The neural architecture of semantic retrieval with and without cues: evidence from neuropsychology and neuroimaging

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Doctor of Philosophy

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Psychology

September 2020

Abstract

Everyday situations are conceptually rich, but not all of this knowledge is relevant at a given time. At the heart of adaptive cognition is flexibility, which allows us to focus on particular mental representations in a way that suits the changing context and goals. Previous work has highlighted the importance of semantic control mechanisms in retrieval, which allow cognition to diverge from dominant associations (Lambon Ralph et al., 2016). However, a clear understanding of the cognitive and neural substrates of semantic flexibility is currently lacking. This work collects evidence from different methods and experimental populations to tackle this broad question. We use novel multimodal semantic cues (i.e. affect and spatial locations) to examine the mechanisms that support flexible patterns of retrieval when the context is helpful or unhelpful. The first two empirical chapters examine behavioural effects of cues and miscues in patients with semantic aphasia (Chapter 2) and investigate whether patients with SA show greater benefits of coherent cue combinations compared to minimal levels of cueing (Chapter 3). The third chapter explores the neural bases of cued semantic retrieval, and tests the predictions of another recent framework which situates the default mode network at the top of a cortical hierarchy of abstraction (Margulies et al., 2016). The final chapter investigates whether the intrinsic connectivity of the brain at rest is predictive of the behavioural efficiency in cued semantic retrieval. Our findings provide evidence for the existence of two qualitatively distinct mechanisms for semantic flexibility, one driven by control processes (impaired in SA) and one driven by the integration of contextual information with long-term semantic knowledge (relatively intact in SA). In line with a growing body of work suggesting a role of default mode network in information integration, we show that more coherent patterns of retrieval which are driven by the context recruit this network. In contrast, multiple-demand regions appear to support more executive aspects of cued retrieval required for the maintenance of cue information. Finally, this thesis provide evidence that affect and location cues are both effective at shaping the activation of semantic knowledge. In summary, this thesis suggests that semantic flexibility is a complex and multi-faceted process which requires an interplay of different cognitive and neural components.

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Acknowledgements

I would like to express my deepest gratitude to my supervisor Beth Jefferies. It’s been a real honour to work alongside this beautiful brain of yours. Never in my life had I met a person who is so intelligent and capable, and yet so modest. Thank you for your flawless supervision, for your endless patience, for your kindness, and for the encouraging words you never failed to provide

A special thanks goes to Jonny Smallwood for the stimulating conversations and for listening to my project updates with great enthusiasm. I feel privileged to have been mentored by such a talented researcher

I would like to thank my TAP members, Aidan Horner and Cade McCall, for their valuable feedback throughout the years. Some people think that TAPs are just a formality. For me, they were fruitful opportunities for critical thinking. Thanks for your genuine interest and for challenging me with thoughtful questions

I am hugely grateful to the Department of Psychology for funding my PhD, and to my examiners Emmanuel Stamatakis and Cade McCall for making my Viva a wonderful experience

Thanks to all the sharp minds in the SemWandering Lab. I am grateful for the thought-provoking conversations and for all the fun times. Special thanks to Tirso, Theo, Deniz, Katya, Sara, Nick, Meichao, Xiuyi and Zhiyao for providing technical and emotional support, and for always doing so with a smile

To the incredible friends I made in York. Dimitris and Christina, my safe *home*, my overseas family. Ioan, a giant of warmth and kindness – we should have done more hikes. Sara, partner of late-night dinners and endless chats – you continue to be my favourite travelling partner, so start planning our next trip! Juliana, strong, fiery and caring - I wish I had met you sooner. Alex, with your unique sense of humour and infinite generosity. Babs, the Bavarian who taught me how to make ragù. Theo, my peppery “philosopher of everything” and skilled conversationist. Tirso, compassionate listener and one of the brightest minds I know. And Eithne, you beautiful Irish sky, thank you for the breeze of change you brought into my life

To my oldest friendships, which miles of land and water could not even scratch. Giulia, Silvia, Laura, Bea, Marta - you have magical powers! *Cin cin* to many more years of learning from each other and laughing at each other, of silliness and serious chats, of laughter and prosecco

My warmest thanks to Petra, for showing me things about myself I did not know

To my super aunt Carla, for loving me and feeding me like a daughter, and to my uncle Paolo, for pretending that I am good at all tech things

I am forever grateful to Tadas for walking a long way with me. For the person you were, for the person you have become, for the nuclear reactor in you. Hopefully one day you will turn back and smile

This PhD wouldn’t have happened without my family. To my father, for his contagious curiosity and his irresistible hunger for knowledge. To my mother, for being a fighter – actually the most loving, thoughtful and compassionate fighter. To my sister, who sees the world through the colourful lenses of imagination, but has not yet realized how beautiful this is

Author’s declaration

I, Lucilla Lanzoni, declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Two chapters of this thesis have been published in the following peer-reviewed journals:

Chapter 2
Lanzoni, L., Thompson, H., Beintari, D., Berwick, K., Demnitz-King, H., Raspin, H., Taha, M., Stampacchia, S., Smallwood, J., Jefferies, E., 2019. Emotion and location cues bias conceptual retrieval in people with deficient semantic control. Neuropsychologia 131, 294–305.
https://doi.org/10.1016/j.neuropsychologia.2019.05.030

Chapter 4
Lanzoni, L., Ravasio, D., Thompson, H., Vatansever, D., Margulies, D., Smallwood, J., Jefferies, E., 2020. The role of default mode network in semantic cue integration. Neuroimage 219, 117019. https://doi.org/10.1016/j.neuroimage.2020.117019

Supervisor’s declaration

As the primary supervisor of Lucilla Lanzoni, I confirm that this thesis is the work of the candidate. Where I am named as co-author, this is due to my role in editing and supervising. The role of other collaborators have been detailed in the acknowledgements section for each empirical chapter.

To Giusi, Stefano, and Chiara.

My light that shines bright.

To Tadas,

Who climbs mountains and knows the most powerful love.

Chapter 1: Review of literature

1. Overview

In everyday situations we rely on semantic cognition for a number of mental processes. We can recognize previously encountered people and objects, make inferences about events, generalize across similar items and contexts, and learn from previous experience. We are able to seamlessly store, retrieve and manipulate the rich knowledge acquired over a lifespan. At the heart of adaptive cognition is flexibility – the capacity to focus on particular mental representations at different points in time, in a way that is appropriate for the ongoing context and goals. Flexibility in semantic cognition allows us to generate coherent patterns of semantic retrieval that diverge from the most accessible associations and features within the long-term semantic store. One contemporary account, referred to as "Controlled Semantic Cognition" (CSC), proposes that semantic cognition emerges from the interplay of conceptual representations and semantic control processes (Jefferies, 2013; Lambon Ralph et al., 2016). Based on the CSC framework - which provides a theoretical grounding for this PhD – meaning retrieval can be shaped (i) in a top-down fashion by applying control over retrieval, but also by (ii) increasing the alignment between external inputs (e.g. the context in which retrieval occurs) and the representations stored in long-term memory. To date, a large body of research has focused on controlled aspects of semantic retrieval (Davey et al., 2016, 2015a; Hoffman et al., 2018; Noonan et al., 2013b; Whitney et al., 2011b; for reviews see Binney and Ramsey, 2020; Jefferies et al., 2020; Lambon Ralph et al., 2016). However, a clear understanding of how flexibility is achieved through the integration of coherent representations is currently lacking. The present thesis examines the ways in which semantic cues can be used to alter the accessibility of long-term representations, and consequently influence the interplay of the neural components underlying semantic cognition.

This opening chapter will firstly describe the evidence for the existence of *multiple components in semantic cognition* drawing on the neuropsychology and the neuroimaging literatures, and it will anticipate the key role of particular brain regions in qualitatively distinct aspects of retrieval. Shifting the focus from individual brain regions to large-scale networks, the chapter will then illustrate that semantic cognition is supported by *functionally interacting large-scale networks*. It will review evidence for a role of heteromodal cortex in global integration and the formation of higher-order conceptual representations, drawing on recent accounts of cortical organization (Margulies et al., 2016). Next, it will anticipate the importance of semantic control and domain-general networks in supporting more controlled aspects of retrieval and working-memory processes. Finally, this chapter will provide a *summary of the research questions* addressed in each chapter and an *overview of the methodologies* used.

2. Distinct components in semantic cognition

The Controlled Semantic Cognition framework (Jefferies and Lambon Ralph, 2006; Lambon Ralph et al., 2016) proposes that flexible semantic cognition emerges from the interaction of conceptual knowledge with semantic control processes, implemented within computationally distinct but interacting brain regions. The first component provides a long-term store of *meanings*, allowing us to make sense of the world which we experience through our senses. As such, it is fundamental for most human behaviours, including verbal and non-verbal communication, action, perception, reasoning, and memory. However, concepts alone are not sufficient. One challenge we face in our everyday life is the need to produce adaptive behaviours in response to the changing environment; different situations require us to focus on different aspects of meaning. Occasionally, we need to access subordinate features of concepts, or even suppress prepotent interpretations of meaning if they are not relevant to the current context and goals. Take the concept “piano” as an example. We know that pianos are large and heavy objects that are played by pressing keys with the fingers. When the task is to play a concerto, features associated with the keys (e.g. corresponding musical notes, pressure that should be applied to produced the desired sound) must be activated to guide behaviour. However, if the task is to load the piano on a truck, this knowledge suddenly becomes irrelevant (Saffran, 2000). Simply put, we store more information about the world than we ever need in any given context. A second component of semantic cognition comes into play to constrain the retrieval of semantic information. *Semantic control* processes manipulate the activation within the representational system, allowing us to focus on currently relevant yet non-dominant aspects of knowledge (Davey et al., 2016, 2015a; Noonan et al., 2013b; Whitney et al., 2011b). In this section I will discuss each component separately, describing evidence from both cognitive neuropsychology and neuroimaging.

2.1 Conceptual knowledge

2.1.1 Hub and Spoke organization of conceptual knowledge

The organization of semantic knowledge has long been a subject of debate in the neuroscientific literature. Different models of semantic cognition disagree on the nature, the number, or even the need for semantic “hubs” or central repositories of meaning (e.g. Martin, 2007; Patterson et al., 2007; Pulvermüller, 2013;

Reilly et al., 2016; Schwartz et al., 2011). Embodied accounts of semantics propose that meaning is computed in dedicated sensory-motor regions (Barsalou, 2008; Pulvermüller, 2012; Pulvermüller and Fadiga, 2010); According to these *distributed-only* theories of semantics, concepts consist of sensory-motor features stored in the same brain systems dedicated to perception and action. Support for this idea comes from patients with category-specific semantic deficits following focal brain lesions (Gainotti, 2010; Warrington and McCarthy, 1987; Warrington and Shallice, 1984). In this view, category-specific disorders of knowledge occur when the lesion compromises the properties that are crucial for defining a category of objects (e.g. visual features for ANIMALS and action-features for TOOLS). Several neuroimaging studies have provided results consistent with the idea of specialized circuits for animate and inanimate objects in the posterior temporal lobe, with the lateral fusiform and superior temporal sulcus processing visual features and motion – crucial for animals, and medial fusiform and posterior middle temporal gyrus (pMTG) responding to action properties – relevant to tool manipulation (for review see Martin, 2007). A major limitation of embodied accounts is the prediction that no focal damage should result into a multimodal semantic deficit, which is instead often observed in degenerative conditions affecting the anterior temporal lobe (Mummery et al., 1999). Moreover, evidence from neuroimaging (Bedny et al., 2008a; Postle et al., 2008; Raposo et al., 2009), transcranial magnetic stimulation (TMS; Papeo et al., 2015, 2009), and lesion studies (Papeo et al., 2010) suggest that modality-specific areas are not always recruited during conceptual processing.

The CSC framework resolves the limitations of embodied theories by proposing that different aspects of knowledge are encoded in modality-specific cortical regions (“spokes”), and brought together within an amodal “hub” in the ventral anterior temporal lobe (vATL; Lambon Ralph et al., 2016; Patterson et al., 2007; Rogers et al., 2004). The *Hub and Spoke* (Figure 1.1.) model of semantic knowledge predicts variations in the coupling between the hub and the spokes – in line with the distinctive features of the concept to be retrieved. For example, concepts that rely heavily on auditory features (e.g. ambulance) will maximally recruit auditory regions, concepts associated with specific motor sequences (e.g. hammer) will involve motor systems, and concepts with salient visual features (e.g. ladybird) will require greater interaction of ATL and visual regions.

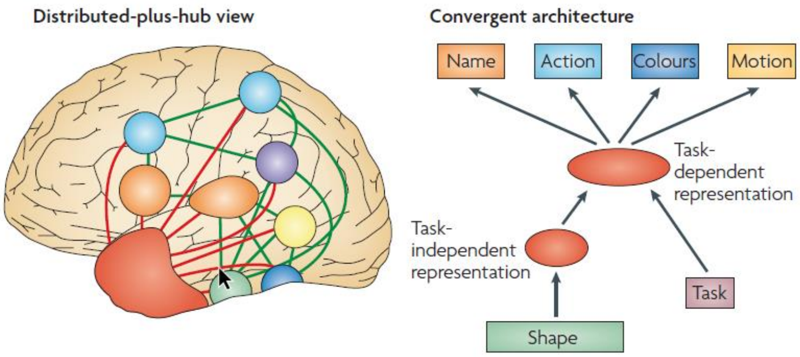

Figure 1.1. Original Hub and Spoke model of semantic memory. In contrast to distributed-only theories, distributed-plus-hub (or Hub and Spoke) model of semantic memory argues that a heteromodal hub (in red) is necessary to create abstract representations. This amodal "hub" located in ATL has bi-directional connections (red lines) to modality-specific regions, which are also interconnected (green lines). Reproduced with permission from Patterson et al., 2007.

Crucially, the ATL hub permits the extraction of abstract representations by encoding concepts at a deeper level than the linear combination of the inputs from the spokes (Reilly et al., 2016). Unlike distributed-only theories, this account offers an explanation for our ability to generalize across experiences and recognize previously encountered concepts even when their appearance changes over time. It also explains why we can confidently group together concepts that belong to the same taxonomic group - even when they share few sensory features (e.g. ORCHID FLOWER and LEAF), or recognize two exemplars as semantically unrelated - despite their similar aspect (e.g. ORCHID FLOWER and ORCHID MANTIS; Figure 1.2.).

Figure 1.2. Two examples of concepts that share common visual properties despite belonging to distinct taxonomic groups. Top row: orchid flower and orchid mantis. Bottom row: leaf and leaf-tailed gecko.

2.1.2 ATL "hub": neuropsychological evidence from semantic dementia

Patients with a degenerative condition known as Semantic Dementia (SD) have provided important insights into the organization of semantic knowledge in the brain. SD arises following progressive degeneration and hypometabolism of bilateral anterior temporal lobe (ATL; e.g. Acosta-Cabronero et al., 2011; Guo et al., 2013), and is characterized by a profound loss of conceptual knowledge, despite intact phonology, spatial attention, and decision-making (e.g. Hodges et al., 1992; Snowden et al., 1989). The semantic loss is evident in tasks that measure comprehension of items presented from different modalities (Bozeat et al., 2000; Coccia et al., 2004; Luzzi et al., 2007), as well as in production tasks such as picture naming (Ralph et al., 2001, 1998; Schwartz et al., 2011) and verbal definitions (Lambon Ralph et al., 1999). Moreover, these patients show consistent difficulties in tasks probing the same concepts in different modalities (Bozeat et al., 2003, 2002, 2000; Jefferies and Lambon Ralph, 2006; Patterson et al., 2007; Rogers et al., 2015), and they are relatively insensitive to phonemic cueing during picture naming (Jefferies et al., 2008b), indicating that the concept itself is degraded. The progressive nature of the disease is reflected in a specific-to-general loss of conceptual knowledge (Hodges et al., 1995; Patterson et al., 2007); patients tend to forget atypical exemplars first (e.g. penguins are birds), suggesting that the boundaries between concepts have become degraded (Mayberry et al., 2010). As the degeneration becomes more widespread, general concepts (e.g. birds are animals) become unavailable. Collectively, these findings provide strong evidence for a core semantic hub in ATL.

2.1.3 ATL "hub": convergent evidence from neuroimaging and brain stimulation

While positron emission tomography (PET) studies have provided initial evidence for a role of ATL in semantic processing (e.g. Bright et al., 2004; Devlin et al., 2000; Rogers et al., 2006), early fMRI studies often failed to detect activation in this region, with a number of semantic studies finding recruitment in regions outside ATL (for reviews see Binder et al., 2009; Martin, 2007; Thompson-Schill, 2003). One explanation for the failure to recover activity in ATL is the signal dropout associated with changes in the magnetic fields in the proximity of air-filled sinuses (Devlin et al., 2000). Since the development of a distortion-corrected spin echo method for fMRI (Embleton et al., 2010; Visser et al., 2010a), the scientific landscape has changed significantly, with a growing number of fMRI studies finding recruitment of ATL during semantic tasks (e.g. Binney et al., 2010; Hoffman et al., 2015; Visser et al., 2010a, 2012; Visser and Lambon Ralph, 2011). Other methods, including repetitive transcranial magnetic stimulation (rTMS; Lambon Ralph et al., 2008; Pobric et al., 2010, 2007), magnetoencephalography (MEG; Marinkovic et al., 2003; Mollo et al., 2017), MEG and EEG decoding (Chan et al., 2011) and fMRI decoding (Correia et al., 2014; Fairhall and Caramazza, 2013; Murphy et al., 2017; Peelen and Caramazza, 2012), have provided converging evidence for a role of ATL in semantics. Moreover, repetitive transcranial magnetic stimulation (rTMS) applied over the left temporal pole in healthy participants produces a selective semantic impairment that mirrors the behavioural pattern in SD, with disrupted picture naming and word comprehension (Pobric et al., 2010, 2007). Collectively, these findings support the notion of an ATL involvement in multimodal semantic processing.

Although the ATL has often been treated as a unitary region (e.g. Patterson et al., 2007), functional specialization within the temporal lobe has been shown across both resting-state and task-based fMRI studies (Binney et al., 2012, 2010; Murphy et al., 2017; Rice et al., 2015; Visser and Lambon Ralph, 2011). For example, the superior ATL shows preferential activation for verbal and auditory stimuli when contrasted with pictures (Moore and Price, 1999; Visser et al., 2012; Visser and Lambon Ralph, 2011). Ventromedial ATL shows the opposite pattern of stronger activations for pictures than words (Visser et al., 2012) and generally activates for concrete objects (Clarke and Tyler, 2015; Hoffman et al., 2015). Polar areas activate more strongly for social concepts (Ross and Olson, 2010; Zahn et al., 2007). A probable explanation for these findings is that representations converge in heteromodal regions in a graded fashion (Bajada et al., 2017b; Buckner and Krienen, 2013; Lambon Ralph et al., 2016; Margulies et al., 2016; Mesulam, 1998; Plaut, 2002). A computational model by Plaut (2002) proposes that semantic representations develop with a "graded modality-specific functional specialisation under the pressure of mediating between multiple input and output modalities". This computational work suggests that regions closer to sensory systems are more important for semantic processing in the specific sensory domain, while regions further away form unimodal cortex (e.g. ATL) are not bound to the sensory modality. In line with this, Margulies et al. (2016) described a "principal gradient" of brain organization, which connects unimodal regions to transmodal default mode cortex. Crucially, the position of heteromodal cortex at the top of the cortical hierarchy suggests a role of regions such as ATL in forming higher-order conceptual representations. Consistently with a graded account, structural connectivity studies in both human and non-human primates show that white matter fasciculi converge in the ATL (Bajada et al., 2017a; Binney et al., 2012; Catani et al., 2002; Kondo et al., 2003; Morán et al., 1987) and selectively connect certain sub-regions of the ATL with other areas in the brain (e.g. Papinutto et al., 2016). Finally, the ATL is known to contain numerous cortical fields with different cytoarchitecture (Blaizot et al., 2010; Brodmann, 1909).

A new formulation of the Hub and Spoke model can account for this pattern of functional specialization and graded convergence within the ATL. According to this framework, semantic knowledge is represented in the brain in a *Graded Hub and Spoke* fashion (Lambon Ralph et al., 2016; Figure 1.3.).

Unlike the original Hub and Spoke model (where all hub units made equal contribution to semantic cognition), this updated account proposes that different ATL sub-regions respond preferentially to certain concepts by virtue of the strength of their connectivity to specific networks in the brain. For example, the temporal pole contributes more to social and emotional concepts by means of its connectivity to the orbitofrontal cortex, the medial ATL responds more to visual or concrete stimuli due to the strong connectivity with visual regions and the STG shows greater activation for auditory stimuli, words, and abstract concepts by virtue of its connectivity to language areas. The broadest integration of conceptual information occurs in the ventro-lateral ATL (vATL) because this region is equally connected to different spoke systems, and distant from all of them (Lambon Ralph et al., 2016; Margulies et al., 2016; Visser et al., 2010b; Visser and Lambon Ralph, 2011). Findings from a recent study by Murphy and colleagues (2017) are consistent with a role of the ventral ATL in processing amodal conceptual knowledge; decoding analyses of task-based fMRI data showed that only the vATL can be trained to classify word-stimuli according to the semantic category irrespective of input modality, while more superior portions of the temporal lobe (i.e. anterior STG) discriminate between input modality regardless of their semantic content. This is in line with the distribution of atrophy in SD – maximal in the polar and ventral ATL (Galton et al., 2001), and with the observation that semantic impairments in SD patients correlate with hypometabolism in ventral – but not in superior - portions of the ATL (Mion et al., 2010).

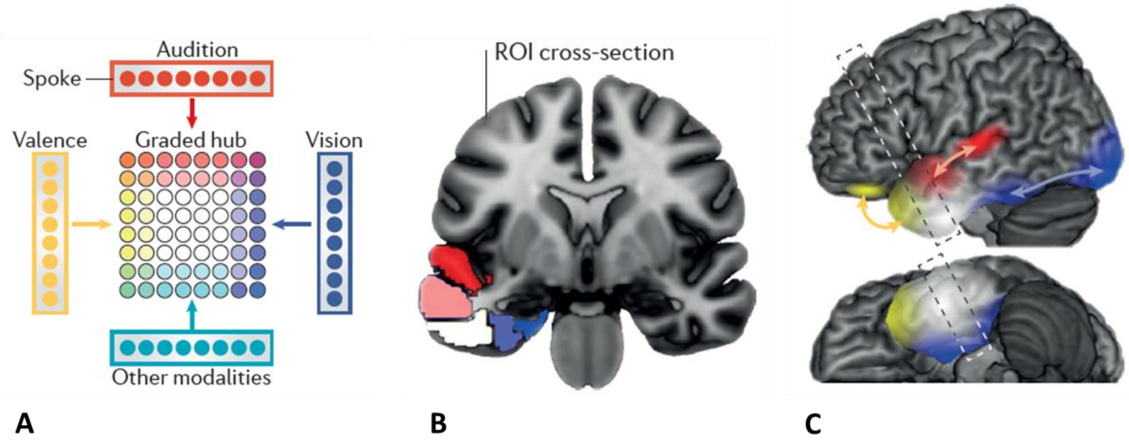

Figure 1.3. Graded Hub and Spoke model. **A** Computational framework showing the graded connectivity between each unimodal spoke (depicted in a different colour) and the heteromodal semantic hub (shown in white). **B** Coronal cross-section illustrating the graded functional specialization within the ATL. **C** Neuroanatomical sketch of the Hub and Spoke model. Reproduced with permission from Lambon Ralph et al. 2017.

2.1.4 The "spokes"

With the exception of *strictly unembodied theories*, that view semantic representations as symbolic and completely independent from sensory and motor systems (Collins and Loftus, 1975; Levelt and Speaking, 1989; Quillian, 1968; for review see Meteyard et al., 2012), most models of semantic memory attribute some degree of functional relevance to regions that represent unimodal information (Binder and Desai, 2011; Lambon Ralph et al., 2016; Meteyard et al., 2012; Pulvermüller, 2013 – for an exception see Mahon and Caramazza, 2008 where it is argued that sensory-motor activation during semantic processing is "epiphenomenal" rather than causally relevant). When we interact with objects in the environment - for example a cup of coffee - our experience includes various sensory (visual, smell, taste) and motor (the action of drinking) features (Meteyard et al., 2012). Consistent with this, several studies have found activation in somatosensory cortex during semantic processing of words with salient perceptual features (for review see Pulvermüller and Fadiga, 2010). For example, concepts expressing different types of visual information ("round" vs. "brown") activate distinct temporal visual regions (Pulvermüller and Hauk, 2005; Simmons et al., 2007). Increased activation has also been observed in the olfactory cortex when the smell is a core feature of the concept ("cinnamon"; González et al., 2006), or in the superior temporal gyrus for words that are semantically related to sounds ("telephone"; Kiefer et al., 2008). Furthermore, words expressing different actions (e.g. "lick" vs. "kick" vs. "pick") activate motor and premotor cortex in a somatotopic fashion - which mirrors the pattern of activation for movements of the tongue, feet or fingers (Hauk et al., 2004; Kemmerer et al., 2013), and a similar pattern of neural recruitment is observed when these words are used in a metaphoric sense (e.g. "she grasped the idea"; Boulenger et al., 2008). Based on this evidence, *embodied* theories attribute a representational role to somatosensory and motor regions dedicated to perception and action (Barsalou, 1999; Pulvermüller, 2001; Zwaan, 2004).

In line with embodied accounts, the *Hub and Spoke* model (Jefferies, 2013; Lambon Ralph et al., 2016; Patterson et al., 2007) proposes that areas proximal to and reciprocally linked to sensory cortices, referred to as "spokes", are necessary to encode modality-specific information. These regions capture the experiential attributes of concepts and events and contribute to the richness of our representations. Unlike classic embodied theories, however, the Hub and Spoke account anticipates a converge of this unimodal information in ATL – which is highly connected to the rest of the brain via major white matter tracts (Binney et al., 2012; Makris et al., 2008; Morán et al., 1987). This region is thought to allow the computation of coherent conceptual representations from combinations of diverse features. While the most commonly discussed spokes within the Hub and Spoke framework are unimodal sensory and motor codes, other spoke systems anticipated by the model are multimodal features. These include praxis - which uses the conjunction of visual and motor information to specify how we should interact with objects, and language - which draws together phonological features from acoustic-motor interactions with word meanings. Other multimodal spokes are valence and spatial location, which are relevant to the empirical work in this thesis and will be discussed in more details in the next few paragraphs. The Graded Hub and Spoke account predicts that "spoke" representations will be able to cue (or miscue) stored representations – depending on whether they are consistent or inconsistent with the current task goals. For example, abstract concepts with few sensory features but strong emotional valence (e.g. suffering, betrayal, friendship) could be made more accessible by activating the relevant emotional valence. Similarly, concepts associated with particular spatial contexts (e.g. siren, parasol) might be supported by activating the relevant locations.

Affect

One organizing dimension for concepts is their degree of pleasantness or unpleasantness, also known as valence. Nearly all experiences can be classified based on their position on this continuum from negative to positive, even though the extent to which valence is a crucial aspect of meaning varies across concepts (e.g. "suffering" vs. "exercise"). In a constructionist view of emotions (Barrett, 2017), valence is part of the broader concept of *core affect* and refers to the representations of the bodily changes that are experienced as pleasant and unpleasant states (Barrett and Bliss-Moreau, 2009; Russell, 2003; Russell and Barrett, 1999). A rich neuroimaging literature implicates the orbitofrontal cortex, ventromedial prefrontal cortex and anterior cingulate cortex in aspects of emotional processing, including the generation of affective states through visceral and autonomic regulation (Gusnard et al., 2001; Öngür and Price, 2000; Sheline et al., 2009), detecting valence in facial expressions (Tsuchida and Fellows, 2012), identifying emotions from facial cues or affective prosody (Hornak et al., 2003; Willis et al., 2014) and the subjective experience of affective states (Rolls and Grabenhorst, 2008; for discussion and meta-analytic review see Lindquist et al., 2015; Satpute and Lindquist, 2019). Brain regions typically involved in the processing of semantic knowledge, such as the anterior temporal lobe, medial temporal lobe and ventrolateral prefrontal cortex (Binder et al., 2009) are thought to use stored semantic representations to interpret the meaning of core affective representations (Lindquist et al., 2014). Collectively, these regions supporting different aspects of emotional processing are part of the same large-scale network known as default mode network (DMN; Buckner et al., 2008; Raichle et al., 2001) which is involved in a number of internally-oriented processes (for review see Andrews-Hanna, 2012).

While affect representations are computed within DMN nodes, the multimodal and highly-abstract nature of valence suggests that these representations may be accessible via different channels or "spokes", including vision and the auditory system. For example, listening to a violin concerto, detecting the emotional prosody in speech or reading emotional cues in a facial expression may activate the same negative affect, and produce a similar representation of sadness. Furthermore, when emotion is conveyed by a facial expression there will be recruitment of face-selective areas such as the occipital face area (Gauthier et al., 2000), the fusiform face area (Kanwisher et al., 1997), and the superior temporal sulcus face area – which has been associated with the detection of changes in the facial expression (Andrews and Ewbank, 2004; Harris et al., 2012; Haxby et al., 2000). Crucially, the heteromodal hub in ventral ATL is highly connected to face-selective regions in the fusiform gyrus (Behrmann et al., 2007; Tavor et al., 2014), and it is connected to orbito-frontal areas via the uncinate fasciculus (Highley et al., 2002; Papinutto et al., 2016; Von Der Heide et al., 2013).

Spatial locations

Spatial representations are also highly relevant to our understanding of concepts. In a similar way to valence, spatial representations are multimodal: they are linked to vision (e.g. recognizing the spatial layout of the kitchen), motor outputs (e.g. navigating the scene), olfactory information (e.g. smelling freshly baked apple cake), and auditory inputs (e.g. hearing the beeping of a kitchen timer). In everyday situations semantic retrieval occurs in physical contexts, and consequently space can be a core part of meaning - especially for concepts that are consistently associated with a given spatial location (e.g. the concept PARASOL is strongly related to beach or pool-side scenarios).

The last five decades of neuroscience research have revealed mechanisms for representing space in the hippocampus and the medial temporal lobe complex (for comprehensive review see Grieves and Jeffery, 2017). Seminal electrophysiology studies in rats have identified hippocampal “place cells” that fire preferentially when the animal’s head is in a specific location of the environment (O’Keefe and Dostrovsky, 1971; O’Keefe and Nadel, 1978). Interestingly, the activity of these cells appears to be unaffected by the rat’s orientation (Muller et al., 1994) or even the absence of visual information caused by blindness (Save et al., 1998), suggesting that abstract or cognitive representations of the environment may be formed in the hippocampus (O’Keefe and Nadel, 1978). Other space-relevant cells were found in the Papez circuit – named “head cells” for their preferential response to specific head directions (Taube et al., 1990a, 1990b), and in entorhinal cortex – known as “grid cells” for their tendency to fire in discrete and regularly spaced locations (Fyhn et al., 2004; Hayman et al., 2008). Although place cells have been found in the human brain (Ekstrom et al., 2003), only a small portion of neurons in the medial temporal lobe seem to respond purely to locations and they are mostly located within the hippocampus (Ekstrom et al., 2003; Grieves and Jeffery, 2017).

Convergent evidence for a role of the hippocampus in representing and remembering space comes from studies showing recruitment of this region in humans during virtual navigation (Burgess et al., 2001b; Maguire et al., 1998; Miller et al., 2013) and during the subsequent recall of navigation-related memories (Miller et al., 2013). Furthering the proposed spatial role of this region, increased hippocampal volume is seen in people who have received extensive navigation training (Maguire et al., 2000). Neuroimaging studies have identified a set of cortical regions beyond the hippocampus that appear to be crucial for spatial memory and navigation: these include the retrosplenial cortex (RSC) and the parahippocampal cortex (PHC) (for reviews see Aminoff et al., 2013; Ranganath and Ritchey, 2012; Vann et al., 2009). Within the posterior PHC, the parahippocampal place area (PPA) shows a selective response to spatial scenes (Epstein and Kanwisher, 1998). These regions have been shown to dissociate, with PPA supporting the perception of the immediate scene, and RSC supporting long-term spatial knowledge (Epstein et al., 2007). In line with this idea, patients with damage to PHC show impaired recognition of scenes (Landis et al., 1986; Takahashi and Kawamura, 2002), while damage to RSC is associated with topographical amnesia (Aguirre and D'Esposito, 1999; Epstein, 2008; Maguire, 2001). The evidence reviewed here suggests that spatial features of concepts may be processed in spatial "spokes" distributed in several medial temporal lobe regions. The ventrolateral ATL is functionally connected to the anterior hippocampus and other medial temporal lobe regions, thought to play a role in representing space and assessing the significance of previously encountered entities (Ranganath and Ritchey, 2012; Ritchey et al., 2014). Bidirectional structural connections via the entorhinal cortex (Squire and Zola-Morgan, 1991) also contribute to the creation of representations capturing spatial context within the medio-temporal complex (Bicanski and Burgess, 2018; Burgess, 2002; Burgess et al., 2002).

In line with the rich connections of ATL with emotional and spatial regions (Chiou and Lambon Ralph, 2019; Lambon Ralph et al., 2016; Ranganath and Ritchey, 2012), the Graded Hub and Spoke account predicts that representations created in these cortical "spokes" will be able to cue (or miscue) stored representations – depending on whether they are consistent or inconsistent with the current task goals. For example, the activation of concepts associated with particular spatial contexts might be boosted by the presentation of the relevant locations. In a similar way, concepts with few sensory features but strong emotional valence could be made more accessible by activating the relevant emotional features. In particular, abstract words which are often semantically linked to knowledge about emotions (Kousta et al., 2011; Ponari et al., 2018) might have strong representations in regions involved in processing emotional information (Vigliocco et al., 2014).

2.1.5 Beyond a single “hub” for semantic knowledge

Moving beyond ATL, other brain areas appear to be involved in the long-term storage of semantic representations. For example, Schwartz et al. (2011) found support for the existence of two parallel yet complementary semantic systems for taxonomic *vs*. thematic information. The study revealed that taxonomic errors in picture naming (e.g. “pear” for “apple”) typically occur in aphasic patients with damage to ATL, while thematic errors (e.g. “worm” for “apple”) are associated with temporo-parietal lesions affecting AG and pMTG. Based on these findings, the authors proposed a *Dual Hub* system of semantic knowledge, whereby ATL and TPJ play different key roles in semantic processing: ATL captures feature similarity and allows grouping by category, and the temporo-parietal cortex computes complementary relationships for the purpose of event processing (see also Mirman, 2003 for a computational model). Interestingly, the proposed role of ATL in extracting taxonomic relations is compatible with Hub and Spoke models of semantics, where feature integration is thought to happen in the ATL (Lambon Ralph et al., 2016; Patterson et al., 2007). However, while the Dual Hub account anticipates a similar role of AG and pMTG as a thematic hub, these two regions often dissociate indicating that they might support qualitatively distinct aspects of semantics (for review see Jefferies et al., 2020).

Informed by a large meta-analysis of neuroimaging studies (Binder et al., 2009) and neuropsychological evidence, Binder and Desai (2011) propose that the content of semantic representations is derived through modality-specific simulations, whereby information relevant to a specific modality is processed in the corresponding sensory-motor system, and then integrated into increasingly abstract representations. Despite the similarities with the Hub and Spoke account, this model does not place ATL at the top of the abstraction hierarchy. Instead, it assumes that multiple levels of abstraction are achieved via several *convergence zones* (for an initial proposal see Damasio, 1989) located throughout the temporal (i.e. MTG and anterior portions of the fusiform gyrus) and parietal (i.e. AG and supramarginal gyri) cortex. These regions have largely been ignored in the embodied literature because of their location outside sensory-motor areas. However, they are reliably recruited in neuroimaging studies of semantic processing (Binder et al., 2009) and have been shown to activate during conceptual processing irrespective of the sensory-perceptual features of the concepts (e.g. Binder, 2016; Bonner and Price, 2013; Fernandino et al., 2016; Kuhnke et al., 2020). The case of parietal cortex is especially interesting for the variety of functions it appears to support. AG is considered in more detail in the next section.

2.1.6 The contribution of parietal cortex to (semantic) cognition

Following Geschwind's (1972) proposal that AG might support multimodal semantic representations, a number of neuroimaging studies have implicated this region in different aspects of semantic processing (e.g. Binder et al., 2005; Graves et al., 2010; Humphries et al., 2007; Seghier, 2013; Seghier et al., 2010). In a meta-analysis of 120 studies of semantic processing (Binder et al., 2009), AG was found to be the most reliable area of activation. Additionally, transcranial magnetic stimulation (TMS) studies have shown that AG is pivotal in the retrieval of dominant aspects of semantic knowledge (Davey et al., 2015a). Some researchers have proposed that activity in this region might reflect automatic, stimulus-driven aspects of semantic cognition, seen in situations in which the cognitive demands of semantic tasks are relatively low (Humphreys et al., 2015). In line with this, AG has patterns of intrinsic connectivity that are partially overlapping with the default mode network (DMN; Davey et al., 2016; Humphreys and Lambon Ralph, 2015; Jackson et al., 2016; Seghier et al., 2010), which typically deactivates in response to demanding tasks (Raichle et al., 2001). Nevertheless, there is also evidence for an involvement of AG even when the tasks are relatively hard (Murphy et al., 2018).

AG might support memory-guided cognition when multiple sources of information can be brought together to form increasingly complex representations. Recent studies of linguistic compositions provide convincing evidence for a role of heteromodal parietal cortex in combinatorial conceptual processing. The construction of complex concepts from simple ones ("JACKET", "PLAID" *vs*. "PLAID JACKET") modulates activity in AG regardless of the modality of presentation, while atrophy in this region results in impaired conceptual combinations (Price et al., 2015). An extensive literature using magnetoencephalography (MEG; Bemis and Pylkkänen, 2013, 2011; Poortman and Pylkkänen, 2016) has identified combinatorial activity across modalities in the left ATL and in AG. These sites show an increased response when nouns are presented in a compositional context (e.g. "RED BOAT") compared to when the same noun is presented in a non-compositional context, such as when preceded by a non-word (e.g. "XQK BOAT") or when part of a list (e.g. "CUP, BOAT"). In line with the MEG literature, anodal transcranial direct current stimulation of the left AG improves the comprehension of semantically meaningful combinations (e.g. "TINY RADISH") compared to non-meaningful combinations (e.g. "FAST BLUEBERRY") (Price et al., 2016).

A role of AG in information integration more broadly is also documented in the episodic memory literature, where increased activation is observed during the retrieval of multi-modal memories compared with unimodal episodes (Bonnici et al., 2016). This region is thought to be crucial for representing details through integration of multimodal information (Shimamura, 2011; Tibon et al., 2019) across temporal frameworks (Ramanan et al., 2017), and for contributing to recollection (Bellana et al., 2019). In line with this, AG shows increased activity during the retrieval of "schema" memories (Wagner et al., 2015) – pre-existing mental frameworks that allow us to organize newly encoded information in relation to existing knowledge. According to Wagner and colleagues, schema retrieval involves the creation of links or mental connections and the "binding or recombination of information", which is thought to be a core function of AG (e.g. Binder et al., 2009; Gilmore et al., 2015; Price et al., 2015; Shimamura, 2011; Wagner et al., 2015).

The evidence reviewed here suggests that although AG and ATL are both implicated in heteromodal semantic processing, AG plays a broader role in cognition. Consistently, a meta-analysis by Humphreys et al. (2015) revealed dissociations in the neural response of these two sites to tasks varying in nature and difficulty. While the pattern of activation of ATL depended on the semantic content of the task, AG was deactivated for both semantic and non-semantic tasks, and this effect was related to difficulty. Another meta-analysis by Humphreys and Lambon Ralph (2015) associated AG with a range of functions beyond semantic memory, including numerical processing, episodic memory retrieval, and sentence-level tasks. Together, these studies support the idea that AG might serve a more domain-general function compared to ATL. To briefly anticipate, AG and ATL show functional coupling at rest and during tasks (Bellana et al., 2017; Davey et al., 2016, 2015b; Hurley et al., 2015; Jackson et al., 2018), and are part of a larger network known as the default mode network (DMN; Raichle et al., 2001). In Section 3, these regions will be discussed in terms of large-scale networks.

2.2 Semantic control processes

Although we retain a wealth of information about any given concept, only a subset of this information is relevant in a particular context (e.g. Barclay et al., 1974; Jefferies, 2013; Schoen, 1988; Yee and Thompson-Schill, 2016). Sometimes, distant associations or less dominant aspects of knowledge are required to achieve a certain goal: we can readily identify that a rolled up newspaper can squash a fly, even though newspapers are normally associated with reading (Corbett et al., 2011; Jefferies, 2013). This semantic flexibility, reflecting the retrieval of non-dominant features of concepts when this is required by the context, is thought to require semantic control processes that are separate from the conceptual store (Jefferies, 2013; Lambon Ralph et al., 2016; Thompson-Schill et al., 1997; Wagner et al., 2001; Whitney et al., 2011b; for review see Badre and Wagner, 2002). In frequently-encountered contexts in which the dominant features of concepts are relevant to ongoing thought and behaviour, the hub can integrate from the spokes and automatically generate an appropriate response without further constraints. When highly accessible information is no longer relevant (for example when using a newspaper to squash a fly), however, this process could generate an erroneous response. Accordingly, semantic control mechanisms come into play to re-establish the alignment with the new context, allowing us to produce flexible and creative solutions (Jefferies, 2013; Lambon Ralph et al., 2016).

2.2.1. Control deficits in semantic aphasia

The study of stroke patients with a condition known as *semantic aphasia* (SA) has suggested that control mechanisms might be supported by distributed left-lateralised prefrontal and temporo-parietal regions, including left inferior frontal gyrus (IFG) and middle temporal gyrus (pMTG) – regions commonly damaged in SA. The term "semantic aphasia" was first introduced by Henry Head (1926) and Luria (1973) who described patients with a high-level deficit in comprehension - visible across modalities and characterized by difficulties in processing relationships between concepts. The association of these deficits with impaired semantic control became more clear in 2006, when the first direct comparison of these patients and patients with SD was published (Jefferies and Lambon Ralph, 2006).

Semantic retrieval in SA appears inflexible and driven by dominant over-learned patterns of associations. For instance, patients show poor comprehension of subordinate interpretations of ambiguous words (e.g. when matching FIRE with RIFLE, as opposed to matching FIRE with HOT) and have difficulty selecting targets in the presence of distractors (Noonan et al., 2010). Critically, these patients show inconsistent performance when the same concepts are probed under different cognitive demands, often performing more accurately in highly constrained tasks in which semantic retrieval is strongly guided by the task itself (Jefferies and Lambon Ralph, 2006; Noonan et al., 2013a; Rogers et al., 2015). In line with difficulty in regulating retrieval, they show strong effects of cueing and miscuing: their performance is improved when the cue is consistent with the required representations (Corbett et al., 2011; Jefferies et al., 2008b; Noonan et al., 2010) and they show severe difficulties when miscues activate irrelevant features that must be suppressed (Noonan et al., 2010; Soni et al., 2009). In line with the idea of a multimodal semantic deficit in retrieval, cueing and miscuing effects are observed across different modalities. For example, phonological cues result in near-perfect picture naming performance in SA (Jefferies et al., 2008b), while miscues (e.g. for TIGER, the phoneme "L") disrupt performance (Soni et al., 2009). Similarly, sentence contexts that clarify the meaning of an ambiguous word ("they served a delicious PUNCH at the party" for PUNCH-FRUIT) facilitate retrieval in SA, while sentence contexts that activate the irrelevant representation of the word (e.g. "the young men like to BOX" for BOX-PACKET) have a detrimental effects of the task (Noonan et al., 2010). Some evidence from the non-verbal domain suggests that picture cues are also effective at priming meaning: SA patients are better at retrieving the action associated with an object when they are presented with a picture showing the recipient (e.g. for HAMMER, a picture of a NAIL; Corbett et al., 2011). At present, the impact of other types of non-verbal cues, such as visuo-spatial contexts, emotional facial expressions and emotional prosody is still unclear. Since language comprehension in everyday situations is likely to be influenced by the environment we are in, this thesis will examine the extent to which patients with SA rely on these cues (Chapter 2 and 3).

Taken together the difficulties observed in SA point to a role of left prefrontal and posterior temporal regions in controlled retrieval. Interestingly, patients with SA have also been described that show similar patterns of impairment despite having more posterior lesions affecting the parietal cortex (Thompson et al., 2015). This observation raises the possibility that a distributed network for semantic control might extend beyond the frequently described left IFG and pMTG regions. This will be discussed in section 3.3.

2.2.2 Comparison of semantic aphasia and semantic dementia

The pattern of impairment in SA is qualitatively distinct from deficits in semantic dementia: although both groups have multimodal semantic comprehension impairment affecting both verbal and non-verbal comprehension, semantic dementia gives rise to a gradual degradation of conceptual knowledge that is (i) highly predictable across tasks, (ii) relatively unaffected by the executive demands of tasks, and (iii) relatively insensitive to distractors (Jefferies and Lambon Ralph, 2006; Patterson et al., 2007). Collectively, these neuropsychological findings resemble the proposed distinction between “storage” (i.e. representations) and “access” (i.e. semantic control) components in semantic dementia and semantic aphasia respectively (Warrington and Cipolotti, 1996; Warrington and McCarthy, 1983). A recent study by Chapman et al. (2020), however, has challenged this idea by suggesting that patients with SA and SD might be less dissimilar than originally thought. They directly contrasted patients’ performance in a number of tasks traditionally used to highlight behavioural differences between SA and SD. Contrary to previous findings that SD are consistent in tasks probing the same semantic representations (Corbett et al., 2009a; Jefferies and Lambon Ralph, 2006; Thompson et al., 2018), the study showed relatively poor item- and task-consistency in both groups. Moreover, despite replicating prior findings of a correlation in SA between semantic tasks with similar cognitive demands, the study also found correlations between tasks with different cognitive demands. Finally, in contrast with previous evidence for a detrimental effect of semantically related distractors in SA (but not in SD), Chapman et al. (2020) found exaggerated effects of distractor strengths in both groups, suggesting that SD and SA might have similar difficulties in inhibiting distractors. Based on these results, the authors propose that, rather than focusing on the storage-access distinction, future research should take into account the possible anatomical overlap in the lesion location, which may be a better predictor of similarities and differences across different examinations.

2.2.2. Neuroimaging evidence for controlled retrieval in lateral PFC and pMTG

Early neuroimaging studies of the contribution of left prefrontal cortex (PFC) to controlled cognition have focused on different aspects of regulatory processing. One prominent theory suggests that left IFG supports the *selection of task-relevant knowledge* among competitors, rather than semantic retrieval *per se* (Thompson-Schill et al., 1997). Thompson-Schill and colleagues examined semantic decisions with varying levels of selection demands. In the "high selection" condition, participants had to judge which of two options was most similar to a probe based on a given feature (e.g. *colour* – SEAGULL: crow, dove). Here, subjects must focus on the relevant property "white" while discarding other semantic information which is not relevant. In contrast, judgements of global semantic similarity presented in the "low selection" condition could be made using any properties or features (e.g. RAISIN: suit, prune), and therefore involved minimal selection. Left IFG showed consistently more activation in the high *vs*. low selection condition, however it did not respond to manipulations of the number of response options (either two or four) – suggesting that it is not the overall amount of semantic knowledge that must be accessed which drives activation in IFG, but rather the selection among competing responses. An alternative view is that the left IFG contributes to *controlled semantic retrieval* more generally (Wagner et al., 2001). In this study participants were presented with semantic decisions in which the associative strength between probe and target was manipulated across conditions. In contrast with Thompson-Schill et al. (1997), increasing the number of response options increased BOLD activity in left IFG. Moreover, this region was more strongly recruited for weak *vs*. strong associations, even when the task did not involve selection between competing options. These findings were interpreted in line with a role of the left IFG in the controlled retrieval of conceptual knowledge. Accordingly, left IFG is thought to guide semantic memory in cases when strong associations are not sufficient and top-down control is needed to retrieve non-dominant associations (Badre and Wagner, 2002).

More recent work has revealed that left IFG is involved in both retrieval and selection (Badre et al., 2005; Bedny et al., 2008b; Gold et al., 2006; Snyder et al., 2011), reconciling these different hypotheses regarding the functional role of this region. Badre et al. (2005) proposed an anterior-to-posterior specialization within this area. Anterior/ventral IFG is involved in controlled retrieval - for example when the task requires the retrieval of weak semantic associations or the cues are insufficient to activate relevant knowledge in a stimulus-driven fashion. This is consistent with previous investigations showing that left anterior IFG responds more strongly when the task requires participants to link semantically distant concepts in the absence of a specific goal (Wagner et al., 2001). In contrast, the mid-IFG is thought to support a generalized selection mechanism that resolves competition between activated representations (Badre et al., 2005). Other studies have reported a different although potentially-related functional specialization within this area, with ventral parts implicated in semantic control and dorsal parts implicated in lexical and phonological control (Devlin et al., 2003; Gough et al., 2005; Poldrack et al., 1999; Snyder et al., 2007; Wagner et al., 2001). Moreover, the most dorsal part of left IFG – extending into the inferior frontal sulcus (IFS) – overlaps with a domain-general executive network known as the multiple-demand network (Duncan, 2010; Fedorenko et al., 2013).

Another site that shows consistent activation during tasks with high control demands is left pMTG, as indicated by an activation likelihood estimation (ALE) meta-analysis by Noonan et al. (2013); however the functional contribution of pMTG to semantic cognition remains controversial. This region often co-activates with IFG across various aspects of semantic cognition, including the retrieval of weak associations, comprehension of ambiguous words, and when competing information must be inhibited (Badre et al., 2005; Bedny et al., 2008a; Rodd et al., 2005; Thompson-Schill et al., 1997; Vitello et al., 2014; Vitello and Rodd, 2015; Whitney et al., 2011a; Zempleni et al., 2007). Moreover, neuroimaging studies have revealed that there are strong functional and structural connections between pMTG and IFG (Anwander et al., 2006; Croxson et al., 2005; Jung and Lambon Ralph, 2016; Rilling et al., 2008; Saur et al., 2010), suggesting these sites form a functional network. In line with the Controlled Semantic Cognition framework (Lambon Ralph et al., 2016), this evidence shows that left pMTG is involved in semantic control.

In addition to its proposed role in semantic control, left pMTG has been associated with the comprehension of actions and events and with relational semantics (for a recent discussion see Jefferies et al., 2020). A recent study using multi-voxel pattern analysis of fMRI data (Wurm and Caramazza, 2019) revealed decoding activity in pMTG for actions presented both as written descriptions and short videos, suggesting a representational role of this region which is independent of stimulus type. This area also activates during action planning (Johnson-Frey et al., 2005), action understanding (Davey et al., 2016; Urgesi et al., 2014), and tool recognition (Ishibashi et al., 2016). Additionally, pMTG responds to verbs more than nouns (Bedny et al., 2014, 2008a; Peelen et al., 2012), and similar patterns of activation are seen when participants must name actions or objects present in an action image (Liljeström et al., 2008). Neuropsychology studies have documented impaired understanding of actions in patients with left temporo-parietal lesions (Tsagkaridis et al., 2014) and a tendency to make thematic errors in picture naming (Schwartz et al., 2011). Together, these observations are compatible with the Dual Hub account, which proposes that pMTG (together with AG) supports long-term knowledge of thematic associations and events (Schwartz et al., 2011). To reconcile the different roles proposed by the Controlled Semantic Cognition and the Dual Hub accounts, Jefferies et al. (2020) propose that, rather than storing long-term knowledge about actions, pMTG may support a broader representation of event structures and contextually-guided retrieval – which is relevant to both action and non-action concepts.

2.2.3 Inhibitory TMS to left IFG and pMTG disrupts semantic control

TMS has been central in establishing the functional contribution of IFG and pMTG to controlled semantic processing. This technique produces relatively focal and temporary “virtual lesions”, thus enabling inferences about the role of a specific area. A study by Whitney and colleagues (2011b) found that inhibitory TMS applied over left IFG and pMTG disrupted executively demanding semantic decisions involving the subordinate meanings of words (i.e. weak associations), while strong and automatic associations remained unaffected. Non-semantic tasks were also unaffected by the TMS stimulation, irrespective of the cognitive requirements of the task, pointing to a specific role of IFG and pMTG in the controlled retrieval of semantic information. Similarly, Davey and colleagues (2015a) showed that semantic judgements to weakly related words were disrupted following inhibitory TMS over pMTG. In contrast, inhibitory stimulation to ventral AG disturbed the efficient retrieval of strong associations, suggesting this site supports the coherent retrieval of concepts from the semantic store. This is consistent with an extensive literature using functional magnetic resonance imaging (fMRI), showing that both ventral AG and ventral ATL show stronger responses during the strong relative to weak associations (e.g. Davey et al., 2016; Humphreys and Lambon Ralph, 2015; Lau et al., 2013; Teige et al., 2019). In line with the proposed role of left IFG and pMTG in semantic control, Krieger-Redwood and Jefferies (Krieger-Redwood and Jefferies, 2014) found that TMS to either site produces similar disruptive effects on naming performance for semantically-related items during the early cycles of a cyclical picture naming task, when retrieval demands are high. Moreover, applying TMS to left IFG in healthy participants slows the comprehension of abstract *vs*. concrete words when they are presented out of context (but not when they are presented following a sentence cue) – mimicking the effects observed in patients with SA and lesions focused on the left ventrolateral PFC (Hoffman et al., 2010).

3. Large-scale networks support qualitatively distinct aspects of cognition

The previous section reviewed evidence in support of the idea of two separable yet interacting components in semantic cognition, namely semantic representations and control processes. The neural bases of the two components were described with reference to neuropsychology and neuroimaging studies showing the involvement of specific brain regions in qualitatively different aspects of semantic retrieval. However, to address the empirical question of how these components interact to support semantic flexibility, it is necessary to adopt a broader view - shifting the focus from individual regions to large-scale networks and their dynamic interplay. Semantic cognition has been shown to overlap with distinct resting-state networks that are recruited differentially depending on the task demands (Badre and Wagner, 2006, 2005; Davey et al., 2016; Hallam et al., 2016; Humphreys and Lambon Ralph, 2015; Jackson et al., 2016; Krieger-Redwood et al., 2015; Noonan et al., 2013b; Seghier et al., 2010; Whitney et al., 2011a; Xu et al., 2016). As reviewed in the previous section, pMTG and IFG are crucial when the task requires to direct retrieval away from dominant representations and focus on non-dominant aspects of knowledge. Here we show that these regions are part of a larger *semantic control network,* involving frontal and temporo-parietal regions (Davey et al., 2016, 2015b; Hallam et al., 2016; Noonan et al., 2013b; Figure 1.4.A). Additionally, spatially adjacent domain-general regions collectively known as the *multiple demand network* (MDN; Duncan, 2010; Duncan and Owen, 2000; Fedorenko et al., 2013; Figure 1.4.B) are thought to support cognitive control across domains and may be required when tasks involve the maintenance of information in working memory, or the controlled application of task rules. This type of control is relevant when semantic representations are used to guide behaviour in a goal-driven fashion (Gonzalez Alam et al., 2018). In contrast, the *default mode network* (DMN; Raichle et al., 2001; Figure 1.4.C) may be relevant for more coherent or integrative aspects of retrieval, for example when the concepts to be retrieved are consistent with the representations stored in semantic knowledge, or when information can be integrated to form higher-order representations (Davey et al., 2016; Jackson et al., 2016; Lau et al., 2013; Wirth et al., 2011). Two regions described in the previous section – AG and ATL, which are considered key regions for the representation of conceptual information – are typically coupled at rest (Bellana et al., 2017; Davey et al., 2016, 2015a; Hurley et al., 2015; Jackson et al., 2018) and both show patterns of intrinsic connectivity allied with DMN (Jackson et al., 2019; Murphy et al., 2017; Vincent et al., 2008).

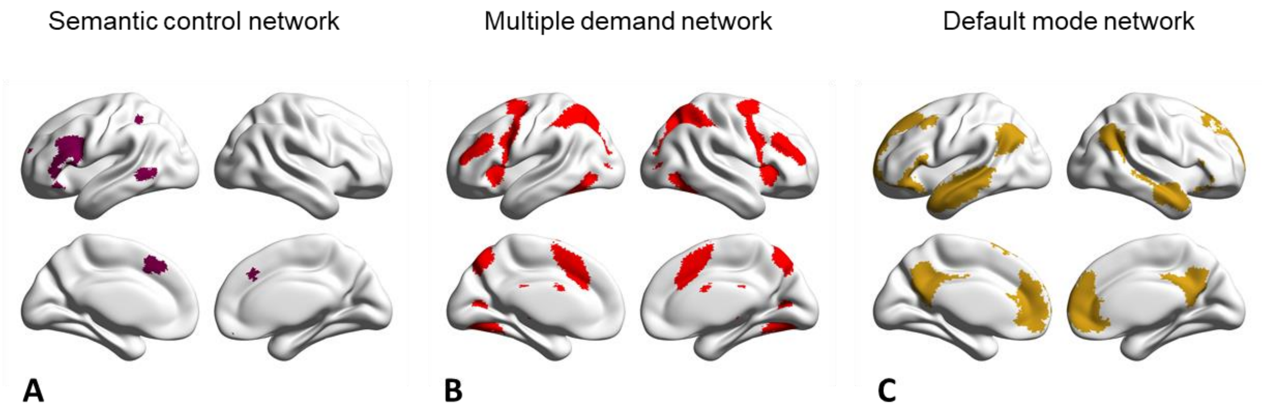

Figure 1.4. Illustration of three large-scale networks involved in semantic cognition. **A** Semantic control network (Humphreys and Lambon Ralph, 2015; Noonan et al., 2013b); **B** Multiple demand network (Duncan, 2010; Fedorenko et al., 2013); **C** Default mode network (Yeo et al., 2011).

3.1 Default mode network

The default mode network (DMN) is an anatomically defined network comprising higher-order association regions such as posterior cingulate cortex, medial PFC, lateral and medial temporal lobes, and AG - collectively known as default mode network (DMN). These regions show strong functional connectivity in resting-state fMRI (e.g. Greicius et al., 2003; Power et al., 2011; Yeo et al., 2011) and during tasks (e.g. Greicius et al., 2004; Simony et al., 2016). Historical views of the default mode network described it as a "task- negative" network (Raichle et al., 2001), which deactivates under cognitively demanding tasks (Mazoyer et al., 2001; Shulman et al., 1997) and is most prominent in the absence of external task demands (Gusnard et al., 2001; Gusnard and Raichle, 2001). Challenging this idea, a growing body of work has shown that DMN actively supports various aspects of cognition (Spreng, 2012), including semantic processing (Binder et al., 2009; Krieger-Redwood et al., 2016), autobiographical recollection of the past and imagining the future (Addis et al., 2007; Andrews-Hanna, 2012; Buckner et al., 2008; Huijbers et al., 2009; Schacter et al., 2012, 2007; Spreng et al., 2009; Svoboda et al., 2006; Szpunar et al., 2007); scene construction (Hassabis et al., 2007; Hassabis and Maguire, 2007), working memory (Konishi et al., 2015; Meyer et al., 2012; Spreng et al., 2014; Vatansever et al., 2015a), and internal generation of emotion (Engen et al., 2017). Notably, many of these tasks involve directing attention internally to generate adaptive patterns of thought. Taken together, this vast neuroimaging evidence points to a role of DMN in supporting "internal mentation", including spontaneous introspective processes which have no basis in the external world (Andrews-Hanna, 2012; Buckner et al., 2008).

3.1.1 Memory-based account of default mode activity

Memory retrieval requires a focus on previously encoded content, as opposed to information present in the environment. Smallwood et al. (2013b) tested the hypothesis that default mode activity might support perceptually decoupled states such as memory, allowing cognition to process representations that are not immediately available to the senses. They used a paradigm in which participants made decisions based on information from memory (i.e. judge whether a previously presented number was odd or even) or perceptually available (i.e. judge whether the number on the screen was odd or even). The study showed that activity in medial PFC and anterior cingulate cortex was associated with faster responses when participants made decisions from memory, and with slower actions if task performance depended on perceptually available information. In line with this, Konishi and colleagues (2015) found greater engagement of DMN during "memory guided decision-making" compared to when decisions were made based on sensory input. These findings also partially overlap with those of Spreng et al. (2014), where DMN activity in a 2-back task was observed when participants made decisions about familiar faces compared to anonymous faces. Spreng et al. suggest that not only recently-encoded information, but also long-term semantic representations (e.g. knowledge associated with a famous face) might be relevant to DMN.

More recently, Murphy et al. (2019, 2018) replicated findings that regions within DMN are engaged when participants make decisions from memory, even when the task demands are greater in this condition. Using a delayed-match-to-sample paradigm, they showed that decisions in a 0-back condition (based on information in the environment) elicited higher activity in unimodal regions along the ventral visual stream, while memory guided decisions (1 back condition) recruited regions within DMN, including bilateral AG, ATL, posterior cingulate cortex and medial PFC. Moreover, the magnitude of this DMN response was greater when decisions involved meaningful objects, relative to judgements about colours (Murphy et al., 2018). These findings provide further support for a role of DMN in memory-guided cognition and suggest that retrieval of meaningful semantic representations might be mediated by DMN. Notably, this study also demonstrates a role of DMN in semantic retrieval even when tasks are relatively hard, thus challenging task-negative accounts of DMN.

3.1.2 Default mode network and semantic cognition

The role of DMN regions in semantic cognition remains controversial: while a meta-analysis by Binder et al. (2009) found peak activation for semantic tasks in AG, others have rejected the proposed role of DMN in semantic cognition, arguing that the spatial overlap between areas identified in a meta-analysis and DMN is not sufficient to draw conclusions about its functional contribution (Humphreys et al., 2015;

Humphreys and Lambon Ralph, 2015; Jackson et al., 2019). In a recent study, Jackson and colleagues used a data-driven multivariate approach known as independent component analysis to test the idea that the semantic network and DMN form distinct networks. First, they extracted components corresponding to the semantic and default mode networks using decomposition of resting-state data. They then examined the relationship between the two components and task-based activation maps (therefore accounting for the spatial overlap), and found that only the semantic network – but not the DMN – was involved in semantic processing. Default mode regions have also been shown to deactivate across semantic and non-semantic tasks, with less deactivation observed in easier tasks (Humphreys et al., 2015) – leading some researchers to attribute the previously reported DMN involvement to differences in task difficulty. This interpretation is challenged by studies that show DMN activity when the demands of semantic and non-semantic tasks are equated (Wirth et al., 2011) or controlled (Binder et al., 2005). Although deactivation is often observed in DMN compared to rest or task-periods (Fox et al., 2005) the degree of deactivation is smaller for semantic memory tasks compared to perceptual or phonological tasks (Binder et al., 2009, 1999; Humphreys et al., 2015; Seghier et al., 2010; Seghier and Price, 2012; Wirth et al., 2011), suggesting that memory is an integral part of DMN.

3.1.3 Relationship between DMN and executive control

The deactivation of DMN during tasks and its anti-correlation with task-positive regions have led to the proposal that DMN is an antagonist system to control (Gusnard and Raichle, 2001; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997); however recent evidence suggests that the relationship might be more complex. For example, Krieger-Redwood et al. (2016) found deactivation in the posterior cingulate cortex during semantic processing, yet this region showed increased coupling with task-positive regions, such as the dorsolateral PFC during the most difficult condition. Contrary to the idea of a task-negative system, Crittenden (2015) found recruitment within DMN during externally focused task switching, especially for large changes of cognitive context. These results, which were replicated by Smith et al. (2019, 2018), indicate a role of DMN in active cognition and suggest that this network might be crucial when the task requires participants to discard previously encoded information and establish a new context. In line with this, Spreng et al. (2010) found increased coupling between DMN and frontoparietal network during a task of autobiographical planning. Moreover, using seed-based analysis of resting state fMRI data, Beaty et al. (2014) found greater coupling between DMN and the right inferior frontal gyrus in people with high creativity. Collectively, these findings suggest that DMN can participate in goal-directed cognition by increasing its communication with regions traditionally implicated in more controlled aspects of cognition.

3.1.4 Default mode cortex supports information integration

Recent work leveraging the intrinsic connectivity of the brain has shed light on the topographical organization of heteromodal default mode cortex (Braga et al., 2013; Buckner and Krienen, 2013; Leech et al., 2012; Margulies et al., 2016). By applying decomposition techniques to brain connectivity, Margulies and colleagues (2016) characterized a principal gradient of cortical organization (Figure 1.5.A) which is anchored at one end by unimodal regions involved in perception and action, and at the other end by transmodal regions including angular gyrus, medial PFC, anterior and posterior cingulate, and anterior temporal lobe. The observation that DMN nodes at the top of the gradient are maximally distant from unimodal cortices (Figure 1.5.B) supports the proposed role of this network in functions that require integration of multiple features (Margulies et al., 2016). The topographic separation of heteromodal default cortex from primary systems suggests that increasingly complex and abstract functions might be formed along the gradient (Figure 1.5.C), where the input from unimodal features is progressively reduced (Buckner and Krienen, 2013; Mesulam, 1998; Plaut, 2002; Schapiro et al., 2013). In this view, complex relationships might be more easily captured where there is greater separation between unimodal "spokes" and association regions in default mode network (Lambon Ralph et al., 2016; Margulies et al., 2016). Distance might also allow the brain to support forms of cognition that require to focus on previously encoded knowledge, as opposed to information in the external environment (i.e. memory; Murphy et al., 2019).

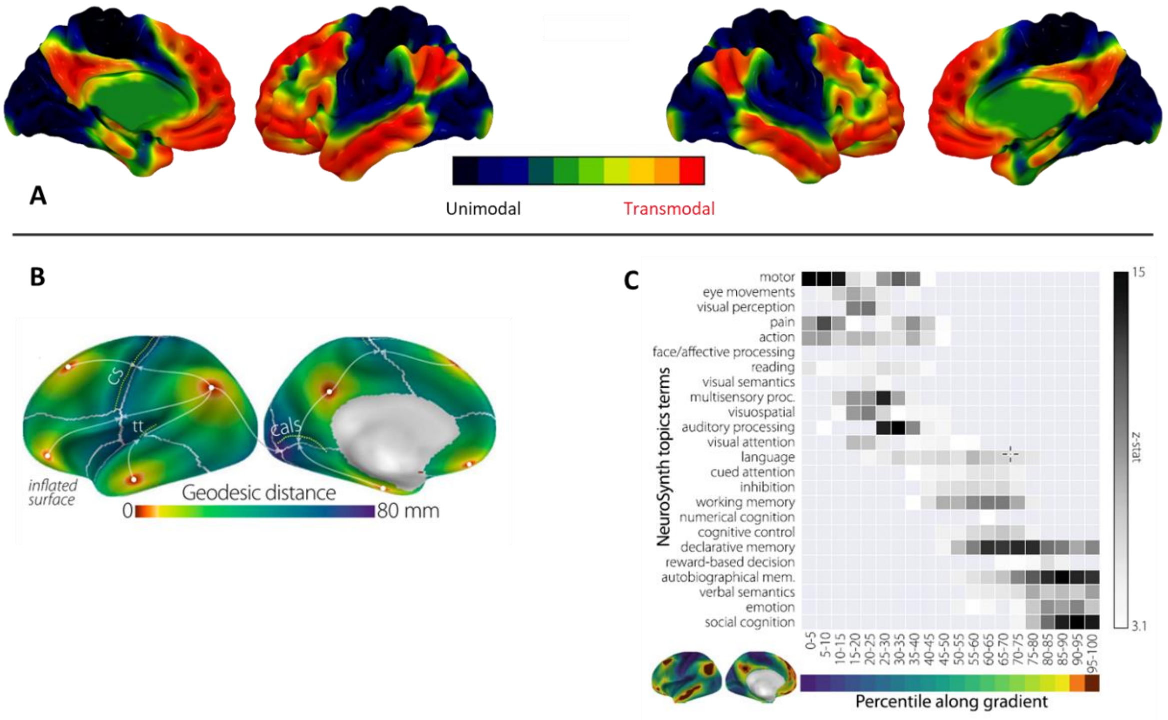

Figure 1.5. A Principal gradient of connectivity projected on a template surface (Margulies et al., 2016). The gradient is a continuous map with values ranging from 0 (in dark blue) to 100 (red). **B** Distance of each point on the cortical surface from seven seeds placed within the default mode network (DMN). Core DMN nodes (red) are located at maximal geodesic distance from landmarks of unimodal function such as the central sulcus (motor cortex) and the calcarine sulcus (visual cortex). This topographical organization divides the cortical surface into distinct "zones" (separated by white lines). **C** Results of a Neurosynth meta-analysis in regions of interest along the gradient, showing increasing abstraction of functions towards the heteromodal end. Reproduced with permission from Margulies et al., 2016.

The proposed topographical organization of cortex with DMN regions at the top of the abstraction hierarchy is consistent with other connectivity studies showing "echoes" or traces of other large-scale networks in default mode cortex (Braga et al., 2013; Leech et al., 2012; Turnbull et al., 2019a). Using decompositions of resting-state fMRI data, Braga and colleagues (2013) were able to show that core nodes of the default mode network, including posterior and anterior cingulate cortex, angular gyrus and middle temporal gyrus, contained neural signals of other established large scale networks. In contrast, unimodal regions presented few traces of other networks and showed a more unitary pattern of intrinsic activity (see also Leech et al., 2012). These results were taken as evidence that DMN regions mediate the communication between different networks and therefore might play a role in the dynamic integration of information (for review see Braga and Leech, 2015). Interestingly, decomposition of the neural signal in the right supramarginal gyrus/AG node has revealed a local topographical organization, such that echoes of multiple large-scale networks were present in spatially adjacent but separable regions (Braga et al., 2013). In addition to supporting a special role of the parietal default mode cortex in global integration, this observation is relevant to understanding why this region is implicated in multiple tasks. The activation of AG could reflect the summation of different neural signals, but in certain circumstances it could reflect the segregation between different components. Congruently with this view, a recent study by Kernbach et al. (2018) revealed that patterns of functional coupling within DMN sub-regions reflected distributed connectivity of large-scale networks, suggesting that a key feature of DMN is to mediate the functional communication between networks. Interestingly, among the candidate regions in their DMN parcellation, the right temporo-parietal junction was found to be the one that explained the most variance in the interplay of DMN and other brain-networks. Convergent evidence for a role of AG in mediating the cross-talk between networks comes from a graph theory study by Xu et al. (2016) showing that AG acts as an "overall connector hub" with strong connections to all modules in the graph.

In line with the proposed role of DMN in information integration, Vatansever et al. (2015b) found evidence for the functional relevance of DMN in goal-directed tasks. Using a working memory paradigm in fMRI and graph theoretical measures, the study revealed that DMN increased interactions with other large-scale networks under higher task demands (1 back *vs*. 0 back), suggesting a role of this network in the flexible integration of elements from memory. More recently, Evans et al. (2020) found that improved performance in a semantic summation task requiring participants to detect weak overlapping patterns of semantic association was related to increased connectivity between DMN and the control network. Similar patterns of connectivity between DMN and other large scale brain systems have been shown to support response inhibition during idea production (Beaty et al., 2017) and creative thinking abilities (Beaty et al., 2018, 2015; for review see Beaty et al., 2016). Moreover, default mode nodes including AG are recruited during the generation of metaphors (Benedek et al., 2014) and chain free associations (Marron et al., 2018), while differences in the DMN intrinsic connectivity are predictive of individual differences in creative thinking abilities (Beaty et al., 2014; Chen et al., 2015; Jauk et al., 2015; Jung et al., 2016). A fundamental component of creativity is the ability to flexibly re-combined stored concepts to produce novel ideas (Beaty et al., 2017). Consequentially, the DMN involvement in creative cognition might be similar to its contribution to other forms of cognition that rely on memory retrieval as opposed to information present in the environment (e.g. Margulies et al., 2016; Murphy et al., 2019). Moreover, recent task-based fMRI studies have suggested that semantic regions allied to DMN (including ATL and AG), support the combination of concepts into meaningful and more complex representations (Bemis and Pylkkänen, 2011; Price et al., 2015; Teige et al., 2019, 2018). Finally, DMN has been shown to support integration over long time-scales during narrative comprehension (Chang et al., 2020; Lerner et al., 2014, 2011; Simony et al., 2016). A study by Lerner et al. (2011) revealed a hierarchy in the temporal lobe responsible for accumulating information over increasing temporal scales. Within this cortical topography, auditory regions responded to fast-changing information reflecting momentary features of the input, adjacent areas in superior temporal gyrus combined information at the time-scale of single sentences, and heteromodal regions overlapping with DMN accumulated information across paragraphs. More recently, Chang et al. (2020) showed re-activation of the neural patterns associated with previously presented stories when the storylines converged and could be integrated.

Taken together, these findings point to a critical role of DMN in conceptual integration and are overall consistent with recent accounts of brain organization (Margulies et al., 2016). In line with the topographical architecture described by the principal gradient increasingly complex and abstract representations – key features of memory retrieval, creative thinking, and semantic integration – might emerge at the top end of the cortical hierarchy in regions overlapping with DMN, where the influence of sensory-motor system is minimal.

3.1.5 Heterogeneity within DMN

One aspect of DMN that remains at odds with the findings described above is the tendency to deactivate during tasks (Raichle et al., 2001). Although this pattern of BOLD response has been reported in several fMRI studies, the functional significance of task-related deactivation is unclear; an alternative possibility to the frequently proposed "task-negative" view (Humphreys et al., 2015) is that deactivation might be functionally relevant, allowing DMN regions to integrate information more selectively from task-relevant networks (Krieger-Redwood et al., 2016; Leech et al., 2012). This proposal is consistent with Granger Causality findings that the intrinsic activity of two major DMN nodes – namely ventromedial PFC and posterior cingulate cortex - exerts causal influence on the respective "anti-networks", suggesting that a fundamental feature of DMN function might be to release externally oriented attention during task performance (Uddin et al., 2009). Notably, a number of recent studies demonstrate that DMN regions can increase their coupling to cognitive control areas when harder tasks are contrasted with easier tasks, even as they deactivate (Krieger-Redwood et al., 2016; Vatansever et al., 2017b, 2015b). Moreover, findings that neural activity in DMN is made of neural signals from multiple networks, or "echoes", suggest that some components of DMN (but perhaps not the entire network) would be deactivated depending on the task and the large-scale network responsible for a given function (Braga et al., 2013). This is consistent with an early fractionation of DMN proposed by Leech et al. (2012), which revealed that ventral posterior cingulate had strong functional connectivity to the rest of DMN, while dorsal parts were connected with the FPN.

The distinct functional roles observed across different studies support the general idea that the DMN is not a unitary network (Andrews-Hanna et al., 2010; Braga et al., 2013; Braga and Buckner, 2017; Leech et al., 2011; Mayer et al., 2010; Yeo et al., 2015). A classic functional and anatomical fractionation of the DMN (Andrews-Hanna et al., 2010) revealed that this network comprises two functionally distinct subsystems that interact with a common "*core*". Using analysis of intrinsic connectivity, combined with graph analytical measures and clustering techniques, this study showed that a *medial temporal lobe subsystem* (comprising bilateral parahippocampal complex, hippocampal formation, ventromedial PFC, posterior inferior parietal lobule and retrosplenial cortex) is recruited when participants make episodic decisions about their personal future. In contrast, making decisions about present mental states recruited a *dorsomedial prefrontal subsystem*, including regions such as dorsomedial PFC, temporo-parietal junction, lateral temporal cortex, and temporal pole. A third component – comprising posterior cingulate cortex and anterior medial PFC – shared functional properties of both subsystems, in line with previous evidence suggesting the existence of a midline "core" (e.g. Buckner et al., 2009). Notably, DMN subsystems might not be equally relevant for semantic memory. Semantic studies and the meta-analysis by Binder (Binder et al., 2009) show strong overlap between the semantic network and the dorsomedial prefrontal subsystem – in regions such as temporal pole, lateral temporal cortex, and temporo-parietal junction – while other default nodes might be less involved in semantic cognition. For example, the medial PFC, hippocampus, parahippocampal gyrus, posterior cingulate cortex and retrosplenial cortex have been identified as regions important for episodic memory retrieval (e.g. King et al., 2015; Rugg and Vilberg, 2013; Watrous et al., 2013).

Further insights into the spatial and functional organization of the larger DMN are provided by a recent study of intrinsic connectivity in which resting-state data from the same subjects scanned 24 times were analysed at the level of the individual (Braga and Buckner, 2017). This is a novel approach, since most previous fractionations are based on group averages (e.g. Andrews-Hanna et al., 2010; Buckner et al., 2008; Leech et al., 2012, 2011; Margulies et al., 2009). The study revealed a novel fractionation within DMN, with two sub-networks (identified as *DN-A* and *DN-B*) arranged in spatially juxtaposed regions. This spatial organization was found to repeat consistently along the cortical surface in several "zones" in dorsolateral PFC, lateral temporal cortex, parietal cortex, and anterior and posterior midline regions. Crucially, the two subnetworks had distinct patterns of functional connectivity with the rest of the brain, suggesting they might serve different functional roles. For example, *DN-A* was coupled with the hippocampal formation, resembling the *medial temporal lobe subsystem* identified by Andrews-Hanna et al. (2010), while *DN-B* did not. Two other networks – the dorsal attentional and frontoparietal networks – were found to have similar properties, with spatially adjacent sub-networks lying side by side in several cortical regions. Interestingly, graded transitions between interdigitated subnetworks were observed in several places. The observed parallel and sequential nature of the sub-networks aligns well with the idea that macroscale gradients are one organizing principle of cortical function (Margulies et al., 2016).

3.2 Semantic control network

3.2.1 Organization of semantic control network

Section 2.2 focused on the role of left IFG and pMTG in semantic control; these regions are commonly recruited during semantic decisions about ambiguous words, for weak *vs*. strong associations, and when the task requires competition to be resolved between alternative meanings (Davey et al., 2016; Rodd et al., 2005; Vitello and Rodd, 2015; Zempleni et al., 2007). Moving beyond the contribution of individual sites, converging evidence from functional imaging, neuropsychology and TMS suggests that these regions are part of a larger network including left prefrontal and posterior temporal regions, as well as dorsal aspects of the parietal cortex. An activation likelihood estimation (ALE) meta-analysis of 53 studies contrasting semantic decisions with high *vs*. low executive requirements highlighted a set of distributed left-hemisphere regions highly overlapping with the lesions in SA patients, including left IFG, pMTG, and the dorsal portion of AG - bordering the inferior parietal sulcus (Noonan et al., 2013b). The largest clusters in the comparison of high *vs*. low-control semantic tasks were observed in PFC and pMTG. Interestingly, the meta-analysis revealed a specialization of function within the semantic control network, with IFG (in ventral PFC) and pMTG responding only to semantic control manipulations, and dorsal PFC being recruited for difficult phonological tasks. These results are consistent with the observation that dorsal aspects of PFC are part of the MDN (Duncan, 2010; Fedorenko et al., 2013), and suggest that semantic control overlaps with domain-general control in PFC. Shared mechanisms for semantic and domain-general control were also observed in the parietal cortex, where the most consistently activated site was dorsal AG/IPS - also part of the MDN (Duncan, 2010; Fedorenko et al., 2013). Congruently, inhibitory TMS applied to IPS has been shown to disrupt executively-demanding semantic and non-semantic decisions (Whitney et al., 2012). Thus, activation of dorsal prefrontal and parietal cortices during semantic tasks with high *vs*. low demands might reflect goal-driven executive processing in MDN regions (for a discussion see Noonan et al., 2013b).

Davey et al. (2015b) found co-activation of left IFG and pMTG for hard *vs*. easy semantic decisions, suggesting that these regions might work in concert to support the flexible retrieval of conceptual information. Next, using a combination of structural and functional MRI techniques, Davey et al. (2016) showed that pMTG and anterior IFG are spatially located between two normally anti-correlated networks implicated in hard *vs*. easy and easy *vs*. hard judgements. A psychophysiological interaction analysis targeting the functional connectivity of pMTG showed increased coupling to both MDN and DMN during tasks involving event and action semantics, which required semantic retrieval to be shaped to suit the context. Seed-based analyses of intrinsic connectivity in an independent dataset confirmed this spatial pattern by showing coupling at rest between pMTG and both IFS (site within MDN showing peak activity for hard *vs*. easy semantic judgements) and ATL (within DMN, showing activity for easy *vs.* hard). In line with findings from the Noonan's meta-analysis and with literature showing functional specializations within PFC (e.g. Badre et al., 2005), a region of interest (ROI) analysis revealed that, while left ventral IFG and pMTG were similarly recruited during event comprehension, dorsal IFG responded to harder feature matching trials – reflecting the proposed role in goal-driven cognition (Duncan, 2010; Fedorenko et al., 2013). Collectively, these findings reinforce the idea of a specialized network for semantic control, comprising left posterior temporal and ventral aspects of PFC, and suggest that the spatial organization of this network within anti-correlated functional networks might have a functional role (this is further discussed in section 3.4).

3.2.2 Functional interactions within the semantic control network

Further support for a distributed network underpinning semantic control has been provided by recent studies showing that functional/structural alterations in specific semantic control sites can have consequences elsewhere in the semantic network (Hallam et al., 2018, 2016; Wang et al., 2018). As reviewed in section 2.2.3, TMS over IFG and pMTG has contributed causal evidence about the functional contribution of these sites (Hoffman et al., 2010; Krieger-Redwood and Jefferies, 2014), for example by showing that stimulation of either site produces equal disruption of difficult semantic decisions thought to require semantic control, while judgements about strong associations remain largely unaffected (Whitney et al., 2011b). More recently, Hallam et al. (2016) used a combination of TMS and fMRI to explore compensatory mechanisms within the semantic control network. First, they measured the BOLD response to weak *vs*. strong semantic associations in healthy participants and recovered a set of semantic control regions previously identified by Noonan et al. (2013b), including left and right IFG, left pMTG, and bilateral pre-SMA. In two subsequent sessions, they applied TMS to the left ventral IFG and then measured brain activity in ROIs defined based on the whole-brain results. Notably, left pMTG and pre-SMA showed higher BOLD signal in the high *vs*. low demand condition following inhibitory stimulation of IFG, reflecting the coordinated action of these regions. In line with these findings, aphasic patients with damage to left IFG showed stronger recruitment of pMTG and ventral ATL during the comprehension of ambiguous sentences compared to age-matched controls (Hallam et al., 2018). Moreover, functional connectivity between pMTG and anterior temporal lobe at rest was found to be predictive of better semantic performance in the patients. Thus, following lesions to left PFC, other brain regions including pMTG and ventral ATL - thought to be key for conceptual processing – can flexibly reorganize to support comprehension, providing evidence for a distributed large-scale network for semantic control.

Supplementing the findings reviewed above, structural MRI has provided insights into the organization of semantic control and its relationship to other large-scale networks. A recent study by Wang et al. (2018) examined the association between structural covariance of semantic control sites and individual differences in the efficiency on a semantic control task (i.e. weak *vs*. strong semantic associations) and an executively-demanding non-semantic task (figure matching). The study revealed increased structural covariance of left pMTG and the anterior left middle frontal gyrus (aMFG) in subjects who were better at difficult semantic decisions. This effect was specific to semantic decisions, since the structural covariance between these regions did not predict performance on the non-semantic task. Left pMTG and aMFG also showed similar patterns of intrinsic connectivity that overlapped with the Noonan et al. (2013) meta-analytic map, reinforcing the idea that they form a network.

3.2.3 Intrinsic connectivity of the semantic control network

Adding evidence to the idea that regions implicated in semantic and executive control are organized in large-scale networks, studies of the intrinsic activity of the brain have shown that left IFG and pMTG are coupled at rest (Davey et al., 2016; Gonzalez Alam et al., 2019; Hallam et al., 2018; Hurley et al., 2015; Wang et al., 2018), and that individual differences in the functional connectivity of these regions with the rest of the brain can predict semantic performance (Mollo et al., 2016; Vatansever et al., 2017a; Wei et al., 2012). Gonzalez Alam et al. (2019) revealed that pMTG and left IFG have highly similar patterns of intrinsic connectivity, consistent with the idea that these regions are part of a larger network for semantic control. They then extracted the intrinsic connectivity of other sites associated with semantic processing but *not* implicated in semantic control (ATL, AG) and examined differences in the patterns of connectivity between each pair. Unsurprisingly, IFG and pMTG showed higher correlations with each other than with either AG or ATL, and they were more correlated in the left hemisphere than the right, reinforcing the idea that control regions form a strong sub-network within the semantic network. In contrast, ventral ATL showed symmetrical connectivity, in line with the proposed heteromodal hub in bilateral ATL (Lambon Ralph et al., 2016; Patterson et al., 2007). Stronger coupling at rest between pMTG and IFG was also reported by Wei et al. (2012), although the focus of the study was on the semantic network rather than on controlled aspects of retrieval. Using canonical correlation analysis, Vatansever et al. (2017a) found that the separation of regions implicated in executive control – namely IFG and pre-SMA – and default mode regions such as AG and posterior cingulate cortex was associated with better performance on harder semantic tasks. This suggests that the ability to apply control over conceptual retrieval may in part depend on the functional segregation between networks that are typically anti-correlated, in line with previous studies of executive control (Hampson et al., 2010; Kelly et al., 2008).

3.3 Multiple demand network

An established body of research suggests that domain-general control is implemented in a bilateral network comprising lateral portions of the frontal lobes – such as the inferior frontal sulcus (IFS) extending into aspects of the inferior frontal gyrus (IFG) and middle frontal gyrus – the anterior insular/frontal operculum (AI/FO), the pre-supplementary motor area (pre-SMA), and parietal regions around the intraparietal sulcus (IPS), which have been collectively termed multiple demand network (MDN; Duncan, 2010; Fedorenko et al., 2013). These areas respond to manipulations of control demands (hard *vs*. easy) across a multitude of tasks, including planning, problem-solving, working memory, stimulus discrimination, learning of novel items, maintenance of task rules and goals, inhibition of prepotent but inappropriate responses, selective coding of task-relevant information, and integration of visual information across successive trials (Dosenbach et al., 2006; Duncan and Owen, 2000; Fedorenko et al., 2013; Naghavi and Nyberg, 2005; Owen et al., 2005; Wen et al., 2018). Multiple-demand regions lie half-way along the principal gradient (between DMN and primary sensory-motor regions on the cortical surface), they show positive correlation at rest (Power et al., 2011; Yeo et al., 2011) and they are typically anti-correlated at rest with DMN regions (Blank et al., 2014; Fox et al., 2005). The observed functional generality of these regions is thought to be achieved through "adaptive coding" – neurons in PFC can selectively represent information that is relevant for the task (Duncan, 2001; Woolgar et al., 2011). Single-cell recordings in monkeys (e.g. Cromer et al., 2010; Freedman and Assad, 2006; Roy et al., 2010) and fMRI studies in humans (e.g. Duncan and Owen, 2000; Woolgar et al., 2011) provide convergent evidence for adaptive neural coding in PFC, showing flexibility in the type of information that the MDN can carry (for review and discussion of the "*adaptive coding model*" see Duncan, 2001).

As would be expected for a domain-general control system, this network is also recruited by demanding semantic tasks when meaning is used to guide behaviour (Davey et al., 2016; Gonzalez Alam et al., 2018; Wang et al., 2020). The involvement of MDN in semantic tasks might reflect the difficulty of maintaining information in a goal relevant fashion and the inhibition of prepotent responses - for example when semantic categorisation is used to drive or withhold a motor response (Gonzalez Alam et al., 2018). In contrast, the semantic control network might be crucial when semantic information itself is the basis for control processes, as it is the case when retrieving weak semantic associations in the absence of a specific instruction about how two words could be linked in meaning, or what aspect of semantic knowledge should be the focus of ongoing retrieval (Davey et al., 2016). Thus, while classic semantic control sites (i.e. IFG, pMTG) are thought to facilitate the retrieval of non-dominant associations and the selection of meanings from the semantic store (Badre et al., 2005; Davey et al., 2015b, 2015a; Lambon Ralph et al., 2016; Noonan et al., 2013b), other aspects of semantic (and non-semantic) cognition, including the maintenance of task-context/goals, response inhibition, and working memory might be supported by a domain-general network. The next sections review evidence for an involvement of MDN in several cognitive abilities which are relevant to semantic cognition, for example when we learn new rules and behaviours, when we interpret events that unfold over time, and when we focus our attention on certain aspects of the environment, while suppressing irrelevant ones.

3.3.1 Creation and maintenance of a "task model"

Duncan et al. (2008) introduced the term "task model", which reflects an internal representation of the task goals, rules, and the relevant steps that must be assembled to achieve a desired behaviour. Evidence from functional neuroimaging indicate that task-context is represented within lateral PFC (Cole et al., 2011; Waskom et al., 2014; Waskom and Wagner, 2017; Woolgar et al., 2011). For example, recent work by Waskom & Wagner (2017) found voxels in PFC which exhibit a preference for certain types of task context (e.g. colour, motion, orientation). Moreover, task-related information can be decoded in prefrontal (Woolgar et al., 2011), and parietal regions overlapping with MDN (Crittenden et al., 2016). Consistently, activation in several MDN nodes - including IFS, pre-SMA and IPS - is observed during the presentation of task instructions, while baseline activity in the distributed MDN increases as new task rules are introduced, reflecting the assembly of a task-model (Dumontheil et al., 2011). In the electrophysiology domain, Kadohisa et al. (2020) recently showed unique patterns of neural activity in the monkey's prefrontal and parietal cortex reflecting different task steps or "phases" (i.e., *encoding* of task rules and *choice* of a target based on previous feedback), consistent with the view that activity in PFC re-organizes across different task steps (e.g. Sigala et al., 2008). Collectively, these findings suggest that one of the key features of MDN might be to represent task rules and goals, effectively establishing a framework for ongoing cognition. This ability is relevant to semantic tasks, for example when two items must be matched based on a shared feature (Davey et al., 2015b; Wang et al., 2020). To use a more naturalistic example, the maintenance of a task-model may be relevant when we are searching for an object, amongst similar items. If we are searching the room for a DVD of the "101 Dalmatians", we need to maintain a clear action-goal which is specified by the concept, however the semantic representation "Dalmatian" does not need to be controlled.

3.3.2 Inhibition of responses

While the application of control to conceptual information typically requires a left-lateralized semantic control that comprises left pMTG, IFG, and dorsal AG (Noonan et al., 2013b), the inhibition of behaviour is associated with right-hemisphere regions within the MDN (Criaud and Boulinguez, 2013; Simmonds et al., 2008; for review see Aron et al., 2014, 2004). Evidence from functional neuroimaging, lesion mapping and electrophysiology (Aron et al., 2014, 2004) situates inhibitory control along a circuit reliant on the right PFC and its connections to anterior insula and subcortical regions. An activation likelihood estimation (ALE) meta-analysis by Criaud and Boulinguez (2013) identified pre-SMA as reliably associated with no-go tasks, while a more recent meta-analysis of 225 studies using response inhibition tasks revealed a right-lateralized network including dorsolateral PFC, pre-SMA and parietal regions (Zhang et al., 2017). Dodds and colleagues (2011) directly contrasted response inhibition and attentional shifting during an online fMRI task and found that, while inhibition recruited the right inferior PFC, attentional shift was associated with greater activation in the left homologue.

Successful semantic cognition involves focussing on the information that is currently relevant and discarding representations that are not supported by the context or current goals. In line with the evidence above, Gonzalez Alam et al. (2018) found activation in a right-lateralized network overlapping with MDN during a go/no-go task in which participants made decisions based on semantic (animals *vs*. objects) or perceptual (i.e. degree of slant of a square) properties. Irrespective of the nature of the stimuli, inhibiting responses in no-go trials recruited regions within MDN – including right IFS, IPS and bilateral occipital cortex. Notably, the semantic control network (Noonan et al., 2013b) was not involved in response suppression, even when the content of the decision was purely semantic. These findings suggests that certain aspects of semantic cognition, for example the ability to suppress responses to certain semantic categories when inappropriate for the task, might be served by right-hemisphere domain-general control regions rather than left-hemisphere semantic control areas.

3.3.3 Working memory

A large body of work implicates prefrontal and superior parietal regions, overlapping with the MDN, as crucial for working memory (Assem et al., 2020; Fedorenko et al., 2013, 2011; Mineroff et al., 2018; Owen et al., 2005; Wen et al., 2018; see also Eriksson et al., 2015 for a general discussion on working memory). PFC is reliably involved in working memory, possibly reflecting the encoding of task relevant information (Baddeley, 2003; Miller and Cohen, 2001). Single-cell recordings in monkey show sustained neural activity during the delay period of working memory tasks (Courtney et al., 1997; Funahashi et al., 1989; Fuster and Alexander, 1971). Consistently, lesion studies indicate that damage to the PFC results in delayed-response tasks, especially if the task involves suppressing distractions (D'Esposito and Postle, 1999), and inhibitory TMS to PFC affects working memory (Brunoni and Vanderhasselt, 2014; Feredoes et al., 2011).

Together with PFC, the superior parietal cortex is often involved in working memory (e.g. Owen et al., 2005). This area is thought to support executive aspects of WM and attentional control (Awh et al., 2006; Collette et al., 2005; Koenigs et al., 2009). In line with this view, a study by Linden et al. (2003) described different load effects in IPS compared to those observed in other MDN regions. While activity in PFC and pre-SMA increased monotonically with the number of items to remember, BOLD in IPS showed a U-shaped curve, peaking when 2-3 objects had to be remembered and then decreasing in higher-load conditions. In contrast, Manelis and Reder (2014) recently found that both frontal and parietal MDN regions - including PFC, anterior cingulate, and IPS - parametrically increased activation with greater working memory load (i.e. 1-back, 2-back, 3-back), which is consistent with previous work by (Manoach et al., 1997) showing increased activity in similar regions for greater WM load. Furthermore, using MVPA, Manelis and Reder (2015) observed that the upcoming working memory load in the n-back task could be decoded from the same regions recruited during task preparation. Thus, these findings are in line with the idea that activity in MD regions is modulated by different types of cognitive demands (Duncan, 2010; Duncan and Owen, 2000; Fedorenko et al., 2013).

Conversely, working memory studies contrasting the maintenance of semantic *vs*. non-semantic verbal material showed involvement of regions overlapping with aspects of the semantic control network (Fiebach et al., 2007, 2006; Shivde and Thompson-Schill, 2004). Shivde and Thompson-Schill (2004) compared the neural response to words that were either semantically (e.g. buy – PURCHASE) or phonologically (e.g. buy – BINE) related to a probe word presented previously and found greater recruitment of left pMTG and IFG for semantic *vs*. phonological working memory, while the reverse contrast elicited activation in the superior parietal cortex. Similarly, Fiebach et al. (2007) found recruitment of regions within the semantic control network – such as the left inferior frontal gyrus, middle and inferior temporal cortex – for a semantic working memory task, as opposed to an item recognition task (where the elements could not be conceptually combined). Taken together, this evidence suggests that both MDN and semantic control might support the attentional and working memory components of semantic tasks, with MDN supporting the general maintenance of information across domains, and the semantic control network being recruited for the maintenance of meaningful relative to non-semantic items.

3.3.4 Heterogeneity within MDN

From an anatomical perspective, the MDN is thought to comprise two distinct networks: a frontoparietal network (FP) including dorsolateral PFC, inferior frontal junction, and IPS, and a cingulo-opercular (CO) network engaging the anterior PFC, anterior insula and pre-SMA/AC (Dosenbach et al., 2008). The same organization has been shown in resting-state data, where correlations between regions in each subnetwork are stronger compared to between-network correlations (Dosenbach et al., 2007). A recent study by Crittenden et al. (2016) has demonstrated that this separation in functional connectivity is present during tasks. Moreover, using MVPA they were able to show stronger decoding of task type in the FP compared to CO subnetwork. In line with the functional division proposed by Dosenbach et al. (2008), this was interpreted as reflecting qualitatively distinct roles of FP and CO, with the former being involved in rapid control and the latter supporting sustained task-maintenance. Another distinction within MDN regions is the one proposed by Corbetta and Shulman (2002), reflecting a separation of ventral attention network (VAN) – supporting bottom-up or stimulus-driven attentional processes and dorsal attention network (DAN) – involved in top down or goal driven control. Interestingly, the DAN has strong functional connections to specific regions within FPN, which show little or negative coupling to DMN sites (Dixon et al., 2018). A recent study by Dixon et al. (2018) using graph theory measures and hierarchical clustering of previously published parcellations (Gordon et al., 2016; Power et al., 2011; Yeo et al., 2011) identified a novel fractionation within FPN, which is stable across individuals and resembles the interdigitated patterns of cortical organization described by Braga and Buckner (2017). The study revealed that FPN fractionates into a system that is functionally coupled with the core DMN and another that is coupled to DAN at rest. The extent to which the two FPN sub-systems coupled with DMN and DAN was also found to vary based on the task demands, in line with the idea that flexible interactions between these networks might support various aspects of cognition.

3.4 Inter-network communication for flexible semantic cognition

A recent upsurge of interest regarding the wider neural architecture of semantic cognition has led to the investigation of modes in which inter-network communication may support semantic processing. Using graph theoretical measures, Xu et al. (2016) explored the intrinsic connectivity of the semantic network focusing on the regions previously identified in the meta-analysis by Binder et al. (2009). They found that semantic nodes are organized into three stable modules corresponding to distinct large-scale networks, namely (i) DMN – encompassing predominantly bilateral midline core regions and AG, (ii) FPN – containing dorsal aspects of the inferior parietal cortex, and (iii) the left perisylvian network (PSN; Friederici, 2011) – covering left-hemisphere regions that have often been described as "high-level language" regions (Fedorenko et al., 2011) and are partly overlapping with the semantic control network (Noonan et al., 2013b). Furthermore, they observed that different modules converged in several hubs located in left IPS (linking DMN and FPN), left ATL (connecting DMN and PSN), and left pMTG (linking PSN and FPN), and that all three modules converged in the left AG, in line with the proposed role of this region in mediating the cross-talk between networks. These findings nicely map onto previous evidence that left ATL serves as a heteromodal hub for conceptual representations (Lambon Ralph et al., 2016; Patterson et al., 2007) and with the idea that ATL might work together with other regions in DMN to support more unconstrained forms of semantic processing that rely on representations stored in memory. In line with previous evidence (e.g. Davey et al., 2016; Gonzalez Alam et al., 2019; Turken and Dronkers, 2011; Wei et al., 2012), pMTG was found to connect language and domain-general control regions, reinforcing its proposed role in controlled aspects of semantic retrieval. Collectively, these findings suggest that multiple large-scale systems are likely to support different cognitive components of semantic processing (for a discussion see Xu et al., 2017).

Furthering this idea, Chiou et al. (2018) elegantly demonstrated that large-scale networks underpinning semantic cognition interact differently depending on the task requirements and the type of information that must be retrieved. In this study, two tasks were used to probe different aspects of semantic processing: (i) semantic pairing, which involved matching items based on their semantic relationship (e.g. MUSTARD – ketchup, hawk) and (ii) colour pairing, in which participants matched semantically unrelated items based on their canonical colour (e.g. MUSTARD – smiley, hawk), which reflects a less typical cognitive operation and is therefore likely to require semantic control. Having established that colour pairing *vs*. unconstrained semantic associations elicited greater activation in left IFG, the authors performed a psychophysiological interaction (PPI) analysis to explore whether the functional connectivity of the left ventral PFC would be sensitive to task demands. Increased coupling between the left IFG seed and various DMN nodes was observed in the semantic pairing task which required the retrieval of global semantic associations. Intriguingly, during the more demanding colour pairing task, the IFG seed showed increased coupling to visual "spokes" in occipital and posterior temporal cortex, as well as to other executive control regions overlapping with both the semantic control network and MDN. Dynamic causal modelling established that the increased coupling reflected directional modulation from IFG to occipito-temporal visual spokes (and not vice-versa), suggesting that semantic control might be involved in the strategic use of colour knowledge (in line with the predictions of the CSC account; Lambon Ralph et al., 2016). These results show that flexible coupling between different large-scale networks supports qualitatively distinct aspects of semantic processing.

Flexible interactions of large-scale networks were also observed in a study by Davey et al. (2016), which showed that pMTG plays a role in integrating information from two normally anti-correlated networks implicated in semantic retrieval and top-down control. A PPI analysis revealed increased coupling of pMTG to regions in DMN and MDN during a task of relational semantics. In line with this, diffusion MRI showed that long-range connections from the same two seeds overlapped in white matter adjacent to pMTG, strengthening the idea that pMTG is a nexus drawing together functionally distinct networks. These findings are consistent with graph-theory work by Xu et al. (2016) and task fMRI analyses by Chiou et al. (2018), and further extend this evidence by showing that large-scale networks are also spatially ordered. The semantic control network lies between two normally anti-correlated networks and simultaneously communicates with both, for the purpose of applying control to semantic retrieval. This topological arrangement of networks might allow relatively-stable long-term semantic representations - acquired over a life-time and modulated by recent experiences - to interact with current demands and goals, thus promoting flexible patterns of retrieval. Intriguingly, these findings raise the question of whether the recruitment of large-scale networks varies in a graded fashion along the cortical gradient depending on the alignment or similarity of the current information with long-term knowledge.

This idea was directly explored in recent work by Wang et al. (2020). In this study participants made decisions to words based on specific features (i.e. shape, size, colour), while the similarity between the probe and the target was varied parametrically – from a nearly complete overlap in shared features (e.g. STRAWBERRY – RASPBERRY) to a minimal overlap, where only the task relevant feature was shared (e.g. TOMATO – POSTBOX). Consistent with the proposed role of DMN in memory-guided cognition, greater conceptual similarity elicited more activation in regions overlapping with DMN. In contrast, semantic decisions with minimal overlap recruited regions within MDN. The "task gradient" obtained from this parametric model was compared to the "connectivity gradient" corresponding to the Principal Gradient, which is anchored at one end by the heteromodal DMN and at the other by unimodal cortex (Margulies et al., 2016). Beyond their striking visual similarity, the two gradients were found to positively correlate across multiple points on the cortical surface, particularly in regions associated with semantics, both at the group level and in individual participants. Moreover, the effect of global feature similarity was found to change systematically along the connectivity gradient, from minimal recruitment at the unimodal end of the gradient, to maximal values at the DMN end. These findings suggest that the abstraction hierarchy described by Margulies and colleagues might reflect the consistency between our current experiences and long-term semantic memory. Additionally, the study showed that the semantic control network was spatially juxtaposed between DMN and MDN, and had values of connectivity and task response that were intermediate to the two large-scale network. This spatial arrangement of the semantic control network was particularly striking in pMTG, and suggests that this network might allow the integration of long term representations (supported by regions allied with DMN) with representations of currently-relevant goals supported by MDN (see also Davey et al., 2016).

In summary, semantic cognition is supported by distinct, yet interacting large-scale networks. The recruitment of these network varies depending on the task requirements and the alignment of the current representations with the structure of long-term memory. When the knowledge required by a task is readily available in long-term memory, for example when one item activates the relevant features of another concept (Wang et al., 2020), regions allied to DMN work closely to interpret new inputs in line with previous experience (Davey et al., 2016; Jackson et al., 2016; Lau et al., 2013; Power and Petersen, 2013; Wirth et al., 2011). In contrast, when the features to retrieve are minimally related to long-term representations but a strong goal is present, as it is the case in a feature matching task, the MDN is essential to maintain goal-relevant information in working memory (Duncan, 2010; Fedorenko et al., 2013). The semantic control network is a nexus between these two distinct networks, allowing the flexible integration of representations and goals. A growing body of evidence suggests that transitions between these large-scale systems are not sudden, but rather gradual along cortical gradients. The macroscale organization of the cortex described by connectivity gradients (Margulies et al., 2016) thus offers an explanation of how high-level cognition occurs from the orderly interaction of different specialized systems.

4. Introduction to thesis

This thesis is an exploration of semantic retrieval when semantic cues are available and can be used to guide the interpretation of meanings *vs*. when they are absent or even unhelpful. In the Controlled

Semantic Cognition theoretical framework (Lambon Ralph et al., 2016), cueing paradigms manipulate the accessibility of semantic features stored in the hub. Cues can increase the short-term availability of concepts if they are aligned with long-term representations, but they can also increase the need for semantic control if irrelevant information is brought to the fore. Consequently, by studying how cues and cue combinations are processed in the brain, we can gain insights into how semantic flexibility is achieved. In this view, flexibility should emerge from the context when the currently available information is in line with the representations stored in memory, or from control processes when task-irrelevant information must be suppressed. The overarching hypothesis states there will be differences in the recruitment of different semantic networks reflecting the coherence between the required pattern of retrieval and the current state of activation of semantic representations in the semantic system. When recent experience is aligned with stored conceptual representations (as it is the case following cues) we expect the retrieval to occur rather automatically, and to be mediated by DMN. On the other hand, when there is a mismatch between the internal representations and the immediate context (or task goals), we might observe a shift in activation from the DMN to the semantic control or multiple demand regions. Moving beyond previous investigations of cueing that focused on language cues, here we used complex multimodal representations such as emotions and spatial locations, which reflect higher-order “spoke” inputs into the semantic system. These modalities are expected to elicit activation within heteromodal cortex in DMN, especially when they are presented simultaneously and form coherent representations, and to affect behavioural patterns of semantic retrieval in both healthy participants and people with deregulated semantic control.

Across four different studies, we explored the psychological and neural correlates of cued semantic retrieval using a combination of different methodologies (i.e. behavioural studies and neuroimaging methods) and experimental populations (i.e. patients with semantic aphasia and healthy participants). The empirical work explored (i) whether patients with semantic aphasia (SA) showed stronger cueing effects compared to healthy controls, due to their deregulated semantic control [Chapter 2], (ii) whether SA patients showed effects of cue combinations, specifically a greater benefit of multiple convergent cues, as opposed to a single cue or no cues [Chapter 3], (iii) the neural bases of semantic cue integration [Chapter 4], and (iv) whether individual differences in the intrinsic connectivity of the brain at rest are predictive of the ability to integrate semantic cues [Chapter 5].

Chapter 2 examined the effect of cues on semantic decisions in people with deregulated semantic control following left hemisphere stroke. Previous studies have shown that these patients are sensitive to phonological and language cues (Jefferies et al., 2008b; Noonan et al., 2010; Soni et al., 2009). Here we used multimodal semantic cues, such as emotional valence (facial expressions and emotional prosody) and visuo-spatial contexts, to prime the interpretation of ambiguous words (e.g. JAM). These cues are important because in everyday situations, patients' comprehension is likely to be influenced by the environment they are in. We manipulated the extent to which emotion and location cues were relevant to the following semantic decisions by presenting positive cues (which probed the correct interpretation of the ambiguous word) and miscues (which probed the alternative – irrelevant – interpretation of the ambiguous words). We hypothesized that patients with SA, compared to healthy controls, would show a greater benefit of cues and a greater detrimental effect of miscues – in line with their deficient control over semantic retrieval.

Having established that comprehension in SA is sensitive to non-verbal cues such as affect and spatial locations, Chapter 3 explored the possibility of additive or supra-additive effects of these cues using neuropsychology. The benefit for positive cues observed in the previous chapter is in line with previous literature suggesting that reducing the control demands of the task improves performance in SA. The findings raise the question of whether combining cues that probe the same interpretation of meaning improves comprehension beyond the effect observed for single cues. To explore the effect of cue combinations, we used a modified version of the paradigm described in the previous study. Rather than focusing on the relevance of cues for the successive semantic decision (cues *vs*. miscues), here we manipulated the number of cues provided. Across different conditions we presented (i) emotion and location cues simultaneously (2 cues condition), either emotion or location presented singly (1 cue condition) or scrambled and meaningless versions of the cues (0 cues condition).

In Chapter 4 we turned to neuroimaging techniques to explore the neural bases of semantic cue combinations. Recent accounts of the default mode network (DMN) place this network at the top of a cortical hierarchy capturing the transition between unimodal regions involved in perception and action, and heteromodal regions (Margulies et al., 2016). Moreover, a vast literature on semantic combinations implicates this network in the formation of complex representations from simple ones. We hypothesised that that regions within DMN would be recruited when multiple convergent sources of information could be combined to guide meaning retrieval. We tested this idea using task-based fMRI and healthy volunteers. We employed the same cueing paradigm described in Chapter 3, which manipulates the number of convergent cues participants see prior semantic decisions (2 cues, 1 cue, 0 cues). Moreover, in this chapter we examined whether the effect of multiple cues occurs in discrete regions, or whether it unfolds along a macro-scale cortical gradient.

Finally, in Chapter 5 we used seed-based analyses of intrinsic connectivity measured with resting-state fMRI to explore whether individual differences in the spontaneous activity of the brain are predictive of the ability to integrate semantic cues during meaning retrieval, measured outside the scanner using the same cueing paradigm described in Chapters 3 & 4. Previous research has shown that specific patterns of spontaneous activity of the brain can be associated with efficiency in semantic tasks. Based on the findings of Chapter 4, we expected to observe increased connectivity (i) between semantically-relevant default mode regions and other default mode sites in people who are more efficient at integrating multiple cues (2 cues *vs*. 1 cue) and (ii) between semantic control regions and other regions associated with working memory in people who benefit most from the presence of a cue *vs*. no cue (1 cue *vs*. 0 cues).

Through the manipulation of cueing, this thesis allows us to describe two qualitatively distinct mechanisms for flexibility in semantic retrieval – one driven by top-down semantic control and one supported by the integration of contextual information with long-term semantic knowledge. We show that the default mode network (DMN) supports this second type of flexibility through the formation of coherent combinations, in line with previous evidence for combinatorial activity in DMN. Our work uniquely adds to the literature by showing that conceptual integration occurs in a graded fashion along the cortical surface, reflecting previously described macro-scale hierarchies. This thesis also highlights the functional relevance of domain-general multiple demand regions in the goal-directed maintenance of conceptual information.

5. Methodologies used

This PhD adopts multiple methods to investigate how semantic processing is influenced by the presence of cues. The first two empirical chapters (Chapter 2 and 3) use similar neuropsychological methods to explore the functional consequences of brain lesions in regions typically associated with semantic control. The two remaining chapters adopt several fMRI methods to explore different aspects the neural architecture of cued retrieval, including task-based univariate analyses and examinations of the Principal Gradient (Chapter 4), and seed-based connectivity analyses combined with meta-analytic decoding (Chapter 5). By combining multiple methodologies, the present work aims to overcome the limitations intrinsic to each approach and provide a multi-faceted description of the phenomenon under investigation. The following sections will briefly outline each methods, focusing on the advantages and the unique insights that each approach can contribute.

5.1 Cognitive neuropsychology

The primary goal of cognitive neuropsychology is to make inferences about the normal cognitive functioning from the examination and description of cognitive impairment. This is enabled by a fundamental assumption known as the “universality assumption” (Caramazza, 1986), which predicts that the architecture of the cognitive system in neurologically intact people is essentially identical - or at least sufficiently similar to allow meaningful conclusions to emerge. Consequently, any systematic change in a given cognitive process following brain damage can be used to draw causal inferences on the neural bases of that process. If a given process breaks down following a circumscribed brain lesion, it can be deduced that the affected neural substrate is directly responsible for the function. Additionally, this method can uncover functional distinctions within the same broad cognitive process through double dissociations. These occur when a brain lesion disrupts a specific cognitive mechanism leaving another one spared, while brain damage in a different area causes the opposite pattern of symptoms in a different patient. For example, in the semantic literature, Jefferies and Lambon Ralph (2006) showed double dissociations between deficits of semantic control in stroke patients with lesions to left prefrontal/frontoparietal areas and deficits of storage in patients with semantic dementia, allowing us to describe the different components of semantic cognition.

While classic neuropsychological studies have often described single-cases (e.g. Hart et al., 1985; Humphreys and Rumiati, 1998; McCarthy and Warrington, 1986), in this thesis we adopted a case-series approach, which has proven useful to test hypotheses about the structure of semantic cognition (Bozeat et al., 2000; Chapman et al., 2020; Corbett et al., 2009a; Jefferies and Lambon Ralph, 2006; Noonan et al., 2010; Thompson et al., 2015; for reviews see Dragoy et al., 2017; Jefferies, 2013; Lambon Ralph et al., 2016; Patterson et al., 2007). In line with a large body of work by our group and others (Almaghyuli et al., 2012; Corbett et al., 2011; Hoffman et al., 2020; Jefferies et al., 2008b; Stampacchia et al., 2019, 2018; Thompson et al., 2018), the present research examines patients with semantic aphasia who have deregulated semantic cognition following left-hemisphere stroke. This is the ideal population to investigate flexibility in cued semantic retrieval, since these patients are highly sensitive to cues and miscues (Jefferies et al., 2008b; Noonan et al., 2010; Soni et al., 2009). We selected patients according to pre-specified criteria, namely co-occurring (i) brain damage in a location of interest (i.e. left IFG) and (ii) specific behavioural pattern (sensitivity to cues, difficulties retrieving non-dominant aspects of meaning, poor performance in the presence of distractors, etc.). To ensure that patients had similar multimodal semantic deficits, background neuropsychological testing was administered, and cases falling below the cut-off score were retained for further investigation.

The primary advantage of neuropsychology is the possibility to draw causal inferences about the functional relevance of certain brain regions to a given mental process. With this method we can directly test the idea that flexibility in semantic retrieval relies on qualitatively distinct processes, and we can examine the extent to which deregulated retrieval affects the way in which cues constrain semantic representations. In particular, we expected patients to have impaired performance when the task required top-down control over semantic retrieval (for example when miscues must be suppressed), and better performance when flexibility could be guided by the context (for example when the features activated by the cues were consistent with long-term memory representations). The neuropsychology method is not free of limitations. One weakness is the need for a control group of healthy participants to establish a behavioural baseline that patients can be compared with. When the task is relatively easy for people without brain damage, near-ceiling performance of the control group can make the interpretation of the findings difficult. However, if the task is appropriately designed for healthy controls, patients may show floor-level performance and fail to show differences between experimental conditions. Another weakness reflects the fact that patients tend to have large lesions, which often span several adjacent large-scale systems. For example, in some patients, damage in the left ventrolateral PFC may extend more posteriorly and affect domain-general control regions within MDN (Duncan, 2010; Fedorenko et al., 2013). Given that these networks are adjacent on the cortical surface (Davey et al., 2016; Wang et al., 2020), associated damage across networks is hard to avoid. To overcome the poor spatial resolution of this method and the difficulties associated with control groups, in this thesis we combine neuropsychology with fMRI methods. Despite these limitations, neuropsychology is extremely important for patient management and rehabilitation, since insights obtained from the study of cognitive impairment can be transferred to real-word environments and therapeutic protocols.

5.2 fMRI methods

Functional magnetic resonance imaging (fMRI) is a non-invasive method that measures brain activity and connectivity (for recent review see Soares et al., 2016). It is based on the underlying concept that increased firing of the neurons will require greater oxygen consumption, and will therefore result in overall higher metabolic activity and blood flow. fMRI measures brain function using a contrast known as blood oxygenation level-dependent (BOLD; Ogawa et al., 1990a, 1990b; Ogawa and Lee, 1990). The BOLD signal is an indirect measure of neural activity which reflects the ratio between arterial oxygenated blood to venous non-oxygenated blood; as the ratio of oxygenated-to-deoxygenated blood increases, the BOLD signal becomes larger. This process has a time-course of several seconds, which reflects the time needed by the vascular system to dilate and facilitate blood flow. For this reason, in fMRI analyses the regressors of interest are typically convolved with a hemodynamic response function (HRF; Buxton et al., 2004;

Handwerker et al., 2012; Miezin et al., 2000) which reflects the physiology and shape of the BOLD signal. In this thesis we used multiple fMRI methods which are described in the following sections.

5.2.1 Activation fMRI

Task-based fMRI paradigms are used to produce activation maps that reflect the level of engagement associated with a given experimental condition. Methods that examine task-related activation can be broadly distinguished into *univariate*, where each voxel's time series is examined independently, or *multivariate*, which analyse spatially distributed patterns of activation. As the current thesis does not contain multivariate analyses, this section will focus on the univariate analysis of fMRI data.

5.2.1.1 Analysis of task-based fMRI data

fMRI analysis starts with several pre-processing steps aimed at correcting for artefacts which are generally introduced during image acquisition. Standard pre-processing protocols typically start with the adjustment of the time-course in each voxel to account for differences in the acquisition time of different slices. This step, known as *slice timing correction*, involves the interpolation of each slice with a reference slice – usually first or last volume (Calhoun et al., 2000; Sladky et al., 2011). Another critical step is the correction of *head motion*, which is commonly achieved by realigning each volume to a reference volume using a rigid body transformation (rotation and translation along x,y,z axes) and discarding data with motion greater than a certain cut-off (e.g. the dimension of the voxels; Johnstone et al., 2006). Subjects' images are then warped into a common space in a step called *normalization*. This step ensures that homologue regions are aligned across individuals, and correspond to one of two standard coordinate systems – Tailarach or MNI. Next, s*patial smoothing* allows to suppress high frequency signal and enhance sensitivity to low frequency by convolving the fMRI signal with a Gaussian Kernel that matches the spatial correlation between adjacent voxels. By averaging the data points with their neighbours, spatial smoothing can improve the signal to noise ratio (SNR) and validity of the statistical analyses by reducing the mismatch between the inherent spatial structure and the model. A final step is *temporal filtering*, in which high-pass filters (~ 0.008–0.01 Hz) are used to remove known frequencies such as scanner drifts, cardiac and respiratory signals (Cordes et al., 2014, 2001). Once the data has been pre-processed, the statistical analysis is usually carried out in two steps: (i) first-level analysis, where the model is set up at the level of individual subjects, and (ii) group-level analysis, where activation maps from multiple subjects are combined and thresholded.

The most commonly used method for the univariate analysis of fMRI data is the general linear model (Friston et al., 1994) The primary aim of GLM is to identify voxels that have time-series which correlate with the experimental manipulation. This is made possible by the fact that the presentation of stimuli in the scanner is time-controlled and events are time-stamped. For each subject, the time-course of each voxel is modelled as a dependent variable resulting from the weighted sum of several predictors (Monti, 2011; Figure 1.6.). Predictors include the experimental conditions (e.g. different levels of cueing in a semantic decision task), nuisance regressors (e.g. motion parameters estimated during the realignment step of pre-processing or other variables that must be regressed out) and an error term. Because the hemodynamic response is a delayed process, it is common to convolve predictors with a canonical HRF that reflects the expected shape of the BOLD signal. By regressing the convolved predictors against the original BOLD signal, this first-level analysis measures the contribution of each predictor or experimental condition to the observed time-course of any given voxels. The resulting statistical map contains the parameter estimates – or regression coefficients – associated with the predictor: large parameter estimates indicate that a voxel responds strongly to the experimental condition, while small parameter estimate suggest that BOLD signal is not predicted by the task. In a second step, statistical maps for each subject are combined into a group-average to capture common patterns and facilitate the interpretation (Holmes and Friston, 1998; Worsley et al., 2002). To correct for the problem of multiple comparisons and the consequent *false positives* (i.e. voxels that are identified as active at the group-level as a result of Type I error), thresholding is applied both at the voxel-level and at the cluster-level (for review see Nichols, 2012). The resulting thresholded map reflect the regions that are significantly recruited by the experimental manipulation.

For statistical inference at the whole brain level, it is common to contrast regressors again each other (e.g. cued > uncued semantic decisions). As contrasts reveal the variance that is uniquely explained by a given regressor, they are extremely useful to capture differences in the pattern of neural activity associated with the experimental manipulation. If the experimenter has predictions about the neural response in specific brain regions, it is also possible to limit the investigation of fMRI signal to a region-of-interest (ROI) and extract the parameter estimates in the pre-specified set of voxels. This approach has several advantages (Poldrack, 2007; Poldrack et al., 2011). One advantage of ROI analysis is to control for type I error by limiting the number of statistical comparisons. Moreover, researchers can interrogate the neural response to the experimental manipulation in a mask that was functionally defined in an independent dataset, for instance a cluster from a meta-analysis, a separate localizer scan, or even a whole brain map (e.g. Principal gradient). Finally, ROI analysis can be particularly useful in complex designs with multiple conditions, where the results observed a the whole brain level might be difficult to interpret. Using an ROI analysis, it is possible to extract the parameter estimates for each condition and plot them against each other and perform further statistical analysis.

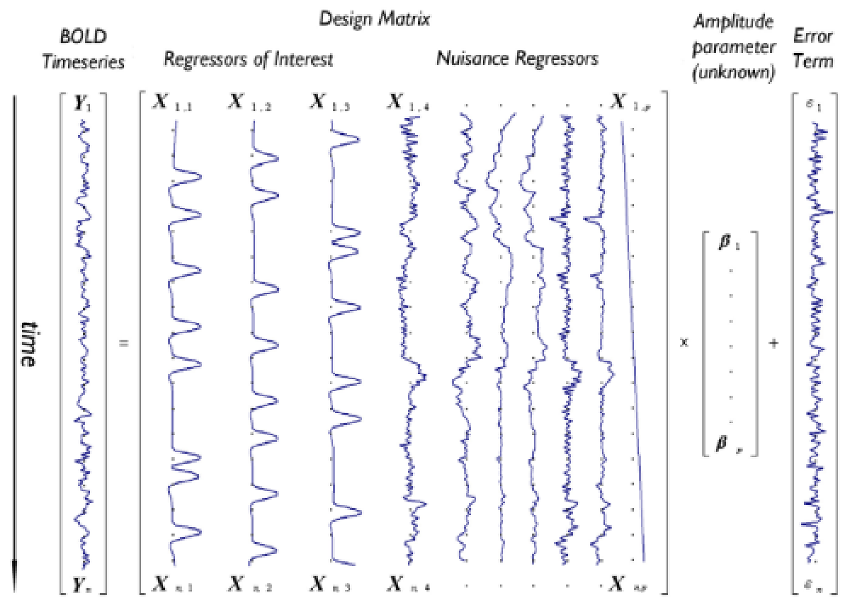

FIGURE 1 | Depiction of the GLM model for an imaginary voxel with time-series *Y* predicted by a design matrix *X* including 10 effects (three regressors of interest – e.g., tasks A,B,C – and seven nuisance regressors – e.g., six motion parameters and one linear drift) of unknown amplitude β_r and an error term.

Figure 1.6. Depiction of the General Linear Model. Reproduced from Monti, 2011

The greatest advantage of task-based fMRI is its spatial resolution, which enables us to examine the brain regions underpinning cued semantic decisions with a greater degree of precision than patient-lesion studies – where the damage is typically widespread and highly variable across individuals. The method also permits whole-brain analyses which may reveal functional contributions of brain regions that are beyond the area typically lesioned in a specific patient group (for example, in the case of semantic aphasia, areas invulnerable to stroke). However, this method has limited power to examine how large-scale systems are dynamically organized, and how this relationship may change over time and/or in different subjects.

5.2.2 Functional connectivity

While activation-based fMRI capturing relative changes in the BOLD signal in response to a task have been widely used to infer the functional relevance of specific regions, this method fails to capture the complex interactions between spatially distinct regions. To overcome this limitation, many studies are moving away from the localization of functions and instead focusing on patterns of functional connectivity between individual brain regions or large-scale networks. As cognition relies on spatially distinct yet functionally associated regions, functional connectivity methods offer the unique advantage of describing and quantifying the dynamic interactions in the brain. These methods can be distinguished according to whether they measure brain connectivity in the context of a task or at rest. Examples of task-based connectivity methods are: psychophysiological interaction analysis (Friston et al., 1997; O'Reilly et al., 2012), structural equation modelling (Büchel and Friston, 1997; McLntosh and Gonzalez-Lima, 1994), dynamic causal modelling (Friston et al., 2003). For the purpose of introducing the empirical work in this thesis, this section will focus exclusively on RS-fMRI approaches (for reviews see Rogers et al., 2007; Soares et al., 2016).

5.2.2.1 Applications of RS- fMRI

Resting-state fMRI (RS-fMRI) measures the spontaneous low frequency fluctuations (<0.1 Hz) in the BOLD signal in the absence of tasks or stimuli, and captures the temporal dependence in the co-activation of different brain regions (Lowe et al., 2000; for review see Lee et al., 2013; Margulies et al., 2010). The underlying assumption is that covariance in the temporal fluctuation in BOLD signal in distinct regions reflects common neural activity (Damoiseaux et al., 2006; Salvador et al., 2005). Following the seminal work by Biswal et al. (1995) showing that the intrinsic activity of a seed region in the left somatosensory cortex was highly correlated with the homologous region in the right hemisphere, several other large-scale networks have been identified. These include the motor system (Lowe et al., 1998; Xiong et al., 1999), visual (Cordes et al., 2000; Hampson et al., 2004; Lowe et al., 2000) and auditory (Smith et al., 2009) networks, a language network (Tomasi and Volkow, 2012), dorsal and ventral attentional systems (Fox et al., 2006; Power et al., 2011; Seeley et al., 2007; Smith et al., 2009), frontoparietal (Vincent et al., 2008), default mode (Greicius et al., 2003). Importantly, these RS-networks are highly overlapping with networks typically engaged during tasks (Fox et al., 2005; Smith et al., 2009), and can be detected reliably across subjects (Damoiseaux et al., 2006; Shehzad et al., 2009) and MRI sessions (Biswal et al., 2010; Shehzad et al., 2009).

The intrinsic activity of the brain has clinical relevance and can be used for pre-surgical localization of relevant cortex in patients with tumours (Zhang et al., 2009) and epilepsy (Liu et al., 2009; Zhang et al., 2011). RS-fMRI has also proven useful in identifying network alterations in multiple disease states (Zhang and Raichle, 2010; for review see Lee et al., 2013). For example, abnormalities in BOLD signal in regions overlapping with the DMN have often been observed in patients with Alzheimer's disease (Dai et al., 2012; Koch et al., 2012; Supekar et al., 2008). Moreover, RS-fMRI can distinguish patients with mild cognitive impairments from healthy controls (Chen et al., 2011), and AD from frontotemporal variants of dementia (Zhou et al., 2010). Changes in functional connectivity have been observed during altered states of consciousness (Luppi et al., 2019; Pappas et al., 2019a, 2019b; Stamatakis et al., 2010; Varley et al., 2020; Vatansever et al., 2020), following traumatic brain injury (Kasahara et al., 2011, 2010), in TBI-induced depression (Moreno-López et al., 2016), and following left-hemisphere stroke (Stamatakis et al., 2005). The main disadvantage of RS-fMRI lies in the correlational nature of this approach, which does not allow causal inferences about the relationships observed. A possible way to overcome this issue is to combine RS-fMRI with other approaches where causal inferences are possible, such as TMS or neuropsychology.

5.2.2.2 Analysis of RS-fMRI data

Pre-processing of BOLD signal for RS-fMRI involves similar steps as those outlined for task-based fMRI: (i) *slice-timing correction* for section-dependent time shifts, (ii) *spatial smoothing* and (iii) *temporal filtering* using low-pass filters (~ < 0.1 Hz), which remove frequencies associated with non-neuronal sources, thus improving the signal to noise ratio (Uddin et al., 2008). A primary source of noise is the signal associated with physiological causes, such as cardiac (~ < 0.15 Hz) and respiratory (~ < 0.3 Hz) signals. These sources of variance are particularly dangerous because they can increase the apparent similarity of time series and thus bias the inferences that can be made from connectivity analyses (Bright and Murphy, 2015; Van Dijk et al., 2012). To circumvent the problem, in addition to temporal filtering, pre-processing of RS-fMRI data also typically involves the inclusion of nuisance regressors, although the effectiveness of nuisance regressors is often a controversial topic. For example, the global signal regression (GSR) – which involves subtracting the mean time-course of the entire brain from each voxel (Macey et al., 2004) – has been shown to introduce negative spurious correlations (Anderson et al., 2011; Murphy et al., 2009). Another source of noise is given by motion artefacts, which can introduce spurious correlation if not adequately corrected (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012). Different approaches for the analysis of RS connectivity are currently available and can be grouped in (i) data-driven approaches, which are free of assumptions and attempt to map connectivity in the whole brain, and (ii) model-driven approaches, which are motivated by *a-priori* hypotheses and typically restricted to specific regions.

One commonly used model-free method is *independent component analysis* (ICA; Beckmann et al., 2005), which uses decomposition of resting-state data to extract maximally independent spatial or temporal components and derive functionally distinct networks (Margulies et al., 2010). The main advantage of this multivariate method is the absence of *a-priori* assumptions or hypotheses regarding the locations of networks. However, the number of desired components must be specified in advance by the investigator, and the selection/interpretation of meaningful components is not always straightforward (Lee et al., 2013). *Clustering* techniques are also gaining popularity in the analysis of resting-state data. This mathematical approach works through the unsupervised classification of data into “clusters” based on a given characteristic; voxels with similar time series will be grouped into the same cluster. Clustering has allowed the description of fractionations within large-scale systems including the default mode (Andrews-Hanna et al., 2010) and frontoparietal network (Dixon et al., 2018). The limitation of this method, known as “cluster validity problem”, is that the experimenter must determine the optimal cluster solution using available algorithms. In a similar way to ICA approaches, clustering is therefore not completely free of human factor (Margulies et al., 2010). An alternative approach is *graph theory*, which describes the intrinsic activity of the brain as a collection of nodes and edges. Within a graph system, nodes correspond to the ROIs, edges represent the functional connectivity between nodes, and modules reflect communities of nodes that are more densely connected with each other than with nodes in other communities. Connectional characteristics of the graph include measures of modularity (the extent to which the system can be divided into separate modules), local clustering coefficient (which examines whether the triangle between three nodes is closed by edges – this indirectly reflects the resilience of the graph and its ability to stay connected once a node is removed; van den Heuvel et al., 2008), and average path length (the average of connections between all pairs of nodes; van den Heuvel et al., 2008). Graph theory offers a unique advantage in describing network topology, however it is not completely model-free, since it often involves a certain degree of assumptions and pre-specification of ROIs (or nodes).

In the present empirical work we used *seed-voxel correlation* mapping, which is perhaps the simplest and most widely used method for connectivity analyses (Biswal et al., 1995; Fox et al., 2005; Fransson, 2005; Raichle et al., 2001). This model-based approach involves the definition of a region-of-interest (or seed region) and the extraction of a model time series from the specified area. In a second step, various statistical analyses techniques can be used to quantify the similarity between the time series of the seed and the time-series of all the voxels in the brain. The main advantage of this technique is the simplicity of use and the high-interpretability of the results, which directly answer the question of how spatially distinct regions interact at rest. Moreover, seed-based correlation can facilitate the detection of functional subdivisions or fractionations within larger regions with a smaller number of participants compared to meta-analytic studies (Margulies et al., 2010). This method has been successfully used in previous studies by our group to describe the functional architecture of semantic cognition (Davey et al., 2016; Gonzalez Alam et al., 2019; Hallam et al., 2018; Krieger-Redwood et al., 2016; Mollo et al., 2016). The primary limitation of this method is the need for an *a-priori* definition of the regions (location, size and shape), which can introduce biases in the results (Cole et al., 2010; Margulies et al., 2010). In an attempt to overcome this limitation, the empirical work in Chapter 5 of this thesis used entire networks as seeds, rather than individual regions. Since semantic cognition is known to rely on large-scale networks, examining patterns of intrinsic connectivity of networks was considered to be a more appropriate approach. Moreover, meta-analytic tools like Neurosynth (Yarkoni et al., 2011; further discussed in the next session) can be used to inform the choice of seeds based on the available literature.

5.2.2.3 Predicting behaviour from individual differences in functional connectivity

While group-average analyses are effective at describing the macro-scale topographical organization of brain networks, they discard important information about inter-individual variability (for discussion on the topic see Dubois and Adolphs, 2016; Kanai and Rees, 2011; Thiebaut de Schotten and Shallice, 2017). Patterns of functional connectivity in the human brain are highly variable (Mueller et al., 2013), particularly in phylogenetically late-developing heteromodal cortices, suggesting that this variability might have an evolutionary root (Mueller et al., 2013). In line with this idea, individual differences in intrinsic connectivity have been associated with behavioural variability in working memory (Alavash et al., 2015; Hampson et al., 2006a; Liu et al., 2017; Magnuson et al., 2015; Stevens et al., 2012), executive control (Seeley et al., 2007), reading abilities (Hampson et al., 2006b; Zhang et al., 2019), face processing (Zhu et al., 2011), intelligence scores (Hearne et al., 2016; Song et al., 2008), content of spontaneous thoughts (Gorgolewski et al., 2014; Smallwood et al., 2016; H.-T. Wang et al., 2018a), and semantic cognition (Evans et al., 2020; Gonzalez Alam et al., 2019; Krieger-Redwood et al., 2016; Mollo et al., 2016; Sormaz et al., 2017; Vatansever et al., 2017a; Wang et al., 2013; Wei et al., 2012). Thus, this growing body of work indicates that the synchronous fluctuations in BOLD observed at rest are functionally relevant, and not just merely epiphenomenal.

In the semantic literature, analyses of individual differences in intrinsic connectivity have been used to examine how changes in the strength and directionality of functional connections might relate to semantic abilities. Often, improved behavioural performance is associated with increased within-network connectivity, when the network is relevant for the task. For example, Wei et al. (2012) showed that increased coupling of pMTG to a distributed set of regions, including left IFG and temporal cortex, was predictive of individual differences in semantic processing efficiency. Similarly, greater coupling within left-hemisphere semantic control regions and other left-lateralized language regions was found to be predictive of semantic performance (Gonzalez Alam et al., 2019). However, other patterns of connectivity have also been reported, for example increased segregation of usually anti-correlated functional networks (Mollo et al., 2016; Vatansever et al., 2017a) or increased coupling of regions belonging to different networks, yet functionally relevant for the task (Evans et al., 2020; Krieger-Redwood et al., 2016).

A common approach to studying individual differences is to combine seed-to-voxel connectivity with measures of behaviour obtained outside the scanner. Typically, a resting-state scan is acquired, then participants are asked to take part in a behavioural session. The analysis then involves two main steps: (i) computing the whole-brain connectivity for the chosen seed, and (ii) entering the behavioural scores as regressors in the group-level analyses. In this way the regression model identifies regions in the brain whose temporal correlation with the seed is significantly predicted by the behavioural scores. An alternative approach to the study of individual differences is canonical correlation analysis (CCA; Hardoon et al., 2004). This multivariate technique allows to identifies “neurocognitive components” from the linear combination of brain activity and behaviour. Using this approach, Vatansever et al. (2017a) described a pattern of brain-behaviour association such that, reduced connectivity between DMN nodes and executive control regions such as IFG and pre-SMA was associated with better performance on harder semantic tasks that required control. Moreover, this method allowed to capture qualitatively distinct aspects of semantic tasks. Specific patterns of connectivity were linked to each participant’s relative strengths and weaknesses in a variety of semantic tasks, for example (i) good performance on picture-based material was associated with poor performance on verbal feature matching, and (ii) good performance in speech production measure alongside poor performance in association judgements. These findings are a clear example of how individual differences can provide unique and complementary insights into the organization of cognitive processes, by capturing systematic changes in the pattern of brain-behaviour associations.

The current thesis used a seed-based approach, which is often preferred to other methods for the high interpretability of the results. To reduce the impact of the biases introduced during the selection of the seed regions, we seeded large-scale networks rather than individual ROIs. Seed-based analyses of the intrinsic connectivity of the brain were combined with behavioural regressions to define the regions in the brain where the functional connectivity with several large-scale networks was associated with performance on a semantic task.

5.2.3 Neurosynth decoding

Neurosynth is an online tool for large-scale synthesis of functional neuroimaging data which combines text-mining, meta-analytic methods and machine learning to aggregate and interpret large amounts of published data (Yarkoni et al., 2011; Figure 1.7.). First, it searches for fMRI studies associated with broad psychological terms (e.g. “semantics”, “memory”, “default mode network”) using text-mining techniques. Then, the peak coordinates reported in the studies are automatically extracted and stored in a database alongside the relative cognitive terms. In a third step, meta-analyses of psychological terms are conducted on the coordinates to produce whole-brain maps (z-stat or t-stat) that are made available in a unthresholded form on the platform. Finally, machine-learning techniques allow to decode activation maps and estimate the probability that the pattern of neural recruitment will be associated with certain terms. In this way, Neurosynth allows for both forward and reverse inference to be made: users can specify a psychological construct (e.g. “semantic control”) and obtain the corresponding activation map using forward inference, or they can obtain the psychological terms associated with a given neural pattern using reverse inference.

This approach offers multiple advantages, including a solution to the reverse inference problem. The ability to decode cognitive states from patterns of neural activity has in fact posed a challenge in neuroscience research, since most studies have focused on capturing the neural changes associated with an experimental manipulation – and not vice versa (Poldrack, 2006). Neurosynth has allowed researchers, for the first time, to perform automated reverse inferences on large amounts of data, thus facilitating the interpretation of the observed neural patterns. The decoding ability of Neurosynth was tested with a naïve Bayes classifier and proved accurate. Additionally, this fully automated tool allows to aggregate and synthetize vast amount of data beyond human capabilities, allowing the comparison of findings from multiple methods and increasing statistical power. Neurosynth, however, is not free of limitations. Firstly, this method relies on lexical decoding and on the assumption that the use of a given psychological term in a study is a proxy for the findings. Consequently, it might fail to capture fine-grained distinction between different cognitive states (e.g. subtle differences in a given emotion) or between terms that are related but have slightly different meanings. Secondly, the fully automated nature of this tool could result in a failure to extract potentially relevant information or introduce errors when different stereotactic coordinates are reported in the studies (but see supplementary materials of Yarkoni et al., 2011 for an algorithm developed to overcome this issue). Neurosynth is used in this thesis for the cognitive decoding of task-based univariate (Chapter 4) and seed-based connectivity (Chapter 5) fMRI maps. By combining this tool with classic statistical analyses, we aim to strengthen the inferences that can be made from the observed pattern of neural activation.

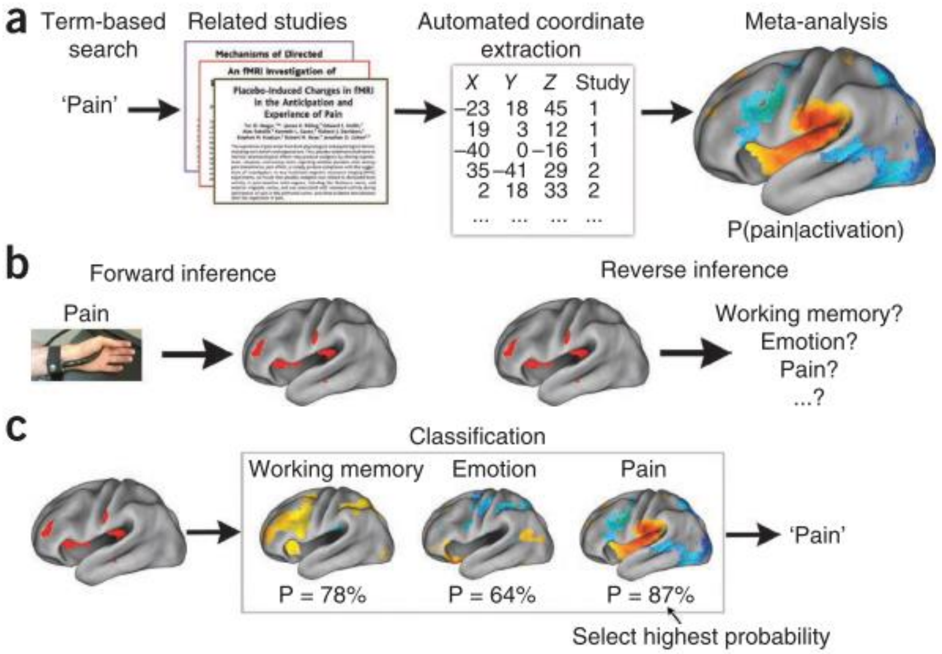

Figure 1.7. Schematic overview of the Neurosynth framework. **A** Published articles associated with psychological terms (e.g. pain) are stored in a database, and the peak coordinates are automatically extracted alongside their cognitive terms. In a third step, meta-analyses of psychological terms are conducted on the coordinates to produce whole-brain maps. **B** Neurosynth allows users to perform both forward and reverse inference. **C** New maps uploaded to Neurosynth can be "decoded" for cognitive terms by comparing them to other maps stored in the database. Reproduced with permission from Yarkoni et al., 2011.

5.2.4 Principal gradient

A complementary method to the ones above allows us to describe the topographical organization of the systems supporting semantic cognition. Using a non-linear decomposition technique of resting-state data known as diffusion embedding, Margulies et al. (2016) extracted multiple overlapping brain gradients corresponding to different components of variability in functional connectivity patterns. The position of cortical points on the gradient reflects connectivity similarities, such that regions close to each other have a similar distribution of correlations with the rest of the brain, whereas areas situated at opposite ends of the gradient have opposing patterns of connectivity. In Margulies et al. (2016), the principal gradient axis which describes the most variance is anchored at one end by primary motor and somatosensory regions, and at the other end by heteromodal cortex overlapping with DMN. The principal gradient matches the intrinsic geometry of cortex, with DMN nodes at the top-end of the hierarchy occupying locations equidistant from unimodal regions. In this way, greater distance along the gradient might allow forms of cognition that require separation from external inputs - such as memory or mind wandering (Mason et al., 2007; Murphy et al., 2019). Moreover, the principal gradient captures orderly transitions between large-scale networks (Yeo et al., 2011) in several locations on the cortical surface, indicating that the spatial layout of intrinsic connectivity is not random. Critically, this macroscale hierarchy is aligned with a continuum of functions spanning acting/perceiving at the unimodal end, and high-order cognition at the heteromodal end of the gradient (Margulies et al., 2016; Figure 1.5.C).

This approach offers multiple advantages. First, it provides an organizing principle for understanding the spatial arrangement of large-scale networks and how this may constrain cognition. Increasingly complex and abstract representations might be formed through the progressive integration of neural signals from unimodal cortex towards high-order integrative hubs. Thus, the topographical organization described by the principal gradient suggests that information converge is expected to occur in regions overlapping with DMN. Second, this analysis provides unique insights by focusing on whole-brain patterns associated with particular aspects of cognition. Unlike traditional univariate activation analyses, which reflect the average engagement of certain regions during a task, the gradient analysis examines how the effect of interest unfolds along the cortical surface. This enables us to shift the focus of our research question from (i) establishing which regions or large-scale networks support semantic flexibility to (ii) quantifying the contribution of different portions of the gradient to the effect of interest. This approach has recently contributed evidence to the role of DMN in active cognition. For example, Murphy et al. (2019, 2018) found increased neural recruitment at the DMN-end of the gradient when participants retrieved information from memory compared to when the relevant features where perceptually available. Furthermore, recent findings from Wang et al. (2020) indicate that the principal gradient can capture the similarity between currently relevant information and representations in long term memory, in line with the proposed convergence hierarchy.

In the present thesis we implemented an ROI-based analysis of the principal gradient. The original gradient map (Margulies et al., 2016) has values ranging from 0 (unimodal end) to 100 (heteromodal end). In line with the methods described in Margulies et al. (2016) and previous studies by our group (Murphy et al., 2019, 2018), we divided the principal gradient map in decile bins; voxels with values 0–10 were assigned to bin1; voxels with values 11–20 to bin 2, etc., yielding 10 bins with near-identical number of voxels. Each bin was then used as a mask in an ROI analysis, where we extracted the parameter estimates for the conditions of interest. In this way, the principal gradient analysis leverages the explanatory power of the macroscale gradient to account for differences between experimental conditions.

5.3 Summary of methods

As reviewed in the previous sections, neuroscience research offers a variety of methods for the investigation of cognitive phenomena. As these methods focus on qualitatively aspects of the mapping between brain and behaviour, it is important to formulate the correct empirical questions – while being aware of the strengths and limitation of each approach. By combining multiple methods and statistical analyses we aim to provide a richer description of the neural architecture supporting cued and uncued semantic retrieval. *Neuropsychological investigations* of patients with semantic aphasia are used in Chapter 2 and 3 to examine the consequences of prefrontal/temporo-parietal lesions on the ability to use contextual information to guide semantic retrieval. In Chapter 4 we use *task-based fMRI* and *principal gradient analyses* to (i) localize the brain regions underpinning semantic cue integration and (ii) describe how the integration effect unfolds along the cortical surface. Finally, in Chapter 5 we examine whether the intrinsic connectivity of the brain is predictive of individual differences in semantic performance using *seed-based analyses* combined with behavioural regressions. To facilitate the interpretation of the results, we perform *cognitive decoding in Neurosynth*.

Chapter 2: Emotion and location cues bias conceptual retrieval in people with deficient semantic control

This chapter is adapted from:
Lanzoni, L., Thompson, H., Beintari, D., Berwick, K., Demnitz-King, H., Raspin, H., Taha, M., Stampacchia, S., Smallwood, J., Jefferies, E., 2019. Emotion and location cues bias conceptual retrieval in people with deficient semantic control. Neuropsychologia 131, 294–305.
https://doi.org/10.1016/j.neuropsychologia.2019.05.030

Acknowledgments and authors' contribution

Lucilla Lanzoni performed the statistical analyses, interpreted the results and wrote the manuscript for publication under the supervision of Prof. Elizabeth Jefferies and Prof. Jonathan Smallwood. The experiment was designed by Dr. Hannah Thompson prior to the start of Lucilla's Lanzoni's research degree. Dr. Thompson also commenced the data collection with the help of Dr. Stampacchia and the following undergraduate students: Danai Beintari, Katrina Berwick, Harriet Demnitz-King, Hannah Raspin, Maria Taha. Data collection was completed by Lucilla Lanzoni in the first year of her PhD. Prof. Jefferies edited manuscript drafts, while Prof. Smallwood provided comments on the final draft.

Emotion and location cues bias conceptual retrieval in people with deficient semantic control

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Acknowledgments

We are indebted to the patients, their carers, and the control participants for their generous support with this study.

Funding

The study was supported by a grant from the Stroke Association [R1425201] and a grant from the European Research Council [FLEXSEM – 771863] awarded to E.J.

Abstract

Visuo-spatial context and emotional valence are powerful cues to episodic retrieval, but the contribution of these inputs to semantic cognition has not been widely investigated. We examined the impact of visuo-spatial, facial emotion and prosody cues and miscues on the retrieval of dominant and subordinate meanings of ambiguous words. Cue photographs provided relevant visuo-spatial or emotional information, consistent with the interpretation of the ambiguous word being probed, while miscues were consistent with an alternative interpretation. We compared the impact of these cues in healthy controls and semantic aphasia patients with deficient control over semantic retrieval following left-hemisphere stroke. Patients showed greater deficits in retrieving the subordinate meanings of ambiguous words, and stronger effects of cueing and miscuing relative to healthy controls. These findings suggest that contextual cues that guide retrieval to the appropriate semantic information reduce the need to constrain semantic retrieval internally, while miscues that are not aligned with the task increase the need for semantic control. Moreover, both valence and visuo-spatial context can prime particular semantic interpretations, in line with theoretical frameworks that argue meaning is computed through the integration of these features. In semantic aphasia, residual comprehension relies heavily on facial expressions and visuospatial cues. This has important implications for patients, their families and clinicians when developing new or more effective modes of communication.

Keywords: stroke; aphasia; context; cueing; semantic; spatial; emotion

1. Introduction

Although we retain a wealth of information about any given concept, only a subset of this information is relevant in a particular context (Jefferies, 2013; Schoen, 1988; Yee and Thompson-Schill, 2016). Sometimes, distant associations or less dominant aspects of knowledge are required to achieve a certain goal: we can readily identify that a rolled up newspaper can squash a fly, even though newspapers are normally associated with reading (Corbett et al., 2011; Jefferies, 2013). This semantic flexibility, reflecting the retrieval of non-dominant elements of concepts in a context-dependent manner, is thought to require semantic control processes that are separate from the conceptual store (Jefferies, 2013; Lambon Ralph et al., 2016; Thompson-Schill et al., 1997; Wagner et al., 2001; Whitney et al., 2011b). According to the Hub and Spoke account of semantic cognition (Lambon Ralph et al., 2016; Patterson et al., 2007), modality-specific features ('spokes') are integrated to form heteromodal conceptual representations within a 'hub' in the ventral anterior temporal lobes (ATL). When the pattern of semantic retrieval required by a task for a specific concept is aligned closely with its dominant features and associations within the semantic store, hub-spoke interactions should readily generate coherent semantic activation that can drive an appropriate response relatively automatically. However, when the most accessible information pertaining to a concept is *not* relevant (for example, when we use newspapers to swat flies), unconstrained semantic activation is less helpful. Accordingly, it is assumed that in these situations, semantic control mechanisms come into play, allowing us to produce flexible patterns of retrieval (Controlled Semantic Cognition account; Jefferies, 2013; Lambon Ralph et al., 2016).

This semantic flexibility is compromised in patients with semantic aphasia (SA) following left-hemisphere inferior frontal and/or temporoparietal stroke (Lambon Ralph et al., 2016; Noonan et al., 2013a; Noonan et al., 2010). Patients with SA have deregulated semantic cognition in both verbal and non-verbal tasks (Corbett et al., 2009a, 2009b; Gardner et al., 2012; Jefferies et al., 2008a; Thompson et al., 2015). They have difficulty selecting targets in the presence of distractors with related meanings and show poorer comprehension of non-dominant interpretations of ambiguous words (e.g. when matching FIRE with RIFLE, as opposed to matching FIRE with HOT; Noonan et al., 2010). Critically, these patients show inconsistent performance when the same concepts are probed under different cognitive demands, often performing the best in more constrained tasks in which semantic retrieval is strongly guided by the task itself (Jefferies and Lambon Ralph, 2006; Noonan et al., 2013a; Rogers et al., 2015). For example, Corbett and colleagues (2011) found that performance in a naturalistic task involving demonstrating the use of an object was significantly improved when SA patients were provided with the actual object (e.g. a hammer) and a picture of the usual recipient (e.g. a nail) compared to when they were verbally instructed to mime the use of the object (e.g. ‘show me how you would use a hammer).

The original definition of semantic aphasia provided by Henry Head (1926) and Luria (1976) referred to a cluster of high-level interpretative deficits across modalities involving processing relationships between concepts. In this study and in previous publications by this group we have used the term semantic aphasia to refer to patients with multimodal semantic problems affecting both words and pictures. Other researchers using this term (e.g. Dragoy et al., 2017), have focused on problems at the sentence level, highlighting the difficulties of their SA cases with logical-grammatical structures and figurative speech. These sets of patients are likely to have overlapping deficits, although the cases reported here and by other studies from our group typically have some degree of impairment for single items, and therefore may have more severe heteromodal deficits of semantic cognition. Overall, this pattern of impairment is qualitatively distinct from deficits in semantic dementia: although both groups have multimodal semantic comprehension impairment affecting both verbal and non-verbal comprehension, semantic dementia gives rise to a gradual degradation of conceptual knowledge that is highly predictable across tasks, following atrophy and hypometabolism focused on the ventral ATL (Desgranges et al., 2007; Diehl et al., 2004; Mion et al., 2010; Mummery et al., 1999; Rosen et al., 2002; Studholme et al., 2004).

This neuropsychological evidence suggests that distinct neurocognitive components support conceptual representation and control, with left inferior frontal gyrus (IFG) and posterior middle temporal gyrus (pMTG) – regions commonly damaged in SA patients – critical for semantic control. Convergent evidence is provided by neuroimaging (Badre et al., 2005; Davey et al., 2015b, 2016; Noonan et al., 2013b; Thompson-Schill et al., 1997) and brain stimulation studies of healthy participants (Davey et al., 2015a; Hallam et al., 2016; Hoffman et al., 2010; Whitney et al., 2011b). These regions commonly activate across a wide range of semantic control manipulations – including for weak vs. strong associations, decisions in the face of strong distractors and for ambiguous words, when there is a need to resolve competition between alternative interpretations (Bedny et al., 2008b; Rodd et al., 2005; Vitello et al., 2014; Vitello and Rodd, 2015; Zempleni et al., 2007). Inhibitory TMS delivered to left IFG and pMTG elicits equal disruption of tasks requiring semantic control, while there is no effect on either easier semantic judgements or non-semantic decisions (Davey et al., 2015a; Hoffman et al., 2010; Whitney et al., 2011b). Left IFG and pMTG show a response to semantic control manipulations across modalities (Krieger-Redwood et al., 2015) and are largely distinct from multiple-demand regions that support domain-general cognitive control (Davey et al., 2016; Noonan et al., 2013b). As these aspects of control occupy adjacent regions along the cortical surface (Davey et al., 2016), they are unlikely to be separable in patients with stroke aphasia who typically have large lesions. Nevertheless, the extent to which semantic deficits and more general executive dysfunction co-occur varies across individuals (as reviewed by Gainotti, 2014). Taken together, these findings suggest that the major areas of lesion overlap in SA – in left inferior prefrontal and temporoparietal cortex – play a crucial role in shaping semantic retrieval to suit the demands of the task or context, accounting for the pattern of inflexible semantic retrieval that these patients show (e.g. Jefferies and Lambon Ralph, 2006; Noonan et al., 2010).

In summary, contemporary accounts of semantic cognition propose that a dynamic interplay of conceptual knowledge with control processes supports the retrieval of meaning in a manner that is tailored to the task or context (Hoffman et al., 2018; Jefferies, 2013; Lambon Ralph et al., 2016). The activation of conceptual representations is thought to be modulated by recent experience and current task goals (Yee and Thompson-Schill, 2016). As a consequence, semantic control demands should reflect the match between the semantic features required by a task and those that are most accessible for the concept (because of recent experience or the strength of long-term learning). In this way, the context in which concepts are presented will strongly influence controlled retrieval demands (Cf. Tulving and Thomson, 1973). Patients with SA provide clear evidence for this claim, since their semantic retrieval is highly sensitive to cueing. Phonological cues result in near-perfect picture naming performance in SA (but not in semantic dementia, reflecting the loss of conceptual knowledge; Jefferies et al., 2008b). Similarly, embedding an ambiguous word in a sentence that disambiguates its meaning yields a positive effect on SA patients' performance (Noonan et al., 2010; e.g. "they served a delicious PUNCH at the party" vs. "the boxer landed a PUNCH on the opponent"). Picture cues are effective at supporting conceptual retrieval in non-verbal tasks: SA patients are better able to retrieve the specific action associated with a tool when shown the typical recipient of the action (Corbett et al., 2011; e.g. for HAMMER, a picture of a NAIL), in line with the proposal that their semantic control deficit is multimodal. However, sometimes concepts have to be processed in a manner that is at odds with the immediately preceding context, or the interpretation needs to change over time. In these circumstances, (mis)cues actually increase semantic control demands, since information that is irrelevant for the task (but potentially dominant for the concept) is made more accessible. SA patients show a greater cost of both phonological miscues in picture naming (Soni et al., 2009; e.g. for TIGER, the phonogical cue "L") and sentence contexts that cue the irrelevant interpretation of ambiguous words (Noonan et al., 2010; e.g. "the young men like to BOX " for BOX - PACKET).

Since heteromodal concepts are thought to draw on a wide range of features (cf. Hub and Spoke model), we would expect different kinds of cues to be effective in patients with SA. In the current study, we moved beyond the phonological and semantic cues used in previous investigations, to investigate the impact of visuo-spatial contexts and emotional cues such as facial expressions and prosody in speech. In everyday situations, patients' comprehension is likely to be supported by the environment they are in – including the location in which conceptual retrieval occurs, and the facial expression and voice intonation of speakers. However, previous studies have not examined whether SA patients rely on these kinds of cues to guide semantic retrieval. This question has become pressing, given the development of telephone and online therapy and support tools, which often lack this information. We used both valence cues (emotional faces and prosody) and pictures of the spatial context in which items commonly occur. These cue types have already been shown to be effective in episodic memory. Memory is improved when the emotional context of an encoding event is reinstated at retrieval (e.g. Bower, 1981; Bower et al., 1978; Bower and Mayer, 1989; Eich, 1995). Similarly, the spatial context in which an event is encoded appears to be an effective retrieval cue (e.g. Burgess et al., 2002; Robin et al., 2018; Robin and Moscovitch, 2014). However, these cue types have rarely if ever been employed in semantic retrieval tasks.

In three different experiments, we provided pictures of facial expressions, emotional prosody sequences using nonsense syllables ("ba-ba-ba"), and spatial context pictures, prior to semantic decisions in which patients were asked to match an ambiguous probe word (e.g. JAM) to a semantically related target presented among distractors (e.g. JAM – blanket, <u>spoon</u>, hospital, union). In some trials, cues were used to prime the correct interpretation of the word. In other trials, the cue was designed to activate the alternative meaning of the ambiguous word, which was not relevant for the task (miscue). We anticipated that both cueing and miscuing effects would be greater for SA patients compared to healthy controls across all tasks since (i) ventral ATL is largely undamaged in SA; consequently, the Hub and Spoke model envisages that diverse cues will influence the accessibility of conceptual information in the semantic store and (ii) damage to semantic control processes makes it difficult for SA patients to retrieve knowledge in the absence of external constraint, and to overcome irrelevant semantic information that is activated.

2. Methods

2.1 Participants

The study was approved by the local ethical committee and informed consent was obtained. Ten SA patients were recruited through stroke and aphasia associations across Yorkshire, UK. The majority (P1-4, P6-9) have been previously described (Stampacchia et al., 2018). All patients had suffered a cerebrovascular accident (CVA) affecting the left hemisphere at least one year before testing. Background details and lesion characteristics for each patient can be found in Table 2.1. Consistent with previous investigations of SA, patients were selected on the basis of multimodal semantic deficits. All patients showed semantic control deficits in both verbal and non-verbal semantic tasks. They performed poorly when retrieving less-dominant meanings of homonyms in a semantic judgement task (Noonan et al., 2010) and non-canonical uses in an object use task (Corbett et al., 2011).

The SA group was compared with sixteen healthy, age and education matched control participants [mean age at recruitment: SA group = 62.2, control group = 69 years, t (24) = 1.6, p = .122; mean age when leaving education: SA group = 16.9, control group = 18.2, t (21.5) = 1.6, p = .135]. The control participants had no history of neurological or psychiatric conditions and showed unimpaired cognitive functioning on the Mini-Mental State Examination with a cut-off point of 24/30 (Folstein et al., 1975). Although the control group was on average a few years older than the SA group (but not statistically significant so), this should have worked against our hypothesis that SA show poorer semantic control.

2.2 Lesion Analyses

MRI scans were available for all 10 patients. An overlay of lesion maps was created using automated lesion identification (Seghier et al., 2008), and is displayed in Figure 2.1. This technique classifies each voxel as grey matter, white matter or cerebrospinal fluid, and identifies lesions as regions of the brain that do not correspond with the expected tissue type.

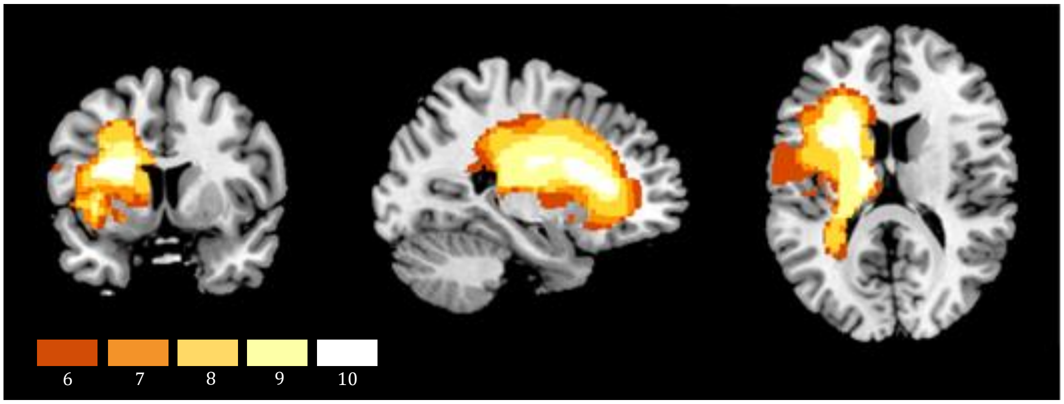

Figure 2.1. Lesion overlay of the sample of SA patients included in the study. Patients' brains were compared to aged-matched controls. Grey matter, white matter and CSF were segmented and changes from the healthy control brains were highlighted as 'lesion' using automated methods (Seghier et al., 2008). Only areas of maximum overlap are included (where at least 6/10 patients had a lesion). The colour bar indicates the number of patients with damage in each voxel.

Details of individual patients' lesions were obtained using Damasio's standardized templates (Damasio and Damasio, 1989) and are displayed in Table 2.1. All of the patients had damage within inferior frontal gyrus (IFG) (especially in pars opercularis and orbitalis). The lesion extended into superior temporal gyrus (STG) and the supplementary motor area (SMA) in the vast majority (9/10). Other areas that showed damage were supramarginal gyrus (SMG, 8/10 patients), posterior middle temporal gyrus (pMTG; 4/10 patients) and dorsolateral prefrontal cortex (DLPFC; 3/10 patients).

					DLPFC		orbIFG	triIFG	opIFG	SMA/PMC	TP	STG	MTG	ITG	FG	POT	AG	SMG
Case	*Age*	*Sex*	*Education (leaving age)*	*Lesion size (%)*	*BA9*	*BA46*	*BA47*	*BA45*	*BA44*	*BA6*	*BA38*	*BA22*	*BA21*	*BA20*	*BA36*	*BA37*	*BA39*	*BA40*
P1	60	F	18	12	1	1	-	1	1	1	1	2	-	-	-	1	1	2
P2	77	M	15	15	2	-	2	2	2	2	-	2	-	-	-	-	-	1
P3	60	F	18	12	-	-	2	1	1	2	-	2	1	-	-	2	1	2
P4	57	M	18	7	-	-	-	1	2	1	-	-	-	-	-	1	1	1
P5	71	M	18	-	-	-	2	2	2	2	-	2	2	-	-	1	1	2
P6	58	F	16	15	-	-	-	-	2	2	-	1	1	-	-	1	1	2
P7	65	M	16	14	-	-	2	1	2	2	-	2	-	-	-	1	1	1
P8	77	F	16	4	-	-	-	-	1	1	-	1	1	-	-	1	-	-
P9	39	F	16	9	-	-	-	1	2	-	-	2	-	-	-	-	-	-
P10	58	F	18	14	-	1	-	2	2	2	-	2	-	-	-	-	-	2

Table 2.1. *Quantification of lesion*: 2 = complete destruction/serious damage to cortical gray matter; 1 = partial destruction/mild damage to cortical gray matter; *Anatomical abbreviations: DLPFC*=dorsolateral prefrontal cortex; *orbIFG*=pars orbitalis in inferior frontal gyrus; *triIFG* = pars triangularis in inferior frontal gyrus; *opIFG* = pars opercularis in inferior frontal gyrus*; SMA/PMC* = supplementary morot area/pontine micturition center; *TP* = temporal pole; *STG* = superior temporal gyrus; *MTG* = middle temporal gyrus; *ITG* = inferior temporal; *FG* = fusiform gyrus; *POT* = posterior occipitotemporal area; *AG* = angular gyrus; *SMG* = supramarginal gyrus.

2.3 Background Neuropsychological Assessment

Here we briefly describe the tests used in the background assessment of our patients. This neuropsychological assessment protocol has been recently described by Stampacchia et al. (2018).

2.3.1 General neuropsychology

Data for individual patients is shown in Table 2.2. In addition to their semantic deficits, patients often displayed more general language and executive impairments. Word repetition (PALPA 9; Kay et al., 1992) was impaired in four out of ten patients (and testing was not attempted in a further two patients because their speech production was very poor). Verbal fluency tasks (category and letter fluency) were under cut-off in seven out of ten patients and not attempted in a further three patients. The “cookie theft” picture description (Goodglass and Kaplan, 1983) revealed non-fluent speech in half of the patients. Executive and attentional impairment was observed in seven out of ten patients across four tasks: Elevator Counting with and without distraction from the Test of Everyday Attention (Robertson et al., 1994); Ravens Coloured Progressive Matrices (RCPM; Raven, 1962); Brixton Spatial Rule Attainment task (Burgess and Shallice, 1997) and Trail Making Test A & B (Reitan, 1958). This is in line with previous studies which found that deregulated semantic cognition in semantic aphasia often correlates with executive dysfunction (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). Visuo-spatial processing, as measured by the Visual Object and Space Perception Battery (Warrington and James, 1991) was spared in nine out of ten patients.

2.3.2 Semantic memory assessment: Cambridge Semantic Battery

Individual test scores are provided in Table 2.3. The Cambridge Semantic Battery (Adlam et al., 2010; Bozeat et al., 2000) measures semantic retrieval for a set of 64 items across four tasks: picture naming, word-picture matching, verbal and pictorial semantic associations (Camel and Cactus Test, CCT). Patients showed large variability during picture naming [correct trials M (SD) = 62.2% (39.3)], in line with their varying degree of impairment in production, while performance was uniformly at ceiling in word-picture matching [M (SD) = 93.4% (5.9)]. When the control demands of the task were higher, such as when secondary associations between concepts were probed on the CCT in either verbal or pictorial format, patients showed greater impairment which was equivalent across modalities [words M (SD) = 80% (16.7); pictures M (SD) = 80% (15.4)].

2.3.3 Tests of semantic control

In line with the inclusion criteria adopted in previous studies by our group (e.g. Stampacchia et al., 2018) the patients in this study had difficulties in retrieving and manipulating concepts in a flexible manner, due to deficient semantic control processes. We report their performance on three tasks that manipulated the control demands of verbal and non-verbal semantic judgements. The task descriptions are taken from Stampacchia et al. (2018) and therefore appear in quotation marks. Individual test scores are displayed in Table 2.3.

i. *Ambiguity task* (Noonan et al., 2010). *"*Semantic judgements (60 items) probed the dominant (MONEY) and subordinate (RIVER) meanings of ambiguous words (e.g. BANK). These semantic decisions were uncued or preceded by a sentence that primed the relevant meaning (cue condition e.g. for MONEY, I WENT TO SEE THE BANK MANAGER) or irrelevant interpretation (miscue condition e.g. THE BANK WAS SLIPPERY). There were four response options on each trial." All patients, with the exception of P5 who only completed the no cue condition, were below the normal cut-off in all conditions. They showed better comprehension for dominant than for subordinate interpretations [no cue condition accuracy: dominant M (SD): 83% (10.4); subordinate M (SD) = 55.3% (13.7)] and had greater difficulties in accessing subordinate meanings following miscues rather than cues [subordinate trials: miscues M (SD) = 51.5% (21); cues M (SD) = 76.3% (15.1)].

ii. *Synonym judgment task. "*We tested synonym judgement with strong or weak distractors (84 trials), using a task from Samson and colleagues (2007); e.g. DOT with POINT [target], presented with DASH [strong distractor] or LEG [weak distractor]. There were three response options per trial." Accuracy was below the cut-off for all patients, with the exception of P5 who did not take part and P10 who scored above the cut-off in the strong distractor condition. Performance was poorer when semantically-related but irrelevant distractors were presented [t (9) = 4, p = .003].

iii. *Object use task.* "The object use task (74 items), from Corbett et al. (2011), involved selecting an object to accomplish a task (e.g. bash a nail into wood), with all items represented as photographs. The target was either a canonical tool, normally used to complete the task (e.g. HAMMER), or an alternative non-canonical option (e.g. BRICK), presented among a set of five unsuitable distractors." Patients were poorer at selecting non-canonical than canonical targets [t (9) = 7.2, p < .001]. One patient (P6) was not below the normal cut-off in the non-canonical condition.

In summary, all ten patients showed impaired performance on one or more non-semantic verbal tasks, while they showed impaired performance on all semantic tasks. The SA group exhibited strong sensitivity to manipulations of semantic control demands across modalities – i.e., more impaired comprehension of subordinate than dominant interpretations of ambiguous words; sensitivity to cues and miscues; better performance with weak than strong distractors and better retrieval of canonical than alternative object use. A composite score reflecting each patient’s deficits in semantic cognition was derived from the Cambridge Semantic Battery and the three semantic control tasks described above using factor analysis. Patients are ordered by this composite score in the tables below.

Test	Max	Cut-off	Patients mean (SD)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Non-semantic language tests													
PALPA 9 real word repetition (tot.)	80	73	53.6 (32.9)	NA	**71**	**42**	79	NA	78	**1**	74	77	**7**
Category Fluency (8)	-	62	43.5 (28.8)	NA	**26**	**15**	**26**	NA	**14**	NA	80	**57**	69
Letter Fluency (F, A, S)	-	21.8	8 (5.4)	NA	**2**	**2**	**6**	NA	**3**	NA	**16**	**9**	**12**
Cookie theft (words/minute)	-	-	28.1 (22.3)	0	18	9	37	NA	60	0	54	37	38
Executive and spatial processing													
TEA: counting without distraction	7	4.2	4.6 (1.3)	**2**	5	6	NT	5	**4**	7	5	7	5
TEA: counting with distraction	10	2.6	1.9 (.9)	**1**	3	**1**	NT	**1**	**2**	7	**2**	6	**3**
Raven's coloured matrices (total)	36	28 ^{a}	29 (5.1)	31	29	31	30	**24**	**19**	34	**21**	33	33
Brixton spatial anticipation (correct)	54	28	25.8 (9.2)	**21**	**7**	**18**	**23**	34	**24**	31	31	30	**39**
Trail Making Test A (correct)	24	24 ^{a}	23.1 (1.6)	**19**	**22**	**23**	**23**	24	24	24	24	24	24
Trail Making Test B (correct)	23	17.4 ^{a}	15.5 (9.2)	**2**	23	**16**	**5**	23	**1**	23	19	22	**21**
Visuospatial processing													
VOSP dot counting	10	8	9.3 (1.2)	**7**	10	10	10	8	10	8	10	10	10
VOSP position discrimination	20	18	19 (1.7)	19	20	**15**	20	20	**17**	19	20	20	20
VOSP number location	10	7	8.6 (1.7)	8	10	**5**	10	8	10	10	**5**	8	8
VOSP cube analysis	10	6	8.9 (1.1)	8	9	**4**	9	9	7	10	10	10	**8**

Table 2.2. Scores are number of correct; NT = unavailable for testing; NA = not attempted because patients were non-fluent. Bold underlined numbers denote impaired scores (less than two standard deviation below mean). PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; TEA = Test of Everyday Attention; VOSP = Visual Object and Space Processing Battery. ^{a} Norms from healthy controls tested at the University of York (cut-off is mean minus two standard deviation). Number of controls as follows: Ravens = 20; Trail Making Test = 14

Test	Max	Cut-off	Patient Mean (SD)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Cambridge Semantic Battery													
Picture Naming	64	59.1	39.8 (25.1)	**1**	61	**19**	**50**	**0**	60	**3**	**56**	62	**46**
Word-Picture Matching	64	62.7	59.8 (3.8)	63	**62**	**60**	**62**	**56**	**62**	**52**	**56**	**62**	63
Word CCT	64	56.6	51.2 (10.7)	**39**	**43**	**29**	**52**	**56**	59	57	61	60	**56**
Picture CCT	64	52.7	51.2 (9.8)	**31**	**44**	**45**	57	61	**45**	54	53	61	61
Ambiguity task													
Miscued dominant	30	30	19.3 (5.6)	**12**	**13**	**13**	**19**	NT	**20**	**21**	**24**	**26**	**26**
Miscued subordinate	30	26.6	15.4 (6.3)	**7**	**10**	**14**	**15**	NT	**10**	**18**	**18**	**19**	28
No cue dominant	30	28.4	24.9 (3.1)	**22**	**18**	**24**	**26**	**25**	**24**	**27**	**28**	**28**	**27**
No cue subordinate	30	27.6	16.6 (4.1)	**11**	**9**	**14**	**17**	**16**	**19**	**19**	**21**	**19**	**21**
Cued dominant	30	30	24.2 (3.5)	**23**	**21**	**19**	**23**	NT	**24**	**23**	**27**	**29**	**29**
Cued subordinate	30	28.8	22.9 (4.6)	**25**	**14**	**20**	**28**	NT	**19**	**24**	**23**	**25**	**28**
Synonym with distractors													
Strong	42	35.4	20.1 (8.1)	**15**	**12**	**13**	**23**	**16**	**21**	**30**	**22**	**17**	38
Weak	42	40.4	30 (4.9)	**25**	**23**	**29**	**30**	**33**	**27**	**31**	**28**	**39**	**36**
Object use													
Alternative	37	33.9[a]	22.8 (7.5)	**14**	**13**	**14**	**22**	**22**	34	**22**	**26**	**29**	**32**
Canonical	37	n.a	34.3 (2.9)	32	31	29	35	35	37	33	37	37	37

Table 2.3. Scores are number of correct; NT = unavailable for testing; NA = testing was not attempted because patients were non-fluent. Bold underlined numbers denote impaired scores (less than two standard deviation below mean). Cut-off scores are from healthy controls tested at the University of York (mean minus 2 standard deviations). Number of controls as follows: Cambridge Semantic Battery = 10; Ambiguity task, Alternative object use, Synonym with distractors = 8.

3. Multimodal cueing paradigms

Three experiments investigated the effects of cues and meaning dominance on semantic judgements. Trials could be cued, miscued, or presented without a cue. The probe word that followed the cue was always an ambiguous word with more than one meaning. In half of the trials, the dominant meaning of the word was probed (e.g. BANK-MONEY), while the remaining trials referred to the subordinate meaning (e.g. BANK-RIVER). Given the multimodal nature of semantic cognition, we investigated whether both modality (for visual vs. auditory emotional cues) and informational content (visuo-spatial vs. emotional) would prime concepts in a similar way. We addressed this question in three separate experiments. In the first, we used facial emotional expressions as cues and miscues – these were consistent or inconsistent with the valence of the ambiguous word that was relevant in the subsequent semantic decision. In the second experiment, we used prosody within short '*ba-ba-ba'* sequences spoken in different emotional tones (e.g. happy or sad voices), which were again consistent or inconsistent with the valence of task-relevant interpretations of the ambiguous words. Finally, in the third experiment, we provided participants with photographs of visuo-spatial scenes: these either cued the relevant interpretation or miscued the irrelevant interpretation of the ambiguous words. The materials and experimental procedure were similar across the three experiments. A thorough description of the methods is provided only for Experiment 1, while for Experiments 2 and 3 we highlight any differences with the original protocol.

3.1 Experiment 1. Facial emotional expressions

3.1.1 Materials

Forty-three ambiguous probe words were selected using published word norms. Thirty-four were selected from the University of Alberta norms of relative meaning frequency (Twilley et al., 1994). In half of the trials, the probe was used in its *dominant* meaning, while in the remaining trials the *subordinate* meaning of the word had to be retrieved. For five additional words, only the dominant meaning was listed; the subordinate meaning was presumed to be rarer. Four remaining words were assigned to the dominant/subordinate conditions using Edinburgh Associative Thesaurus (Kiss et al., 1973). Whenever possible, we chose meanings with different emotional valence (e.g. strawberry jam is typically thought to be nice, whereas traffic jams are normally associated with negative emotions). Target words for the dominant and the subordinate interpretations were matched for lexical frequency (CELEX database; Baayen et al., 1993) ($t(84) = 0.1$, $p = .887$), length ($t(84) = 0.4$, $p = .680$), number of syllables ($t(84) = 0.3$, $p = .774$) and imageability ($t(84) = 0.6$, $p = .571$) in the N-Watch database (Davis, 2005). Each probe was presented alongside four alternatives, namely a semantically related target and three semantically unrelated distractors.

We manipulated the control demands of the task by showing facial expressions that were either consistent with the relevant interpretation of meaning (*cue condition* - e.g. /happy face/ JAM [jelly]), or with the alternative and therefore irrelevant interpretation (*miscue condition* - e.g. /angry face/ JAM [traffic jam]). The same image was used as a cue in one trial, and as a miscue in another trial. In one third of the trials, the probe was presented in the absence of a cue (*no cue condition*). Images included the eight basic emotions from the Radboud Faces Database (Langner et al., 2010): happy, angry, sad, contemptuous, disgusted, neutral, fearful, surprised. These were supplemented with images of more nuanced emotional expressions (see Figure 2.2.). These images only included the face and shoulders on a neutral background. Participants saw each probe word 6 times, once in each combination of cue-condition/meaning dominance (see Figure 2.2.). Target words also appeared as distracters on a different trial. After the experiment, we asked control subjects to judge the valence of these words (e.g. “do they leave you with either good or bad feelings?”) on a scale from 0 (not at all) to 7 (very much). Ratings were collected for the probes presented alone, as well as for each probe-target combination. This allowed us to remove any non-emotional pairings.

Figure 2.2. The six possible combinations of *cue condition* and *dominance* for the probe word “jam”.

3.1.2 Procedure

The experiment was run using E-Prime v1.1 (Schneider et al., 2002). Before the beginning of each block, patients received verbal and written instructions about the nature of the task, while healthy controls received written instructions only. On any given trial, a probe word was presented for two seconds (alongside an image of a facial expression in the *cue* and *miscue* conditions), then the target and three distracters appeared in written format below the probe. These were read aloud by the experimenter to facilitate patients' comprehension. Participants had ten seconds to respond, before the next trial was presented and an error was recorded. As most of the patients had motor impairments at the time of testing, patients gave their response by pointing to one of the options and the experimenter pressed the corresponding key on their behalf. All participants had ten seconds to respond before the next trial was presented and an error was recorded. Accuracy and response time (RT) were recorded on each trial. Multiple researchers were involved in collecting this data but the conditions were counterbalanced across sessions in each experiment, reducing the impact of variability in the way RT was recorded. Moreover, the experimenter maintained one finger on each of the four possible keys to minimize the time between the patients' decision and the actual keypress.

Two practice items were presented before the start of each block. A total of 258 trials were arranged in 6 blocks of 43 trials each, with each probe used once per block. Block order was counterbalanced across participants, and trial order was randomized to control for possible effects of the order of presentation. Within a session, both meanings of the probe word were primed. Cue type was counterbalanced, such that a roughly equal number of cue/miscue/no cue trials appeared in each block. At the end of the experiment, control participants rated the stimuli for how emotive they were (see Materials section).

The responses to seven ambiguous words were removed from the main analysis, due to consistently poor performance on those trials in the control participants. We identified items for removal by collapsing accuracy data across cueing conditions and obtaining average scores for dominant and subordinate trials. Ambiguous words which did not have both dominant and subordinate average scores above 50% accuracy in control participants were not carried forward into the analyses. This brought the number of ambiguous words in each of the six conditions to 36.

3.1.3 Statistical analyses

At the group level, accuracy and response efficiency (median RT/mean accuracy) data were analyzed separately using three-way mixed ANOVAs, with cue condition (3 levels: cue, miscue, no cue) and dominance (2 levels: dominant, subordinate) as within-subjects factors, and group (2 levels: controls, patients) as a between-subjects factor. Pairwise comparisons for all significant interactions were Bonferroni-corrected. All statistical analyses were performed in SPSS version 24 (IBM, Armonk, NY).

3.1.4 Results

Mean accuracy and median response efficiency are displayed in Figure 2.3. ANOVA results are reported in Table 2.4. In Experiment 1, there were main effects of group, cue type, and ambiguity plus two-way interactions of group with cue type (significant only in response efficiency) and group with ambiguity. Overall, patients were less accurate and less efficient than controls. Bonferroni-corrected pairwise comparisons of the group by cue type interaction indicated that patients' efficiency on miscue trials was significantly lower compared to cue trials (p = .002), while the same was not true for healthy controls (p = 1). Performance was also less accurate and less efficient for the subordinate meaning of the ambiguous word. Post-hoc tests of accuracy data revealed that both groups were less accurate when retrieving subordinate meanings (patients: p < .001; controls: p = .002). This effect was greater in the patients, in line with the expected pattern of deregulated semantic control in SA (see Figure 2.3.). Patients were also less efficient on subordinate compared to dominant trials (p < .001), while controls did not show a significant difference (p = .417).

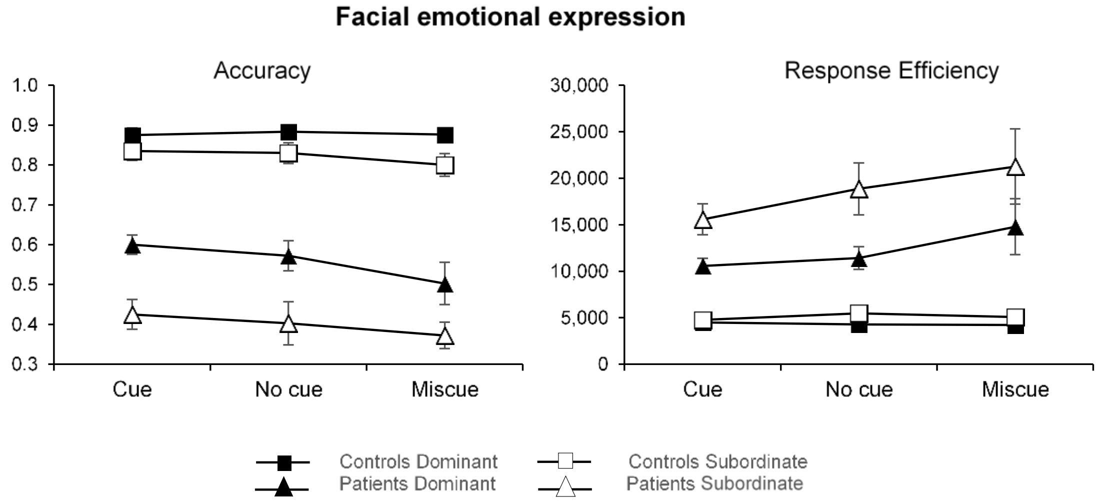

Figure 2.3. Mean accuracy (left) and median response efficiency (right) for patients and controls in the six different combinations of cue condition and dominance. Small numbers indicate poorer performance in the accuracy graph (left), while they reflect better performance when expressed as response efficiency (right). Error bars show Standard Error of the Mean (SEM).

3.2 Experiment 2. Emotional prosody

3.2.1 Materials

While in the previous task we presented participants with visual emotional cues (faces), here we used sound cues featuring different emotions. These consisted of simple monosyllabic sounds spoken with emotional prosody. Twenty-four items were recorded from either a male or female voice repeating 'ba-ba-ba-ba' sounds in a way that reflected a variety of emotions (e.g. happy, irritated, surprised), as rated by control participants after the experiment. The stimuli lasted between 2 and 3 seconds and background noise was removed using Audacity software (ver. 2.1.2; (Mazzoni and Dannenberg, 2000). The same set of ambiguous words presented in Experiment 1 was used.

3.2.2 Procedure

At the beginning of each trial, an ambiguous word appeared in the middle of the screen. Participants were instructed to press the spacebar to hear the cue sound, which could be either emotionally congruent or incongruent with the relevant interpretation of the ambiguous word. At the offset of the sound, the four options were presented below the probe. As before, the task was to select the word that was semantically related to the probe, while discarding the three distracters. There were four blocks, containing 172 trials. As the word stimuli were identical to those in Experiment 1, data for the no cue condition were taken from this experiment. Ambiguous words with an average of < 50% accuracy for controls across cue, no cue and miscue conditions were removed from the analysis, bringing the number of ambiguous words in each of the 4 conditions to 36.

3.2.3 Results

Mean accuracy and median response efficiency are displayed in Figure 2.4. ANOVA values are reported in Table 2.4. There were significant main effects of group and ambiguity in both accuracy and response efficiency, while the effect of cue condition approached significance ($p = .057$) in response efficiency. There were two-way interactions between group and dominance, and cue type by dominance (this last one being significant only in response efficiency). The interaction between group and cue approached significance in the accuracy data ($p = .058$). Performance was poorer when the task required participants to retrieve the subordinate meaning of the ambiguous word. As in experiment 1, both groups were less accurate with subordinate meanings (patients: $p < .001$; controls: $p = .009$), with the patients showing a stronger effect, but only the SA group had lower efficiency on subordinate vs. dominant interpretations (patients: $p < .001$;

controls: p = .317). Moreover, pairwise comparisons of the cue type by dominance interaction revealed that people were more efficient at retrieving the subordinate meaning of words following a cue compared to when no cue was provided (p = .016). The same was not true for dominant trials (p = 1).

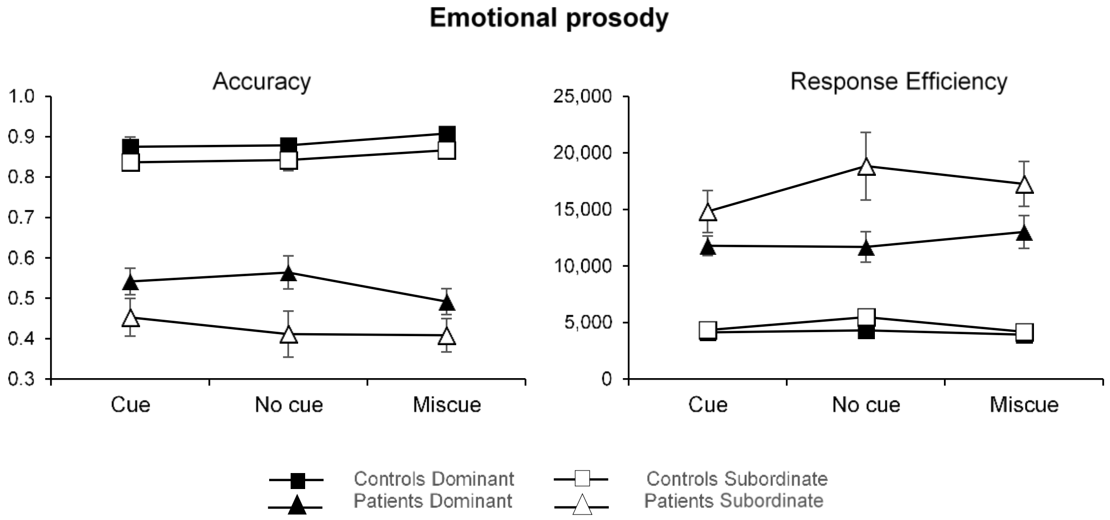

Figure 2.4. Mean accuracy (left) and median response efficiency (right) for patients and controls in the six different combinations of cue condition and dominance. Small numbers indicate poorer performance in the accuracy graph (left), while they reflect better performance when expressed as response efficiency (right). Error bars show SEM.

3.3 Experiment 3. Visuo-spatial context

3.3.1 Materials

Here, the cue consisted of a visuo-spatial context, rather than an emotional one. Stimuli were photographs of scenes (Figure 2.5.) linked to either the relevant meaning (*cue condition*) or an alternative interpretation (*miscue condition*) of an ambiguous word. For example, the cue for BAT-team could be a picture of a baseball field, whilst BAT-night could be an image of a cave. Forty-five ambiguous words were used, of which fifteen were also presented in Experiment 1 and 2. Of the remaining, twenty-seven were taken from Elston-Guttler and colleagues (2005) and three from the Edinburgh Association Thesaurus (Kiss et al., 1973). Target words for the dominant and the subordinate interpretations were matched for lexical frequency (CELEX database; Baayen et al., 1993) (t (88) = 0.6, p = .532), length (t (88) = 0.2, p = .799), syllable length (t (74) = 1.8, p = .080) and imageability (t (88) = 0.4, p = .704) using the N-Watch (Davis, 2005).

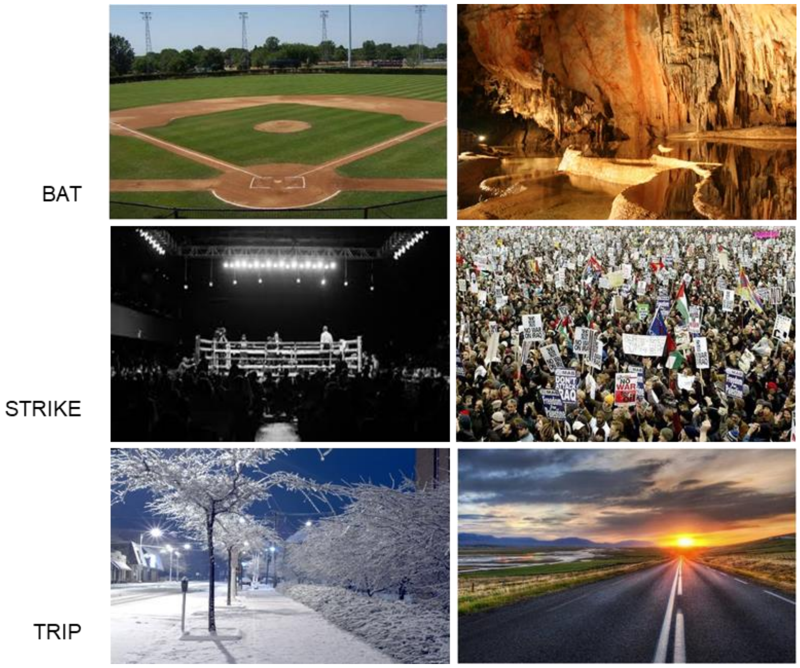

Figure 2.5. Location cues for three probes words used in the dominant meaning (left) and in the subordinate meaning (right). From top to bottom: BAT- team / BAT – night; STRIKE – bruise / STRIKE – union; TRIP – balance / TRIP - car

3.3.2 Procedure

The procedure followed Experiment 1 and 2. A visuo-spatial scene was presented simultaneously with the ambiguous probe for two seconds. At the end of this period, four options appeared below. The participants' task was again to select the semantically associated word while discarding the distracters. Trials in which controls had poor accuracy were removed, as in Experiment 1 and 2. Of the original 45 ambiguous words presented in each condition, 36 were carried forward into the analyses.

3.3.3 Results

Mean accuracy and median response efficiency are displayed in Figure 2.6. ANOVA values are reported in Table 2.4. We found a three-way interaction between group, dominance, and cue type. Separate ANOVAs were conducted for accuracy and response efficiency in the patients and in the control group. We found a significant interaction between cue condition and dominance in the patient group, in both accuracy (F (2, 18) = 8.9, p = .002) and median response efficiency (F (2, 18) = 4, p = .036), but no interaction in the control group. Bonferroni-corrected comparisons of accuracy in the patient group revealed more errors for miscues compared to both cues (t (8) = -9.1, p < .001) and the no cue condition (t (8) = -8.9, p < .001) for the dominant interpretation. When the subordinate meaning was required, the provision of a cue significantly improved accuracy relative to the miscue (t (8) = 4.4, p = .005) and no cue (t (8) = 4.7, p = .004) conditions. The same pattern of results was obtained for response efficiency: for the dominant interpretation, patients were impaired by miscues relative to cues (t (8) = 5.9, p = 001) and no cue trials (t (8) = 5.5, p = 001), while for the subordinate meaning, the same positive effect of cueing compared to miscues (t (8) = -5.7, p = .001) and no cue (t (8) = -4.8, p= .003) was obtained. A Cochran's Q test was used to compare the three levels of *cueing* at the individual level. This test revealed that 7 out of 10 patients showed a significant difference between the three cue conditions (p = .010 to p < .001).

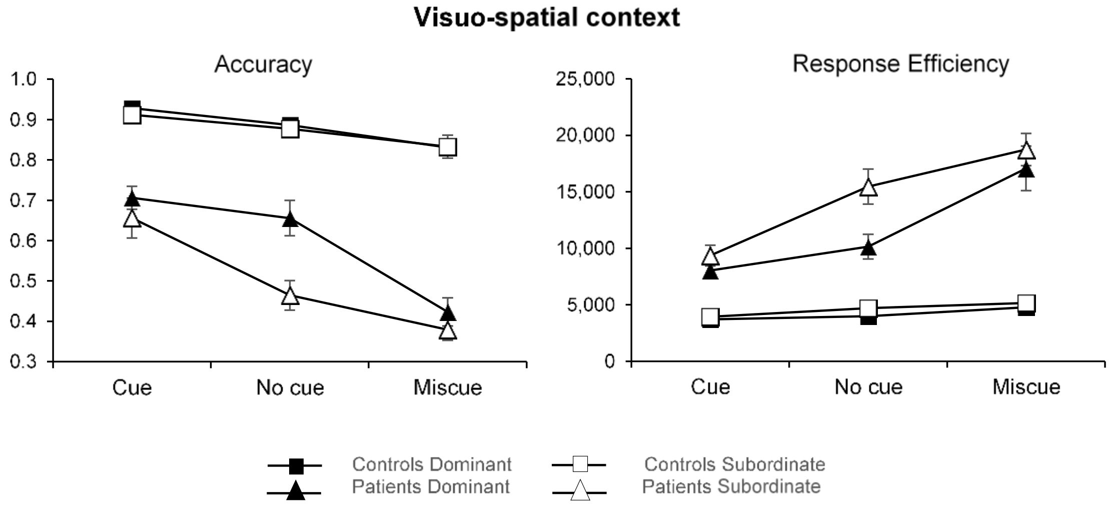

Figure 2.6. Mean accuracy (left) and median response efficiency (right) for patients and controls in the six different combinations of cue condition and dominance. Small numbers indicate poorer performance in the accuracy graph (left), while they reflect better performance when expressed as response efficiency (right). Error bars show SEM.

			Group	Cue Condition	Dominance	Cue condition x Group	Dominance x Group	Cue condition x Dominance	Cue condition x Dominance * Group
FACIAL EMOTIONS	Accuracy	F	**140.9***	**3.8***	**68.0***	1.4	**15.2***	0.0	1.3
		df	1, 24	2, 48	1, 24	2, 48	1, 24	2, 48	2, 48
		p	**<.001**	**.029**	**<.001**	.249	**.001**	.953	.296
		partial η2	0.9	0.1	0.7	0.1	0.4	0.0	0.0
	Response Efficiency	F	**53.4***	**5.7***	**21.4***	**5.7***	**13.0***	0.7	0.1
		df	1, 24	2,48	1, 24	2,48	1,24	1.3, 30.0	2,48
		p	**<.001**	**.006**	**<.001**	**.006**	**.001**	.426	0.862
		partial η2	0.7	0.2	0.5	0.2	0.4	0.0	0.0
PROSODY	Accuracy	F	**146.2***	0.1	**44.3***	3.0	**10.0***	1.3	1.6
		df	1, 24	2,48	1, 24	2,48	1, 24	2,48	2,48
		p	**<.001**	.894	**<.001**	.058	**.004**	.284	.210
		partial η2	0.9	0.0	0.6	0.1	0.3	0.1	0.1
	Response Efficiency	F	**68.7***	3.0	**39.5***	1.8	**25.2***	**5.3***	2.0
		df	1, 24	2,48	1, 24	2,48	1, 24	2,48	2,48
		p	**<.001**	.057	**<.001**	.182	**<.001**	**.009**	.153
		partial η2	0.7	0.1	0.6	0.1	0.5	0.2	0.1
VISUO-SPATIAL	Accuracy	F	**144.7***	**62.8***	**17.8***	**17.0***	**12.7***	**6.9***	**6.5***
		df	1, 24	1.6, 38.3	1, 24	2, 48	1, 24	2, 48	2, 48
		p	**<.001**	**<.001**	**<.001**	**<.001**	**.002**	**.002**	**.003**
		partial η2	0.9	0.7	0.4	0.4	0.3	0.2	0.2
	Response Efficiency	F	**109.2***	**61.2***	**24.7***	**37.2***	**13.2***	**7.5***	**4.9***
		df	1, 24	2,48	1, 24	2,48	1, 24	2,48	2,48
		p	**<.001**	**<.001**	**<.001**	**<.001**	**.001**	**.001**	**.012**
		partial η2	0.8	0.7	0.5	0.6	0.4	0.2	0.2

Table 2.4. Accuracy and response efficiency effects revealed by three-way mixed ANOVAs of the data for Experiments 1, 2, and 3. Significant results and interactions are reported in bold and marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

4. Discussion

This study explored the effect of multi-modal cues on conceptual tasks in SA patients with deregulated retrieval following left-hemisphere stroke. Across three experiments we presented emotional facial expressions (Experiment 1), emotional prosody (Experiment 2) and visuo-spatial contexts (Experiment 3), which were designed to cue or miscue the currently-relevant or irrelevant interpretations of ambiguous words. SA patients were highly sensitive to these cues, showing better performance when external information was consistent with semantic knowledge to be retrieved, and poorer performance when the cue was misleading. Both emotional and visuo-spatial cues were effective.

Previous studies by our group have shown that patients with SA are highly influenced by semantic ambiguity, with poorer performance when the task requires the less dominant interpretation of the word (Noonan et al., 2010). Across all three experiments we replicated this effect of ambiguity in an independent sample. In line with previous findings of cueing and miscuing effects, performance was modulated in both positive and negative directions by the provision of information that was relevant or irrelevant to the task. However, we used emotional and spatial cues, which have not been previously investigated. Since heteromodal concepts are thought to draw on a wide range of features, we expected different kinds of cues to be equally effective in patients with SA. Perhaps not surprisingly, the strongest effect of cueing was observed in Experiment 3. Visuo-spatial contexts are likely to provide a highly concrete and vivid interpretation of the word, constraining semantic retrieval to a large extent. Emotional cues also influenced performance, at least when presented using facial expressions (Experiment 1). On the other hand, the effect of cueing in the emotional prosody task (Experiment 2) only approached significance. Facial expressions might be stronger cues to emotion than prosody. Nevertheless, given the known right-hemisphere dominance for emotional processing (as reviewed by Gainotti, 2019), we expected our left-hemisphere stroke patients to be able to extract the valence of the emotional stimuli, regardless of the modality of presentation (visual vs. auditory).

Our results are consistent with contemporary accounts of semantic cognition such as the Controlled Semantic Cognition account (Jefferies, 2013; Lambon Ralph et al., 2016), which anticipates interactions between semantic representations and control processes in conceptual retrieval. This framework proposes a 'graded hub' for conceptual representation in ventral ATL – an area relatively invulnerable to stroke, and largely spared in SA patients. This region is thought to allow the computation of coherent conceptual representations from combinations of diverse features – including valence and visuospatial context, as well as visual and auditory inputs. While there is most evidence for the graded combination of vision and audition, recent work has suggested that the ATL hub region integrates emotional valence (Olson et al., 2013; Ross and Olson, 2010), via connections from orbitofrontal cortex via the uncinate fasciculus (Highley et al., 2002; Papinutto et al., 2016; Von

Der Heide et al., 2013). Several studies have shown an involvement of portions of the ATL in representing and retrieving social knowledge (Binney et al., 2016; Olson et al., 2013; Rice et al., 2018; Ross and Olson, 2010). Representations capturing spatial context within the medio-temporal complex (Bicanski and Burgess, 2018; Burgess, 2002; Burgess et al., 2002) are also likely to contribute to conceptual processing in ventral ATL, with bidirectional connections via the entorhinal cortex (e.g. Squire and Zola-Morgan, 1991). The ventral ATL is equidistant from all these diverse inputs along the cortical surface, and this is thought to facilitate the formation of heteromodal concepts (Lambon Ralph et al., 2016; Margulies et al., 2016; Visser et al., 2010b; Visser and Lambon Ralph, 2011).

The Graded Hub account predicts that these inputs to ventral ATL can be potent cues or miscues, depending on whether they are consistent or inconsistent with current task demands. Consequently, cues that increase the accessibility of task-relevant features reduce semantic control demands, while miscues that increase the accessibility of task-irrelevant features increase semantic control demands. Here we provide further evidence for this theoretical framework by showing that emotional and spatial cues modulate the accessibility of semantic representations. Spatial context is known to play a key role in episodic memory (Burgess et al., 2002, 2001a; Hazen and Volk-hudson, 2018; O'Keefe and Nadel, 1978; Robin et al., 2018). Similarly, emotional cues have been shown to be powerful cues in episodic memory (as reviewed by Buchanan, 2007). For example, mood induction and mood congruency paradigms have provided strong evidence for the idea that episodic retrieval is improved when there is emotional congruency between encoding and retrieval (Bower et al., 1978; Bower and Mayer, 1989; Robinson and Rollings, 2011; Xie and Zhang, 2018). At present, the contribution of these feature types to semantic retrieval has been little investigated. A key contribution of the current study is to show that these features are effective cues and miscues, particularly in people with a reduced capacity to internally constrain their semantic retrieval. However, as the multimodal cueing paradigm implemented here has not been used before, replicating the effects in a larger sample will help to clarify their magnitude, and whether spatial cues and facial expressions are more potent than emotional prosody.

The semantic control regions typically damaged in SA are spatially distinct from, but adjacent to, multiple-demand regions that support domain-general cognitive control (Davey et al., 2016; Noonan et al., 2013b). Patients with SA have large lesions, and domain-general control and semantic control networks are likely to be damaged together. Patients with SA have a broad range of deficits, as observed by Head and Luria in their seminal characterizations of the syndrome (Head, 1926; Luria, 1976). In our sample, neuropsychological tests show that 9/10 patients have some degree of executive impairment, mirroring the initial results of Jefferies and Lambon Ralph (2006) who studied an independent sample of SA cases. Given these considerations, we cannot conclude that increased sensitivity to cues in semantic tasks specifically reflect semantic control deficits in SA – this pattern may also reflect the influence of domain-general executive deficits.

The observation that semantic aphasia patients are sensitive to emotional and spatial cues is relevant to clinical practice and patient management. Showing that semantic retrieval can be influenced by emotions and spatial contexts in a semantic task might provide an explanation for why patients with SA appear to function well in everyday contexts. Real-world situations are generally very rich and characterized by both emotional and spatial cues, which can support comprehension when they are coherent with the message being communicated. Moreover, our findings suggest that patients will be vulnerable to being misled by emotional expressions and spatial context when these are not consistent with the information required in a certain situation. For example, they might be more likely to be confused when sad news is conveyed with a smile, or when a familiar object has to be used in a novel spatial context. Being aware that patients rely on contextual cues but can also be misled by them has important implications for patients, their families and therapists, since the context in which semantic retrieval occurs can be controlled to afford good understanding. A final consideration is that real-world situations are much richer than any experimental tasks designed to investigate semantic retrieval. Further research is required to investigate the potential additive effects of cues, as well as the efficacy of more ecological cues, closer to every-day situations.

Chapter 3. Semantic cue integration following deregulated semantic control

Having established that patients with deregulated semantic control are sensitive to non-verbal cues such as emotional facial expressions and visuo-spatial contexts, the next study explored whether combining these cue types might have an additional beneficial effect, beyond that observed for single cues. Such pattern of results would be expected if multiple cues that are consistent with the semantic knowledge needed by the task constrained retrieval to a larger extent than single cues. This question has practical relevance for patient management and rehabilitation, since language comprehension in everyday situations occurs in rich multimodal contexts. Evidence that patients benefit from convergent emotion and location cues could be incorporated in language protocols, and real-world environments could be enriched with these cues to facilitate patients' comprehension.

Studying cue combinations also has theoretical relevance for our understanding of the different components underlying semantic cognition. Converging evidence from neuropsychology and neuroimaging has highlighted the role of semantic control mechanisms when less dominant aspects of knowledge are retrieved in the absence of a context (Controlled Semantic Cognition account; Jefferies, 2013; Lambon Ralph et al., 2016). Providing contextual support in the form of a single cue, however, reduces the control demands of the task and improves comprehension in patients with semantic aphasia (Lanzoni et al., 2019). A question that remains open is whether integrating multiple cues requires the intervention of control processes, or whether cue integration occurs rather automatically whenever there is coherence between inputs. If the latter is true, we would expect integration to be relatively intact in patients with deregulated semantic control.

We developed a paradigm in which semantic decisions to ambiguous words were preceded by different levels of cueing: participants saw both affect and location cues simultaneously (2 cues condition), either affect or location cues presented singly (1 cue condition), or scrambled and meaningless versions of the images (0 cues condition). In this chapter, we compare semantic retrieval in patients with semantic aphasia and healthy controls using neuropsychology. In the remainder of this thesis we used the same cueing paradigm in combination with different neuroimaging methods: in Chapter 4 we investigated the neural bases of semantic cue integration using task-based fMRI, while in Chapter 5 we explored whether individual differences in the spontaneous activity of the brain (measured with resting-state fMRI) are predictive of the ability to integrate semantic cues during meaning retrieval, measured outside the scanner using the same cuing paradigm.

Acknowledgments and authors' contribution

Lucilla Lanzoni, Prof. Elizabeth Jefferies, and Prof. Jonathan Smallwood developed the main ideas in this chapter and the experimental paradigm (this was readapted from Lanzoni et al., 2020). Patients' data were collected by Lucilla Lanzoni with the help of the following research assistants: Suzanne Pegg, Marcus Glennon and Amelia Shelton. Controls' data were collected by Annabelle Harding, Emma Parker and Ellicia Swindells as part of their UG final year project. Lucilla Lanzoni performed the statistical analyses, interpreted the results, wrote and edited the chapter. Prof. Jefferies helped with editing drafts of this chapter.

Abstract

Patients with deregulated semantic cognition following left-hemisphere stroke are sensitive to task manipulations which reduce the need to internally constrain semantic retrieval, such as the provision of sentence cues that are consistent with the relevant interpretation of a word. Recently we showed that multimodal contextual cues, such as facial expressions and visuo-spatial context, are also effective at guiding meaning retrieval in patients with aphasia (Lanzoni et al., 2019). This study aimed to extend the findings reported in the previous chapter by exploring the possibility that patients with semantic aphasia might show even stronger effects when semantic retrieval is constrained by multiple semantic cues. We investigated (i) whether patients are able to use the combination of facial expressions and visuo-spatial context pictures, presented simultaneously, to facilitate interpretations of ambiguous words, and (ii) whether combining these cue types improves patients' performance more than single cues. We manipulated the number of cues provided prior to semantic decisions: participants saw both affect and location cues simultaneously (2 cues condition), either affect or location cues presented singly (1 cue condition), or scrambled and meaningless versions of the images (0 cues condition). Compared to healthy controls, patients' retrieval of less frequent interpretations of ambiguous words was improved by the provision of one cue, in line with previous findings, but combining different cue types did not yield any additional benefits. While comprehension deficits in SA are ameliorated by the provision of information that constrains retrieval to suit the task, several factors might explain why we did not observe additional facilitation following multiple cues.

1. Introduction

A crucial aspect of semantic cognition is the ability to call upon different aspects of knowledge to guide behaviour according to the changing circumstances. Often we need to retrieve non-dominant aspects of knowledge or distant semantic associations that are currently relevant. This flexibility requires semantic control processes, which allow us to manipulate stored conceptual representations in a goal-driven fashion. People with semantic aphasia (SA) following a stroke to left fronto-parietal regions lack this top-down flexibility. They are highly influenced by the control demands of the task, showing inconsistent performance when the same concepts are probed under different cognitive demands (Jefferies and Lambon Ralph, 2006). They perform poorly on semantic tasks that require to select a target among competing responses, and have difficulty activating less frequent meanings of homonyms (Noonan et al., 2010). These effects also occur in the non-verbal domain, for example, when SA patients are asked to select the appropriate alternative object to perform a given action when the canonical object is not available (e.g. Corbett et al., 2011).

One way of reducing the control demands of a task is through the provision of external constraints such as cues. In line with the idea of deregulated top-down control, performance in SA is significantly improved when verbal and non-verbal cues are provided (Corbett et al., 2011; Hoffman et al., 2010; Jefferies et al., 2008b; Lanzoni et al., 2019; Soni et al., 2009). For example, patients' understanding of distant associations (e.g. when matching BANK with RIVER as opposed to matching BANK with MONEY) is enhanced if the ambiguous word is embedded in a sentence that biases the activation toward the relevant meaning (e.g. "the bank is slippery", Noonan et al., 2010). Additionally, patients with SA benefit from phonological cues during picture naming (e.g. "e – ele – elef" for ELEPHANT; Jefferies et al., 2008b; Soni et al., 2009); these cues are incompatible with semantically-related competitors and consequently reduce the need for top-down control over retrieval. Most recently we have shown that multimodal cues such as emotional faces and visuo-spatial contexts are also effective at supporting semantic decisions to ambiguous words (Lanzoni et al., 2019). Words were preceded by pictorial cues corresponding to emotional facial expressions or visuo-spatial contexts that were consistent with the interpretation of the word being probed on that trial (*cue* condition), or consistent with the alternative and irrelevant interpretation (*miscue* condition). We also tested semantic decisions in the absence of cues (*no-cues* condition). Compared to healthy controls, patients showed stronger effects of cueing and miscueing for facial emotional expressions (Experiment 1) and visuo-spatial contexts (Experiment 3), and these were greater when retrieving the subordinate meanings of ambiguous words. These results suggest that comprehension in SA relies heavily on contextual cues, and that meaning understanding can be improved by providing relevant cues. Furthermore, the findings raise the question of whether combining affect and location cues, which are both effective at reducing the control demands of the task, might yield even larger beneficial effects on comprehension. Such effects of cue combinations are expected if patients can benefit from the provision of two complementary sources of information.

A rich neuroimaging literature implicates anterior temporal lobes (ATL) and angular gyrus (AG) in processing conceptual combinations. Increased activity in AG is observed when participants integrate single items (e.g. "jacket" and "plaid") into coherent concepts (e.g. "plaid jacket"; Price et al., 2016, 2015), while meaningful combinations (e.g. “red boat”) elicit activation in ATL, compared to the same word preceded by an unpronounceable string (e.g. “xkq boat”; Bemis and Pylkkänen, 2013, 2011; Pylkkänen, 2020, 2019; Teige et al., 2019, 2018). In line with this, Hub and Spoke models of semantic cognition propose that conceptual knowledge emerges through the convergence of unimodal sensory features - encoded in cortical ‘spokes’, within an amodal ‘hub’ in the ventral ATL (Jefferies, 2013; Lambon Ralph et al., 2016; Patterson et al., 2007; Rogers et al., 2004). This region, which receives a double blood supply from the anterior temporal cortical artery of the middle cerebral artery and the anterior temporal branch of the distal posterior cerebral artery (Borden, 2006; Conn, 2008), is relatively invulnerable to strokes. Moreover, strokes rarely affect both hemispheres. Instead, lesions are frequently observed in inferior frontal gyrus (IFG) and posterior middle temporal gyrus (pMTG), within the classic territory of the middle cerebral artery, and more rarely in AG - if the stroke affects the posterior cerebral artery. This explains why conceptual representations stored in ATL are intact in semantic aphasia and can be successfully cued by external constraints. Although patients lack top-down control over semantic retrieval following damage to regions important for semantic control, semantic access is rather preserved if a context is present and can guide retrieval. It follows that, when cues from different modalities (e.g. facial expressions and visuo-spatial contexts) provide convergent information, patients should be able to process the integrated meaning of the cues.

A further possibility is that patients might actually show a greater benefit of cue combinations, compared to when minimal cues are provided. If this is the case, we should observe better comprehension when the constraining context is richer and provides a more circumscribed interpretation of the word. This question has important practical implications for patient management. In everyday situations, patients’ comprehension is influenced by the environment they are in, including the facial expression of the speaker or the spatial context in which a situation unfolds. Evidence that combining multiple cues provides additional constraint beyond the effect of individual cues, could prove relevant to patients’ managament and rehabilitation. The primary goal of speech and language therapy is to ameliorate comprehension deficits in real-world contexts. If providing emotions and locations together could reduce the need to constrain retrieval internally, this evidence could be incorporated into therapy protocols and everyday environments could be enriched with these cues for the benefit of patients.

In this experiment we tested these possibilities using a modified version of the single-cueing paradigm described in Lanzoni et al. (2019). This paradigm was originally designed to explore the neural bases of semantic integration and it is described in Chapter 4. Across three different conditions we manipulated the amount of cueing provided prior to semantic decisions about ambiguous words. Participants were shown either affect or location cues (1 cue condition), both cue types simultaneously (2 cues condition) or scrambled versions of these cues (0 cues conditions). They were then asked to match an ambiguous probe word (e.g. JAM) to a semantically related target preseneted among unrelated distarctors (JAM – spoon, intruder, history). We anticipated that (i) patients should show a benefit of cued semantic decisions vs. uncued decisions (as revealed by a contrast of 1 cue vs. 0 cues), replicating findings from Lanzoni et al., 2019, as well as previous literature showing a positive effect of external cues. (ii) Furthermore, we hypothesized that patients would show normal effects of cue combinations over and above single cue effects, since the regions important for processing conceptual combinations were largely spared in our sample. (iii) A final possibility is that extracting the combined meaning of multiple cues would result in an additional benefit, beyond that observed by single cues (as revealed by a contrast of 2 cues vs. 1 cue). This pattern would be expected if cue combinations can have a more constraining effect on conceptual retrieval than individual cues, and consequently ameliorate patients' control deficits to a greater degree.

2. Methods

2.1 Participants

Fourteen patients with SA were recruited from stroke and aphasia groups across Yorkshire. All patients had suffered a cerebrovascular accident affecting the left hemisphere at least one year before testing. Nine patients (coded as P1, P2, P6-P10, P12, and P14 in the current study[1]) had previously taken part in the investigation of semantic cues described in Chapter 2. All of the patients had damage within inferior frontal gyrus (IFG) (especially in pars opercularis and orbitalis), which extended into superior temporal gyrus (STG) and the supplementary motor area (SMA) in the majority of cases. Lesion characteristics and a lesion overlay for these patients are provided in Chapter 2 (Table 2.1. and Figure 2.1.). MRI scans were not available for newly recruited participants (P3-P5, P11, P13) due to the closure of scanning facilities during the COVID-19 pandemic. A CT scan was instead available for P11 and showed left fronto-parietal damage. In line with previous investigations of SA, patients were selected on the basis that they showed multimodal semantic deficits affecting both verbal and non-verbal comprehension. All patients showed some hallmarks of semantic control deficits in both verbal and non-verbal semantic tasks: they performed poorly when retrieving less-dominant meanings of homonyms in a semantic judgement task (Noonan et al., 2010) and non-canonical uses in an object use task (Corbett et al., 2011).

The SA group was compared with 16 healthy control participants [mean age at the time of testing: SA group = 61.1, control group = 70.5 years, t(25) = -2.4, p = .024; mean age when leaving education: SA group = 16.8, control group = 18.6, t(18.4) = -1.7, p = .102]. Nine of the controls had

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[1] Patient ID does not match across the two experiments, but the patients who took part in both studies can be identified in Table 3.2. and 3.3.

previously taken part in the experiment described in Chapter 2. The control participants had no history of neurological or psychiatric conditions and showed unimpaired cognitive functioning on the Mini-Mental State Examination with a cut-off point of 24/30 (Folstein et al., 1975). The study was approved by the local ethical committee and informed consent was obtained prior to the experiment.

2.2 Background Neuropsychological Assessment

The protocol for the neuropsychological assessment of the newly recruited SA patients was identical to that used by Lanzoni et al. (2019) described in Chapter 2. To facilitate the interpretation of the test scores for the new participants, a description of the tasks is provided again here[2].

2.2.1 General neuropsychology

Data for individual patients are shown in Table 3.2. In addition to their semantic deficits, patients often displayed more general language and executive impairments. Word repetition (PALPA 9; Kay et al., 1992) was impaired in four out of fourteen patients (and testing was not attempted in a further two patients because their speech production was very poor). Verbal fluency tasks (category and letter fluency) were under cut-off in ten out of fourteen patients and not attempted in a further four patients. The "cookie theft" picture description (Goodglass and Kaplan, 1983) revealed non-fluent speech in five patients. Executive and attentional impairment was observed in eleven out of fourteen patients across four tasks: Elevator Counting with and without distraction from the Test of Everyday Attention (Robertson et al., 1994); Ravens Coloured Progressive Matrices (RCPM; Raven, 1962); Brixton Spatial Rule Attainment task (Burgess and Shallice, 1997) and Trail Making Test A & B (Reitan, 1958). This is in line with previous studies which found that deregulated semantic cognition in semantic aphasia often correlates with executive dysfunction (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010). Eight out of fourteen patients had performance under cut-off in at least one task of the Visual Object and Space Perception Battery (VOSP; Warrington and James, 1991), which measures visuo-spatial processing.

2.2.2 Semantic memory assessment: Cambridge Semantic Battery

Individual test scores are provided in Table 3.3. The Cambridge Semantic Battery (Adlam et al., 2010; Bozeat et al., 2000) measures semantic retrieval for a set of 64 items across four tasks: picture naming, word-picture matching, verbal and pictorial semantic associations (Camel and Cactus Test, CCT). Patients showed large variability during picture naming [correct trials M (SD) = 63% (38.8)], in line with

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[2] The text below has been taken from section *2.3. Background Neuropsychological Assessment* of Chapter 2, and has been edited to include the new group means.

their varying degree of impairment in production, while performance was uniformly at ceiling in word-picture matching [M (SD) = 94.2% (5.3)]. When the control demands of the task were higher, such as when secondary associations between concepts were probed on the CCT in either verbal or pictorial format, patients showed greater impairment which was equivalent across modalities [words M (SD) = 81.5% (14.5); pictures M (SD) = 82.9% (14.1)].

2.3.3 Tests of semantic control

In line with the inclusion criteria adopted in previous studies by our group (e.g. Stampacchia et al., 2018), the patients in this study had difficulties in retrieving and manipulating concepts in a flexible manner, due to deficient semantic control processes. We report their performance on three tasks that manipulated the control demands of verbal and non-verbal semantic judgements. The task descriptions are taken from Stampacchia et al. (2018) and therefore appear in quotation marks. Individual test scores are displayed in Table 3.3.

i. *Ambiguity task* (Noonan et al., 2010)*. "*Semantic judgements (60 items) probed the dominant (MONEY) and subordinate (RIVER) meanings of ambiguous words (e.g. BANK). These semantic decisions were uncued or preceded by a sentence that primed the relevant meaning (cue condition e.g. for MONEY, I WENT TO SEE THE BANK MANAGER) or irrelevant interpretation (miscue condition e.g. THE BANK WAS SLIPPERY). There were four response options on each trial." The majority of patients were below the normal cut-off in all conditions. They showed better comprehension for dominant than for subordinate interpretations [no cue condition accuracy: dominant M(SD): 86.2% (7.7); subordinate M(SD) = 60% (16.7), t(13) = 8.38, p < .001] and had greater difficulties in accessing subordinate meanings following miscues rather than cues [subordinate trials: miscues M(SD) = 54.2% (18.5); cues M(SD) = 78.1% (14.5), t(11) = -5, p < .001]. P5 and P8 only completed the no cue trials of the task.

ii. *Synonym judgment task. "*We tested synonym judgement with strong or weak distractors (84 trials), using a task from Samson and colleagues (2007); e.g. DOT with POINT [target], presented with DASH [strong distractor] or LEG [weak distractor]. There were three response options per trial." Accuracy was below the cut-off for all patients, with the exception of P5 who did not take part and P14 who scored above the cut-off in the strong distractor condition. Performance was poorer when strong distractors were presented [strong M(SD) = 48.5% (18.1), weak M(SD) = 72.7% (11.4), t(12) = -5, p < .001].

iii. *Object use task.* "The object use task (74 items), from Corbett et al. (2011), involved selecting an object to accomplish a task (e.g. bash a nail into wood), with all items represented as photographs. The target was either a canonical tool, normally used to complete the task (e.g.

HAMMER), or an alternative non-canonical option (e.g. BRICK), presented among a set of five unsuitable distractors." Patients were poorer at selecting non-canonical than canonical targets [alternative M(SD) = 65.1 (20.2), canonical M(SD) = 87.6 (17.7), t(13) = -3.5, p = .004]. One patient (P7) was not below the normal cut-off in the non-canonical condition.

In summary, all fourteen patients showed impaired performance on one or more non-semantic verbal tasks, while they showed impaired performance on all semantic tasks. The SA group exhibited strong sensitivity to manipulations of semantic control demands across modalities – i.e., more impaired comprehension of subordinate than dominant interpretations of ambiguous words; sensitivity to cues and miscues; better performance with weak than strong distractors and better retrieval of canonical than alternative object use. A composite score reflecting each patient's deficits in semantic cognition was derived from the Cambridge Semantic Battery and the three semantic control tasks described above using factor analysis. Following the same procedure as Lanzoni et al., 2019, principal components analysis was used as a method of extraction[3]. The first component explained 53% of the total variance (Table 3.1.). Factor scores for each patient for component 1 were extracted using a regression method and patients are ordered by this composite score in Table 3.2. and 3.3.

		Component	
		1	**2**
	Eigenvalue	4.8	1.6
	Total variance explained	53%	17%
Loading of semantic tasks	Word picture matching (CSB)	-0.093	0.871
	Picture naming (CSB)	0.273	0.791
	Synonym with distractor (strong)	0.628	-0.163
	Synonym with distractor (weak)	0.806	0.115
	Pictures CCT (CSB)	0.807	-0.04
	Object use (canonical)	0.838	0.147
	Word CCT	0.863	0.094
	Ambiguity (nocue)	0.869	0.225
	Object use (alternative)	0.888	0.277

Table 3.1. Loading of each semantic task onto the first two components extracted using principal component analysis (sorted by component 1). The rotated solution is displayed here.

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[3] Extraction was based on Eigenvalues greater than 1; Varimax rotation was applied

Test	Max	Cut-off	Patient Mean (SD)	P1*	P2*	P3	P4	P5	P6*	P7*	P8*	P9*	P10*	P11	P12*	P13	P14*
Non-semantic language tests																	
PALPA 9 real word repetition (tot.)	80	73	59.4 (29.3)	NA	**42**	74	**67**	NA	**7**	79	78	NA	**1**	75	74	79	77
Category Fluency (8)	-	62	38.0 (24.3)	NA	**15**	**18**	**15**	NA	69	**26**	**14**	NA	NA	**45**	80	**41**	**57**
Letter Fluency (F, A, S)	-	18	8.5 (4.9)	NA	**2**	**8**	**3**	NA	**12**	**6**	**3**	NA	NA	**13**	**16**	**13**	**9**
Cookie theft (words/minute)	-	-	44.2 (23.5)	0	9	16	34	NA	38	37	60	NA	0	80	54	77	37
Executive and spatial processing																	
TEA: counting without distraction	7	4.2	5.3 (1.4)	**2**	6	6	6	NT	5	NT	**4**	5	7	6	5	5	7
TEA: counting with distraction	10	2.6	3.4 (2.6)	**1**	**1**	3	4	NT	**3**	NT	**2**	**1**	7	9	**2**	**2**	6
Raven's coloured matrices (total)	36	28.3	28.6 (5.4)	31	31	**27**	**20**	32	33	30	**19**	**24**	34	32	**21**	34	33
Brixton spatial anticipation (correct)	54	28	27.0 (9.3)	**21**	**18**	**18**	30	**6**	**39**	**23**	**24**	34	31	32	31	41	30
Trial Making Test A (correct)	24	24	22.7 (2.8)	**19**	**23**	23	24	**14**	24	**23**	24	24	24	24	24	24	24
Trial Making Test B (correct)	23	17.4	16.4 (8.1)	**2**	**16**	20	19	NT	21	**5**	**1**	23	23	20	19	22	22
Visuospatial processing																	
VOSP dot counting	10	8	9.2 (1.1)	**7**	10	8	9	NT	10	10	10	8	8	9	10	10	10
VOSP position discrimination	20	18	18.4 (2.0)	19	**15**	**15**	**17**	**16**	20	20	**17**	20	19	20	20	20	20
VOSP number location	10	7	8.3 (1.9)	8	**5**	8	**4**	9	8	10	10	8	10	10	**5**	10	8
VOSP cube analysis	10	6	8.3 (1.8)	8	**4**	**5**	**5**	NT	**8**	9	7	9	10	10	10	9	10

Table 3.2. Scores are number of correct; NT = unavailable for testing; NA = not attempted because patients were non-fluent. Bold underlined numbers denote impaired scores (less than two standard deviation below mean). PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; TEA = Test of Everyday Attention; VOSP = Visual Object and Space Processing Battery. [a] Norms from healthy controls tested at the University of York (cut-off is mean minus two standard deviation). Number of controls as follows: Ravens = 20; Trail Making Test = 14. Patients marked with a * had previously taken part in the experiment described in Chapter 2 (**P1*** = P1, **P2*** = P3, **P6*** = P4, **P7*** = P6, **P8*** = P5, **P9*** = P8, **P10*** = P7, **P12*** = P9, **P14*** = P10)

Test	Max	Cut-off	Patient Mean (SD)	P1*	P2*	P3	P4	P5	P6*	P7*	P8*	P9*	P10*	P11	P12*	P13	P14*
Cambridge Semantic Battery																	
Picture Naming	64	59.1	40.3 (24.9)	**1**	**19**	**51**	**54**	**NA**	**50**	60	**0**	**56**	**3**	63	62	**59**	**46**
Word-Picture Matching	64	62.7	60.3 (3.4)	63	**60**	**59**	**62**	**61**	**62**	**62**	**56**	**56**	**52**	**62**	**62**	64	63
Word CCT	64	56.6	52.1 (9.3)	**39**	**29**	**45**	**48**	**50**	**52**	59	**56**	61	57	59	60	59	**56**
Picture CCT	64	52.7	53.1 (9.0)	**31**	**45**	**51**	**44**	59	57	**45**	61	53	54	59	61	62	61
Ambiguity task																	
Miscued dominant	30	30	20.4 (4.7)	**12**	**13**	**21**	**16**	NT	**19**	**20**	NT	**24**	**21**	**25**	**26**	**22**	**26**
Miscued subordinate	30	26.6	16.3 (5.6)	**7**	**14**	**13**	**13**	NT	**15**	**10**	NT	**18**	**18**	**18**	**19**	**22**	28
No cue dominant	30	28.4	25.9 (2.3)	**22**	**24**	**22**	**25**	**27**	**26**	**24**	**25**	**28**	**27**	30	**28**	**27**	**27**
No cue subordinate	30	27.6	18.0 (5.0)	**11**	**14**	**12**	**12**	**17**	**17**	**19**	**16**	**21**	**19**	**26**	**19**	28	**21**
Cued dominant	30	30	25.2 (3.4)	**23**	**19**	**24**	**23**	NT	**23**	**24**	NT	**27**	**23**	30	**29**	**28**	**29**
Cued subordinate	30	28.8	23.4 (4.3)	**25**	**20**	**15**	**19**	NT	**28**	**19**	NT	**23**	**24**	29	**25**	**26**	**28**
Synonym with distractors																	
Strong	42	35.4	20.4 (7.6)	**15**	**13**	**13**	**17**	NT	**23**	**21**	**16**	**22**	**30**	**13**	**17**	**27**	38
Weak	42	40.4	30.5 (4.8)	**25**	**29**	**24**	**25**	NT	**30**	**27**	**33**	**28**	**31**	**35**	**39**	**35**	**36**
Object use																	
Alternative	37	33.9	24.1 (7.5)	**14**	**14**	**9**	**29**	**24**	**22**	34	**22**	**26**	**22**	**29**	**29**	**31**	**32**
Canonical	37	n.a	32.4 (6.5)	32	29	28	12	33	35	37	35	37	33	35	37	34	37

Table 3.3. Scores are number of correct; NT = unavailable for testing; NA = testing was not attempted because patients were non-fluent. Bold underlined numbers denote impaired scores (less than two standard deviation below mean). Cut-off scores are from healthy controls tested at the University of York (mean minus two standard deviations). Number of controls as follows: Cambridge Semantic Battery = 10; Ambiguity task, Alternative object use, Synonym with distractors = 8. Patients marked with a * had previously taken part in the experiment described in Chapter 2 (**P1*** = P1, **P2*** = P3, **P6*** = P4, **P7*** = P6, **P8*** = P5, **P9*** = P8, **P10*** = P7, **P12*** = P9, **P14*** = P10)

2.3 Materials

The present study used the cueing paradigm designed for the task-fMRI investigation of semantic cue integration (see Chapter 4). The following description is reproduced from Chapter 4.

"The cueing paradigm, adapted from Lanzoni et al. (2019), presented pictures of facial expressions and spatial locations prior to semantic judgements about ambiguous words. The stimuli are available on the Open Science Framework (https://osf.io/wp6a7/)[4]. Thirty English homonyms were selected from the Free Association Norms of Twilley et al. (1994), and the Gawlick-Grendell and Woltz norms (1994). We chose items where the different interpretations were associated with different facial expressions (e.g. jam with *traffic* is associated with frustration while jam with *strawberry* is associated with pleasure). We also chose items where different interpretations were associated with different locations (e.g. a motorway for *traffic* jam and a supermarket for *strawberry* jam). We then generated four target words for each probe, two for each interpretation. This resulted in 120 probe-target pairs. For instance, the probe jam appeared in four trials, twice paired with a target referring to *traffic* (jam-horn or jam-delay) and twice paired with a target referring to the alternative interpretation (jam-spoon or jam-bread). Although we did not manipulate the difference in frequency between the two alternative meanings, one interpretation of the homonym was dominant over the other (i.e., a larger proportion of subjects generated words linked to that interpretation, as reported in Twilley et al. (1994). Dominance was controlled by counterbalancing the assignment of each interpretation to the different experimental conditions across participants. For each combination of probes and targets, two unrelated distractors were selected. Latent Semantic Analysis (as implemented in lsa.colorado.edu) was used to calculate the similarity in semantic space between the probe and the targets vs. probe and distractors (parameters used: space – General reading up to 1st year college, comparison type - term to term, number of factors – maximum). This confirmed that the strength of the relationship between probe and distractor (M = .08, SD = .04) was significantly weaker compared to the association between probe and target (M = .22, SD = .10; t (29) = 7.17, p < .001). Distractors and target words were matched for lexical frequency (SUBTLEX-UK database, van Heuven et al., 2014; t = .89, p = .380), word length (t = -1.44, p = .154), and concreteness (Brysbaert et al., 2014; t = .58, p = .564).

Pictures of facial emotional expressions and spatial locations were used to prime the relevant meaning of the homonym. Each picture was used only once across the entire experiment, making it impossible for participants to predict the following probe word on the basis of the cue. Images of facial expressions were chosen from the Radboud Faces Database (Langner et al., 2010) and included eight basic emotions: happy, angry, sad, disgusted, contemptuous, surprised, neutral, fearful. In selecting

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[4] The images of spatial locations are not included in the collection due to potential copyright restrictions.

the affect cues we ensured that the same face from the Radboud Database would not be presented in the same emotional expression in other trials. Therefore, for trials that required the same emotional expression we chose different actors. Pictures of spatial contexts were downloaded from Google images.

The emotion and location cues could appear together in the same trial (2 cues condition), they could be presented alone (1 cue affect or location conditions), in which case they were paired with one meaningless scrambled image, or two scrambled images were provided (0 cues condition). Images were converted to greyscale, matched for luminance and scrambled using the SHINE toolbox (Willenbockel et al., 2010). Images were also brought to a fixed dimension (600 x 400 pixels for location and 260 x 400 for affect cues) using Matlab (The MathWorks Inc., Natick, MA, US). Figure 3.1.B shows the 4 cue conditions, which were used to examine three levels of constraint on semantic retrieval. The location of the emotion and location cues (to the left or right of the screen) was counterbalanced within each run."

In the original paradigm described in Chapter 4, one of the distractors was related to either the emotional or the visuo-spatial cue to ensure that people could not make their semantic decisions based only on the cue. Here we removed this additional level of difficulty by re-shuffling the distractors and ensuring that they had no semantic relationship with the probe.

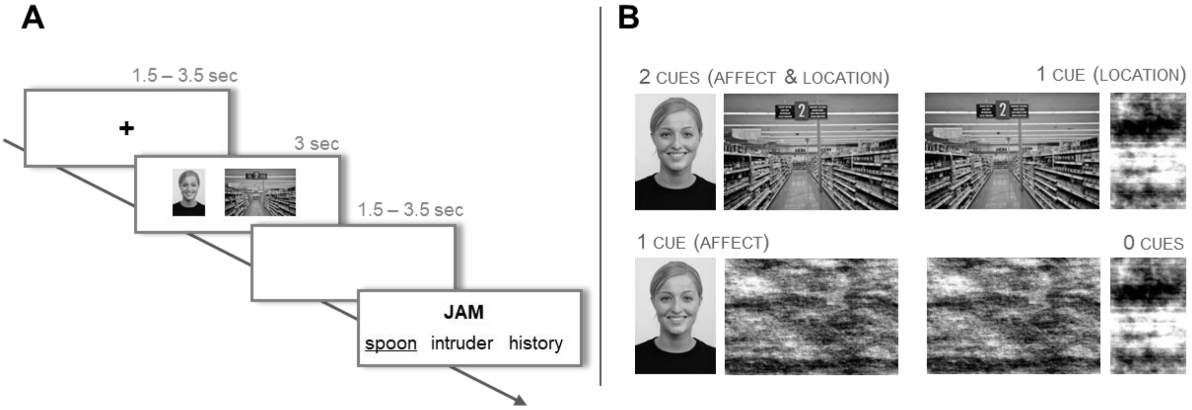

Figure 3.1. A Experimental design. After an initial fixation cross (1500 – 3000ms), participants were presented with cue images for 3000ms, before moving to a blank screen (1500 – 3000ms). Then a probe word was presented above a target and two unrelated distracters, triggering the onset of the decision-making period. The probe and choices remained visible until a response was made. **B** The four levels of the variable cue.

2.4 Procedure

An example of a trial is shown in Figure 3.1.A. The experiment was run using Psychopy 2 (Peirce et al., 2011) and unfolded in the similar manner as the task-based fMRI (see Chapter 4, section 2.2 Procedure). Each trial started with a fixation cross of random duration between 1500 and 3000ms

(Figure 3.1.A). Two cue pictures or scrambled cues were then presented for 3s, followed by a blank screen (ISI: 1500 – 3000ms). Next, four words appeared on screen – a probe word at the top and three response options underneath, marking the start of the semantic task. These were read aloud by the experimenter to facilitate patients' comprehension. Participants were asked to decide which of the three options had the strongest semantic relationship to the probe. Unlike the original paradigm where the time to respond was fixed, in the present study participants were allowed to complete the semantic decision at their own pace. Nevertheless, they were encouraged to respond as quickly as possible and they were told that response time would be measured. As most of the patients had motor impairments at the time of testing, patients gave their response by pointing to one of the options and the experimenter pressed the corresponding key on their behalf. Consistently with the experiment described in Chapter 2, the experimenter maintained one finger on each of the three possible keys to minimize the delay between the patients' decision and the actual keypress. Control participants were also encouraged to maintain their fingers on the keyboard to speed up their responses. Accuracy and response time (RT) were recorded on each trial.

Participants received written and verbal instructions prior to the start of the experiment. They then completed a practice block of 30 trials where they received feedback on the accuracy of their choice. In case of a missed trial, the experimenter explained the semantic relationship between the target and the probe. This was done following a written script, to ensure consistency between different researchers. A total of 120 trials were arranged in four blocks of 30 trials each, with each probe used once per block. Within each block, trials were split into three mini-blocks of ten trials each. Participants were allowed to take a quick break at the end of each mini-block. The order of presentation was randomized and stimuli were counterbalanced so that, across all participants, each probe-target combination appeared in all four cue conditions. As a consequence of this design, it is not possible to directly compare the magnitude of cueing effects in different participants (since different items were assigned to conditions across cases). Testing was performed over two separate sessions of one hour each, during which time, participants completed 2 blocks of the cueing task and other neuropsychological tasks. Within a session, both meanings of the probe word were primed.

2.5 Statistical analyses

Although we did not directly manipulate the dominance of the alternative interpretations of the ambiguous words, previous investigations have shown strong effects of dominance in SA patients (Jefferies and Lambon Ralph, 2006; Lanzoni et al., 2019; Noonan et al., 2010). Dominance values were available for each interpretation of the ambiguous words probed in the study (as reported in Twilley et al., 1994). For the purpose of the statistical analysis, we performed a median-split of these values (median = .385) and transformed the scale variable into a categorical predictor with two levels:

dominant and subordinate. This allowed us to maintain consistency with the work described in the previous chapter, and examine how cueing affected the retrieval of relatively dominant and subordinate items. At the group level, accuracy and response efficiency (median RT/mean accuracy) data were analysed separately using three-way mixed ANOVAs, with cue condition (3 levels: 0 cues, 1 cue, 2 cues) and dominance (2 levels: dominant, subordinate) as within-subjects factors, and group (2 levels: controls, patients) as a between-subjects factor. Pairwise comparisons for significant effects were Bonferroni-corrected. All statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY).

3. Results

3.1 Group-level analyses of patients and healthy controls

Mean accuracy and median response efficiency for patients and controls are displayed in Figure 3.2. The results of the ANOVA are provided in Table 3.4. As expected, control participants performed more accurately [$F(1,25) = 50.9$, $p < .001$, $\eta^2 = .7$] and more efficiently [$F(1,25) = 30.3$, $p < .001$, $\eta^2 = .6$] than patients. We found a three-way interaction between group, dominance, and cue type in both accuracy ($F(2,50) = 4.8$, $p = .012$, $\eta^2 = .2$) and efficiency ($F(2,50) = 3.8$, $p = .030$, $\eta^2 = .1$). Separate ANOVAs were conducted for the patient and control groups. We found a significant interaction between cue condition and dominance in the patient group, in both accuracy ($F(1.3, 16.5) = 7.1$, $p = .012$, $\eta^2 = .4$) and median response efficiency ($F(1.3, 17.2) = 4.2$, $p = .046$, $\eta^2 = .2$), but no interaction in the control group. Statistical values are reported in Table 3.5. Bonferroni-corrected comparisons of accuracy in the patient group revealed more errors for semantic decisions about subordinate meanings in the absence of a cue compared to when a single cue was provided ($t(12) = -4$, $p = .005$), while the difference between providing a single cue or two cues was not significant ($t(12) = 0$, $p = 1$). When the dominant meaning was probed, there were no significant differences between different levels of cueing. In the response efficiency data, no comparisons survived Bonferroni correction (all p values > .017). These results show that retrieval of the non-dominant meanings of homonyms is improved in the patients by the provision of a cue, and that combining different types of cues does not yield an additional benefit.

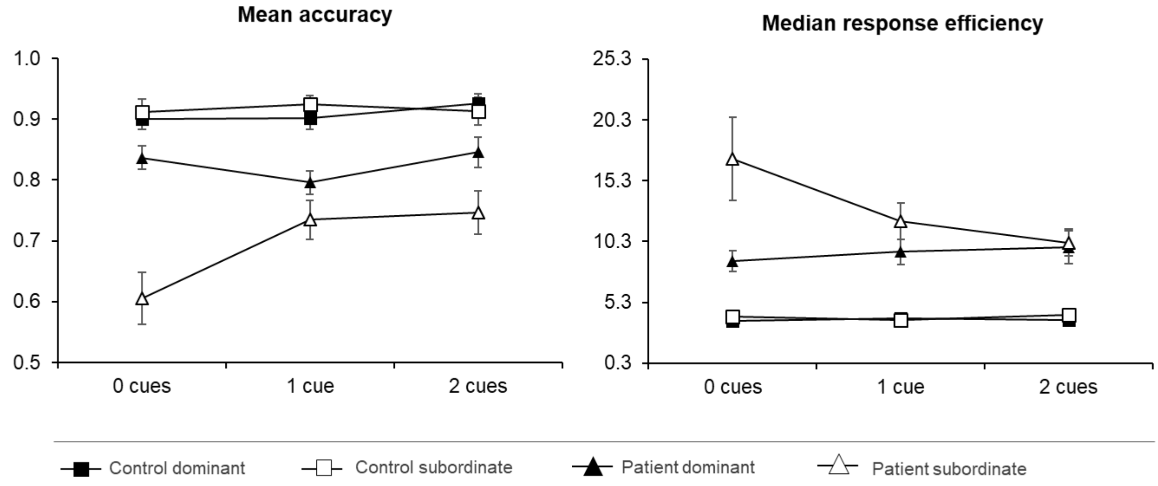

Figure 3.2. Descriptive statistics for the two groups. Mean accuracy and median response efficiency were plotted as a function of the cue condition and the level of dominance of the interpretation of meaning. Dominance values were median-split to transform the variable into a categorical predictor. Large numbers indicate better performance in the accuracy graph, and reflect worse performance when expressed as response time and response efficiency. Error bars show standard error of the mean (SEM).

		Group	**Cue**	**Dominance**	**Cue x group**	**Dominance x group**	**Cue x dominance**	**Cue x dominance x group**
Accuracy	F	**50.9***	**3.2***	**24.7***	1.5	**30.9***	**4.8***	**4.8***
	df	1, 25	2, 50	1, 25	2, 50	1, 25	1.5, 37	2, 50
	p	**<.001**	**.048**	**<.001**	.227	**<.001**	**.022**	**.012**
	partial η2	0.7	0.1	0.5	0.1	0.6	0.2	0.2
Response Efficiency	F	**30.3***	2.1	**12.3***	2.4	**9.7***	**3.9***	**3.8***
	df	1, 25	1.5, 37.2	1, 25	2, 50	1, 25	1.3, 33.3	2, 50
	p	**<.001**	.131	**.002**	.104	**.005**	**.044**	**.030**
	partial η2	0.6	0.1	0.3	0.1	0.3	0.1	0.1

Table 3.4. Accuracy and median response efficiency effects revealed by 3-way mixed ANOVAs with group as a between-subject factor and cue condition as a within-subject factor. Significant results and interactions are reported in bold and marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

		PATIENTS			CONTROLS			
		Cue	**Dominance**	**Cue x dominance**		**Cue**	**Dominance**	**Cue x dominance**
Accuracy	F	3.1	**48***	**7.1***	F	0.4	0.2	0.6
	df	2, 26	1, 13	1.3, 16.5	df	2, 24	1, 12	1.3, 15.7
	p	.062	**< .001**	**.012**	p	.695	.651	.486
	partial η2	0.2	0.8	0.4	partial η2	0	0	0.1
Response Efficiency	F	2.2	**12.5***	**4.2***	F	0.5	0.7	1.1
	df	2, 26	1, 13	1.4, 17.2	df	2, 24	1, 12	2, 24
	p	.107	**.004**	**.046**	p	.588	.421	.340
	partial η2	0.2	0.5	0.2	partial η2	0	0.1	0.1

Table 3.5. Two separate 2-way ANOVAs were performed on patients and controls. Significant results and interactions are reported in bold and marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

3.2 Comparison of cue types in the patient group

Since the previous analysis revealed a benefit of 1 cue vs. 0 cues in patients' accuracy in the subordinate trials, we explored whether emotion and location cues were equally effective in constraining semantic retrieval. A 1-way repeated measure ANOVA with cue condition (3 levels: 0 cues, 1 cue affect, 1 cue location) as within-subject factor was performed on patients' accuracy in subordinate trials. We found a significant main effect of cue (F(2, 26) = 9.7, p = .001, η^2 = 0.4). Pairwise comparisons revealed that patients were more accurate when subordinate trials were cued by a visuo-spatial context, compared to when no cues were provided (t(12) = -4.5, p = .002). The difference between uncued trials and semantic decisions following a single affect cue only approached significance (t(12) = -2.6, p = .065), suggesting that facial emotional expressions might not be as effective as spatial cues in priming the interpretation of ambiguous words.

4. Discussion

In this study, we explored whether patients with semantic aphasia following a left-hemisphere stroke (i) showed a benefit of cued vs. uncued semantic decisions (replicating findings in Lanzoni et al., 2019), (ii) were able to process semantic cue combinations, and (iii) showed a greater benefit of multiple cue types compared to when a single cue type was provided. We contrasted semantic decisions following the presentation of affect and visuo-spatial cues together (2 cues), affect or location cues presented singly (1 cue), or scrambled versions of the images (0 cues). Compared to healthy controls, patients' understanding of less frequent meanings of ambiguous words was improved by the provision of one cue relative to scrambled images (contrast of 1 cue vs. 0 cues). When the two cue types were analysed separately, only visuo-spatial contexts were significantly associated with better accuracy in the task. Finally, presenting emotional expressions and locations simultaneously to further constrain meaning did not ameliorate comprehension deficits above and beyond the effects resulting from one cue type (contrast of 2 cues vs. 1 cue).

Our previous experiment showed that patients' comprehension of ambiguous words is constrained by contextual cues (i.e. facial emotional expressions and visuo-spatial contexts), particularly when the task requires to access less frequent meanings of words (Lanzoni et al., 2019). Here, we replicated these findings by showing that the presentation of a single cue improved patients' retrieval of subordinate interpretations of words, relative to uncued trials. This is in line with the predictions made by the Controlled Semantic Cognition framework (Jefferies, 2013; Lambon Ralph et al., 2016), which anticipates interactions between semantic representations and control processes in conceptual retrieval. The semantic hub in ventral ATL is thought to allow the computation of meaning through the integration of different features (including valence and visuo-spatial contexts). Since the semantic control regions typically damaged in SA patients are spatially distinct from temporal lobe regions that store representations, patients maintain the different interpretations of meaning, but they might fail to access the relevant one. In line with the existing literature, our study demonstrates that 'online' manipulation of semantic representations is ameliorated by the presence of cues. Comparing semantic decisions following 2 cues vs. 1 cue allowed us to tackle a new question of whether patients' comprehension can be improved even further by providing rich and highly constrained multi-modal contexts. Such question is extremely relevant for patient management and rehabilitation; if comprehension can be ameliorated by embedding multi-modal cues in a conversation setting, this could be implemented by caregivers and speech and language therapists. Patients' performance in semantic decisions following 2 cues was not significantly different than following a single cue, suggesting that conceptually-richer contexts might not facilitate comprehension beyond the benefit observed for one cue.

There are at least two potential explanations for the lack of a cue-additive effect. First, our task may have been insufficiently challenging for SA patients to fully benefit from the presence of multiple cues. Following the presentation of a single cue, patients' retrieval of subordinate meanings reached the same level of efficiency observed for dominant meanings, suggesting that there might not have been an opportunity for a further improvement. Our results also indicate that a single visuo-spatial cue may have been rather constraining, thus reducing the need to process the emotion cue when both cues were presented. Additionally, the experimental manipulations proved ineffective for the control group, where similar (and near-ceiling) levels of accuracy and efficiency were observed for both dominant and subordinate aspects of meaning, and across cue conditions. Taken together, this evidence suggests that the cueing paradigm did not effectively manipulate the control demands of the task. Real-life situations, however, are more complex than experimental scenarios: language in the real world contains multiple sources of ambiguity (e.g. in the word meaning, in the non-verbal behaviour of the speaker, in the sensory aspects of objects and people etc.). It remains possible that in more demanding situations, where multiple uncertainties must be resolved simultaneously, patients will show effects of cue combinations. A follow up study could address this question by using a parametric manipulation of the complexity of semantic decisions and comparing the effect of cues at different levels of semantic difficulty. Alternatively, the absence of cue combination effects for the patients might relate to the computational cost of processing multiple sources of information. Cue pictures were presented for 3 seconds before being replaced by the semantic decision and this may have been insufficient time for patients to pay attention to both cues. Future studies could extend the interval in which the cues are shown, or present the cues and the semantic judgement simultaneously.

In line with our previous findings (Lanzoni et al., 2019), the present study established that our sample of patients with SA largely benefits from non-verbal cueing, even when a single cue is provided. The presence of a single semantic cue vs. scrambled images improved comprehension to such an extent that it was impossible to fully establish the effect of multiple cues. The results are consistent with dual-system accounts of semantic cognition, which anticipate the interaction of two distinct routes to semantic flexibility (CSC framework; Lambon Ralph et al., 2016) – one driven by the context and relatively spared in SA patients, and a second one which requires the intervention of semantic control processes. In the presence of a constraining context, conceptual integration mechanisms in ventral ATL may be sufficient to support semantic retrieval. When recently activated conceptual representations (i.e. inputs from the environment) are in line with long-term semantic knowledge, patients may be able to produce heteromodal representations by combining different aspects of knowledge, which remain intact. In many situations, however, we need to access subordinate aspects of meanings in the absence of a constraining context, or establish relationships between semantically distant representations. This second type of flexibility is damaged in SA, but it can be improved by applying external constraints, as highlighted by the interaction of cue condition and dominance in our experiment. Although this study does not allow us to draw conclusions about the direct benefit of combining different cue types on patients' communication, these findings do stress the importance of controlling the spatial context in which communication occurs to make it as consistent as possible with the message being conveyed.

Chapter 4. The role of default mode network in semantic cue integration

In the previous chapter we examined whether patients with damage to left-hemisphere semantic control regions are able to integrate convergent semantic cues. Previous research has established the role of regions within the default mode network (largely spared in our patient sample) in conceptual combinations. Accordingly, we hypothesized that patients' understanding of cue combinations should be relatively preserved, if cue combinations are formed automatically without the intervention of control processes. Findings that patients show normal or greater-than-normal effects would provide convergent evidence for a role of DMN in semantic integration.

The study failed to provide this evidence, and there were limitations of our methods. The lack of a behavioural effect did not allow us to draw conclusions about the ability of our patients to integrate cues – and consequently about the role of DMN regions in cue integration. It is possible that we would have recovered an effect with a different task design. A more general limitation is that neuropsychology studies lack the anatomical precision required to define a network. Stroke patients tend to have relatively large lesions, which can sometimes extend beyond the typically damaged networks.

In the present chapter we used fMRI to overcome these limitations and defined the neural bases of semantic cue integration with greater precision[5]. Crucially, fMRI can recover the large-scale networks responsible for different aspects of semantic cognition. Based on the previous literature, we predicted that making semantic decisions following multiple convergent cues would recruit DMN regions, largely distinct from the neural substrate for uncued or minimally cued decisions. We tested this hypothesis by contrasting the BOLD response when participants made decisions to ambiguous words after the presentation of two vs. one cue or after the presentation of a single cue vs. no cues.

This chapter is adapted from: Lanzoni, L., Ravasio, D., Thompson, H., Vatansever, D., Margulies, D., Smallwood, J., & Jefferies, E. (2020). The role of default mode network in semantic cue integration. *NeuroImage*, 117019.
https://doi.org/10.1016/j.neuroimage.2020.117019

Part of the data collection for this study was conducted outside the period of PhD registration, when Lucilla Lanzoni worked as a research administrator in the group (employed by Prof. Elizabeth Jefferies

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[5] The experiment in this chapter was completed before the Neuropsychology study described in Chapter 3, but it was decided to present the two neuropsychological studies in adjacent chapters of this thesis.

under a grant from the Stroke Association: R1425201) from March to October 2017. The data collection was completed by Lucilla Lanzoni upon returning to the PhD.

Acknowledgments and authors' contribution

Lucilla Lanzoni, Prof. Elizabeth Jefferies, and Prof. Jonathan Smallwood developed the main ideas in this chapter and the experimental paradigm. Daniela Ravasio, a visiting scholar in the group, helped to create the experimental stimuli and collected pilot data. Lucilla Lanzoni performed the fMRI data collection with the help of a research assistant - Oliver Hodgkinson – who acted as Level 0 operator in a few scanning sessions, and an UG student - Sophie Cawkwell – who helped with the behavioural training in a few occasions. Lucilla Lanzoni performed the statistical analyses. Dr. Deniz Vatansever provided technical help when needed, and Dr. Daniel Margulies developed the Principal Gradient methodology used in the statistical analyses (Margulies et al., 2016). The interpretation of the results, writing and editing of the chapter were also completed by Lucilla Lanzoni. Prof. Jefferies and Prof. Smallwood edited drafts of this chapter.

The role of default mode network in semantic cue integration

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Funding

The study was supported by a grant from the Stroke Association [R1425201] and a grant from the European Research Council [FLEXSEM – 771863] awarded to E.J.

Abstract

Recent accounts of large-scale cortical organisation suggest that the default mode network (DMN) is positioned at the top of a principal gradient, reflecting the separation between heteromodal and unimodal sensory-motor regions in patterns of connectivity and in geodesic distance along the cortical surface (Margulies et al., 2016). This isolation of DMN from external inputs might allow the integration of disparate sources of information that can constrain subsequent cognition. We tested this hypothesis by manipulating the degree to which semantic decisions for ambiguous words (e.g. JAM) were constrained by preceding visual cues depicting relevant spatial contexts (e.g. SUPERMARKET or ROAD) and/or facial emotions (e.g. HAPPY vs. FRUSTRATED). We contrasted (i) the effects of a single preceding cue with a no-cue condition employing scrambled images, and (ii) convergent spatial and emotion cues with single cues. Single cues elicited stronger activation in the multiple demand network relative to no cues, consistent with the requirement to maintain information in working memory. The availability of two convergent cues elicited stronger activation within DMN regions (bilateral angular gyrus, middle temporal gyrus, medial prefrontal cortex, and posterior cingulate), even though behavioural performance was unchanged by cueing – consequently task difficulty is unlikely to account for the observed differences in brain activation. A regions-of-interest analysis along the unimodal-to-heteromodal principal gradient revealed maximal activation for the convergent cue condition at the heteromodal end, corresponding to the DMN. Our findings are consistent with the view that regions of DMN support states of information integration that constrain ongoing cognition and provide a framework for understanding the location of these effects at the heteromodal end of the principal gradient.

Keywords: default mode, integration, principal gradient, semantics, cueing

1. Introduction

The context in which we encounter concepts in our daily life influences the manner in which we think about them. Hearing the word *jam* at the kitchen table, for example, one might activate a number of concepts related to food, its taste and emotional valence. The same word *jam* on the traffic news, however, might bring up very different thoughts and emotions. Although studies have manipulated sentence contexts to constrain the interpretation of ambiguous words (e.g. Noonan et al., 2010; Rodd et al., 2016, 2013, 2005, 2004; Vitello and Rodd, 2015), cues beyond language have rarely been employed (for an exception see Lanzoni et al., 2019). Consequently, relatively little is known about how non-verbal cues, such as spatial location and affect, constrain meaning retrieval or the neural mechanisms that underlie this effect. The current study addressed this issue by manipulating the availability of spatial and facial emotion cues prior to semantic decisions about ambiguous words.

Contemporary models of semantic cognition suggest that retrieval is supported by a dynamic interplay of conceptual knowledge with retrieval processes (Hoffman et al., 2018; Jefferies, 2013; Lambon Ralph et al., 2016). Conceptual representations are rich and comprise features from multiple sensory modalities (e.g. an apple is a *sweet* fruit, with a *rounded* shape and a *smooth hard* surface which is often *red*, *yellow* or *green*). According to the Hub and Spoke model of conceptual representation, the ventrolateral anterior temporal lobe (ATL) 'hub' integrates features encoded in sensory-motor cortical 'spokes' to generate coherent representations – e.g. our concept 'apple' (Chiou and Lambon Ralph, 2019; Lambon Ralph et al., 2016; Patterson et al., 2007). However, hub and spoke representations are not sufficient to support *flexible* semantic cognition; we also dynamically vary the aspects of knowledge that we retrieve about concepts depending on the context. Semantic processing may draw on different large-scale networks depending on whether retrieval is usefully constrained or miscued by the context.

In line with this view, semantic sites have been shown to overlap with distinct large-scale networks that are recruited differentially depending on the task demands. When non-dominant associations are required by a task, or the prior context is unhelpful, a 'semantic control network' is recruited (including left inferior frontal gyrus and posterior middle temporal gyrus), which may shape retrieval to suit the circumstances (Badre and Wagner, 2006, 2005; Davey et al., 2016; Hallam et al., 2016; Krieger-Redwood et al., 2015; Noonan et al., 2013b; Whitney et al., 2011). In contrast, other key sites for semantic cognition, such as lateral ATL and angular gyrus (AG), have patterns of intrinsic connectivity that are partially overlapping with aspects of the Default Mode Network (DMN) (Davey et al., 2016; Humphreys and Lambon Ralph, 2015; Jackson et al., 2016; Seghier et al., 2010). The role of DMN regions in semantic cognition remains controversial: a meta-analysis by Binder and colleagues (2009) found peak activation for semantic tasks in AG, while other researchers have characterized AG as a task-negative region which deactivates across semantic and non-semantic tasks (Humphreys et al., 2015; Humphreys and Lambon Ralph, 2015; Mollo et al., 2017). DMN regions, including AG, typically show anti-correlation with task-positive regions within the multiple demand network (MDN; Blank et al., 2014; Davey et al., 2016; Fox et al., 2005). Nevertheless, TMS studies have shown that AG plays a critical role in the efficient retrieval of dominant aspects of knowledge (Davey et al., 2015a). There are also demonstrations of a role for the DMN in semantic retrieval even when tasks are relatively hard. For example, Murphy et al. (2018) found greater DMN recruitment both when participants made judgements based on their memory of preceding trials (as opposed to stimuli present on the screen), and when the decisions involved semantic categories as opposed to perceptual features.

Recent studies have suggested that semantic regions allied to DMN, including AG, support the combination of concepts into meaningful and more complex representations (e.g. Price et al., 2015; for review see Pylkkänen, 2019). These regions show a stronger response when coherent conceptual combinations or heteromodal features are presented (Bemis and Pylkkänen, 2011; Price et al., 2016, 2015; Pylkkänen, 2019; Teige et al., 2019, 2018). The suggested critical role of the DMN in conceptual integration fits well with the observation that the DMN lies at the top of a cortical hierarchy. Through decomposition of resting-state connectivity, Margulies et al. (2016) identified a principal gradient of macroscale organization, anchored at one end by sensory regions and at the other end by heteromodal cortex, corresponding to the DMN. This separation of DMN from unimodal cortex in intrinsic connectivity relates to geodesic distance – DMN sites are located relatively far away from primary sensory-motor cortex along the cortical surface (Margulies et al., 2016). Greater distance along the gradient might allow the brain to support forms of cognition that rely on memory, as opposed to information in the external environment (Murphy et al., 2019). Distance might also support increasing levels of abstraction from sensory-motor features, allowing the formation of heteromodal conceptual representations from the integration of these diverse sources of information (Buckner and Krienen, 2013; Mesulam, 1998; Patterson et al., 2007; Smallwood, 2013). In line with this idea, default mode regions might show a greater response in semantic tasks when multiple aspects of a concept are activated during retrieval.

In the present study, we tested the view that semantically-relevant regions within the DMN, in particular AG, contribute to conceptual integration. We adopted a paradigm recently developed to assess the impact of non-verbal cues in patients with semantic aphasia, who have deficits of semantic control (Lanzoni et al., 2019). Participants were shown 0, 1 or 2 cues that were relevant to the subsequent interpretation of an ambiguous word: they saw photographs of spatial contexts, facial emotions or scrambled meaningless versions of these cues. The cues alone were not sufficient to prime the concepts and did not influence behavioural performance (for example, SUPERMARKET and HAPPY FACE can be linked in many ways and do not strongly anticipate JAM AS FOOD). Nevertheless, the cues allowed the subsequent semantic decisions to unfold in a conceptually-rich context. If semantic integration occurs in the DMN, comparing semantic decisions in the context of multiple convergent cues as opposed to single cues should reveal increased activation within this network and in particular in AG – even though semantic decisions to ambiguous words are relatively cognitively effortful. In contrast, brain regions that selectively encode and maintain semantic cue information *prior* to integration should be spatially distinct from DMN: the neural basis of cue maintenance might be maximally revealed by a contrast of single cue over no cue trials (as this contrasts situations where there are working memory demands versus no requirement to maintain information). MDN is a candidate network for attentional and working memory components of the cueing task, since this network is associated with executively demanding aspects of cognition, including working memory and the maintenance of task rules, across domains (e.g. Dosenbach et al., 2006; Naghavi and Nyberg, 2005; Owen et al., 2005). For example, a study by Dumontheil et al. (2011) found activation in several parts of MDN during the presentation of task instructions, which might reflect the creation of a task-model or framework for ongoing cognition.

Additionally, we predicted that the effect of conceptual integration but not cue load would be located at the heteromodal end of the principal gradient (Margulies et al., 2016), providing a framework for understanding *why* information integration effects occur where they do within the cortex: these effects should be greatest at the DMN apex of the gradient, which is maximally separated (both in terms of physical distance and in connectivity terms) from unimodal input or 'spoke' regions associated with processing specific features. In contrast to our standard whole-brain cluster-corrected contrasts, the focus of this analysis was not on the functional contribution of specific regions, such as AG, to cue integration, but instead on whole-brain patterns that include similar functional transitions between heteromodal and unimodal cortex in distant cortical regions.

2. Materials and Methods

2.1 Participants

Twenty-seven healthy right-handed native English-speaking participants with normal or corrected-to-normal vision were recruited from the University of York (9 males, mean age 21.5, SD 2.9, range 19-30). Participants received monetary compensation or course credits. One dataset was excluded due to technical problems that resulted in no behavioural responses being recorded, leaving 26 subjects in the final sample. In a subsequent analysis we examined resting-state fMRI data from 86 participants (22 males; mean age 20.3, range 18–32 years), twelve of whom were also in the main sample. The research was approved by the York Neuroimaging Centre Ethics Committee and participants provided written informed consent.

2.2 Materials

The cueing paradigm, adapted from Lanzoni et al. (2019), presented pictures of facial expressions and spatial locations prior to semantic judgements about ambiguous words. The stimuli are available on the Open Science Framework (https://osf.io/wp6a7/)[6]. Thirty English homonyms were selected from the Free Association Norms of Twilley et al. (1994), and the Gawlick-Grendell and Woltz norms (1994). We chose items where the different interpretations were associated with different facial expressions (e.g. JAM with *traffic* is associated with frustration while JAM with *strawberry* is associated with pleasure). We also chose items where different interpretations were associated with different locations (e.g. a motorway for *traffic* JAM and a supermarket for *strawberry* JAM). We then generated four target words for each probe, two for each interpretation. This resulted in 120 probe-target pairs. For instance, the probe JAM appeared in four trials, twice paired with a target referring to *traffic* (JAM-horn or JAM-delay) and twice paired with a target referring to the alternative interpretation (JAM-spoon or JAM-bread). Although we did not manipulate the difference in frequency between the two alternative meanings, one interpretation of the homonym was dominant over the other (i.e., a larger proportion of subjects generated words linked to that interpretation, as reported in Twilley et al. (1994). Dominance was controlled by counterbalancing the assignment of each interpretation to the different experimental conditions across participants. For each combination of probes and targets, two unrelated distractors were selected. Latent Semantic Analysis (as implemented in lsa.colorado.edu) was used to calculate the similarity in semantic space between the probe and the targets vs. probe and distractors (parameters used: space – General reading up to 1st year college, comparison type - term to term, number of factors – maximum). This confirmed that the strength of the relationship between probe and distractor (M = .08, SD = .04) was significantly weaker compared to the association between probe and target (M = .22, SD = .10; t (29) = 7.17, p < .001). Distractors and target words were matched for lexical frequency (SUBTLEX-UK database, van Heuven et al., 2014; t = .89, p = .380), word length (t = -1.44, p = .154), and concreteness (Brysbaert et al., 2014; t = .58, p = .564).

Pictures of facial emotional expressions and spatial locations were used to prime the relevant meaning of the homonym. Each picture was used only once across the entire experiment, making it impossible for participants to predict the following probe word on the basis of the cue. Images of facial expressions were chosen from the Radboud Faces Database (Langner et al., 2010) and included eight basic emotions: happy, angry, sad, disgusted, contemptuous, surprised, neutral, fearful. In selecting

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[6] The images of spatial locations are not included in the collection due to potential copyright restrictions.

the affect cues we ensured that the same face from the Radboud Database would not be presented in the same emotional expression in other trials. Therefore, for trials that required the same emotional expression we chose different actors. Pictures of spatial contexts were downloaded from Google images.

The emotion and location cues could appear together in the same trial (2 cues condition), they could be presented alone (1 cue affect or location conditions), in which case they were paired with one meaningless scrambled image, or two scrambled images were provided (no-cue condition). Images were converted to greyscale, matched for luminance and scrambled using the SHINE toolbox (Willenbockel et al., 2010). Images were also brought to a fixed dimension (600 x 400 pixels for location and 260 x 400 for affect cues) using Matlab (The MathWorks Inc., Natick, MA, US). Figure 4.1.B shows the 4 cue conditions, which were used to examine three levels of constraint on semantic retrieval. The location of the emotion and location cues (to the left or right of the screen) was counterbalanced within each run. Finally, to ensure that people could not make their decisions based only on the cue, in each trial one of the distractors was related to either the emotional cue or the visuo-spatial cue presented before the semantic task (in Figure 4.1.A, the distractor 'bag' is related to the location cue – supermarket). The assignment of the emotion-related and location-related distractors to the different conditions was counterbalanced within participants, such that each probe appeared twice with an emotion-related distractor and twice with a location-related distractor.

2.3 Procedure

The MRI session included a high-resolution structural scan, a FLAIR sequence and four functional runs of approximately nine minutes each. Each trial started with a fixation cross of random duration between 1500 and 3000ms (Figure 4.1.A). Two cue pictures or scrambled cues were then presented for 1s, followed by another jittered inter-stimulus interval (ISI: 1500 – 3000ms). Participants were asked to pay attention to the cues, and they were told that these would be helpful images on some trials, and meaningless images on other trials. Next, four words appeared on screen – a probe word at the top and three response options underneath, marking the start of the semantic task. Participants were asked to decide which of the three options had the strongest semantic relationship to the probe, and they were encouraged to make the semantic decision based on the words and not on the previously seen images. Although the time to respond was fixed (4s), participants were asked to respond as quickly and accurately as possible. Each of the 30 probes was presented once within each run, resulting in 30 semantic trials. The order of presentation was randomized and stimuli were counterbalanced so that, across all participants, each probe-target combination appeared in all four cue conditions. Each run had a total of eight non-semantic trials, in which words were replaced with strings of the letter 'X' matched in length to the words. Here the task was to press any key. The scrambled images used in non-semantic trials were created equally often from face and location photos. Two null trials were also included to improve task modelling. During null trials participants saw a blank screen for the same duration of 4 seconds.

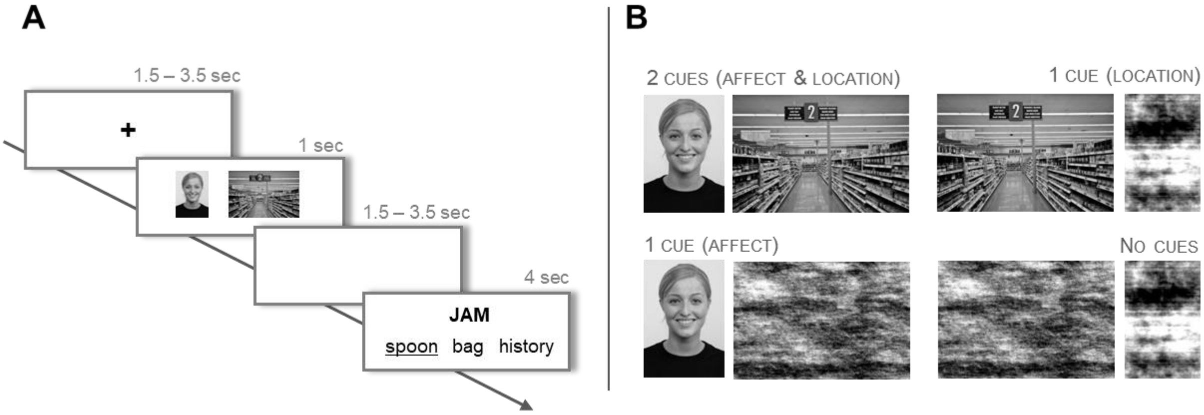

Figure 4.1. A After an initial fixation cross (1500 – 3000 ms), participants were presented with cue images for 1000 ms, before moving to a blank screen (1500 – 3000 ms). Following that, a probe word was presented above a target and two unrelated distracters, triggering the onset of the decision-making period. The probe and choices remained visible for a fixed interval of 4000 ms. **B** The four levels of the variable cue are shown.

2.4 fMRI acquisition

Whole brain fMRI data acquisition was performed using a GE 3 Tesla HDx Excite MRI scanner. Structural MRI data acquisition in all participants was based on a T1-weighted 3D fast spoiled gradient echo sequence (TR = 7.8ms, TE = minimum full, flip-angle = 20°, matrix size = 256x256, 176 slices, voxel size = 1.13×1.13×1 mm). A gradient-echo EPI sequence was used to collect functional data from 60 interleaved bottom-up axial slices aligned with the temporal lobe (TR = 3s, TE = 18.9 ms, FOV = 192x192x180 mm, matrix size = 64x64, slice thickness = 3mm, slice-gap = 3mm, voxel size = 3x3x3 mm^3, flip-angle = 90°). An intermediary FLAIR scan with the same orientation as the functional scans was collected to improve the co-registration between subject-specific structural and functional scans.

2.5 Data pre-processing

2.5.1 Behavioural pre-processing and analysis

We examined accuracy, median response time (RT), RT variability and response efficiency in separate repeated-measures ANOVAs to characterise differences in performance across the 4 semantic conditions (0 cues, 1 cue affect, 1 cue location, 2 cues: affect and location). One keypress was not recorded for two participants and these missing RT values were replaced with the group median for that condition. Response efficiency scores were used to account for any speed-accuracy trade-offs: the median RT for correct responses for each subject in each condition was divided by the mean accuracy in the same condition (Townsend and Ashby, 1983). We also examined trial-to-trial variability, using the standard deviation of RT for each participant in each condition.

2.5.2 MRI data pre-processing

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.0, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration of the high resolution structural to standard space (Montreal Neurological Institute – MNI) was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Pre-processing of the functional image included motion correction using MCFLIRT (Jenkinson et al., 2002), slice-timing correction using Fourier-space time-series phase-shifting (interleaved), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5mm, grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s).

2.6 Statistical modelling

Pre-processed time series were modelled using a general linear model using FILM correcting for local autocorrelation (Woolrich et al., 2001). We used an event-related design. We built two separate models, a *semantic decision model* to look for brain changes during semantic decisions following different levels of cueing, and a *cue model* to identify brain regions that responded to the presentation of the cues. Our key focus was on the semantic decision model, since this established whether specific networks or gradient patterns were associated with making semantic decisions in the context of single or convergent cues. The *semantic decision model* included 8 EVs: correct semantic decisions following each of the 4 experimental conditions (0 cues, 1 cue affect, 1 cue location, 2 cues), non-semantic trials where strings of "Xs" were presented, remaining time in the semantic trials after making a decision before the start of a new trial, cue presentation period (combining all the cue presentation events, irrespective of the cue condition), and incorrect semantic trials. Given that this model revealed two distinct networks associated with the maintenance of single cues as opposed to no cues, and the convergence of multiple cues vs. a single cue, we then elected to examine the response during cue presentation in a second stage of the analysis. The *cue model* included 6 Explanatory Variables (EVs) corresponding to the 4 cue conditions (0 cue condition containing scrambled images, 1 face cue + scrambled image, 1 location cue + scrambled image, 2 cues: face and location), the semantic task, and the non-semantic task. The cue model established whether MDN regions responding to one > no cues showed load-dependent effects during cue encoding, consistent with increasing working memory demands of cue maintenance. However, it is important to acknowledge that the study was not designed to examine the cue phase in this fashion, and there are limitations of this exploratory analysis

– in particular, the study did not de-confound the order of the cue presentation and semantic decision phases, as cues were always followed by the semantic task (albeit separated by a jittered interval; see limitations in Discussion). All regressors were modelled using a variable epoch model, with the appearance of the words (or the cue images, for the *cue model*) as the start of the event and the response time (or the duration of the cue presentation) as the duration of the event. Convolution of the hemodynamic response was achieved using a Gamma function (phase = 0, SD = 3, mean = 6). Temporal derivatives were added to each regressor. Nuisance regressors included standard + extended motion parameters. Absolute framewise displacement ranged from 0.05 mm to 0.64, with a mean value of 0.21 mm across the 4 runs.

We then averaged contrast estimates over the four runs within each subject using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). The group analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $z > 3.1$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001). Our analysis focused on the comparison between semantic decisions which followed different levels of cue: 2 cues > 1 cue (collapsing across emotion and location cues) and 1 cue > 0 cues.

Cognitive decoding of the main contrasts of interest was performed in Neurosynth, an automated meta-analysis tool (Yarkoni et al., 2011). Unthresholded z maps were uploaded to Neurosynth to obtain psychological terms associated with the patterns of activation in our results. Where multiple terms had the same meaning (e.g. default, default mode, DMN, network DMN, default network), only the word with the highest correlation value was retained. This analysis provides additional evidence about the functional role of the regions within different maps, by comparing the results to previous studies which have reported similar patterns of activation.

Finally, we wanted to examine whether the observed pattern of BOLD response in DMN regions reflected the macroscale cortical organization captured by the principal gradient (Margulies et al., 2016). In line with previous studies by our group (Murphy et al., 2019, 2018), this analysis leverages the explanatory power of the unimodal to heteromodal gradient to account for differences between experimental conditions. Consistently with our predictions of greater DMN recruitment during information integration, we expected to observe a higher response in regions towards the heteromodal end of the gradient in the 2>1 contrast. Decile bins along the gradient were calculated using the methods outlined by Margulies et al. (2016). The original gradient map provided values from 0 to 100 for each voxel in the brain (0 = unimodal end; 100 = DMN). This map was then divided into ten-percentile bins: all voxels with values 0–10 were assigned to bin1; voxels with values 11–20 to bin 2, etc., yielding 10 bins in total. The total number of voxels in each bin was near-identical (each contained 6133 to 6135 voxels). This analysis provides unique insights by focusing on whole-brain patterns associated with particular aspects of cued semantic retrieval, as opposed to the role of specific brain regions. The analysis can establish whether peaks associated with cue integration across the cortex are located at the apex of the gradient from heteromodal to unimodal processing, in line with the expectation that heteromodal cortex supports information convergence.

3. Results

3.1 Behavioural results

A repeated measures ANOVA examining response efficiency revealed no significant differences across conditions [F(3,75) = .62, p = .605, η^2 = .02], indicating that semantic decisions following two cues were not easier than trials with less contextual support (one cue or no cue). The means and standard error for each condition are provided in Figure S4.1. and Table S4.1. (Supplementary Materials). There were also no significant differences between conditions in accuracy [F(3,75) = .14, p = .939, η^2 = .01], median response time [F(3,75) = .95, p = .420, η^2 = .04] or response time variability [F(3,75) = 1.26, p = .296, η^2 = .05]. All statistical values are provided in Table S4.2.

3.2 fMRI results

First, we report the whole-brain univariate results for models examining (i) how the BOLD response during semantic decision-making changes as a consequence of cues (semantic decision model) and (ii) the response to cue presentation (cue model). The coordinates for cluster peaks are reported in Table S4.3. (Supplementary Materials) and statistical maps are available in Neurovault (https://neurovault.org/collections/6198/). Next, to test one account of the response to single cues vs. no cues during semantic decision-making, we present a region of interest (ROI) analysis examining the response to different numbers of cues during cue presentation, in regions defined by the semantic decision model. This exploratory analysis establishes whether these regions behave in a load-dependent manner during cue encoding. Finally, we examine whether integration effects in DMN regions are captured by a macroscale gradient of cortical organization, using a series of ROIs positioned from the heteromodal to the unimodal end of this gradient. Figures were created using BrainNet Viewer (Xia et al., 2013; http://www.nitrc.org/projects/bnv/) and Surf Ice (https://www.nitrc.org/projects/surfice/).

3.2.1 Whole-brain results

Semantic decision model

Figure 4.2.A shows the contrast between uncued semantic decisions and responses to letter strings (also uncued), while Figure 4.3. shows the response to different cue contrasts (1 cue vs. 0 cues; 2 cues vs. 1 cue). The supplementary materials provide contrasts between semantic and letter string trials for each of the cue conditions separately (Figure S4.3.). These maps show a similar semantic response across conditions, which resembles the contrast of 0 cues over letter strings.

The contrast between semantic decisions without cues and non-semantic trials revealed activation in brain areas previously associated with semantic cognition (in studies that largely did not employ cues; e.g. Binder et al., 2009; Bright et al., 2004; Chee et al., 2000; Gold et al., 2005; Noonan et al., 2013b; Seghier et al., 2004; for reviews see Hoffman et al., 2018; Jefferies, 2013; Lambon Ralph et al., 2016), in left-hemisphere semantic areas such as inferior frontal gyrus and posterior temporal gyrus, as well as in medial temporal lobes, medial prefrontal and posterior cingulate cortex (Figure 4.2.A).

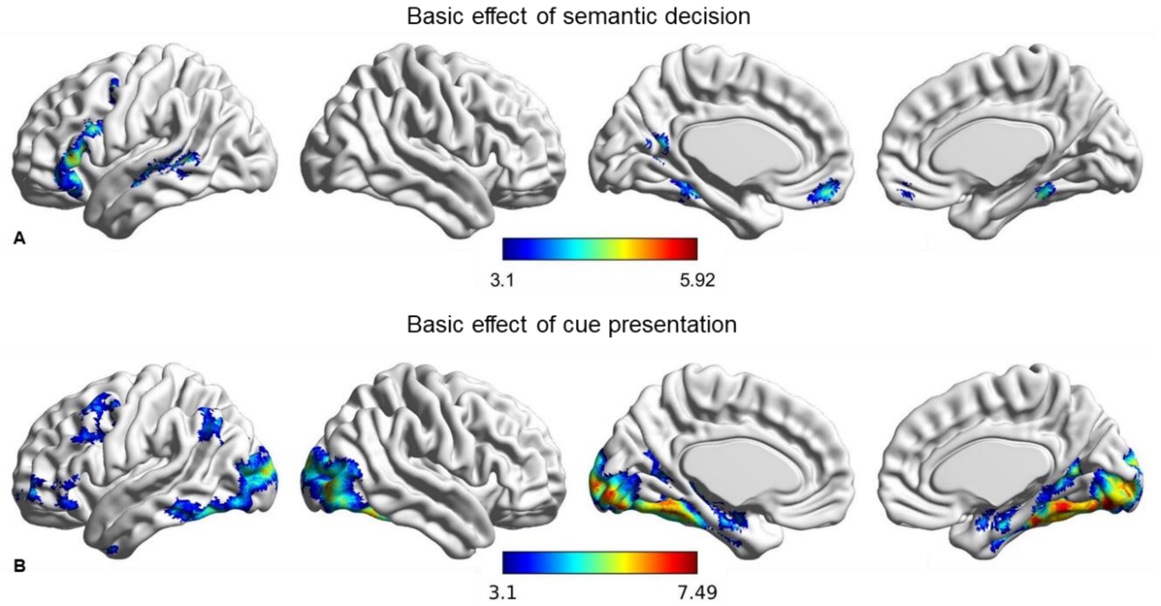

Figure 4.2. A Basic effect of uncued semantic decision (semantic no cue > letter strings at decision time period). **B** Basic effect of cue presentation (2 cues + 1 cue > 0 cue at cue time period). Coordinates of cluster peaks for these basic comparisons are reported in Table S4.3.

We then explored cueing effects by contrasting semantic decisions in the presence of different levels of constraint. The contrast of semantic decisions following 1 cue > 0 cues identified clusters in task-positive regions overlapping with the MDN (Duncan, 2010), consistent with the cognitive demands of maintaining cues. We found recruitment of inferior and middle frontal gyrus (with the peak in inferior frontal sulcus), precentral gyrus, bilateral paracingulate gyrus and pre-supplementary motor area, temporo-occipital cortex and visual cortex. Interestingly, the effect of multiple cues compared with a single cue (2>1) did not elicit stronger activation within these regions, even though the amount of information to be maintained was increased. Instead, this contrast elicited activation in regions overlapping with the DMN, including in bilateral angular gyrus/lateral occipital cortex, middle temporal gyrus, medial prefrontal cortex, posterior cingulate cortex, and left middle frontal gyrus. The thresholded maps for the two contrasts can be found in Figure 4.3.A. Parameter estimates for the three conditions over the implicit baseline were extracted in both the 1>0 cue and 2>1 cue regions (see Supplementary Figure S4.4.). Overall, 1>0 regions showed task-related activation (with more activation when cues had to be maintained in working memory, compared with the no cue condition) while 2>1 regions exhibited task-related deactivation (with less deactivation when people made semantic decisions following 2 convergent cues compared with 0 or 1 cue).

We examined the overlap of the contrast maps with published maps of the MDN (Duncan, 2010) and DMN (Yeo et al., 2011; Figure 4.3.C). Consistent with the hypothesized role of DMN in semantic integration, 36.2% of the total voxels in the 2>1 cue map overlapped with the DMN, while only 1% of voxels overlapped with MDN. For the 1>0 cue map, the opposite pattern was observed, with 31.8% of total voxels overlapping with MDN and only 2.4 % with DMN. We submitted the unthresholded z maps for the 2>1 and 1>0 cue contrasts to Neurosynth for cognitive decoding and produced word clouds using the top 10 terms positively associated with the maps (Figure 4.3.B). The terms recovered for the 2>1 and 1>0 cue maps suggest the involvement of DMN and MDN respectively. The contrast of 2 > 0 cues (Figure S4.3.), shows activation in regions overlapping with 1 > 0, such as left middle and inferior frontal gyrus, left middle temporal gyrus, but also in regions within the 2 > 1 map, such as left angular gyrus. This pattern of activation suggests that both cue mainteinance and cue integration might be visible in this map.

As the DMN is known to show anti-correlation with task-positive regions captured by the MDN (Blank et al., 2014; Davey et al., 2016; Fox et al., 2005), we also explored whether this would be the case for our contrast maps. In an independent sample of 86 participants, whole-brain connectivity maps for the 2>1 and 1>0 contrasts were generated using CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012). Full methods are in the Supplementary Materials. The analysis revealed two functionally distinct and anti-correlated networks, comprising DMN for the 2>1 cue contrast and MDN regions involved in domain-general executive control for the 1>0 cue contrast (Figure S4.5.).

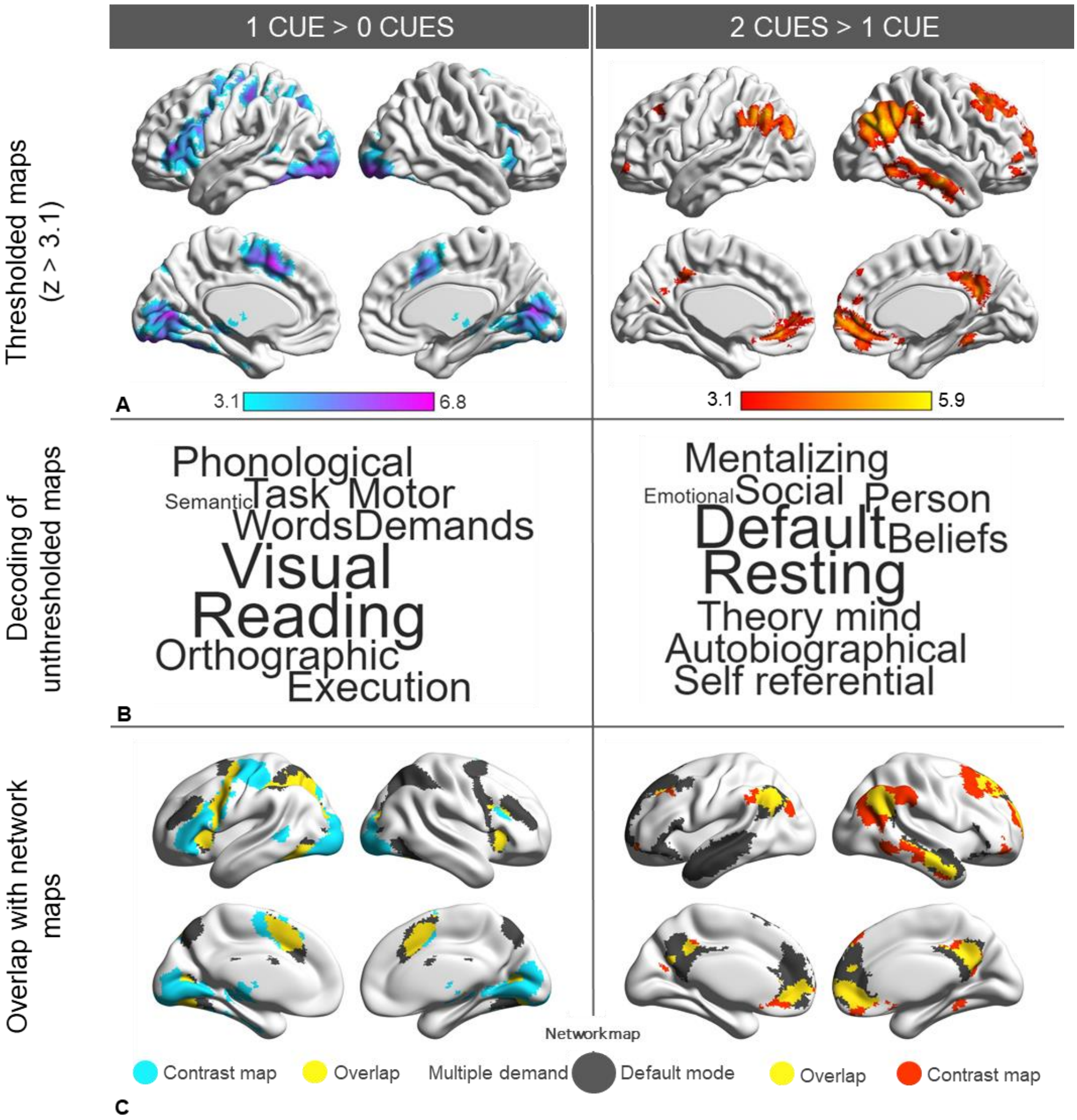

Figure 4.3. Results for the main contrasts of interest in the semantic decision model: the left side of the figure contains results for 1 cue > 0 cues, while the 2 cues > 1 cue contrast is shown on the right. **A** Contrast maps thresholded at z > 3.1. **B** Word clouds produced by plotting the top 10 terms positively associated with the contrast map. **C** Overlap of the 1 > 0 contrast with the multiple demand network (Duncan, 2010) and the contrast of 2 >1 with the default mode network (Yeo et al., 2011).

Cue model

To check whether the two distinct networks identified as relevant for conceptual cueing also showed different responses to load during the encoding of cue information, we constructed a second model to look at the cue presentation period. This was an exploratory analysis, since our main focus was on how cues modulate the neural basis of semantic decisions. Our paradigm was not designed to deconfound the order of the cues and the semantic decisions. Nevertheless, if the regions showing a stronger response to semantic decisions following 1 vs. 0 cues reflect the working memory demands of cue maintenance, we would expect to see load-dependent effects from cue encoding in these regions – i.e. stronger responses when more cues are presented.

First, we used a contrast of 2 cues + 1 cue > 0 cues across the whole brain to define the basic effect of cue presentation (see Figure 4.2.B). This elicited bilateral activation in occipital visual regions, extending into the posterior ventral stream in the left hemisphere. In addition, we found bilateral recruitment of the inferior frontal sulcus (IFS), within the multiple demand network, and the inferior frontal gyrus, in line with the idea of load demands of processing and maintaining cues (this interpretation is further explored in paragraph 3.2.2 'ROI analysis of cue load). Activation in the left hemisphere was also observed in AG.

The Supplementary Figure S4.2. shows other cue presentation contrasts. The contrast of 2 > 0 cue presentation revealed activation in occipital cortex and in left-hemisphere control regions. Similar control regions were recruited by the contrast of 2 > 1 cue presentation, although this map had less extensive activation overall. The contrast of 1 cue > 0 cue presentation revealed activity in visual regions largely overlapping with 2 cues > 0 cues, and a cluster in left angular gyrus. Finally, the contrast of 1 cue location > 1 cue affect recruited visual regions in occipital cortex and bilateral paracingulate gyrus, while the reverse contrast did not yield significant results.

3.2.2 ROI analysis of cue load

To test possible accounts of the different patterns of activation observed in the decision-making phase (*semantic decision model*) for the contrasts of 2 > 1 and 1 > 0 cues, we conducted a post-hoc ROI analysis of the activation in these regions prior to the decision, when the cues were on the screen (*cue model*). The recruitment of cognitive control areas (i.e. inferior and middle frontal gyrus, inferior frontal sulcus, precentral gyrus, anterior cingulate gyrus, and pre-supplementary motor area, falling within the multiple demand network) for semantic decisions that followed the presence vs. absence of cues (1 > 0 cues) suggests that these regions might be engaged in active maintenance of task-relevant information; in which case, cues might be processed in a load-dependent way during the cue period. To test this idea, the regions that responded to the contrasts of 1>0 and 2>1 cues during the semantic task (semantic decision model) were used to mask the BOLD response for cue presentation (cue model). We extracted and compared the parameter estimates for the three conditions against the implicit baseline: no cues (scrambled images), one cue (average of face emotion and location cue) and two cues (both face emotion and location image presented). If the semantic task activation observed for the 1>0 contrast reflects a demand-relevant state associated with maintaining the cues, then the activation of these regions during cue presentation should increase as the number of cues is increased; i.e. 2 cues > 1 cue, 1 cue > 0 cues. This is because information about the cues is required to be maintained from their onset. In contrast, regions responding more to semantic decisions following multiple cues (2>1 cues) might not be expected to show a load-dependent effect during the cue period. These regions responded more when multiple sources of information could be used to constrain semantic retrieval – and this form of information integration is unlikely to occur prior to the onset of the semantic decision (since the cues themselves were not easy to link in the absence of the probe concept – for example HAPPY FACE and SUPERMARKET are consistent with a wide range of concepts and do not strongly prime JAM). Consistent with these predictions, we found that activation in the 1>0 cue regions increased in a linear fashion with a higher number of cues [F (1, 25) = 48.39, p < .001, η^2 = .66] (Figure 4.4.A). However, there was no significant difference between cue conditions within regions responsive to the 2>1 cue contrast [F (2, 50) = .39, p = .682, η^2 = .02] (Figure 4.4.D).

The results of this ROI analysis show that regions responding more to semantic decisions following 1 > 0 cues also respond in a load-dependent way during the encoding of cue information. However, this ROI map includes both cognitive control regions within MDN and visual cortex, making it difficult to separate the effects of increasing visual stimulation from cognitive load. To further characterize the effect, we divided the 1 > 0 semantic decision map into regions that fell within the occipital cortex (Harvard-Oxford probabilistic map – 25%) and outside MDN regions (1997 voxels – Figure 4.4.B), and within MDN after masking out occipital regions (10658 voxels – Figure 4.4.C). The BOLD response showed a similar linear increase with the number of cues presented on the screen in visual cortex (F (1, 25) = 54.96, p < .001, η^2 = .69) and in MDN (F (1, 25) = 53.73, p < .001, η^2 = .68).

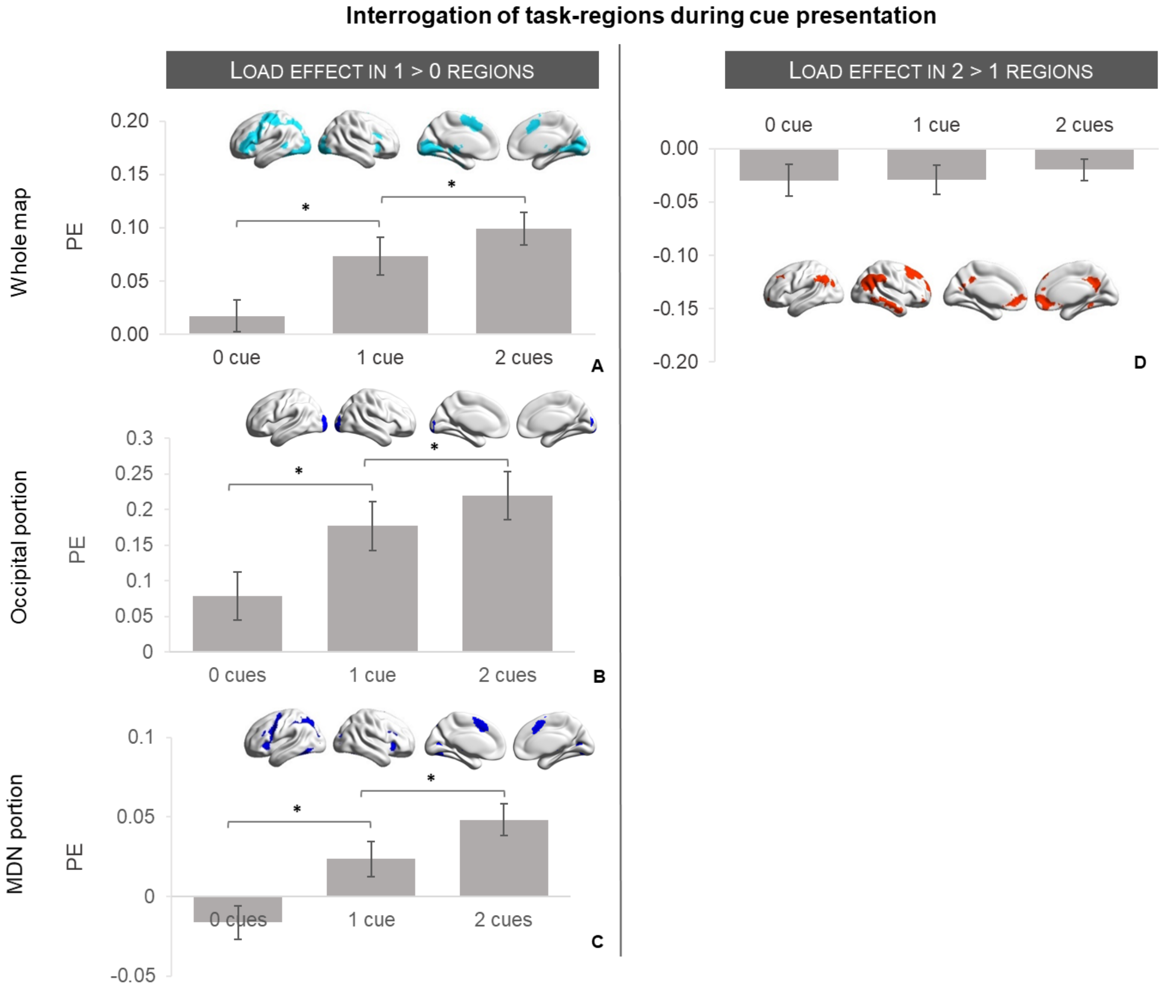

Figure 4.4. ROI analysis extracting the parameter estimates (PE) for the three levels of cue processing over the implicit baseline (cue model) in the 1 > 0 and 2 > 1 maps obtained in the semantic decision model. Three separate ROIs were conducted for the 1 > 0 regions (left panel): whole map (**A**), voxels that fell within the occipital cortex (**B**) and voxels that fell in the MDN (**C**). While the effect of number of cues is present in the 1 > 0 regions across the different masks used, no effect is observed in the integration regions (**D**) at the time-point of processing cue pictures. Bonferroni-corrected pairwise comparisons in the 1 > 0 regions confirmed that PE for 0 cues were significantly lower than 1 cue, and PE for 1 cue were significantly lower than 2 cues (all p values < .025; p value corrected for 2 multiple comparisons).

3.2.3 Gradient analysis

To further characterize the involvement of DMN regions in integrating information, we interrogated the response to semantic decisions along the Principal Gradient (Margulies et al., 2016). Unlike traditional univariate activation maps, which localize activation in certain regions, this gradient analysis examines how the effect of cueing unfolds along the entire cortical surface and measures the contribution of different portions of the gradient to the effects of interest. This analysis can highlight systematic functional change along the cortical surface, and explain why similar functional transitions are observed in multiple locations.

The gradient map was divided into 10-percentile bins (see Methods section) and each bin was used as a mask in ROI analyses where we extracted mean parameter estimates for the contrasts of 2 cues vs. 1 cue and 1 cue vs. 0 cues within each bin (see Figure 4.5.). We then explored the effect of gradient bin on each univariate contrast using a two-way repeated measure ANOVA with *cue contrast* (2 levels: 2 cues vs.1 cue and 1 cue vs. 0 cues) and *gradient bin* (10 levels) as within-subject variables. This analysis revealed a significant interaction of cue contrast and gradient bin (F(2, 51) = 28.33, p < .001, η^2 = .53), suggesting that the effect of gradient was different for 2 > 1 and 1 > 0 contrasts. Next, we performed two one-way repeated measure ANOVAs looking at the effect of *gradient bin* on each contrast separately. For 2>1 cues, we found a significant linear effect for gradient bin (F(1, 25) = 47.13, p < .001, η^2 = .65), as well as complex higher-order contrast effects (values reported in Table S4.5.). The comparison of semantic decisions following 2 vs. 1 cues elicited maximal activity at the heteromodal end of the gradient, suggesting that DMN regions at this end of the principal gradient responded more strongly when multiple sources of information were integrated to support semantic cognition. For 1>0 cues, we found the opposite pattern, with more activation at the unimodal end of the gradient for the single cue condition compared to when no cues were provided. Again, the effect of context vs. no-context along the principal gradient was complex, with linear (F(1, 25) = 24.80, p < .001, η^2 = .50), as well as higher-order contrasts reaching significance. Full details of the statistical outcomes are reported in Supplementary Tables S4.4., S4.5., S4.6.

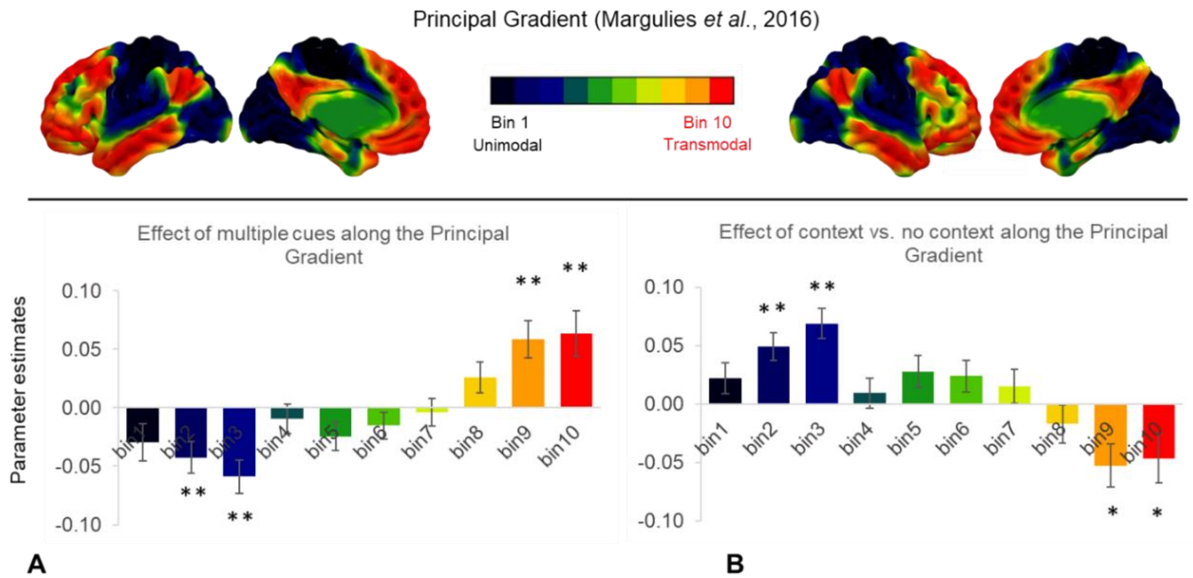

Figure 4.5. A Semantic decisions in the presence of multiple cues (contrast of 2>1 cues) maximally recruited regions at the heteromodal end of the principal gradient. **B** The effect of context vs. no context (contrast of 1>0 cues) showed an effect in the opposite direction, with maximal activation toward the sensory end of the gradient. ** Highlights portions of the gradient where the BOLD response is significantly different from 0 when the Bonferroni correction is applied (all p values ≤ .005), while * denotes p values < .05.

4 Discussion

Recent accounts of the default mode network (DMN) place this system at the top of a cortical hierarchy, maximally distant from unimodal sensory regions (Margulies et al., 2016) in both geodesic and connectivity space. The separation of heteromodal DMN regions from unimodal cortex may underpin our capacity to form conceptual representations that are not dominated by a particular type of feature but instead draw on multiple types of information – including affect or spatial location. To test this idea, we contrasted semantic decisions made following the presentation of multiple cues (depicting facial emotional expressions and locations), only one of these cues, or no cues. In this way, we manipulated the extent to which semantic retrieval occurred in a rich and meaningful context, in which multiple convergent features were available. Our results indicate that the cueing paradigm involved distinct mental processes that were supported by different networks. First, from the onset of the cues, information was maintained in working memory: MDN regions were activated for the contrast 1 cue > 0 cues, and the response of these regions during cue presentation was load-dependent. These findings are in line with previous research showing that the multiple demand network supports the maintenance of goal-relevant information (Duncan, 2010; Woolgar et al., 2011). Secondly, DMN regions were activated by the contrast 2 cues > 1 cue, consistent with a role of this network in convergent information integration. In line with our prediction that information integration occurs at the heteromodal end of the Principal Gradient, we found greater recruitment at this end when semantic decisions occurred in the presence of multiple cues. In contrast, activation was greater towards the unimodal end of the gradient (in regions overlapping with visual cortex) when semantic decisions were made in the presence vs. absence of cues. These novel findings provide important insights into the neural mechanisms supporting semantic integration and suggest a framework for understanding the location of these effects at the heteromodal end of the principal gradient.

According to “task-negative” accounts of the DMN, apparent semantic activation of this network occurs when an easy task is contrasted with a hard task (Humphreys et al., 2019, 2015; Humphreys and Lambon Ralph, 2015). This account is unlikely to provide an adequate explanation of our data since we found no behavioural differences between conditions (unlike other reports of cueing effects; Lanzoni et al., 2019; Noonan et al., 2010; Rodd et al., 2016, 2013). Our findings are instead consistent with a rich neuroimaging literature implicating ATL and AG in the formation of conceptual combinations. Integrating items (e.g. “jacket” and “plaid”) into coherent concepts (i.e. “plaid jacket”) modulates activity in AG regardless of the modality of presentation, while atrophy in this region results in impaired conceptual combinations (Price et al., 2015; see also Price et al., 2016). Similarly, magnetoencephalography (MEG) studies show increased activity in left ATL and AG for meaningful conceptual combinations (e.g. “red boat”) compared to the same words preceded by unpronounceable consonant strings (e.g. “xkq boat; Bemis and Pylkkänen, 2013, 2011; Pylkkänen, 2019), particularly when these combinations are more predictable or share more overlapping semantic features (Teige et al., 2019). Activation in the left superior ATL is also observed during semantic decisions following meaningful sentence cues, while IFG shows the opposite pattern (i.e. increased activation following irrelevant vs. relevant contexts), consistent with a role in semantic control (Hoffman et al., 2015). Moving beyond the language stimuli used in previous studies on conceptual combinations, here we show that semantic integration in DMN occurs for non-verbal material (i.e. pictures), in line with the heteromodal nature of these regions. Our findings uniquely add to this literature by showing that these effects of conceptual combination are maximal at the heteromodal end of the principal gradient, which situates DMN at the top of functional hierarchy (Margulies et al., 2016). Consequently, effects of information integration are seen not only in classic semantic regions such as AG and anterior middle temporal gyrus, but also in other DMN regions highlighted by our 2 > 1 cues contrast (e.g., superior frontal gyrus; medial prefrontal and posterior cingulate cortex).

The role of DMN in semantic cognition appeared to be largely restricted to the impact of convergent cueing during semantic decision-making: in contrast, a distinct anti-correlated network overlapping with MDN was associated with the selective attention and working memory demands of encoding and maintaining individual cues. Moreover, the basic effect of making semantic decisions in the absence of cues, relative to the letter string trials, did not reveal activation in DMN regions. At first, this result may seem at odds with accounts of the DMN that attribute a crucial role in semantic cognition to this network. However, our semantic task was considerably more demanding than the letter string baseline: studies have shown that although DMN regions can respond to the contrast of semantic vs. non-semantic tasks, they typically do so when the semantic task is not more demanding than the comparison task (Binder et al., 2009; Humphreys et al., 2015). Moreover, activation in DMN regions is often associated with ‘automatic’ patterns of retrieval or conceptual combinations (Bemis and Pylkkänen, 2013, 2011; Davey et al., 2016; Price et al., 2016; Teige et al., 2019), while our task required participants to match an ambiguous words to a target word while discarding distractors and as such, it might involve more ‘controlled’ aspects of retrieval supported by regions such as left IFG which lie outside DMN.

In line with other studies, we found that DMN regions responding to cue integration (i.e. the 2>1 cue contrast during semantic decisions) showed differential deactivation across conditions, relative to the implicit baseline, while MDN regions responding to cue maintenance (i.e. the 1>0 cue contrast during semantic decisions) showed differential activation. The functional significance of task-related deactivation is a topic of considerable debate; while some authors have interpreted deactivation as suggesting that sites are irrelevant to ongoing cognition (e.g. Humphreys et al., 2015), another possibility is that deactivation might be functionally relevant, as it might allow DMN regions to integrate information more selectively from task-relevant networks (Krieger-Redwood et al., 2016). According to this “cognitive tuning” hypothesis, we might expect more deactivation of DMN regions when only a limited set of features are relevant to ongoing cognition (for example, in the 0 and 1 cue conditions, when emotion and location representations are not necessarily task-relevant). There are already studies demonstrating that DMN regions can increase their coupling to cognitive control areas when harder tasks are contrasted with easier tasks, even as they deactivate (Krieger-Redwood et al., 2016; Vatansever et al., 2017b, 2015a).

The effect of convergent cueing was not found within one specific semantic region, such as AG, but across multiple distributed nodes of DMN. We then turned to the Principal Gradient of intrinsic connectivity to provide a potential explanation for why cue integration effects were observed where they were across the cortex. The separation between DMN and unimodal systems, captured by the Principal Gradient, is thought to (i) allow heteromodal representations to emerge (cf. Hub and Spoke account) and (ii) support forms of cognition that require separation from the external environment, such as states that draw on heteromodal representations in memory. The latter observation is particularly important for explaining the similarity of our results with recent findings from our group (Murphy et al., 2019, 2018). Using a 1-back/0-back paradigm, Murphy et al. showed that decisions based on the immediately available perceptual input (0 back condition) elicited higher activity towards the unimodal end of the Principal Gradient, while decisions drawing on information from memory (1 back condition) maximally recruited the heteromodal end of the gradient (Murphy et al., 2019). Critically, DMN involvement in memory-guided cognition was maximised when the decisions involved meaningful objects that were not perceptually-identical, increasing reliance on conceptual knowledge, relative to simpler unidimensional decisions based on colour (Murphy et al., 2018). Building on these findings, the results of the current study suggest that this pattern of activation within DMN arises because heteromodal cortex at the top end of the gradient supports the integration of disparate and convergent sources of information; these regions are more involved when we match meaningful objects based on their identities extracted from a multitude of features, as opposed to single features. Nevertheless, Murphy et al. also showed that tasks based on memory recruit representations at the heteromodal end of the gradient, even when these tasks only probe a single feature and therefore arguably do not place strong demands on information integration: this pattern might arise because in the absence of perceptual inputs, heteromodal regions may play a key role in generating patterns of cognition needed for the task (i.e., visual imagery). Importantly, the regions at the top of the gradient responded similarly to memory-based decisions irrespective of whether these decisions concerned colour or shape; in this way, the function of these sites still reflects the heteromodal nature of DMN. In contrast, distinct unimodal sites responsive to colour and shape are expected to support these decisions when perceptual information is present. In summary, the principal gradient relating to the separation of heteromodal from unimodal processing can potentially explain both the increased response in heteromodal DMN when cognition involves multiple convergent features, and the common response in heteromodal DMN when cognition involves decisions about single features in the absence of perceptual input.

There are a number of limitations of this study. It does not fully establish the form of the relationship between the number of cues and DMN activation at retrieval, since we did not manipulate cueing parametrically. Activation in DMN regions may not increase linearly with the number of cues (0, 1, 2 cues). Instead, the contrast of 1 > 0 cues elicits activation in MDN regions and towards the unimodal end of the principal gradient, suggesting that the presence vs. absence of context involves additional cue encoding and maintenance in working memory. A follow up study could use a parametric manipulation of the number of cues to better identify how responses in MDN and DMN scale with the number of cues. Moreover, in our experiment, integration unfolded over time, with semantic decisions occurring roughly 2 seconds after the presentation of the cue. A recent study by Branzi and others (2020) suggests that ventral AG supports the integration of meanings during time-extended narratives (see also Bonnici et al., 2016; Ramanan et al., 2017). Future research should establish whether semantic integration that emerges over time leads to a different pattern of activation along the principal gradient compared with the integration of simultaneously-presented information.

Furthermore, although our cueing paradigm allowed us to recover a set of regions within DMN recruited during semantic integration, it is unclear whether we would observe the same pattern of activation with other types of cues. Future studies could examine tasks that involve simple sensory features, for example, semantic decisions about concrete concepts such as DOG following visual and auditory feature cues (e.g. image of tail and sound of dog barking) to establish if a similar integration effect occurs in DMN. The current experiment used complex stimuli depicting emotional affect and locations, which are known to be relevant to the DMN. The DMN is closely associated with the classic limbic network for emotional processing (e.g. Chanes and Barrett, 2016; Greicius et al., 2003; Raichle et al., 2001; Simpson et al., 2000). Moreover, the hippocampus, which has strong functional ties with the default mode network (Andrews-Hanna et al., 2010; Kernbach et al., 2018; Leech and Sharp, 2014; Raichle et al., 2001) is known to play a role in representing spatial locations (Bellmund et al., 2016; Burgess, 2002; Burgess et al., 2002; Robin et al., 2018). Our findings demonstrate that when semantic decisions are made in the context of both emotional and spatial information, as opposed to only one of these cue types, DMN ramps up its response in line with its hypothesised role in higher-order information integration. Contrary to previous literature showing the recruitment of the parahippocampal place area for spatial scenes (e.g. Epstein and Kanwisher, 1998) and the fusiform face area for faces (e.g. Kanwisher et al., 1997), our contrasts of 1 cue type over the other aligned only partially with previous evidence. The failure to reach statistical significance for the contrast of 1 cue affect > 1 cue location could reflect a lack of statistical power, since much of the data acquisition was devoted to the semantic decisions. Moreover, the different size and aspect ratio of the images (with location images being wider and larger) may have influenced the results.

A final limitation of the study concerns the statistical model used to examine activation during cue presentation, which was used to test possible interpretations of the univariate results in the main model in a post-hoc fashion. As the experiment was not originally designed to look at the cue presentation, we did not include trials in which facial expressions and location cues were not followed by semantic decisions. Whenever a meaningful cue picture was presented, this was always followed by a semantic decision. The inclusion of trials where cues were followed by a blank screen would have facilitated the temporal separation of the cue and task events, allowing us to draw stronger conclusions from the cue model. In this way, future research could directly test the idea that integration requires a component of maintenance supported by the MDN, in addition to a combination of conceptual features within DMN.

5. Supplementary materials

Group behavioural performance

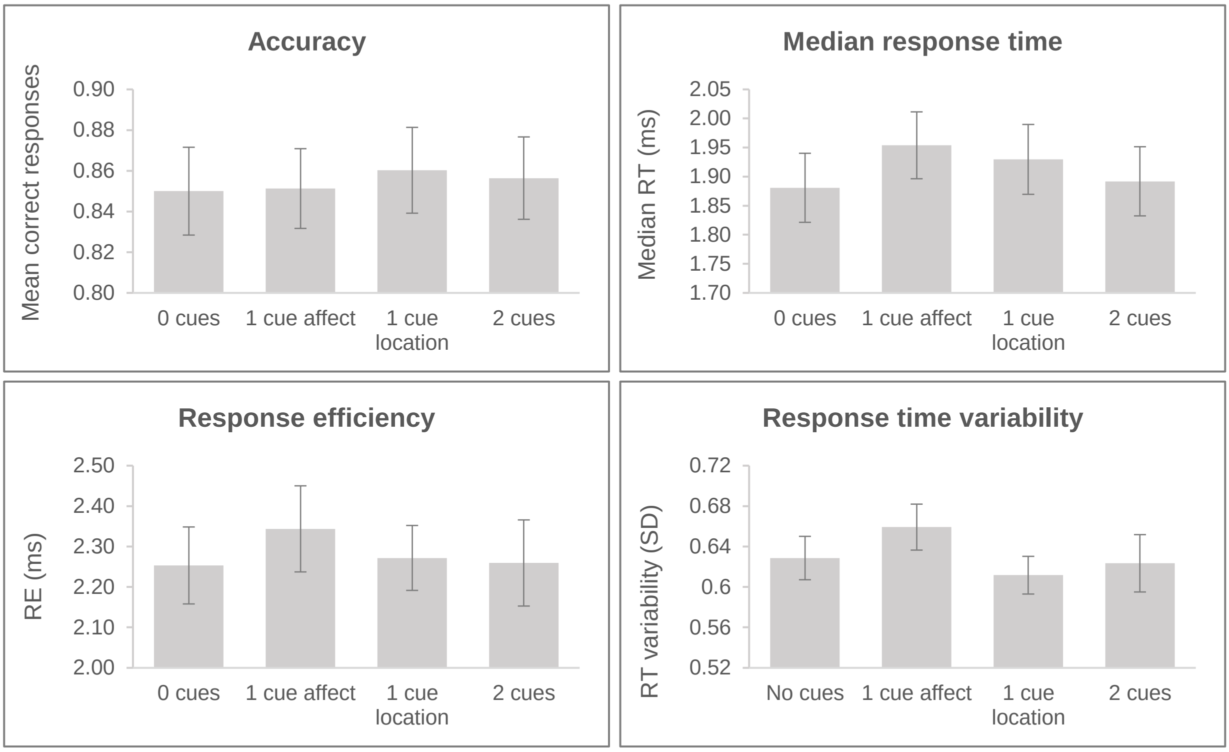

Figure S4.1. Accuracy (mean correct responses), median RT for correct trials (milliseconds), response efficiency scores (median RT/mean correct responses), and RT variability (mean standard deviation per participant per condition) do not differ significantly across conditions. Error bars show standard error of the mean (SEM).

Summary statistics

	Accuracy	**Median RT**	**Response efficiency**	**RT variability**
0 cues	0.85 (0.11)	1.88 (0.30)	2.25 (0.49)	0.63 (0.11)
1 cue affect	0.85 (0.10)	1.95 (0.29)	2.34 (0.54)	0.66 (0.12)
1 cue location	0.86 (0.11)	1.93 (0.31)	2.27 (0.41)	0.61 (0.10)
2 cues	0.86 (0.10)	1.89 (0.30)	2.26 (0.54)	0.62 (0.14)

Table S4.1. Descriptive statistics for the cueing task. Mean and (standard deviation) values are provided.

Supplementary behavioural analyses

1- way repeated measures ANOVAs on cue condition

	Accuracy	Median RT	Response efficiency	RT variability
F	0.14	0.95	0.62	1.26
df	3, 75	3, 75	3, 75	3, 75
p	0.939	0.420	0.605	0.296
partial η2	0.01	0.04	0.02	0.05

Table S4.2. Behavioural performance did not differ significantly across cue conditions, as revealed by 1-way ANOVAs on accuracy, median response time, response efficiency, and response time variability.

Univariate contrasts of activation during cue presentation

Below we report the group-level statistical maps ($z > 3.1$) for the cue model. In this model we looked at changes in the BOLD response in response to the presentation of the visual cues. Semantic decisions (which happen subsequently to the presentation of cues) were modelled separately; the statistical maps that survived the threshold of $z > 3.1$ can be seen in the body of the manuscript (Figure 4.2.A and 4.3.).

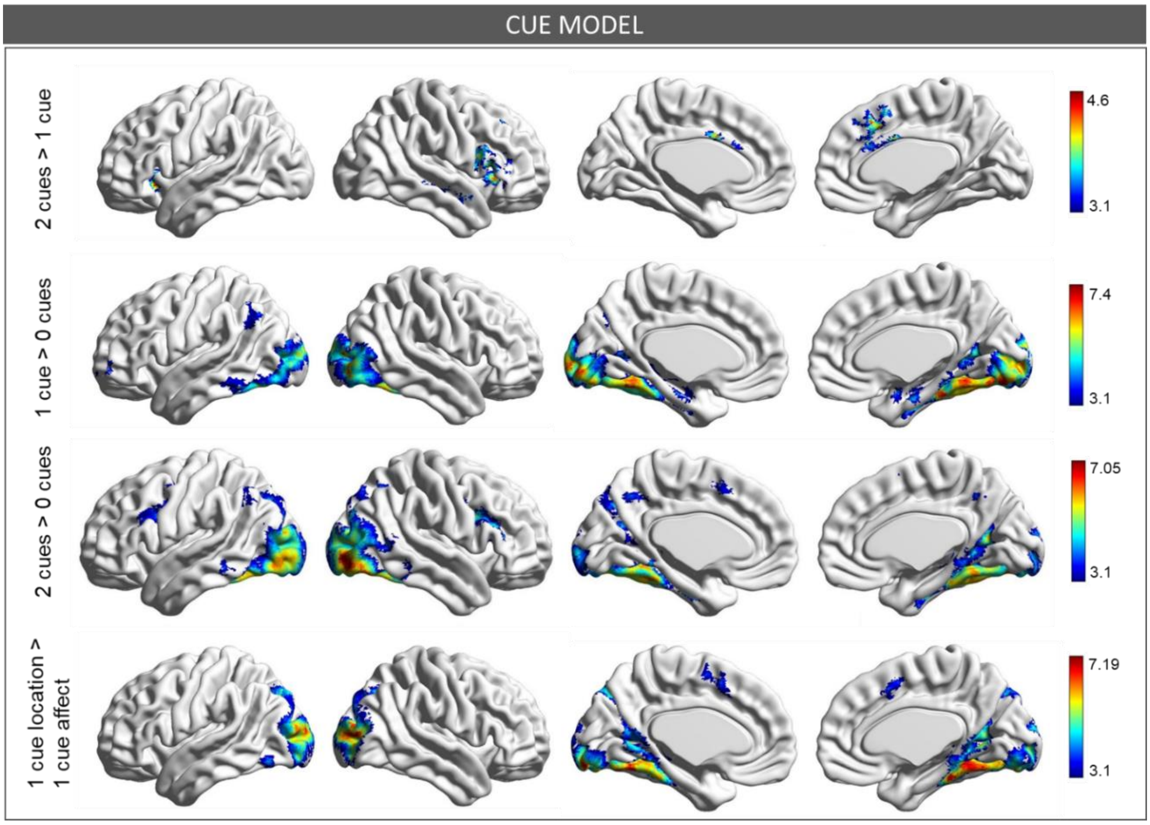

Figure S4.2. Univariate results for the cue model (i.e. when the cues were presented, prior to the semantic decision). From top to bottom: 2 cues > 1 cue (processing of 2 cues > 1 cue [average of affect and location]), 1 cue > 0 cues (processing of 1 cue [average of affect and location] > 0 cues [scrambled images]); 2 cues > 0 cues; 1 cue location > 1 cue affect. The reverse contrast (1 cue affect > 1 cue location) yielded no clusters. Coordinates of cluster peaks for these comparisons are reported in Table S4.3.

Basic effect of semantic decisions

In the main manuscript we defined the semantic regions recruited during the task using a contrast of 0 cues > letter strings (Figure 4.2.A). Below we report the contrasts of each of the other task conditions against the presentation of letter strings (i.e. non semantic task).

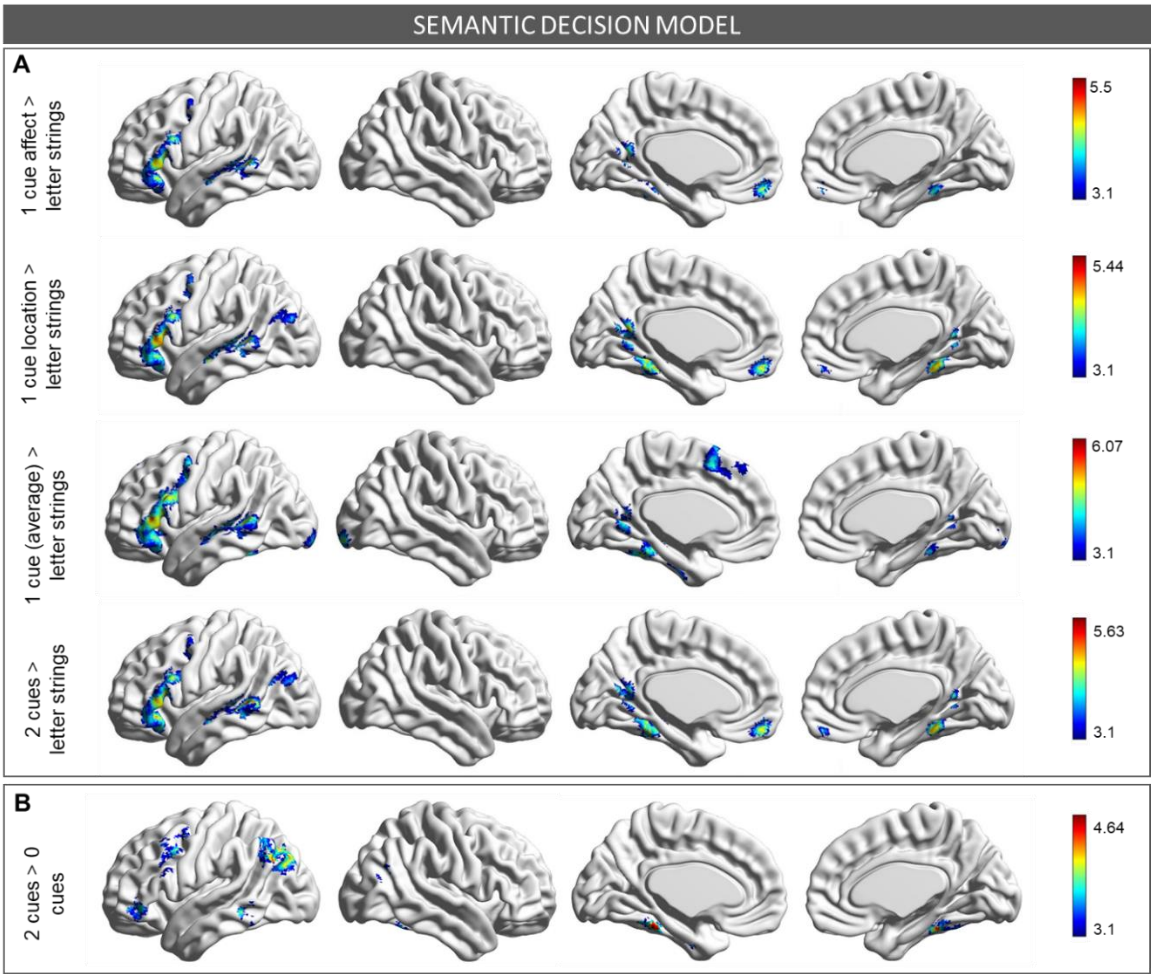

Figure S4.3. A Basic effect of semantic decisions as estimated by contrasts of the task conditions > letter strings (i.e. non-semantic task). These univariate contrasts for the semantic decision model (i.e. when participants were making decisions following the presentation of 0, 1, 2 cues) reveal a similar pattern of activation. **B** Semantic decisions following 2 cues vs. 0 cues.

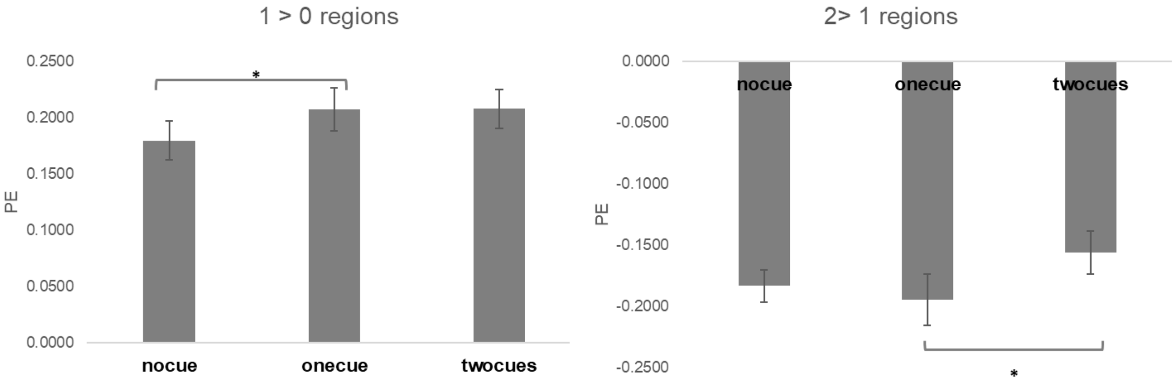

Figure S4.4. ROI analysis extracting the parameter estimates (PE) for the three conditions over the implicit baseline at the time of making semantic decisions (semantic decision model) in the 1 > 0 and 2 > 1 maps. We ran two repeated measures ANOVAs that found that the recruitment is different across cueing conditions in both 1 > 0 [F (2,50) = 3.36, p = .043, $\eta^2 = .12$] and 2 > 1 [F (2,50) = 3.47, p = .039, $\eta^2 = .12$] regions. Bonferroni-corrected pairwise comparisons revealed reduced activation for 0 cue condition compared to 1 cue in 1 > 0 regions [t(25) = -2.59, p = .016], and reduced de-activation in 2 cues compared to 1 cue in 2 > 1 regions [t(25) = -3.03, p = .006].

Peak co-ordinates for clusters identified by the cue model and semantic decision model

Contrast	Region	Voxels	Z-score	MNI coordinates (x, y, z)		
	Cue model					
2 + 1 > 0	R. Lingual gyrus, occipital fusiform gyrus, occipital pole	26628	7.49	8	-82	-12
	L. Middle frontal gyrus, superior frontal gyrus	769	4.51	-36	22	54
	L. Frontal pole	766	4.99	-42	54	-4
	L. temporal pole, inferior temporal gyrus (anterior), temporal fusiform gyrus (anterior)	130	4.29	-42	4	-42
2 > 0	R. Lateral occipital cortex (inferior), occipital pole	21099	7.05	42	-86	-8
	R. Precentral gyrus, inferior frontal gyrus, middle frontal gyrus	866	5.11	38	10	28
	L. Inferior frontal gyrus (pars opercularis), precentral gyrus, middle frontal gyrus	850	4.63	-40	16	22
	Bilateral precuneus	189	4.11	0	-56	46
	L. Supplementary motor cortex, paracingulate gyrus, superior frontal gyrus	177	4.29	-4	6	54
2 > 1	R. Frontal operculum cortex, inferior frontal gyrus (pars opercularis), inferior frontal gyrus (pars triangularis)	940	4.48	46	18	6
	R. Paracingulate gyrus, superior frontal gyrus, cingulate gyrus (anterior)	585	4.38	6	24	44
	R. Middle frontal gyrus, superior frontal gyrus, frontal pole	267	4.55	28	32	44
	R. Superior temporal gyrus (anterior), middle temporal gyrus (anterior), superior temporal gyrus (posterior), middle temporal gyrus (posterior)	199	4.35	54	-6	-16

	L. Insular cortex	152	4.51	-28	20	-6
1 > 0	R. Occipital fusiform gyrus, lingual gyrus	21130	7.38	24	-72	-14
	L. Lateral occipital cortex (superior), angular gyrus	229	4	-50	-66	40
	L. Frontal pole	229	4.51	-40	58	2
	R. Cerebellum	198	4.24	28	-74	-44
1 location > 1 affect	R. Occipital pole, lateral occipital cortex	17891	7.19	36	-88	8
	Bilateral paracingulate gyrus, supplementary motor cortex	411	4.31	0	10	50
	Semantic decision model					
0 > letter strings	L. Inferior frontal gyrus (pars triangularis), frontal pole, middle frontal gyrus	1672	5.92	-54	32	8
	L. Superior temporal gyrus (posterior), middle temporal gyrus (posterior), supramarginal gyrus (posterior)	953	5.52	-56	-42	4
	R. Cerebellum	644	5.04	10	-82	-36
	L. Temporal fusiform cortex (posterior), parahippocampal gyrus (posterior), inferior temporal gyrus (posterior)	400	4.51	-38	-30	-18
	L. Cerebellum	280	4.62	-8	-60	14
	L. Frontal medial cortex, frontal pole	256	4.66	-4	52	-16
	R. Temporal occipital fusiform, Lingual gyrus, parahippocampal gyrus (posterior)	220	4.91	22	-42	-16
	L. Precentral gyrus, middle frontal gyrus	153	4.7	-38	0	46
1 affect > letter strings	L. Inferior frontal gyrus (pars triangularis), frontal pole, middle frontal gyrus	1684	4.91	-56	32	6
	L. Middle temporal gyrus (temporo-occipital part), middle temporal gyrus (posterior)	926	5.5	-56	-44	4
	R. Cerebellum	571	4.81	10	-82	-36
	L. Temporal fusiform (posterior), parahippocampal gyrus (posterior), inferior temporal gyrus (posterior)	261	4.2	-38	-30	-18
	L. Precuneus, intracalcarine cortex, supracalcarine cortex, cingulate gyrus (posterior)	258	4.65	-8	-60	14
	L. Medial frontal cortex, frontal pole	186	4.6	-2	52	-16
	R. Temporal fusiform (posterior), parahippocampal gyrus (posterior), lingual gyrus	138	4.19	24	-38	-18
	L. Precentral gyrus, middle frontal gyrus	125	4.11	-38	0	44
1 location > letter strings	L. Inferior frontal gyrus (pars triangularis), frontal pole, middle frontal gyrus	2000	5.44	-56	32	8
	L. Middle temporal gyrus (temporo-occipital part), middle temporal gyrus (posterior)	1107	5.04	-58	-44	4
	R. Cerebellum	910	5.12	12	-78	-30
	L. Temporal fusiform (posterior), parahippocampal gyrus (posterior), inferior temporal gyrus (posterior)	773	5.06	-38	-30	-18
	L. Precuneus, intracalcarine cortex, lingual gyrus, supracalcarine cortex, cingulate gyrus (posterior)	723	4.93	-8	-60	10

	R. Lingual gyrus, occipital fusiform gyrus, parahippocampal gyrus (posterior), temporal fusiform (posterior)	375	5.4	20	-40	-16
	L. Medial frontal cortex, frontal pole	230	4.71	-2	52	-16
	L. Precentral gyrus, middle frontal gyrus	205	4.61	-38	0	44
	L. Lateral occipital cortex (superior)	176	3.97	-44	-84	26
1 > letter strings	L. Inferior frontal gyrus (pars triangularis), frontal pole, middle frontal gyrus	3459	5.65	-54	30	8
	L. Middle temporal gyrus (temporo-occipital part), middle temporal gyrus (posterior)	2493	5.41	-56	-44	4
	R. Cerebellum	1165	6.07	12	-78	-28
	L. Precuneus, lingual gyrus, intracalcarine cortex, cingulate gyrus (posterior), supracalcarine cortex	371	4.73	-6	-58	8
	L. Paracingulate gyrus, superior frontal gyrus, juxtapositional lobule	337	4.56	-6	14	52
	R. Occipital pole	275	4.89	18	-100	-12
	L. Occipital pole	235	4.91	-34	-98	-14
	R. Precuneus, lingual gyrus, intracalcarine cortex, cingulate gyrus (posterior), supracalcarine cortex	127	4.54	14	-56	6
	R. temporal fusiform (posterior), parahippocampal gyrus (posterior), lingual gyrus	118	4.37	28	-36	-20
2 > letter strings	L. Inferior frontal gyrus (pars triangularis), frontal pole, middle frontal gyrus	2239	5.51	-56	32	8
	L. Middle temporal gyrus (temporo-occipital), middle temporal gyrus (posterior), supra-marginal gyrus (posterior), , superior temporal gyrus (posterior)	1175	5.63	-48	-44	-2
	R. Cerebellum	794	4.79	10	-82	-34
	L. Temporal fusiform (posterior), temporal occipital fusiform, parahippocampal gyrus (posterior), lingual gyrus	695	4.95	-26	-42	-20
	L. Precuneus, lingual gyrus, intracalcarine cortex, cingulate gyrus (posterior), supracalcarine cortex	458	4.77	-8	-58	10
	R. Temporal occipital fusiform, Lingual gyrus, temporal fusiform (posterior), parahippocampal gyrus (posterior)	367	5.6	22	-40	-16
	L. Angular gyrus, lateral occipital cortex (superior), lateral occipital cortex (inferior)	265	4.4	-40	-60	18
	L. Frontal medial cortex, frontal pole	237	4.82	-2	52	-16
	R. Precuneus, Intracalcarine cortex, cingulate gyrus (posterior), lingual gyrus, supracalcarine cortex	201	4.67	16	-54	8
2 > 1	R. Lateral occipital cortex (superior)	5247	5.94	52	-70	30
	R. Frontal pole, paracingulate gyrus, frontal medial cortex	4395	5.57	4	56	0
	L. lateral occipital cortex (superior), angular gyrus, supramarginal gyrus (posterior)	1639	5.27	-50	-62	42
	R. Precuneus, cingulate gyrus (posterior)	1521	5.17	8	-56	26
	L. Cerebellum	745	4.77	-26	-78	-36
	L. Middle frontal gyrus	304	4.46	-36	26	42

	R. Frontal pole	191	4.35	40	48	-10
	L. Frontal pole	172	4.33	-30	62	-2
	R. Temporo-occipital fusiform, lingual gyrus, parahippocampal gyrus	143	4.72	24	-42	-16
1 > 0	R. Cerebellum	30503	6.81	4	-74	-28
	L. Supplementary motor cortex, paracingulate gyrus, superior frontal gyrus, cingulate gyrus (anterior)	2167	6.57	-4	8	52
	R. Inferior frontal gyrus (pars opercularis), middle frontal gyrus, inferior frontal gyrus (pars triangularis), precentral gyrus	714	5.59	42	22	20
	L. Middle temporal gyrus (temporo-occipital), supra-marginal gyrus (posterior), middle temporal gyrus (posterior), superior temporal gyrus	254	4.85	-56	-46	4
2 > 0	L. Lateral occipital cortex (superior), angular gyrus	1431	4.55	-46	-66	32
	R. Lateral occipital cortex (inferior), occipital fusiform gyrus	533	4.55	38	-74	-24
	L. Middle frontal gyrus, precentral gyrus, inferior frontal gyrus (pars opercularis)	472	4.04	-46	12	40
	L. Temporal fusiform cortex (posterior), temporal occipital fusiform cortex, parahippocampal gyrus (posterior)	441	4.64	-26	-40	-20
	L. Occipital fusiform gyrus	283	4.55	-46	-72	-26
	L. Frontal pole, frontal orbital cortex, inferior frontal gyrus (pars triangularis)	153	3.94	-52	40	-8
	L. Middle temporal gyrus (posterior), middle temporal gyrus (temporooccipital)	128	3.97	-60	-40	-8
	R. Lateral occipital cortex (superior), angular gyrus	125	3.94	52	-64	24

Table S4.3. Coordinates of cluster peaks for the main contrasts of interest. From top to bottom: cue model – 2 + 1 > 0 (processing of cues > scrambles images), 2 > 0 (processing of 2 cues [affect and location] > 0 cues [scrambled images]), 2 > 1 (processing of 2 cues [affect and location] > 1 cue [average of affect and location]), 1 > 0 (processing of 1 cue [average of affect and location] > 0 cues [scrambled images]), 1 affect > 1 location; semantic decision model - 0 cues > letter strings (semantic decisions in the absence of a semantic cue > non semantic decisions in the absence of cues), 1 affect > letter strings, 1 location > letter strings, 1 > letter strings (semantic decision following 1 cue [average of affect and location] > non semantic decisions in the absence of cues), 2 > letter strings, 2 > 1 (semantic decisions following multiple cues > semantic decisions following 1 cue), 1 > 0 (semantic decisions following 1 semantic cue > semantic decisions in the absence of a semantic cue). The location of the peaks is labelled according to the Harvard-Oxford Structural Cortical Atlas tool available in FSL. Caption: R = right hemisphere, L = left hemisphere, cluster corrected at z > 3.1.

Supplementary analyses examining activation for the semantic task along the Principal Gradient

2 (cue contrast: 2 vs. 1, 1 vs. 0) x 10 (gradient bin: bin1 - bin10) ANOVA

	Test of within-subjects effect			Test of within-subjects contrasts			
	Cue contrast	Gradient bin	Cue contrast x gradient bin	Cue contrast	Gradient bin	Cue contrast x gradient bin	
F	0.33	1.82	28.33	0.33	1.53	37.27	Linear
p	.571	.164	<.001*	.571	.227	<.001*	
partial η^2	0.01	0.07	0.53	0.01	0.06	0.60	
F					0.06	12.37	Quadratic
p					.815	.002*	
partial η^2					0.00	0.33	
F					2.26	6.47	Cubic
p					.145	.018*	
partial η^2					0.08	0.21	
F					0.79	0.28	Order 4
p					.382	.601	
partial η^2					0.03	0.01	
F					20.44	111.60	Order 5
p					<.001*	<.001*	
partial η^2					0.45	0.82	
F					1.06	9.51	Order 6
p					.312	.005*	
partial η^2					0.04	0.28	
F					5.07	38.85	Order 7
p					.033*	<.001*	
partial η^2					0.17	0.61	
F					2.50	64.54	Order 8
p					.127	<.001*	
partial η^2					0.09	0.72	
F					1.07	66.73	Order 9
p					.311	<.001*	
partial η^2					0.04	0.73	

Table S4.4. Values for the 2-way repeated measure ANOVA on cue contrast (2 levels: 2 cues > 1 cue; 1 cue > 0 cues) and gradient bin (10 levels: bin1 – bin10). Degrees of freedom for the Test of Within-subjects Effects: cue condition [1, 25]; gradient bin [2.37, 59.16]; cue contrast x gradient bin [2.04, 51.01]. Degrees of freedom for the Test of Within-subjects Contrasts: cue contrast, gradient bin, cue contrast x gradient bin [1, 25]. Significant results and interactions are marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

1 way RM ANOVA on 2 cues > 1 cue along the gradient

	Test of within-subjects effect	Test of within-subjects contrasts	
	Gradient bin	Gradient bin	
F	31.50	47.13	Linear
p	<.001*	<.001*	
partial η^2	0.56	0.65	
F		11.38	Quadratic
p		.002*	
partial η^2		0.31	
F		3.03	Cubic
p		.094	
partial η^2		0.11	
F		0.06	Order 4
p		.813	
partial η^2		0.00	
F		70.22	Order 5
p		<.001*	
partial η^2		0.74	
F		7.66	Order 6
p		.010*	
partial η^2		0.23	
F		31.30	Order 7
p		<.001*	
partial η^2		0.56	
F		48.60	Order 8
p		<.001*	
partial η^2		0.66	
F		50.58	Order 9
p		<.001*	
partial η^2		0.67	

Table S4.5. Values for the 1-way repeated measure ANOVA on the parameter estimates for the univariate contrast of 2 cues > 1 cue extracted along the gradient (10 levels: bin1 – bin10). Degrees of freedom for the Test of Within-subjects Effects: 2.13, 53.30. Degrees of freedom for the Test of Within-subjects Contrasts: 1, 25. Significant results and interactions are marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

1 way RM ANOVA on 1 cue > 0 cues along the gradient

	Test of within-subjects effect	Test of within-subjects contrasts	
	Gradient bin	Gradient bin	
F	21.37	24.80	Linear
p	<.001*	<.001*	
partial η^2	0.46	0.50	
F		11.48	Quadrati
p		.002*	
partial η^2		0.31	
F		7.44	Cubic
p		.011*	
partial η^2		0.23	
F		0.52	Order 4
p		.478	
partial η^2		0.02	
F		116.31	Order 5
p		<.001*	
partial η^2		0.82	
F		8.61	Order 6
p		.007*	
partial η^2		0.26	
F		40.27	Order 7
p		<.001*	
partial η^2		0.62	
F		62.44	Order 8
p		<.001*	
partial η^2		0.71	
F		64.32	Order 9
p		<.001*	
partial η^2		0.72	

Table S4.6. Values for the 1-way repeated measure ANOVA on the parameter estimates for the univariate contrast of 1 cue > 0 cues extracted along the gradient (10 levels: bin1 – bin10). Degrees of freedom for the Test of Within-subjects Effects: 2.05, 51.22. Degrees of freedom for the Test of Within-subjects Contrasts: 1, 25. Significant results and interactions are marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

Analysis of intrinsic connectivity

As there is evidence that DMN is anti-correlated with task-positive regions captured by MDN (Blank et al., 2014; Davey et al., 2016; Fox et al., 2005), we predicted that our contrast maps of 1 > 0 and 2 > 1 should fall within regions with distinct patterns of intrinsic connectivity at rest, given their spatial similarity with the MDN and with the DMN, respectively.

Materials and Methods

Participants

Whole-brain intrinsic connectivity maps for the two contrasts (1 > 0 and 2 > 1) were produced using a sample of 86 participants recruited as part of a different study. The study was approved by the Ethics Committees of the York Neuroimaging Centre and the Department of Psychology, University of York. Volunteers provided written consent and were debriefed after the experiment.

MRI data acquisition

Structural and functional MRI data were acquired using a 3T GE HDx Excite MRI scanner at the York Neuroimaging Centre, University of York. Structural MRI acquisition was based on the same protocol used for the main sample of this experiment (see Materials and Methods– *fMRI acquisition*). Resting-state fMRI data was recorded from the whole brain using single-shot 2D gradient-echo-planar imaging (TR=3s, TE=minimum full, flip angle=90°, matrix size=64x64, 60 slices, voxel size=3x3x3mm3, 180 volumes). Participants were asked to passively view a fixation cross and not to think of anything in particular for the duration of the resting-state scan (9 minutes). A T1 weighted FLAIR scan with the same orientation as the functional scans was collected to improve co-registration between subject-specific structural and functional scans (TR=2560ms, TE=minimum full, matrix size=64x64, voxel size=3x3x3mm3).

Pre-processing

The pre-processing of resting state data was performed using the CONN functional connectivity toolbox V.18a (http://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon, 2012). The following steps were performed on the functional volumes: (1) slice-time (bottom-up, interleaved) and motion-correction, (2) skull-stripping and co-registration to the high-resolution structural image, (3) spatial normalisation to Montreal Neurological Institute (MNI) space using the unified-segmentation algorithm, (4) smoothing with a 6mm FWHM Gaussian kernel, and (5) band-passed filtering (0.008-0.09Hz) to reduce low-frequency drift and noise effects. Nuisance regressors in the pre-processing pipeline included: (i) motion (12 parameters: the six translation and rotation parameters and their temporal derivatives), (ii) scrubbing (outliers were identified through the artefact detection algorithm included in CONN based on scan-by-scan change in global signal above z=3, subject motion threshold above 5mm, differential motion and composite motion exceeding 95% percentile in the normative sample), (iii) CompCor components (the first 5) attributable to the signal from white matter and CSF (Behzadi et al., 2007), and (iv) a linear detrending term, eliminating the need for global signal normalisation (Chai et al., 2012; Murphy et al., 2009).

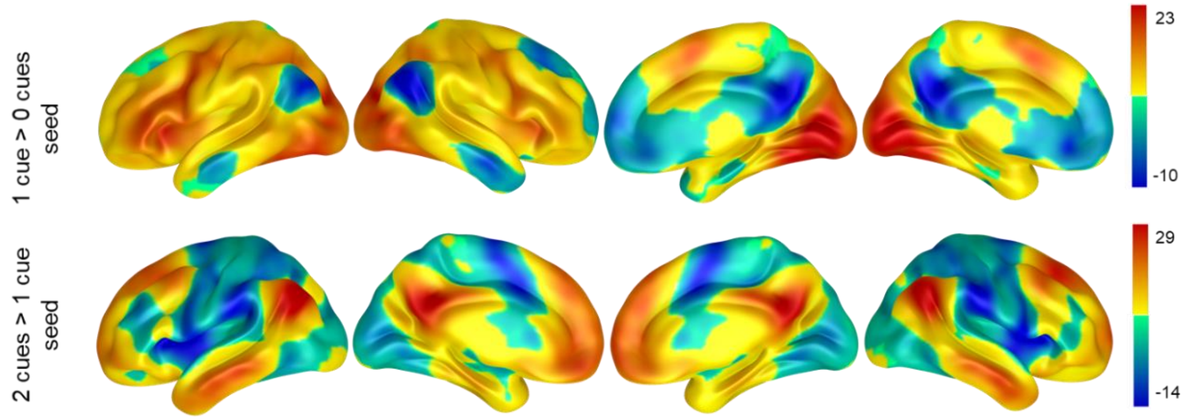

Figure S4.5. Intrinsic connectivity maps obtained in a separate sample of 86 participants using the thresholded (z > 3.1) contrast maps of 2 cues > 1cue and 1 cue > 0 as seeds in a resting state analysis. These reveal two functionally distinct and anti-correlated networks, comprising multiple demand regions for 1>0 and default mode regions for 2>1.

Chapter 5. Individual differences in semantic cueing and their relationship to intrinsic connectivity measured with resting-state fMRI

The findings described in Chapter 4 suggest that our cueing paradigm involves distinct mental processes that are supported by different networks. We found evidence that the maintenance of cues in working memory involves regions within the multiple demand network, while the integration of convergent sources of conceptual information is supported by the default mode network. Having examined the neural bases of semantic integration, here we explored the extent to which individual differences in the patterns of intrinsic connectivity of these large scale networks may relate to behavioural differences in the cueing task. We hypothesize that the strength and directionality of connections between the two networks supporting different aspects of semantic integration and the rest of the brain will influence peoples' ability to efficiently (i) maintain currently-relevant information and (ii) integrate convergent conceptual representations. To test these hypotheses, we examined intrinsic connectivity measured through resting-state fMRI, combined with measures of behavioural efficiency obtained outside the scanner. Compared to task-based fMRI analyses, which localize cognitive processes by describing the relative changes in the BOLD signal in response to a task, functional connectivity can capture interactions between spatially distinct regions. By combining seed-based analyses of intrinsic connectivity and behavioural measures we aim to provide complementary insights into the functional architecture of semantic integration.

Acknowledgments and authors' contribution

Lucilla Lanzoni, Prof. Elizabeth Jefferies, and Prof. Jonathan Smallwood developed the main ideas in this chapter. The experimental paradigm was developed by Lucilla Lanzoni and has recently been published in Lanzoni et al. (2020). Fiona Lancelotte helped with the data collection as part of her final year UG project. Lucilla Lanzoni completed the data collection, implemented the statistical analyses, interpreted the results, wrote and edited the chapter. Dr. Gonzalez-Alam and Dr. Krieger-Redwood provided technical advice on seed-based connectivity analyses. Prof. Jefferies helped editing drafts of this chapter.

Abstract

Flexible semantic cognition involves maintaining and integrating currently-relevant information. In a recent fMRI study (Lanzoni et al., 2020), we showed that distributed regions within the default mode network (DMN) support semantic decisions that follow the presentation of multiple convergent cues - in line with the proposed role of DMN in information integration. In contrast, maintaining cues requires the involvement of working memory and control processes, supported by the multiple demand (MD) network. Here we explored the idea that patterns of intrinsic connectivity between large-scale networks relevant to semantic cognition might influence the efficiency with which we access heteromodal concepts in these different circumstances. We used seed-based analyses of intrinsic connectivity measured with resting-state fMRI to examine whether individual differences in the spontaneous activity of the brain would be predictive of the ability to integrate semantic cues during meaning retrieval, measured outside the scanner using the same cueing paradigm described in the previous chapter. We defined seeds based on the literature: we examined semantically-relevant default mode regions and a network of regions involved in semantic control. We found that decoupling of the DMN seed from a cluster in the right angular gyrus (rAG) was associated with better performance when information about a single cue had to be maintained, relative to semantic decisions without this working memory requirement. We then examined the connectivity of rAG to the univariate contrast maps from Lanzoni et al. and found an opposite pattern across subjects: participants with stronger connectivity from rAG to DMN regions implicated in conceptual integration exhibited weaker connectivity of rAG to executive regions involved in the maintenance of cues. Taken together, these results are consistent with our previous investigation of semantic cue integration, indicating that integration of long-term memory and contextual features might rely on the interplay of distinct networks.

1. Introduction

Flexible semantic cognition is supported by the maintenance of currently-relevant conceptual information, which guides ongoing interpretations about the meanings of words and events, as well as the capacity to integrate conceptual features into coherent representations. While Chapter 4 provides a description of the brain regions supporting these two aspects of semantic integration, the present study set out to explore the link between patterns of intrinsic connectivity (measured through resting-state fMRI) and behavioural efficiency in semantic decisions with different levels of cueing (measured outside the scanner). This methodology can provide complementary evidence to our task-based fMRI findings by highlighting specific patterns of connectivity between regions implicated in semantic cue integration, and their association with behavioural efficiency. We aimed to (i) examine whether individual differences in the brain activity at rest are predictive of individual abilities in semantic cue maintenance and integration and (ii) further characterize the functional role of two large-scale networks that appear to support distinct aspects of conceptual integration – namely semantically-relevant default mode network (DMN) and semantic control regions. According to the Controlled Semantic Cognition (CSC) framework (Jefferies, 2013; Lambon Ralph et al., 2016; Patterson et al., 2007), an interplay of these two networks is crucial for an adaptive semantic retrieval. Semantic representations are formed in the ventrolateral anterior temporal lobe (ATL; the '*hub*'), allied with DMN, through the convergence of features from unimodal areas (or '*spokes*'). Semantic control mechanisms, centered in a left-lateralized network comprising frontal and temporo-parietal regions such as inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG) and pre-supplementary motor area (pre-SMA), come into play to regulate activation in a task-relevant fashion, allowing us to produce flexible patterns of retrieval. By studying the intrinsic connectivity of the brain, the present study further examines the relationship between these two distinct components and semantic cue integration.

Recent studies have suggested that semantic regions allied with DMN, including the ATL and angular gyrus (AG), support the combination of concepts into meaningful and more complex representations (e.g. Price et al., 2016, 2015; for review see Pylkkänen, 2019). These regions show a stronger response when coherent conceptual combinations or heteromodal features are presented (Bemis and Pylkkänen, 2013, 2011; Price et al., 2015; Pylkkänen, 2019; Teige et al., 2019, 2018). In line with this, DMN has been argued to support self-reinforcing patterns of semantic retrieval, where the task goals are consistent with long-term memory representations (Davey et al., 2016, 2015a; Murphy et al., 2018; Spreng et al., 2014). Additionally, Vatansever et al. (2017b, 2015a) have shown that core DMN nodes (including AG) display greater engagement with other large-scale networks with increasing task demands, suggesting an important role of this network in representing and integrating information. The idea of the DMN as a global integrator has gained traction in recent years, with a growing number of studies showing a role of DMN regions in mediating the functional interplay between large scale networks (Braga et al., 2013; Braga and Leech, 2015; Bzdok et al., 2013; de Pasquale et al., 2013, 2012; Kernbach et al., 2018; Leech et al., 2012; van den Heuvel and Sporns, 2011). Moreover, recent work using dimensionality-reduction techniques of spontaneous brain activity found that neural regions are organized along a principal gradient of macroscale organization, anchored at one end by unimodal regions and at the other end by heteromodal cortex corresponding to the DMN (Margulies et al., 2016). The positioning of DMN nodes equidistant from sensorimotor regions makes this network the ideal candidate for creating increasingly complex representations that require separation from sensory inputs.

In addition to conceptual combinations, flexible semantic cognition requires an additional component of selective maintenance of conceptual information, which allows relevant semantic integration to occur over time. The ability to maintain relevant information is crucial in our daily life, for example when we process the meaning of a sentence, when we interpret events that unfold in time, or when we focus our attention on different aspects of the environment. As such, regions typically implicated in working memory, such as prefrontal cortex and posterior parietal cortex (see Eriksson et al., 2015 for a review on working memory), might show involvement in conceptual integration. The lateral prefrontal cortex is thought to encode task-relevant information in working memory (Baddeley, 2003; Miller and Cohen, 2001) and shows sustained neural activity during the delay period of working memory tasks (Courtney et al., 1997; Funahashi et al., 1989; Fuster and Alexander, 1971). Moreover, this region is critical for tasks that require access to a specific subset of relevant semantic knowledge (Badre et al., 2005). The rostral portion of prefrontal cortex is part of a larger fronto-parietal network associated with executively demanding cognitive tasks, including working memory, maintenance of task rules, creation of mental programs, selective coding of task-relevant information, and integration of visual information across successive trials (e.g. Dosenbach et al., 2006; Naghavi and Nyberg, 2005; Owen et al., 2005). Described initially in the primate brain, the human multiple demand (MD) network includes regions such as the inferior frontal sulcus, the anterior insula and frontal operculum, the pre-supplementary motor area and the adjacent anterior cingulate cortex, the intraparietal sulcus (Duncan, 2010). Activation in several MDN nodes has been observed during the presentation of task instructions (Dumontheil et al., 2011), possibly reflecting the creation of a task-model or framework for ongoing cognition. Additionally, surgical disconnection of frontal and parietal regions in MDN in the monkey brain results in the animal's inability to integrate visual information across successive trials (Browning et al., 2006). In the semantic domain, working memory studies contrasting the maintenance of conceptual information vs. non-semantic verbal material find recruitment of regions such as the left inferior frontal gyrus, posterior inferior and middle temporal cortex (Fiebach et al., 2006; Shivde and Thompson-Schill, 2004), which belong to the semantic control network (Noonan et al., 2013b). Taken together, this evidence suggests that both semantic control and MD regions might support the attentional and working memory components of the cueing task.

In a recent task-based fMRI study (Lanzoni et al., 2020), we showed that distinct large-scale networks were implicated in the maintenance of currently-relevant semantic information versus the integration of multiple types of information in a conceptual task. Participants were shown 0, 1 or 2 cues that were relevant to the subsequent interpretation of an ambiguous word: they saw photographs of spatial contexts, facial emotions or scrambled meaningless versions of these cues. When semantic decisions followed multiple convergent cues (contrast of 2 cues > 1 cue), we observed increased activation in regions within the DMN, including bilateral AG, middle temporal gyrus, medial prefrontal cortex, posterior cingulate cortex, and left middle frontal gyrus. A different set of brain regions overlapping with the MD network was recruited when semantic decisions following a cue were contrasted with trials without cues (contrast of 1 cue > 0 cues), in line with the demands of cue maintenance on working memory. Taken together, these findings suggest that conceptual integration and the maintenance of task-relevant cues rely on the interplay of distinct networks, with DMN regions supporting integration of diverse sources of information, while cognitive control regions support our capacity to retain conceptual cues in working memory.

At present, little is known about the extent to which individual differences in the spontaneous activity of these networks at rest might relate to differences in the ability to maintain and integrate conceptual information. Analysis of intrinsic connectivity (recorded at rest using fMRI) can investigate the functional architecture of the brain (for a review see Lee et al., 2013), and has the potential to answer this question. This method extracts low frequency synchronous fluctuations in the hemodynamic activity of distinct brain regions, in the absence of a task. Correlations in the BOLD signal across spatially distinct regions have allowed the identification of the classic resting state networks (RSNs), such as somatosensory (Biswal et al., 1995), default mode (Greicius et al., 2003; Raichle et al., 2001), visual (Beckmann et al., 2005; De Luca et al., 2006; Power et al., 2011; Smith et al., 2009; Yeo et al., 2011), and auditory networks (Smith et al., 2009). Previous studies have successfully associated the spontaneous activity of the brain at rest with individual differences in semantic cognition (e.g. Evans et al., 2020; Gonzalez Alam et al., 2019, 2018; Krieger-Redwood et al., 2016; Mollo et al., 2016; Vatansever et al., 2017a). The underlying assumption is that the strength of specific patterns of connectivity might alter the efficiency with which participants can complete a certain task. Often, better performance on a task is associated with increased *within-network* connectivity, when the network is relevant for the task. For example, increased coupling between a language region in the middle temporal gyrus (overlapping with the DMN) and medial prefrontal cortex (also within DMN) has been linked to better reading comprehension (Zhang et al., 2019). Similarly, greater coupling of left-hemisphere semantic control regions to other left-lateralised language regions predicts more efficient semantic retrieval, as would be expected for a strongly left-lateralized network (Gonzalez Alam et al., 2019). Individual differences at rest can also be seen in the of the *cross-network* connectivity between large-scale networks, however the link with behaviour is less clear. Some studies have observed that increased coupling between regions situated in different networks (yet functionally relevant for the task) is associated with greater efficiency on the task (Evans et al., 2020; Krieger-Redwood et al., 2016). Other studies have found an association between better behavioural performance and greater segregation of networks that are usually anti-correlated (Hampson et al., 2010; Kelly et al., 2008; Mollo et al., 2016; Smallwood et al., 2013a; Vatansever et al., 2017a). These two patterns of results may not be contradictory, since studies observing increased cross-network coupling highlight specific functionally-relevant patterns, which might relate to the capacity for certain brain regions to participate in multiple networks.

In the present study we examined the association between the connectivity at rest of two semantic networks and individual variation in efficiency on the cueing task. Following our recent fMRI investigation of cued semantic decisions, we hypothesized that our cueing paradigm involves at least two cognitive processes, represented by distinct networks: integration of convergent information is supported by the DMN, while maintaining individual cues recruits regions in the MD network. Semantic sites have been shown to overlap with distinct networks that are recruited differentially depending on the task demands (Badre and Wagner, 2006, 2005; Davey et al., 2016; Hallam et al., 2016; Humphreys and Lambon Ralph, 2015; Jackson et al., 2016; Krieger-Redwood et al., 2015; Seghier et al., 2010; Whitney et al., 2011b) – these include both default mode and control networks. While the CSC framework proposes a role of these networks in representing conceptual representations and regulating semantic retrieval respectively (Lambon Ralph et al., 2016), here we are interested in exploring how they relate to conceptual integration. To examine how these semantic networks map onto the different mental processes involved in the cueing task, we selected two seed maps: 1) semantically relevant DMN regions and 2) a combined map of semantic control and semantically-relevant MD regions, excluding any voxels falling within the DMN. Based on the fMRI findings in Chapter 4, we hypothesized that better semantic performance could relate to stronger within-network coupling (i.e. from our seed networks to multiple regions within the same network). Different networks are expected to be associated with different aspects of performance (i.e. DMN with better performance following coherent cue combinations, and control networks with better single cue maintenance). Alternatively, specific patterns of coupling between our network seeds and sites that can participate in multiple networks might be associated with individual differences in these aspects of the task. To anticipate, our analysis identified a site in right angular gyrus (rAG) that showed patterns of contrasting connectivity to DMN and executive regions across participants. Decoupling of this site from our DMN seed was associated with better cue maintenance in working memory.

2. Materials and methods

2.1 Study overview

In this study we used seed-based analyses of intrinsic connectivity measured with resting-state fMRI to explore whether individual differences in the spontaneous activity of the brain are predictive of the ability to integrate semantic cues during semantic decisions, measured outside the scanner. A schematic summary of the analysis is provided in Figure 5.2. First, we defined two seed regions based on the literature: semantically-relevant DMN regions and semantic control network (Figure 5.2.A – step 1). We then generated the intrinsic connectivity maps of the seeds and regressed behaviour onto the group connectivity (Figure 5.2.B – step 2). The behavioural regressions allowed us to recover clusters where the connectivity to the seeds is correlated with behavioural performance on the task. With the aim of establishing patterns of intrinsic connectivity of these regions, we re-seeded the clusters in independent participants and we submitted the unthresholded maps to Neurosynth for cognitive decoding. In a final stage of the analyses, we used the same independent sample to quantify the strength of the connectivity of the rAG cluster (recovered in Step 2) to the networks involved in semantic integration and establish whether the patterns of connectivity are in competition (Figure 5.2.C – step 3).

2.2. Participants

A total of 104 healthy right handed, English-speaking participants, with normal or corrected-to-normal vision were recruited at the University of York (27 males, mean age 20.2, range 18-32). Of these, twelve had previously taken part in Lanzoni et al., (2020). The study was approved by the Ethics Committee of the York Neuroimaging Centre, and participants provided written informed consent prior to their participation in the study. Participants received monetary compensation or course credits. An independent sample of 155 participants (58 males, mean age 20.3, range 18 - 31) was pre-processed for the supplementary analyses. This sample is a subset of the larger cohort of 206 volunteers recruited at the University of York, whose data have been used in previous studies by our group (Gonzalez Alam, 2019; Karapanagiotidis et al., 2017; Poerio et al., 2017; Turnbull et al., 2019b; Vatansever et al., 2017a; H.-T. Wang et al., 2018b, 2018a). Following removal of subjects with missing data, poor behavioural performance and excessive brain motion, a total of 86 datasets were carried forward into the main analyses, and 151 were left in the independent sample. The exclusion criteria are explained in more details in the Pre-processing section.

2.3 Behavioural task

Following the acquisition of the brain scans, we invited participants to come back for a behavioural session where they were tested on five tasks. Results for one of these have been reported in Evans et al. (2020), while the remaining three are described in Gonzalez Alam (2019). The 'combined cueing' task used in the current analyses was taken from Lanzoni et al. (2020) and it involved making semantic decisions to ambiguous words following the presentation of images featuring facial expressions or spatial locations. The amount of cueing provided was manipulated across four different conditions, such that in a given trial participants could be presented with both affect and location cues (2 cues condition), either affect or location (1 cue affect & 1 cue location), or scrambled versions of the cues (0 cues condition). Figure 5.1. contains an illustration of the experimental design (while a detailed description of the cueing task is provided in Chapter 4). To ensure consistency with the task-based fMRI investigation of semantic cue integration, the same Python script was used to collect behavioural data for the present analyses.

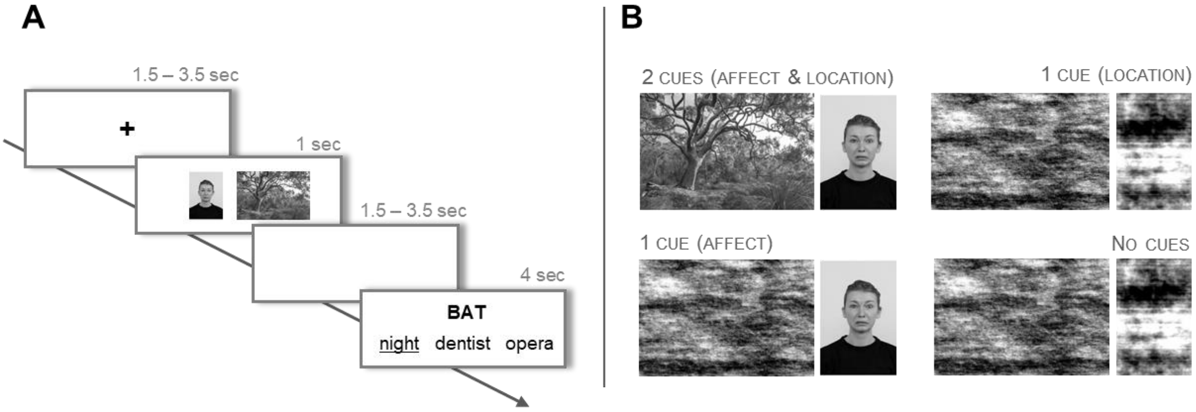

Figure 5.1. Experimental design of the task (see also Figure 4.1 for an example of a homonym generally associated with positive affect). **A** After an initial fixation cross (1500 – 3000 ms.), participants were presented with cue images for 1000 ms., before moving to a blank screen (1500 – 3000 ms.). Following that, a probe word was presented above a target and two unrelated distracters, triggering the onset of the decision-making period. The probe and choices remained visible for a fixed interval of 4000 ms. **B** The four levels of the variable cue are shown.

2.4 MRI data acquisition

Structural and functional MRI data were acquired at the York Neuroimaging Centre at the University of York with a 3T GE HDx Excite MRI scanner, using an eight-channel phased array head coil. Structural MRI acquisition was based on a T1-weighted 3D fast spoiled gradient echo (TR = 7.8s, TE = minimum full, flip angle = 20°, matrix size = 256 x 256, 176 slices, voxel size = 1.13 x 1.3 x 1 mm^3). A T1-weighted FLAIR sequence was then collected to improve co-registration between subject-specific structural and functional scans (TR = 2560 ms, TE = minimum full, matrix size = 64 x 64, voxel size = 3x3x3 mm^3).

Resting state data was obtained from the whole-brain using a single-shot 2D gradient-echo-planar imaging (TR=3s, TE=minimum full, flip angle=90°, matrix size=64x64, 60 slices, voxel size=3 x 3 x 3 mm^3, 180 volumes). During the 9-minute resting state scan, participants were asked to focus on a fixation cross and not to think of anything in particular. The scan always took place prior to the behavioural session, such that cognitive testing could not influence the patterns of intrinsic connectivity that were observed.

2.5 Pre-processing

Pre-processing of brain data

Two subjects were excluded prior to the analyses because of missing resting state scans, while four more were excluded as they were scanned under a different protocol from the rest of the sample. Ten subjects were excluded because of problems with the behavioural data (see *Pre-processing of behavioural data*). The remaining 88 resting state scans were pre-processed using the CONN functional connectivity toolbox V.18a (http://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon, 2012) using a standard pipeline. The following steps were performed on the functional volumes: (1) slice-time (bottom-up, interleaved) and motion-correction, (2) skull-stripping and co-registration to the high-resolution structural image, (3) spatial normalisation to Montreal Neurological Institute (MNI) space using the unified-segmentation algorithm, (4) smoothing with a 6mm FWHM Gaussian kernel, and (5) band-passed filtering (0.008-0.09Hz) to reduce low-frequency drift and noise effects. Nuisance regressors in the pre-processing pipeline included: (i) motion (12 parameters: the six translation and rotation parameters and their temporal derivatives), (ii) scrubbing - outliers were identified through the artefact detection algorithm included in CONN based on a composite metric (scan-by-scan change in global signal above z = 3, subject motion threshold above 5mm, differential motion and composite motion exceeding 95% percentile in the normative sample), (iii) CompCor components (the first 5) attributable to the signal from white matter and CSF (Behzadi et al., 2007), and (iv) a linear detrending term, eliminating the need for global signal normalisation (Chai et al., 2012; Murphy et al., 2009). Following pre-processing, we produced quality insurance (QC) plots and extracted average values per participant for the following metrics: invalid scans (cut-off 20% of total scans: 36 (180 volumes), mean motion (cut off 3 mm), mean global signal change (GSC; cut off z = 3). Two participants were removed due to excessive mean global signal change (z > 3) and removed from the main sample, leaving 86 subjects for statistical analyses. The same pre-processing pipeline was used for the independent sample of 155 participants. Four subjects with GSC of z >3 were removed, leaving 151 subjects in the additional sample. All figures were created using BrainNet Viewer (http://www.nitrc.org/projects/bnv/; Xia et al., 2013). Scatterplots were created in Python 3.4 using the Seaborn data visualization library.

Pre-processing of behavioural data

Six participants were excluded at the start due to technical problems that resulted in no behavioural responses being recorded. Four additional subjects were excluded from the sample because their accuracy was lower than 50% in at least one condition.[7] This additional step allowed us to discard participants with poor performance at the start, before pre-processing the resting-state data for the remaining 88 datasets. Following the removal of two participants with brain motion (see above), a total of 86 participants remained in the final sample. Accuracy, median response time for correct trials, and efficiency scores (median response time/accuracy) were computed for each subject in each condition. Response efficiency (RE) scores provide an overall measure of performance, allowing to account for differences in the way participants trade-off speed and accuracy. Higher efficiency scores indicate poorer performance, however these were inverted in the functional connectivity analyses to facilitate the interpretation of seed-cluster connectivity. Outliers were defined as scores exceeding ±2.5 standard deviations from the mean of the condition and were replaced with the value of the cut-off. Five participants out of 86 had one mean efficiency score imputed.

2.6 ROI selection

Figure 5.2.A shows the two seed maps used in the main functional connectivity analyses. To form these seed maps, we used three previously published network maps: i) default mode, defined by a parcellation of intrinsic connectivity data from 1000 subjects (Yeo et al., 2011); ii) semantic control, extracted from a meta-analysis of 53 studies contrasting semantic decision with high vs. low executive demands (Humphreys et al., 2015; Noonan et al., 2013b); iii) multiple demand, defined as a set of frontal and parietal regions involved in domain-general executive control (Duncan, 2010; Fedorenko et al., 2013). Each network map was then masked by a meta-analytic map of 1031 studies that contain the word "semantic", generated using Neurosynth (accessed in October 2018 - http://neurosynth.org/analyses/terms/semantic/; (Yarkoni et al., 2011). This procedure allowed us to identify semantically-relevant voxels within the original network masks. Voxels in the DMN map that overlapped with semantic control as defined by Noonan et al. (2013b) were removed from the DMN seed map and were retained in the semantic control map, to ensure that no voxels were contained in more than one map. This resulted in a total of 14% of DMN voxels being removed from the DMN map.

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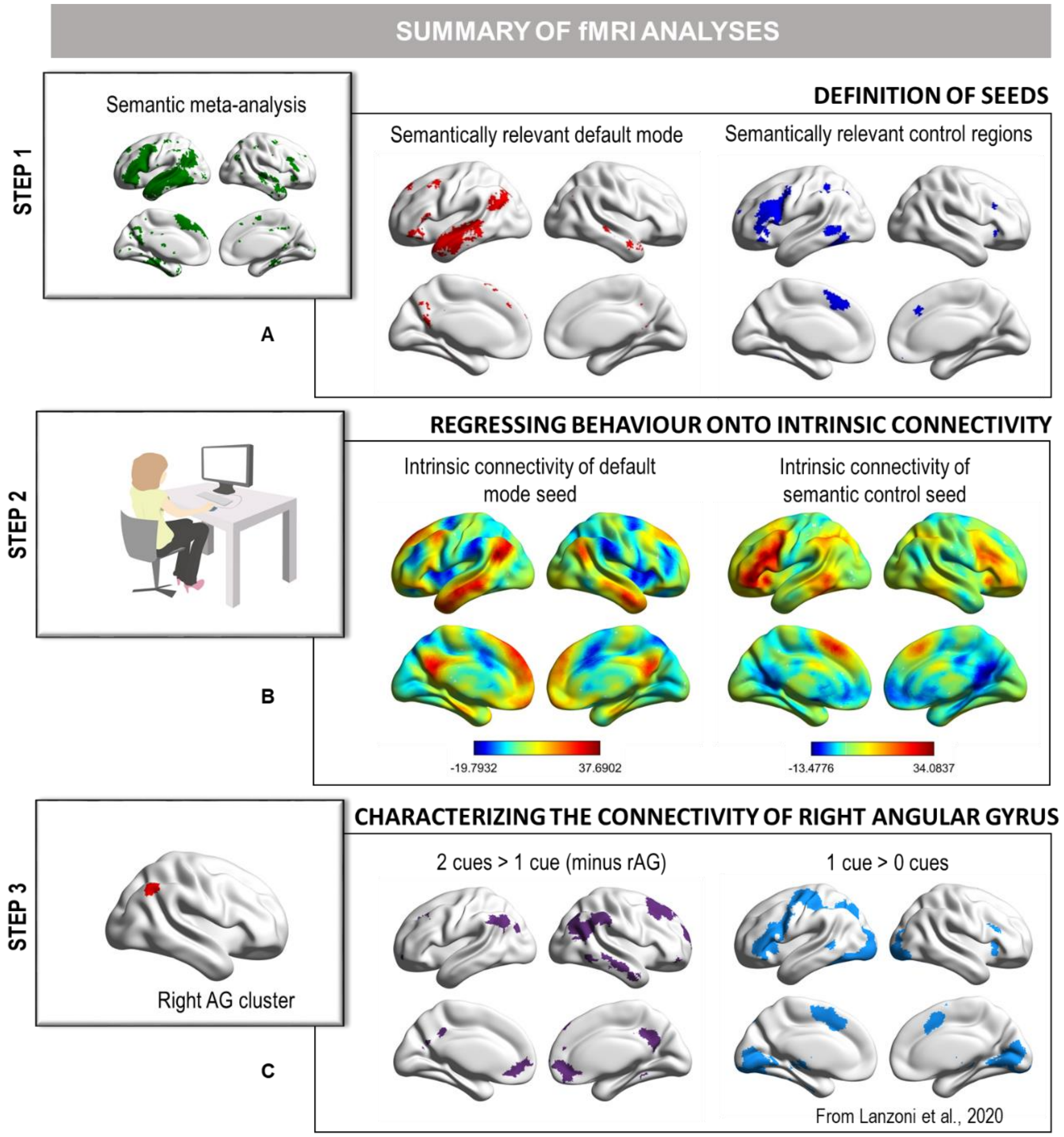
[7] Despite chance level being 30.3%, we implemented a stricter cut-off of 50%, since previous investigations of this task revealed mean accuracy above 85% (Chapters 3 and 4).

Having established that 70.9% of voxels in the MDN map were also contained in the semantic control map, these two networks were merged into a single seed map of semantically relevant control regions. Similar maps were recently used in a study by (Evans et al., 2020).

In a supplementary analysis, we seeded the two maps that were recovered in our previous investigation of semantic cue integration (z > 3.1; Figure 5.2.C) and are likely two reflect the two distinct processes underlying conceptual integration. These reflect: i) semantic decisions in the presence of multiple converging cues, as defined by a contrast of 2 cues > 1 cue and ii) semantic decisions in the presence vs. absence of a context, as defined by a contrast of 1 cue > 0 cues.



From Lanzoni et al., 2020

Figure 5.2. Schematic overview of the stages of the fMRI analysis. **A** Step 1 - Definition of seed regions. A meta-analytic map of 1031 studies which contain the term ‘semantic’ was used to define the semantic portions of DMN

and semantic control network. The final seed maps are also shown here: *semantically relevant default mode network*, given by the Yeo et al. (2011) DMN minus the overlap with semantic control as defined by Noonan et al. (2013b), and *semantically relevant control regions*, derived by combining maps of semantic control (Noonan et al., 2013b) and MD network (Duncan, 2010; Fedorenko et al., 2013). The two seeds are non- overlapping and contain respectively 3741 and 5215 voxels. **B** Step 2 – Regressing behaviour onto intrinsic connectivity. Behavioural performance on the cueing task measured outside the scanner was regressed onto the unthresholded intrinsic connectivity maps generated from the two seeds. These behavioural regressions allowed us to recover regions that show a pattern of connectivity to the seeds which is correlated with behavioural performance on the task (significant clusters are presented in Figure 5.3.B and Figure 5.4.B). **C** Step 3 – Characterizing the connectivity of right angular gyrus. To test the idea that the right AG might display a pattern of variable connectivity with the networks relevant for semantic integration, we performed an additional analysis quantifying the strength of intrinsic connectivity between right angular gyrus (rAG) and regions implicated in 2 > 1 and 1 > 0 cue effects. The seeds were the contrast maps from Lanzoni et al. (2020): *2 cues > 1 cue* (minus rAG) and *1 cue > 0 cues*.

2.7 Resting-state fMRI analysis

Main sample

This analysis examined associations between individual differences in the intrinsic connectivity of our seeds to the rest of the brain and behavioural performance on the combined cueing task, measured outside the scanner. At the first-level, we computed the whole-brain seed-to-voxel connectivity for each of the two seeds. In the group-level analysis, we entered as explanatory variables (EVs) in the GLM analysis the mean-centred response efficiency scores for the four conditions of the cueing task (0 cues, 1 cue affect, 1 cue location, 2 cues) and a nuisance regressor given by the z-scored mean values of the framewise displacement for each subject. The response efficiency behavioural regressors were inversed to facilitate the interpretation of connectivity results (as higher efficiency scores now indicate better performance). We convolved the signal with a canonical haemodynamic response function. Analyses were carried out in CONN including both seeds in the same model. First, we examined the group intrinsic connectivity of the two seeds. Then we explored the following contrasts: 2 cues > 1 cue (assigning the same weight to affect and location 1 cue conditions), 1 cue > 0 cues, 2 > 0 cues, 1 cue affect > 0 cues, 1 cue location > 0 cues, and the main effects of each of the four conditions. Two-sided tests were used to determine the significance of clusters. Group-level analyses were cluster-size FWE corrected and controlled for the number of seeds (Bonferroni corrected $p < .025$, corresponding to a $p < .05$ corrected for 2 seeds). A threshold of $z > 3.1$ (p-FWE=0.001) was applied to define contiguous clusters (Eklund et al., 2016). This analysis allowed us to explore whether differences in the ability to integrate semantic cues correlated with differences in intrinsic connectivity. We extracted the mean connectivity between the seed and the cluster for each participant using the REX toolkit implemented in CONN. These values were plotted against behaviour to determine the direction of each effect.

The REX toolbox was also used to extract values of intrinsic connectivity between our seed maps and the maps recovered in the task-based fMRI analyses (Lanzoni et al., 2020). For each seed - map pair, the REX toolbox computed the mean connectivity to each of the clusters in the fMRI map. Since the largest cluster in the 1 > 0 fMRI map (30502 voxels) contained almost six times more voxels than the largest cluster in the 2 > 1 map (5247 voxels), we discarded connectivity values for clusters other than the largest in the 1 > 0 map. Connectivity values between the seeds and all nine clusters in 2 > 1 were retained and averaged. We then entered these values into a repeated measure ANCOVA with performance for 0, 1 and 2 cues as the dependent variables and the average connectivity values between the seed maps and networks in implicated in cue maintenance and cue combination as covariates (results are displayed in Table 5.2). In order to standardize the distributions, all values were de-meaned prior to the analysis.

Independent sample

The meta-analytic tool Neurosynth (http://neurosynth.org/analyses/terms/semantic/; Yarkoni et al., 2011) was used to obtain psychological terms often associated with the patterns of activation in our results (accessed in January 2020, 1307 studies). First, we seeded the results in the independent sample of 151 participants and generated the whole-brain connectivity network associated with the clusters. We then submitted the unthresholded t maps to Neurosynth for decoding. Anatomical terms (e.g. inferior parietal, angular gyrus) were removed. Where multiple terms had the same meaning (e.g. default, default mode, DMN, network DMN, default network), only the word with the highest correlation value was retained.

Finally, we described the pattern of connectivity of the rAG cluster (recovered in the behavioural regressions) to the networks involved in semantic integration (from Lanzoni et al., 2020). We seeded the task-based fMRI masks of 1 cue > 0 cues and 2 cues > 1 cue (minus the rAG cluster) in an independent cohort of 151 participants. We then generated the whole-brain connectivity map of each seed, while controlling for the variance explained by the other one, and extracted the neural signals in our cluster of interest using the REX toolbox.

3. Results

3.1 Behavioural results

Table 5.1. shows means and standard deviations for accuracy and median RT (on correct trials only), and the efficiency scores computed by dividing median RT in each condition by mean accuracy. The imputed response efficiency scores were submitted to a 1-way repeated-measures ANOVA with Greenhouse-Geisser correction, including cue condition as within-subject factor (3 levels: 0 cues, 1 cue,

2 cues). This revealed a significant effect of cue ($F (1.87, 158.34) = 4.59$, $p = .013$, $\eta^2 = 0.051$). Bonferroni-corrected pairwise comparisons indicated significantly better performance in the 2 cues condition compared with the 0 cues condition ($t (85) = -2.93$, $p = .004$), suggesting a facilitation when semantic decisions occur in a richer context.

	Accuracy		Median response time		Response efficiency	
Condition	Mean	SD	Mean	SD	Mean	SD
0 cues	0.84	0.09	2.00	0.33	2.42	0.54
1 cue	0.85	0.08	1.96	0.28	2.36	0.50
2 cues	0.86	0.08	1.94	0.31	2.28	0.46

Table 5.1. Group behavioural performance as measured by accuracy, median RT for correct trials, and a composite efficiency score (RE: time/accuracy). Only RE were used in the statistical analyses of behavioural performance.

3.2 Functional connectivity results

Using a seed-to-voxel analysis, we explored whether individual differences in the intrinsic connectivity of the seeds at rest relate to behavioural differences in the cueing task. We also examined the connectivity of the two seeds at rest in the absence of behaviour; the significant clusters ($z > 3.1$, $p < .005$) are reported in the Supplementary Materials (Table S5.1.), while the unthresholded maps can be seen in Figure 5.2.B.

Semantic control seed

Increased connectivity between semantic control regions (Figure 5.3.A) and a cluster located at the intersection of pre- and post-central gyrus and supramarginal gyrus (Figure 5.3.B) was associated with better performance ($r = .40$) on semantic decisions in the absence of a cue. The scatterplot in Figure 5.3.C shows the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency score in the 0 cues. As this was a main effect of one condition, and not a contrast between conditions, post-hoc analyses were used to examine the correlation between this pattern of connectivity and performance on the other conditions. The inspection of these scatterplots (Figure 5.3.D and Figure 5.3.E) suggests that this relationship might be specific to the 0 cues condition, however we do not have direct evidence in favour of this interpretation.

We then determined the network associated with the supramarginal gyrus cluster by seeding it in an independent cohort of 151 participants (Figure 5.3.F). The resulting unthresholded intrinsic connectivity map was uploaded to Neurosynth for cognitive decoding. The psychological terms associated with connectivity of this region relate to motor function (e.g. primary motor, hand, execution; Figure 5.3.G). Taken together, these results suggest that the execution of semantic judgments in the absence of cues is more efficient in people with stronger coupling between semantic control and motor regions.

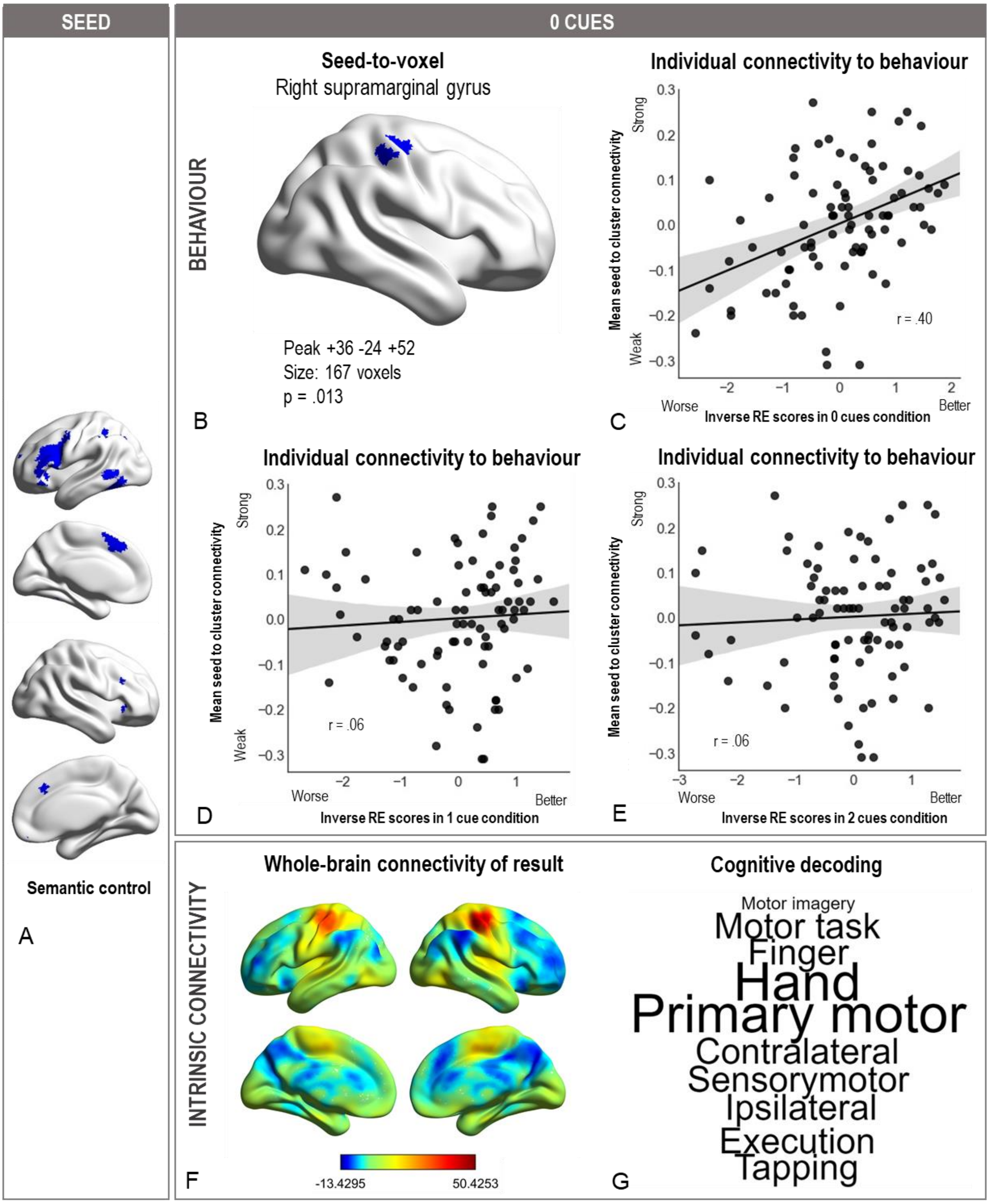


Figure 5.3. Results for the semantic control seed. **A** Lateral and medial view of the seed. **B** Connectivity between this motor region and the semantic control seed is associated with behavioural performance in the cuing task

(cluster correction z > 3.1, p < 0.025 - Bonferroni corrected for 2 seeds). **C** The scatterplot shows the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency in the 0 cues condition. Better performance in the absence of cues is associated with increased connectivity between the seed and the cluster. **D** Scatterplot showing the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency in the 1 cue condition (post-hoc analysis). **E** Scatterplot showing the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency in the 2 cues condition (post-hoc analysis). **F** The binarized cluster mask was used as seed in an independent cohort of 151 participants to generate the group intrinsic connectivity of the region. The unthresholded map is displayed here. **G** Word cloud containing the top 10 terms obtained from the cognitive decoding of the unthresholded intrinsic connectivity map of the seed in Neurosynth (Yarkoni et al., 2011).

Semantic DMN seed

Better performance in the 1 cue condition compared to the 0 cues condition was associated with weaker connectivity between the DMN semantic seed (Figure 5.4.A) and a cluster in the rAG (also within DMN; Figure 5.4.B). We found a negative correlation between connectivity and behavioural efficiency in the 1 cue condition (r = -.27, Figure 5.4.D). Scatterplots showing the relationship between connectivity and performance in the other conditions are presented in Figure 5.4.C and 5.4.E.

As with the previous result, we determined the network associated with this cluster by seeding it in an independent cohort of 151 participants (Figure 5.4.F), and uploaded the resulting map into Neurosynth for cognitive decoding. The psychological terms generated by Neurosynth were largely overlapping with previous investigations of the DMN (e.g. default mode, autobiographical, mental states. Figure 5.4.G). Overall, this result suggests that a separation between the DMN seed and rAG, also allied to the DMN, might be more beneficial when the semantic task involves the maintenance of cue information in working memory. This is consistent with the fMRI results described in the previous chapter, showing minimal involvement of the DMN in a contrast of 1 cue > 0 cues (only 2.4% of the voxels in the 1>0 map overlapped with the classic DMN).

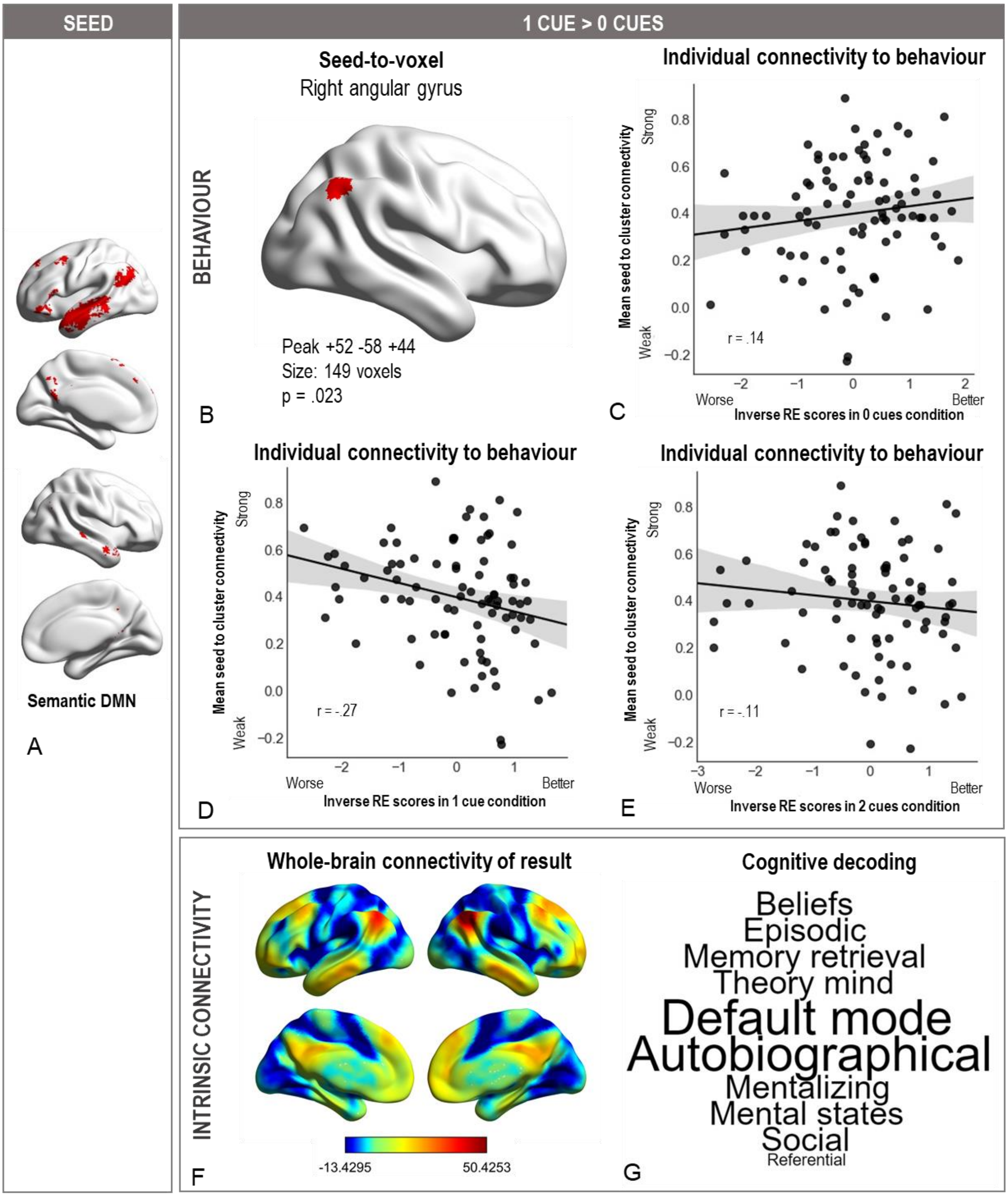


Figure 5.4. Results for the default mode network seed. **A** Lateral and medial view of the seed. **B** Connectivity between right angular gyrus (rAG) and the default mode seed is associated with behavioural performance in the cuing task (cluster correction z > 3.1, p < 0.025 - Bonferroni corrected for 2 seeds). **C** The scatterplot shows the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency in the 0 cues condition. Better performance in the 0 cues condition is associated with stronger connectivity between the seed and the cluster. **D** Scatterplot showing the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency in the 1 cue condition. Better performance in the 1 cue condition is associated with reduced connectivity between the seed and the cluster. **E** Scatterplot showing the mean connectivity of the seed to the cluster for each participant as a function of their behavioural efficiency in the 2 cues condition (post-hoc analysis). **F** The binarized cluster mask was used as seed in an independent cohort

of 151 participants to generate the group intrinsic connectivity of the region. The unthresholded map is displayed here. **G** Word cloud containing the top 10 terms obtained from the cognitive decoding of the unthresholded intrinsic connectivity map of the seed in Neurosynth (Yarkoni et al., 2011).

The cueing paradigm used in this study involves at least two distinct mental processes, which are supported by different networks. In task fMRI (Lanzoni et al., 2020) we found that default mode regions, including right AG, showed increased activation for semantic decisions with multiple cues (contrast of 2 cues > 1 cue, Figure 5.5.A – left), consistent with a role of this network in convergent cue integration. In contrast, MDN regions were recruited for the contrast 1 cue > 0 cues (Figure 5.5.C - left), and the response of these regions during cue presentation was load-dependent. Building on these findings, we hypothesised that individual differences in the pattern of connectivity of our seeds with the 2>1 and 1>0 regions might explain behavioural differences on the cueing task outside the scanner. In particular, we expected to observe stronger connectivity between the DMN and 2 > 1 map in people who are better at integrating multiple convergent cues, in line with the fMRI results. We also expected that connectivity between control regions and the 1 > 0 map would predict performance in the 1 cue condition. Although we did not observe such effects at the whole brain level, this could be due to a lack of power of our analysis in detecting subtle effects. As a follow up to guard against type 2 errors, we extracted the mean connectivity between each seed and each of the two fMRI maps and we entered them as covariates in a within-subject ANCOVA with cue condition as dependent variable (3 levels: two cues, one cue, no cue). This analysis recovered no significant main effect of cue and no interactions between cue condition and connectivity pattern (all values are reported in Table 5.2.).

		ANCOVA			
		DF	F	p	η^2
Cue		1.87, 151.08	0	1	0.00
Cue by connectivity of:	DMN to 2 > 1 map	1.87, 151.08	1.26	.29	0.20
	DMN to 1 > 0 map	1.87, 151.08	0	1	0
	Sem. control to 2 > 1 map	1.87, 151.08	0.34	.7	0
	Sem. control to 1 > 0 map	1.87, 151.08	2.37	.1	0.03

Table 5.2. Values for the repeated measure ANCOVA on cue condition (3 levels: 0 cues, 1 cue, 2 cues). The strength of the connectivity between our seeds and the maps recovered in the fMRI experiment using the same task (Chapter 3) were entered in the model as covariates. All values were mean-centered prior to the analysis. Significant results and interactions are reported in bold and marked with *. A Greenhouse-Geisser correction was applied where the assumption of sphericity was not met.

Variable patterns of connectivity from right angular gyrus

The observed decoupling within the default mode network in people with better performance on 1 cue > 0 cues is broadly consistent with our previous fMRI findings suggesting that DMN is not relevant to this behavioural contrast (thought to relate to the maintenance of cue information in working memory). Several DMN nodes, including AG have been shown to contain ‘echoes’ of neural signals from other large-scale networks (Braga et al., 2013; Braga and Leech, 2015; Leech et al., 2012; Turnbull et al., 2019a). Moreover, the right temporo-parietal junction is thought to be a key player in mediating functional dynamics between brain networks (Bzdok et al., 2013; Kernbach et al., 2018), flexibly coupling with different networks at rest. We hypothesized that stronger intrinsic connectivity between rAG and MDN regions (implicated in cue maintenance by the contrast of 1 cue > 0 cues) might be associated with weaker connectivity to other DMN regions (implicated in cue combination). By this view, rAG is a nexus between two largely anti-correlated networks, potentially explaining why separation within DMN is associated with better controlled maintenance of relevant conceptual information. To test the idea that the right AG might display a pattern of variable connectivity with the networks relevant for semantic integration, we performed an additional analysis quantifying the strength of intrinsic connectivity between rAG and regions implicated in 2 > 1 and 1 > 0 cue effects. Consistently with our prediction, participants with stronger connectivity between 2 cues > 1 cue regions and rAG had significantly weaker connectivity between 1 cue > 0 cues regions and AG (r = -.230; Figure 5.5.B).

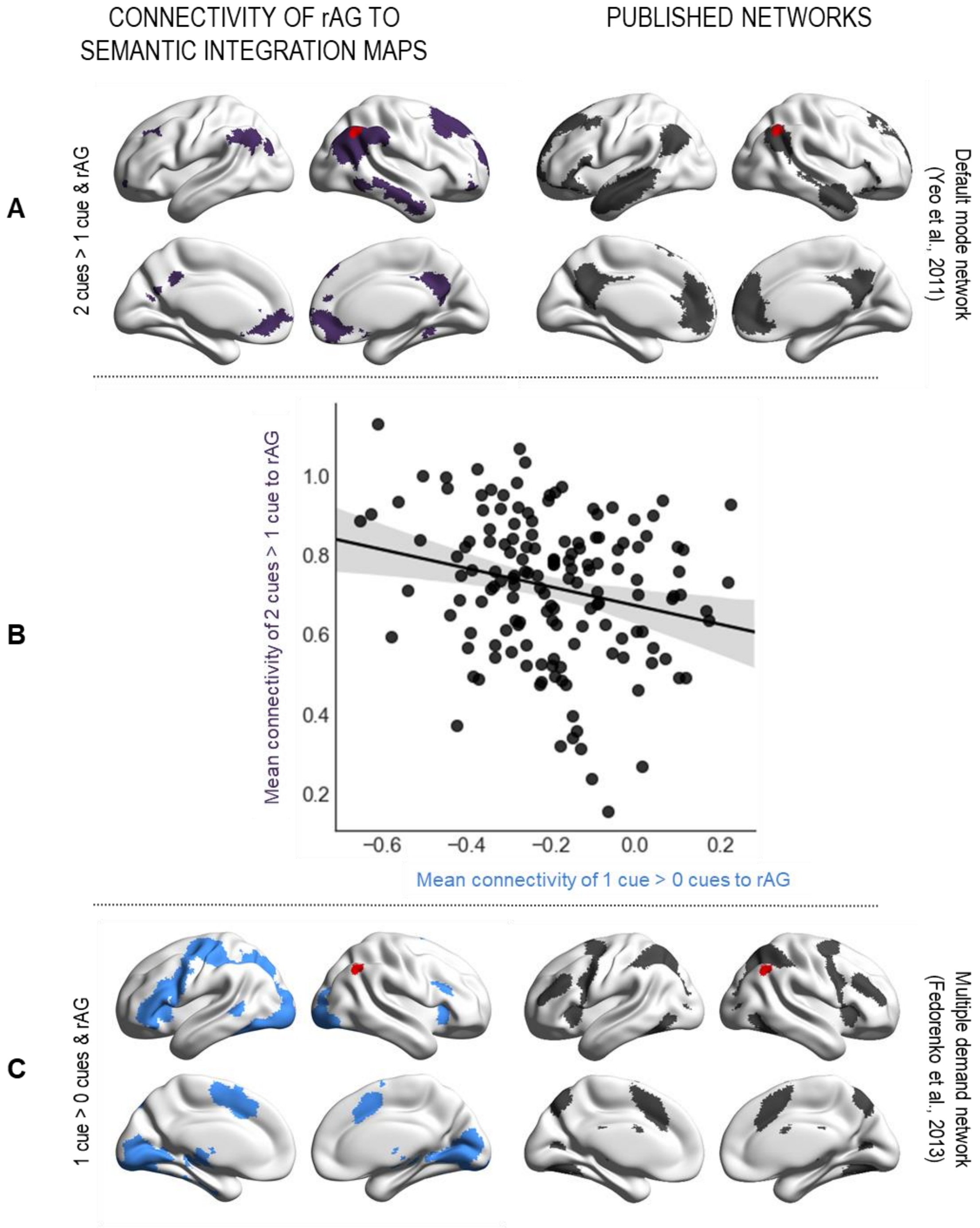


Figure 5.5. A The rAG cluster recovered in the behavioural regressions (shown in red) overlaps with the 2 cues > 1 cue map from the fMRI study (shown in purple) and also with the classic default mode network (Yeo et al., 2011; shown in dark grey). **B** Scatterplot showing a negative relationship between the connectivity at rest of rAG to 2 > 1 and 1 > 0 regions. This analysis reveals that rAG has a pattern of variable connectivity at rest with the networks relevant for semantic integration. **C** The rAG cluster does not overlap with 1 > 0 regions (shown in light blue), but it is adjacent to MD regions (Duncan, 2010; shown in dark grey) in inferior parietal sulcus.

4. Discussion

The current study investigated the neural architecture supporting our ability to integrate semantic cues to guide meaning retrieval. We used seed-based functional connectivity analyses to relate the intrinsic activity of two large-scale semantic networks (i.e. semantic control, default mode network) to individual differences in performance in a cued semantic decision task measured outside the scanner. Increased coupling between the semantic control seed and a cluster located at the intersection of primary motor and somatosensory cortex was associated with better performance without cues, suggesting that task execution might be more efficient in people with stronger coupling between semantic and motor regions. The semantic default mode seed exhibited a pattern of within-network functional decoupling, with reduced connectivity to the right AG being predictive of more efficient semantic retrieval in the 1 cue condition, relative to no cues. Additionally, this cluster was found to have opposite connectivity at rest to DMN regions involved in semantic integration and to MD regions involved in cue maintenance (as defined by Lanzoni et al., 2020). Taken together, these findings are in line with our recent investigation of semantic cue integration (Lanzoni et al., 2020) and provide further support for the idea that some core nodes of the DMN might mediate the communication between other large scale networks (e.g. Braga et al., 2013; Bzdok et al., 2013; Kernbach et al., 2018).

By comparing semantic decisions in the presence vs. absence of a meaningful location or emotion context, the contrast of 1 cue > 0 cues taps processes that support the maintenance of cue information, such as selective attention and cognitive control, whilst controlling for semantic decision-making common to both tasks. Decoupling of right AG from other DMN regions might allow this site to increase its functional connectivity with other networks overlapping with the MD system that are more relevant to the selective maintenance of cue information. As such, the connectivity of rAG to multiple demand and default mode sites might vary across individuals. We tested this hypothesis and found that people with lower connectivity from rAG to semantic integration default mode regions also exhibited stronger connectivity between the same rAG cluster and multiple demand regions involved in cue maintenance. This finding is in line with several studies that have placed rAG at the centre of communication between functionally distinct networks. Bzdok et al. (2013) proposed that the right temporo-parietal junction (rTPJ) might link antagonistic networks implicated in internal vs. external information processing. Using connectivity-based parcellation techniques, they recovered two distinct clusters in the right TPJ: an anterior cluster showing connectivity with action and motor control areas and a posterior cluster linked to DMN regions involved in social cognition and memory. More recently, Kernbach et al. (2018) employed canonical correlation analysis to explore whether patterns of connectivity within DMN could explain functional relationships between large-scale networks. Among the candidate regions in their DMN parcellation, rTPJ was found to be one that explained the most variance in the interplay of DMN and other brain-networks. Further evidence for the idea of AG as a connector hub comes from the presence of ‘echoes’, or traces of multiple large-scale networks in association cortex and in several core nodes of the DMN (for a review see Braga and Leech, 2015). Through decomposition of resting-state neural signals, Braga et al. (2013) were able to distinguish between functionally distinct but spatially overlapping regions within DMN correlated with different large-scale networks. By representing “echoes” or converging signals from multiple networks, AG can engage with different networks and participate in multiple tasks.

There are a number of limitations that should be borne in mind when considering our findings. While this study shows that weaker intrinsic connectivity between rAG and other DMN nodes is associated with efficient conceptual decisions following a single cue, the regions we recovered are quite sparse. One question that remains unanswered is whether efficiency in contextually guided semantic decisions (vs. unconstrained decisions) is predicted (i) by the separation of DMN to rAG specifically, or (ii) whether it is attributable to more general segregation within the DMN. A study with greater statistical power might have recovered a broader network of regions showing the pattern observed for rAG. We speculate that other regions beyond rAG might show echoes of other networks, consistent with their role in information integration. This possibility could be explored directly using multivariate techniques similar to those implemented in Leech et al. (2012). Moreover, contrary to our prediction, we failed to observe an association between improved efficiency in the 2 cues > 1 cue and connectivity of the brain at rest. Based on the results from the previous study we might have expected increased connectivity within DMN nodes in individuals with enhanced performance on semantic decisions with multiple cues. This could be due to the small sample size (although similar sample sized have been used before, e.g. Mollo et al., 2016).

In addition, we used large network-based seeds, created by combining a meta-analytic semantic map with a DMN parcellation and a task-based semantic control map. Consequently we cannot establish (i) if a more specific region within this map is the source of the association with rAG, and (ii) if additional significant results might have emerged if individual sites implicated in conceptual working memory had been taken as seeds. Our strategy allowed us to probe the functional significance of much of the semantic network, whilst avoiding the use of many models designed to interrogate different seeds. Future studies can address this issue by using more circumscribed seeds in locations known to be relevant for working memory, examining the contribution of each of these sites separately. A final limitation concerns the interpretation of the result for the semantic control seed. Our analysis revealed that increased connectivity between our seed and a motor cluster in primary-motor cortex was associated with better performance in the 0 cues condition. However, as this was a main effect of one condition and not a contrast of conditions, we cannot interpret the effect as being specific to the 0 cues. Future studies with greater statistical power might be able to recover a contrast of conditions.

Despite these limitations, the study revealed two functionally distinct components within DMN that are relevant to semantic integration. We characterized rAG based on its position within a 17-network cortical parcellation of 1000 brains based on patterns of intrinsic (Yeo et al., 2011; https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011). The cluster showed high overlap (50% of total number of voxels) with a ‘core default mode network’ (*17Network_16*: medial prefrontal, posterior inferior parietal, posterior cingulate, dorsal prefrontal, orbitofrontal, temporal), but not with the ‘lateral DMN’ (*17Networks_17*: dorsal prefrontal, temporal, anterior inferior parietal). The rAG cluster also showed some overlap (30% of voxels) with the ‘lateral frontoparietal’ network (*17Networks_13*: lateral posterior prefrontal, lateral anterior prefrontal, inferior parietal, temporal, posterior frontal), consistent with the view that this cluster can connect to both DMN and control networks. In contrast, the semantic DMN that was used as seed was almost entirely overlapping with the lateral DMN (*17Networks_17*), and showed almost no overlap with core DMN (*17Networks_16*). This distinction is highly coherent with previous fractionations of the DMN (Andrews-Hanna et al., 2010; Yeo et al., 2011) and supports the general idea that the DMN is not a unitary network (Braga et al., 2013; Braga and Buckner, 2017; Leech et al., 2012; Mayer et al., 2010; Yeo et al., 2015). In this view, people who show a greater separation between different components of the same system might be facilitated in situation that require to maintain cue information. Increased segregation of usually anti-correlated functional networks has been reported in previous studies of executive control (Hampson et al., 2010; Kelly et al., 2008), language (Mollo et al., 2016), reading comprehension (Smallwood et al., 2013a), semantic abilities (Vatansever et al., 2017a), and general intelligence (Sripada et al., 2019). Here we observe that participants who were better at making semantic decisions following a cue showed more segregation of lateral DMN, implicated in semantic processing, from AG, a key region within the core DMN that is less clearly implicated in controlled semantic processing. Our findings are consistent with our previous investigations of semantic cue integration and provide additional evidence for a role of AG in mediating the communication of functionally distinct large-scale networks.

5. Supplementary materials

		Cluster	voxels	p (FEW)	cluster peak		
					x	y	z
Semantic DMN seed	Increased	L AG	129959	0	-50	-60	24
		L cerebellum	1679	0	-26	-80	-38
		L occipital pole	908	0	-28	-100	-12
		R pre- post- central gyrus	648	0	28	-26	52
		L pre- post- central gyrus	482	0.000006	-34	-24	58
		R post- pre- central gyrus	224	0.002661	66	-4	26
	Decreased	R inferior temporal gyrus, occipital fusiform	239	0.001779	52	-52	-14
		R thalamus	211	0.0038	14	-18	20
		brain stem	175	0.010592	4	-10	-32
		L pallidum	149	0.023131	-18	-12	-4
Semantic control seed	Increased	L inferior frontal gyrus (pars opercularis), middle frontal gyrus	113798	0	-46	18	24
		R caudate, pallidum	856	0	14	6	10
		L pre- post- central gyrus	309	0.00028	-4	-36	74
		L precuneus	219	0.002895	-6	-28	-34
		occipital pole	156	0.017957	0	-94	26
	Decreased	R parietal operculum	769	0	42	-28	24
		R superior frontal gyrus	227	0.002326	22	28	36

Table S5.1. Connectivity at rest of the semantic DMN and semantic control seed (z > 3.1, p < .005)

Chapter 6: General discussion

1. Overview

The overarching aim of this PhD was to explore the neurocognitive mechanisms that support flexibility in semantic retrieval. This is an interesting avenue for investigation, since in everyday situations we are immersed in conceptually rich and high dimensional environments, but not all of this knowledge is relevant at a given time. Consequently, we are faced with the fundamental challenge of shaping our internal representations of the world to produce adaptive behaviours. At present, a clear understanding of the cognitive and neural substrates of semantic flexibility is still lacking. While most research has focused on the role of semantic control processes (Badre et al., 2005; Bedny et al., 2008b; Davey et al., 2015b; Noonan et al., 2013a, 2010; Wagner et al., 2001; Whitney et al., 2011b), much less attention has been devoted to explore the ways by which multimodal contextual information can be used to guide flexible retrieval. The present thesis used a cueing paradigm and a combination of methodologies and experimental populations to tackle different aspects of this broad question. Cues offer a unique opportunity to study context-based retrieval by establishing a conceptual framework in which subsequent meanings can unfold. In this view, flexibility arises from the integration of conceptual information available in the context.

Much of the work in this thesis is motivated by a recent framework of semantic cognition, the Controlled Semantic Cognition account (CSC; Lambon Ralph et al., 2016), which anticipates that modality-specific information represented in cortical spokes will aggregate in a heteromodal hub in ventral anterior temporal lobe (ATL) – where abstract representations are formed. This region is relatively invulnerable to strokes and largely spared in semantic aphasia (SA) patients. Thus, by using cues in this population (Chapter 2 and 3) we were able to test a prediction of the CSC framework that it should be possible to alter the state of long-term representations in the semantic hub from information in modality-specific regions. Next, task-based fMRI techniques (Chapter 4) allowed us to explore the neural recruitment during cued retrieval and test the predictions of another contemporary framework of brain organization, which situates the default mode network (DMN) at the top of a cortical hierarchy (Margulies et al., 2016). According to the Principal Gradient account, information integration should occur along the cortical surface and it should be maximal towards the heteromodal end of the gradient, in regions overlapping with DMN. Additionally, using seed-based analyses of functional connectivity (Chapter 5) we related individual differences in intrinsic connectivity to differences in the efficiency with which individuals can combine conceptual representations to guide semantic retrieval.

2. Novel empirical findings

This section discusses four themes relevant to the novel findings of this PhD. First, the chapter discusses evidence for the existence of two qualitatively distinct routes to semantic flexibility, one driven by control processes and one driven by the context. Second, our research shows that context-based flexibility involves different cognitive processes, which are represented in different large-scale networks. Furthermore, the empirical work in this thesis sheds light on the topographical organization of context-driven flexibility, demonstrating that integration of conceptual features into complex representations occurs in a graded fashion along the cortical surface, reflecting previously described macro-scale hierarchies. Finally, the last theme discusses the nature of the cue stimuli used. Since communication in real-world environments is likely to be influenced by the emotional expression of the speaker and the spatial setting in which conceptual representations are accessed, we examined two types of contexts – affect and location – and both types of cues proved to be effective at shaping the activation of semantic knowledge.

2.1 Two routes to semantic flexibility

2.1.1 Summary of findings

A large body of work has focused on the role of semantic control processes in regulating semantic retrieval (Jefferies, 2013; Lambon Ralph et al., 2016; Thompson-Schill et al., 1997; Wagner et al., 2001; Whitney et al., 2011b). This PhD provided a richer and novel description of the mechanisms responsible for semantic flexibility by focusing on an alternative way in which flexible patterns of retrieval can occur. This process involves the progressive integration of currently available information with long-term conceptual representations. In the healthy brain these two mechanisms typically coexist, allowing retrieval to be shaped by the context when the currently available information is line with the representations stored in memory, and by control processes when weak associations must be brought to the fore or when irrelevant information must be suppressed. When the latter mechanism is damaged, the pattern of retrieval is marked by profound rigidity – as observed in patients with SA following frontal and temporo-parietal stroke. In Chapter 2 we found that, when flexibility given by control mechanisms is lacking due to deregulated semantic control, patients are still able to use information from the context. Compared to healthy participants, patients relied on cues to guide semantic retrieval, especially when the task required participants to retrieve the subordinate meaning of ambiguous words. Nevertheless, this mechanism can fail in certain circumstances – for example when the cues provide misleading information that must be suppressed. In our experiment we found detrimental effects of miscues, for example when a *happy face* or a picture of a *supermarket* was used to prime the alternative meaning of JAM as “traffic jam” (Chapter 2). In Chapter 3 we replicated the positive effect of cues on meaning retrieval in SA, providing convergent evidence for the idea that multimodal information available in the context can activate long-term representations (even when control mechanisms are damaged). Patients' performance on subordinate trials was significantly improved by the provision of a single cue relative to scrambled images (while combining different cue types did not yield an additional benefit). Notably, the effect of cueing in our patient sample (in both Chapter 2 and 3) was greater for non-dominant meanings – which are thought to have higher control demands, suggesting that context-based retrieval may offer a compensatory mechanism when the top-down route to flexibility is impaired.

While the first two empirical chapters provide convincing evidence for the idea that semantic flexibility can be achieved through the integration of recent experience (i.e. cues) with long-term representations, the widespread nature of the patients' damage did not allow us to separate the regions involved in this process. To support the claim of the existence of two qualitatively distinct routes to semantic flexibility, it is paramount to show that a specific set of regions is active when participants use contextual information to constrain retrieval, and that this network is distinct from the semantic control network. Chapter 4 addressed this question directly using fMRI; we found activation within DMN when participants performed semantic decisions following multiple cues – indicating that the ability to integrate conceptual information to guide retrieval is supported by heteromodal cortex, largely distinct from the semantic control network responsible for processes that constrain retrieval in a top-down way.

2.1.2 Relation to broader literature

Human behaviour is highly flexible; we can modify our actions and thoughts based on previous experience, but also based on inferences from information present in the environment. Despite the key role that flexibility plays in our everyday life, a clear understanding of how this process emerges in the brain is currently lacking. Recent theories rooted in the spatial-navigation literature propose the existence of domain-general mechanisms supported by place- and grid-cells in the medial temporal complex, which would allow the formation of "cognitive maps" across a variety of spatial and non-spatial contexts (Behrens et al., 2018; but see Tolman, 1948). By encoding relationships between states (i.e. "possible configurations of the world"), these cognitive maps can abstract information and generalize knowledge for flexible behaviours. While this framework provides a fascinating explanation of how medial temporal lobe structures in DMN may contribute to conceptual integration, flexibility in semantic cognition is likely to require a more complex organization. Consistent with component-based accounts of semantic cognition (Lambon Ralph et al., 2016), this PhD provides evidence for two alternative routes to flexible retrieval, one driven by semantic control mechanisms located in prefrontal and temporo-parietal regions (and compromised in patients with SA), and one driven by the context in which information is retrieved, whereby presently available information is integrated with long term representations.

The last twenty years of research have provided solid evidence for the role of the left inferior frontal gyrus (IFG) in supporting flexible patterns of semantic retrieval (Badre et al., 2005; Badre and Wagner, 2005, 2002; Davey et al., 2016; Thompson-Schill et al., 1997). More recently, posterior middle temporal gyrus (pMTG) has been shown to serve a similar function of controlling the retrieval of semantic representations (Davey et al., 2016; Noonan et al., 2013b). In line with fMRI findings, inhibitory TMS to left IFG and pMTG interferes with controlled aspects of semantic retrieval (Davey et al., 2015a; Hoffman et al., 2010; Krieger-Redwood and Jefferies, 2014; Whitney et al., 2011b). Following damage to left IFG, pMTG and in some cases dorsal aspects of AG (Thompson et al., 2015), semantic retrieval becomes inflexible and dominated by strong and over-learned associations (Jefferies and Lambon Ralph, 2006; Noonan et al., 2010; Rogers et al., 2015; Thompson et al., 2015; Thompson and Jefferies, 2013). Crucially, patients' efficiency in retrieving meaning of words and pictures is improved by the provision of cues which reduce the control demands of the task, and it is disrupted by cues that probe irrelevant information (Jefferies et al., 2008b; Noonan et al., 2010; Soni et al., 2009).

Building on this observation, this PhD used cues and miscues to manipulate the accessibility of semantic information. Here we moved beyond language cues previously used to study deregulated semantic control in SA patients; semantic decisions were preceded by non-verbal cues related to specific features of the concept, namely valence and visuo-spatial contexts. Our findings that cues improved performance in SA compared to uncued trials (Chapter 2 and 3) are broadly consistent with previous studies showing positive effects of phonological cues on picture naming (Jefferies et al., 2008b; Soni et al., 2009) and sentence cues on semantic comprehension (Noonan et al., 2010). Conversely, retrieving meanings in the absence of a supportive context or following misleading cues requires more internally-generated control that can shape activation within the semantic store. As expected, when miscues primed the alternative interpretation of the ambiguous word, patients seemed unable to inhibit the irrelevant representations (Chapter 2). While miscuing effects in SA have been found before (Jefferies et al., 2008b; Soni et al., 2009), the work in this PhD uniquely adds to this literature by revealing that even rather abstract *features* of concepts such as valence can be sufficient to disrupt retrieval if not in line with the task. These findings are consistent with the *Hub and Spoke* model's prediction that concepts are formed through the integration of sensory and affective features into abstract representations (Jefferies, 2013; Lambon Ralph et al., 2016; Patterson et al., 2007). Moreover, the overall pattern of impairment observed in our SA patients is in line with the prediction of the CSC framework (Lambon Ralph et al., 2016) which suggests that flexibility will emerge from the interaction of semantic control and stored representations. Our neuropsychological findings are suggestive of a disrupted control-based route to flexibility in SA, but an intact mechanism for a more automatic type of flexibility. As long as the context provides information which primes the correct representations in the semantic store, semantic retrieval will be relatively unimpaired.

Chapter 4 provides further support for the idea of an alternative route to flexibility which does not require semantic control. We showed that in situations in which retrieval was supported by the context (i.e. when participants were able to integrate multiple convergent cues to constrain meaning), activation increased across a set of DMN regions which are spatially non-overlapping with the typical sites of brain damage in SA. Interestingly, one of the largest clusters was in angular gyrus (AG), which has been described as a second semantic hub (Schwartz et al., 2011) or a “convergence zone” (Binder et al., 2009; Binder and Desai, 2011). The neural bases of this process will be discussed in Theme 2.3.

2.2 Semantic integration involves distinct cognitive components supported by different large-scale networks

2.2.1 Summary of findings

While the first two empirical chapters provide convincing evidence for the idea that semantic flexibility can be achieved through the integration of recent experience (i.e. cues) with long-term representations, the widespread nature of the patients’ damage does not allow us to study the neural bases of this bottom-up route to flexibility. Chapter 4 addressed this question directly using task-based fMRI; we manipulated the extent to which semantic retrieval occurred in a rich and meaningful context by providing 0, 1 or 2 cues that were relevant to the following interpretations. As this type of flexibility is thought to depend on the ability to integrate coherent features into more complex and abstract representations, we reasoned that the neural substrate would be largely distinct from control regions. Interestingly, we found that semantic integration involves two different mental processes supported by distinct networks. Contrasting cued vs. uncued decisions revealed activation in domain-general control regions within the multiple demand network (MDN), including middle and inferior frontal gyrus, inferior frontal sulcus and pre-supplementary motor area, and the response of these regions during cue presentation was load-dependent. These findings suggest that maintaining cue information requires working memory supported by MDN (Duncan, 2010; Fedorenko et al., 2013). In contrast, integrating different cue types to guide semantic retrieval activated the DMN, compared to when a single cue was provided. We found an increased BOLD response in bilateral angular gyrus, middle temporal gyrus, medial prefrontal cortex, and posterior cingulate, in line with the proposed role of DMN in information integration (Braga et al., 2013; Bzdok et al., 2013; Margulies et al., 2016; Price et al., 2015; Pylkkänen, 2020; van den Heuvel and Sporns, 2011; Vatansever et al., 2017b, 2015b).

Seed-based connectivity analyses of resting-state fMRI in Chapter 5 revealed associations between the connectivity of these networks and individual variation in the efficiency on the task. We found that behavioural efficiency following a single cue vs. no cues was related to greater separation between the semantically relevant DMN and a cluster in right angular gyrus (rAG) – also within DMN. The observed decoupling within different DMN regions is consistent with the fMRI result showing that this network is not relevant for maintaining cue information, which instead recruited MDN regions in Chapter 4. Additionally, consistent with the division of labour observed for DMN and MDN, the cluster in rAG was found to have opposite connectivity at rest to the whole brain maps recovered in the previous experiment: participants with greater coupling between rAG and DMN regions linked to conceptual combination exhibited reduced coupling between the same rAG cluster and MDN regions involved in cue maintenance. Collectively, findings from Chapter 4 and 5 support the idea of two neurocognitive components underlying semantic integration, one involving domain-general executive control to facilitate the maintenance of cues in a goal-driven fashion, and one involving heteromodal cortex within DMN which supports the integration of multiple conceptual cues.

2.2.2 Relation to broader literature

A crucial finding of this PhD is the observation that semantic integration involves at least two separate cognitive processes which are supported by distinct large-scale networks (Chapter 4). Maintaining cue information during semantic decisions recruited prefrontal and superior parietal regions within MDN (Figure 6.1.A – left), in line with previous literature showing involvement of this network in working memory (e.g. Assem et al., 2020; Fedorenko et al., 2013, 2011; Mineroff et al., 2018; Wen et al., 2018). Moreover, these regions responded in a load-dependent fashion during the encoding of cue information. This was unsurprising, since both functional activation and functional connectivity in MDN nodes are known to increase with greater working memory loads (Kim et al., 2012; Linden et al., 2003; Ma et al., 2012; Manelis and Reder, 2014; Manoach et al., 1997; for meta-analytic evidence see Owen et al., 2005; Rottschy et al., 2012). While the contrast of cued compared to uncued decisions mostly overlapped with domain-general executive regions (31.8% of voxels overlapped with MDN), some activation was also observed in left-hemisphere regions typically involved in semantic control, including pMTG, IFG and paracingulate gyrus (Figure 6.1.A – right; 6.37% of voxels overlapped with the semantic control network). This is in line with recent findings from working memory studies which examined the maintenance of semantic material (Fiebach et al., 2007, 2006; Shivde and Thompson-Schill, 2004).

This observation is also relevant to the interpretation of the cueing effects observed in patients with deregulated semantic control in Chapter 3: we found that patients were able to benefit from the presence of context despite the working memory demands associated with maintaining cue information until the subsequent semantic decisions. Interestingly, Figure 6.1.B shows that the areas of maximum lesion overlap in our patient sample are focused around the left prefrontal cortex, thus leaving a large portion of the neural substrate for cue maintenance relatively unaffected. In this way, patients could still rely on more posterior MDN regions for the use of contextual information.

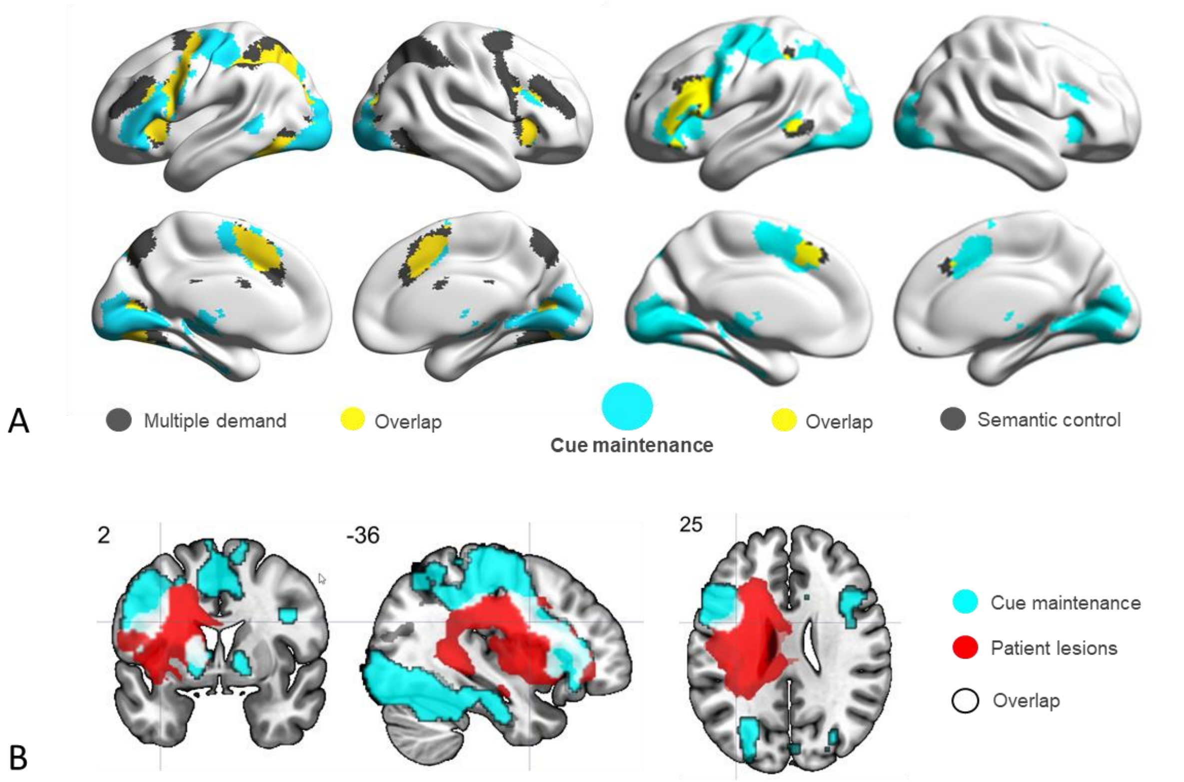


Figure 6.1. A The yellow areas show the overlap of the univariate contrast from Lanzoni et al (2020) reflecting the maintenance of cue information during semantic decisions (1 cue > 0 cues) with the Multiple Demand Network (Duncan, 2010; *left panel*) and with the semantic control network (Humphreys and Lambon Ralph, 2015; *right panel*). **B** Regions in white show the overlap between the areas of highest-density lesion in our sample of stroke patients (red) and the univariate contrast of 1 cue > 0 cues (cyan).

In contrast, the availability of convergent information from multiple cues during semantic decisions elicited activation in a set of regions overlapping with the DMN, which were largely distinct from the MDN regions responding to cued vs. uncued decisions, and the effect could not be explained in terms of task difficulty. The recruitment of AG when participants drew on multiple sources of information is consistent with a rich literature implicating this region in the formation of conceptual combinations (Flick and Pylkkänen, 2020; for reviews see Pylkkänen, 2020, 2019). For example, increased activation in left AG has been observed for meaningful conceptual combinations (e.g. “red boat”) compared to the same words preceded by unpronounceable consonant strings (e.g. “xhl boat”; Bemis and Pylkkänen, 2013), or when participants integrate simple items (e.g. “jacket” and “plaid”) into coherent concepts (i.e. “plaid jacket”; Price et al., 2016, 2015). Combinatorial activity in AG has also been documented in the episodic literature, with several studies suggesting a role of this region in multi-modal feature integration during episodic retrieval (e.g. Bonnici et al., 2016; Tibon et al., 2019). Another classic site associated with conceptual integration is the left ATL (Bemis and Pylkkänen, 2013, 2011; Westerlund et al., 2015), however we did not recover activity in this region (this is further discussed in section 3.4). Instead, increased BOLD during semantic decisions with multiple compared to single cues was observed in ventromedial prefrontal cortex (PFC), which is consistent with previous evidence from linguistic composition studies (Bemis and Pylkkänen, 2011; Pylkkänen et al., 2014).

In line with these findings, in Chapter 5 we found that participants who were more efficient at cued relative to uncued semantic decisions had greater separation between DMN and a cluster in rAG, also within DMN. This result suggests that a separation between the DMN and rAG might be more beneficial when the semantic task involves a working memory component, and is therefore consistent with our previous fMRI findings showing that cue maintenance recruits regions largely distinct from DMN. Interestingly, the rAG region was found to have opposite connectivity at rest to MDN areas involved in cue maintenance and DMN areas involved in cue combinations. This pattern of coupling is consistent with a growing body of studies which place AG at the nexus of the functional communication between large-scale networks (Braga et al., 2013; Braga and Leech, 2015; Bzdok et al., 2013; Kernbach et al., 2018). For example, Vatansever et al. (2017b, 2015b) have shown that AG displays greater engagement with other large-scale networks with increasing working memory demands, suggesting an important role of this region in network-communication. By this view, decoupling between rAG and other DMN nodes might enable this region to strengthen the connectivity with other regions which are more relevant for the task. This interpretation resonates with the Process-Specific Alliances (PSAs) account of network organization (Cabeza et al., 2018), which anticipates that the same brain region can form “flexible, temporary and opportunistic” alliances with other regions to support distinct cognitive processes.

2.3 Principal gradient and conceptual integration

2.3.1 Summary of findings

The effect of convergent cues in Chapter 4 was not only seen in classic semantic regions such as AG and middle temporal gyrus, but also within other DMN regions including medial prefrontal cortex, posterior cingulate and superior frontal gyrus. To further characterize this effect we interrogated the neural response along the Principal Gradient of connectivity described by Margulies et al. (2016), which is anchored at one end by unimodal regions, and at the other end by heteromodal cortex overlapping with DMN. This analysis offers a complementary approach to univariate activation analyses by describing systematic changes on the cortical surface, thus shifting the focus away from individual regions. Crucially, we found that the effect of semantic integration increased in a linear fashion along the gradient and was maximal at the DMN end. Maintaining a single cue relative to uncued decisions had the opposite topographical arrangement, with maximal activation towards the unimodal end of the principal gradient, in regions overlapping with visual cortex. These novel findings go some way in helping to characterize the role of DMN in semantic cognition. Not only was there consistent evidence for a role of DMN in multimodal feature integration (Bonnici et al., 2016; Braga et al., 2013; Bzdok et al., 2013; Margulies et al., 2016; Price et al., 2015; Pylkkänen, 2020; van den Heuvel and Sporns, 2011; Vatansever et al., 2017b, 2015b), but the thesis findings also suggest that this effect of convergent cues is graded, in a way that reflects the increasing separation of heteromodal cortex from sensory regions dedicated to perceiving and acting.

2.3.2 Relation to broader literature

A core principle in neuroscience is that the topographical arrangement of the cerebral cortex governs its function. In his seminal work, Mesulam (1998) proposed a hierarchical architecture of cortical organization, whereby increasingly abstract features of cognition are formed through the progressive integration of neural signals from primary sensory and motor regions toward transmodal cortices. Unlike primary cortex, association regions in transmodal cortex are "untethered" from the hierarchies and constraints that govern the functional specialization of sensory systems (Buckner and Krienen, 2013). In this way, the progressive spatial distance from structural landmarks corresponding to primary sensorimotor cortex (Margulies et al., 2016), and the increasing divergence from the microstructural constraints that determine the functional specialization of unimodal areas (Paquola et al., 2019) may underpin the capacity of association cortex to integrate information from multiple modalities. Recent work by Margulies et al. (2016) demonstrated that DMN nodes are located at maximal geodesic distance from unimodal systems, supporting the view that increasingly complex and abstract representations are formed where the input from unimodal features is reduced (Buckner and Krienen, 2013; Mesulam, 1998; Plaut, 2002; Schapiro et al., 2013). Consequently, the separation of heteromodal DMN regions from unimodal cortex may be at the core of our ability to form conceptual representations that are not dominated by a particular type of feature but instead draw on multiple types of information (Margulies et al., 2016). In a similar way, the Graded Hub and Spoke framework (Lambon Ralph et al., 2016) predicts a graded convergence of conceptual features from primary sensory and motor cortices into the heteromodal ATL. Following this prediction, conceptual retrieval that follows multiple cue types is likely to be less reliant on unimodal systems – which may support individual cue types, and more reliant on heteromodal cortex – which can capture the convergence of these cues.

This thesis was therefore motivated by the hypothesis that integrating information from valence and location contexts would produce a shift along the gradient, with greater recruitment moving toward heteromodal cortex at the top end of the gradient when multiple cues are presented. Our findings are consistent with the idea of a hierarchy of abstraction, whereby increasingly complex relationships are captured as the pattern of neural activation moves away from primary systems (Buckner and Krienen, 2013; Lambon Ralph et al., 2016; Mesulam, 1998; Patterson et al., 2007; Plaut, 2002; Schapiro et al., 2013). Environmental cues such as affect and spatial location provide complex sources of information, which can be integrated into coherent meanings through a process of abstraction or separation from the unimodal systems dedicated to perception. Evidence that semantic decisions following affect and location cues elicit activation in DMN regions at the top of the principal gradient indicates that one key role of heteromodal cortex is to extract regularities that are invariant to changes in task features (Patterson et al., 2007) to form a highly integrative contextual framework.

The observation that the pattern of neural activation for cue combinations followed the graded organization of cortex is consistent with recent work showing that increasing conceptual similarity gradually recruits regions at the top of the gradient (Wang et al., 2020). In this study participants made yes/no decisions to words based on specific features, while the global similarity between the probe and the target was manipulated parametrically. The response to this parametric task manipulation varied along the principal gradient; at the DMN end of the connectivity gradient, the neural response was maximal for items that had the highest global similarity, while at the sensorimotor end, it was greatest for items that only shared the task-relevant feature. Crucially, this effect could not be explained by task difficulty, as the same pattern was also observed for non-matching trials (in which target and probe did not share the relevant feature e.g. TOMATO - CUCUMBER based on *colour*) – for these trials, global similarity made the judgements more difficult, but more activation was still observed for DMN. These findings suggest that the cortical hierarchy described by Margulies and colleagues (2016) might reflect the consistency between our current experiences and long-term semantic memory. In line with this idea, the present thesis revealed involvement of DMN when the context was aligned with representations in long-term memory (i.e. when convergent cues activated the same conceptual representation) even though behavioural performance was unchanged by the presence of multiple sources of information. Although the DMN has often been associated with task-induced deactivation (Humphreys et al., 2015; Humphreys and Lambon Ralph, 2015), the systematic change along the gradient observed for cue combinations in Chapter 4 and the effect of global similarity (Wang et al., 2020) argue against an interpretation of the gradient as a hierarchy of difficulty. Instead, this novel evidence supports the idea that increased recruitment of DMN might reflect states of information integration, even when the task is more difficult.

The findings in this thesis have similarities and differences with studies showing recruitment of heteromodal cortex during operations that require the separation of cognition from the external environment, such as states that draw on heteromodal representations in memory (Konishi et al., 2015; Murphy et al., 2019, 2018; Smallwood et al., 2013b). For example, Murphy et al. (2019) found that decisions based on memory (1-back) elicited maximal activity at the DMN end of the gradient, whereas decisions based on perceptually available information (0-back) recruited regions at the unimodal end of the gradient, and this effect was greater for meaningful stimuli (Murphy et al., 2018). Similarly, in our study, cues were not perceptually available when participants retrieved semantic associations, and consequently the activation at the top end of the gradient might reflect the integration of convergent information based on memory. Nevertheless, although our cueing paradigm unfolded over time, an important difference with Murphy et al. is that decisions were not "perceptually decoupled" but they were made in response to words presented on screen (which were modulated by the cues presented in the previous screen). Moreover, Murphy et al. (2018) showed recruitment at the DMN end of the gradient even when the tasks only probed a single feature and therefore placed little demands on information integration. Conversely, our paradigm had strong integration requirements but working memory was not manipulated in a systematic fashion.

Taken together, the available empirical evidence suggests that the heteromodal end of the gradient may support different cognitive functions, including decoupled or memory-guided decisions (Murphy et al., 2019, 2018), retrieval of items with high conceptual similarity (Wang et al., 2020), and information integration (Lanzoni et al., 2020). As such, a single cognitive label is unlikely to capture the different behaviours associated with DMN. An alternative way of describing the cognitive profile of the gradient may aim to extract the commonalities between the psychological processes observed at the top of the gradient. In this way, the DMN end appear to sustain types of cognition where the computation requires separation from perceptual systems, which is common to memory-guided decisions, semantic cognition, and integration of multimodal information. Consequently, a greater need to produce patterns of cognition that are separated from unimodal system may elicit greater activation toward the heteromodal end of the gradient. This interpretation raises questions for future investigation, which are discussed in Section 3.3.

Clustering approaches applied to the resting-state data have revealed a tri-partite organization of DMN, with a medial temporal lobe (MTL) subsystem focused on parahippocampal structures, ventromedial prefrontal cortex and posterior inferior parietal lobule; a dorsomedial prefrontal cortex (DMPFC) subsystem anchored in the lateral temporal cortex, temporoparietal junction and dorsomedial prefrontal cortex; and a third "core" subsystem engaging midline regions including anterior and posterior cingulate (Andrews-Hanna et al., 2010). Andrews-Hanna et al. suggest that these components might be functionally distinct, with the MTL subsystem involved in scene construction, the DMPFC supporting metalizing, and the midline core recruited when participants make self-relevant affective decisions. Given the functional-anatomic heterogeneity of this network, an important question is whether different DMN components equally contribute to conceptual integration. Although we did not test this directly in our experiment, an overlay of the cue combination effect and the three DMN subsystems (Andrews-Hanna et al., 2010; Yeo et al., 2011) suggests that the different subsystems participate in information integration to different extents (Figure 6.2.). Combining multiple sources of information during semantic decisions predominantly recruits “core” regions (33% of the voxels overlap with this subsystem) in line with the proposed integrative function of these midline and parietal structures (Andrews-Hanna et al., 2014; Bzdok et al., 2013; Leech et al., 2012), however some overlap is also visible with the MTL (4.7%) and DMPFC (9.2%) subsystems. An interesting observation is that cue combinations overlap with all three DMN components in spatially adjacent areas in parietal cortex, mirroring the interdigitated organization of networks revealed by Braga and Buckner (2017). This is consistent with the idea that AG may serve as a functional hub, allowing external and internal inputs to be integrated with long-term representations (Andrews-Hanna et al., 2014; Binder and Desai, 2011; Seghier, 2013).

In summary, an upsurge of interest has focussed on the spatial arrangement of whole-brain connectivity patterns and their role in constraining cortical function (for review see Huntenburg et al., 2018). Gradients supporting increasingly abstract levels of representation have been observed in several domains (Huntenburg et al., 2018; Sepulcre et al., 2012; van den Heuvel and Sporns, 2013), including object recognition in the ventral occipito-temporal stream (Goodale and Milner, 1992; Mishkin and Ungerleider, 1982; Patterson et al., 2007; Visser et al., 2012), semantic processing in the anterior temporal lobe (Bajada et al., 2017b), episodic memory in the hippocampus (Brunec et al., 2018; Dalton et al., 2019; Sekeres et al., 2018), and goal abstraction in prefrontal cortex (Badre, 2008; Badre and D’Esposito, 2009). The work presented in this thesis adds to this literature by demonstrating that situations in which the context supports retrieval activate the cortical surface in a graded fashion which reflects the separation of heteromodal cortex from unimodal systems. The shift toward the DMN end of the gradient for decisions following multiple is compatible with a role of DMN in information integration. More broadly, our findings provide support for the functional relevance of cortical gradients in understanding aspects of cognition.

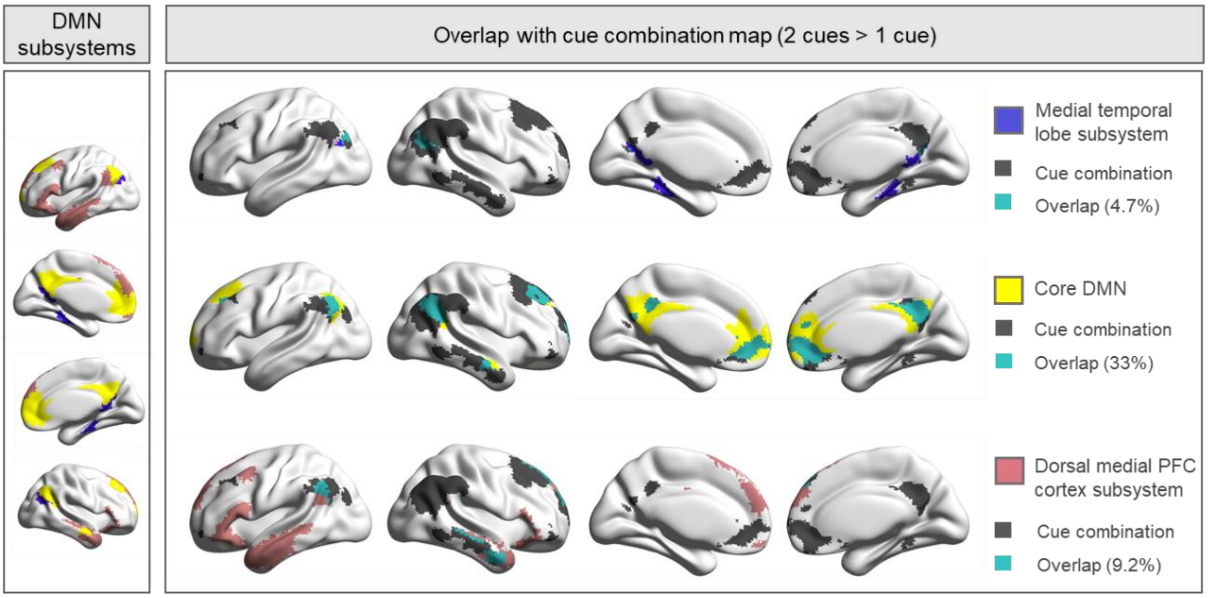


Figure 6.2. Overlay of cue combination map (contrast of 2 cues > 1 cue at the time of semantic decisions; from Lanzoni et al., 2020) and DMN subsystems (Andrews-Hanna et al., 2010; Yeo et al., 2011). The % overlap reported in the legend indicates the percentage of the cue combination map that overlaps with each DMN subsystem.

2.4 Effects of affect and location cues

2.4.1 Summary of findings

This PhD used valence cues (emotional faces and prosody) and pictures of the visuo-spatial contexts in which items commonly occur to prime the meaning of ambiguous words. To our knowledge, this is the first time that affect and location cue types have been used in semantic retrieval tasks. Because concepts are rich and comprise features from different modalities, it is important to understand the extent to which multi-modal features can facilitate retrieval within the semantic system and focus activation on different aspects of concepts. Based on the Hub and Spoke model (Jefferies, 2013; Lambon Ralph et al., 2016; Patterson et al., 2007), we expected that emotional faces, emotional prosody and location cues would influence the accessibility of word meanings in patients with deregulated semantic control. The results described in Chapter 2 confirmed our predictions, but also suggested that different cue types may not be equally effective in priming conceptual representations: emotional facial expressions were only effective when used as miscues, while visuo-spatial contexts were associated with both positive effects of cues and detrimental effects of miscues. In contrast, effects of emotional prosody only approached significance, indicating that valence presented in an auditory format might be a more subtle cue to word meaning (consequently, prosody was not carried forward into the following experiments). In Chapter 3 we replicated findings that semantic retrieval in patients with aphasia is improved by the presence of a context, whilst a direct comparison of cue types revealed that only visuo-spatial contexts were significantly associated with better accuracy in the task.

Together, these findings suggest that contexts such as valence and spatial location cues can influence the accessibility of long-term representations in patients with deregulated semantic control; however photographs of associated spatial locations constrain meaning retrieval to a greater extent.

Although we did not observe behavioural effects of cues in healthy participants in Chapter 4, the task-based fMRI analyses revealed distinct patterns of neural recruitment associated with cued semantic decisions. Location cues activated medial temporal lobe regions typically involved in processing spatial scenes and representing long-term knowledge about spatial locations (Epstein and Kanwisher, 1998; Epstein et al., 2007). We found increased activation in domain-general control regions overlapping with MDN (Duncan, 2010; Fedorenko et al., 2013) when subjects made decisions following one cue (average of affect and location) compared to uncued decisions. When the two cue types were presented simultaneously in the same trial several nodes of the DMN showed increased activation at retrieval, and the effect of combining multiple convergent cues was maximal at the heteromodal end of the principal gradient (Margulies et al., 2016). Collectively, these results suggest that the brain is sensitive to the presence of multi-modal context during semantic retrieval, even though the behavioural output may not always be affected. In line with this idea, when we used a larger sample size to examine individual differences in patterns of brain-behaviour associations in Chapter 5, we observed a behavioural facilitation of cued compared to uncued decisions in healthy people – resembling the cueing effects observed in SA in the two Neuropsychology chapters. Moreover, our seed-based analyses of intrinsic connectivity provided evidence consistent with the idea that context-guided decisions have a specific neural architecture.

Taken together, these findings suggest that, at a behavioural level the effect of cues is relatively subtle, and consequently it may only emerge in a large sample (Chapter 5) or when the cues are used as an alternative strategy to compensate for difficulties in controlled retrieval (Chapter 2 and 3). Nevertheless, semantic decisions with different levels of cueing gave rise to specific patterns of neural activity (Chapter 4) and were associated with distinct patterns of intrinsic connectivity (Chapter 5), suggesting that the brain is sensitive to the integration of multi-modal information.

2.4.2 Relation to broader literature

Most studies of cued retrieval in SA have focused on language contexts, for example the sentence in which an ambiguous word appears (e.g. “They look at *cell* aging”; Noonan et al., 2010) or the initial phonemes of a word in picture naming provided one at a time until the correct response is produced (e.g. for squirrel, /s@/, /sk@/, /skw@/, /skwI/, etc. Jefferies et al., 2008). Pictures of everyday objects have sometimes been used as cues to examine the impact of task-constraint on naturalistic object use in SA, typically yielding a facilitation effect compared to verbal instructions (Corbett et al., 2011). Overall, these cues facilitate comprehension by boosting activation for the relevant features of the concept, while reducing the activation of the semantic competitors. In contrast, other types of non-verbal contexts do not appear to facilitate semantic retrieval. For example, when patients with SA are tested on their ability to recover unusual uses for everyday objects, the action-goal context (e.g. “kill a fly”) is not sufficiently helpful to select an alternative object (e.g. newspaper) when the canonical object (e.g. fly swat) is missing from the options (Corbett et al., 2011). As the majority of work on the topic has focused on language cues, and only a relatively small number of studies have examined non-verbal cues, this PhD provides unique insights into the effect of non-language contexts on retrieval. We showed that multimodal features that prime the relevant aspects of knowledge can be used by SA to produce flexible patterns of behaviour, even when they are not straightforwardly associated with the concepts (e.g. a picture of a supermarket does not directly prime the concept JAM). On the other hand, patients can be seriously misled by cues that are not consistent with information to be retrieved. Beyond the theoretical implications for component-based theories of semantic memory (cf. Hub and Spoke), these findings have important practical implications for patient management and rehabilitation. Being aware that patients benefit from multimodal cues (but can also be deceived when bad news is communicated with a smile or when objects are presented in unusual settings) may help families and caregivers to build richer and more controlled everyday contexts to support comprehension.

Despite being relatively unexplored in the semantic memory literature, affect and location contexts have often been examined in relation to episodic memory. The spatial context in which an event is encoded plays a fundamental role in episodic retrieval (Burgess et al., 2002, 2001a; O’Keefe and Nadel, 1978), serving as a “spatial scaffold” for episodic memory (Hassabis and Maguire, 2009, 2007; Nadel, 1991; O’Keefe and Nadel, 1978; Robin et al., 2016; Robin and Moscovitch, 2017, 2014; for review see Robin, 2018). Congruent environments at encoding and retrieval can facilitate object memory for items encountered in a virtual reality (VR) setting (Pacheco et al., 2017), while crossing a spatial boundary during the exploration of a VR environment can disrupt memory for the order of the objects encountered (Horner et al., 2016). Moreover, spatial cues probing specific scenes have been associated with more detailed episodic memories compared to people cues (e.g. "You are with Joanna"; Robin et al., 2016) and event cues which are not tied to a specific location (e.g. "holiday celebrations"; Sheldon and Chu, 2017). Notably, real-world spatial contexts are effective cues to memory retrieval both when they are presented as pictures (Robin et al., 2019) or in the form of short narratives (e.g. “You are in front of the Eiffel tower”; Robin et al., 2016). Similarly, emotional cues have been shown to be powerful cues in episodic memory (for review see Buchanan, 2007). In particular, mood induction paradigms have consistently shown that episodic retrieval is improved when there is emotional congruency between encoding and retrieval (for review see Eich, 1995; Lewis and Critchley, 2003), and the effect has been observed for different types of materials, including verbal material

(Bower, 1981; Bower et al., 1978; Bower and Mayer, 1989), autobiographical experiences (Bower, 1981; Eich et al., 1994), two-dimensional symbols (Robinson and Rollings, 2011), faces (Robinson and Rollings, 2011), and everyday objects (Xie and Zhang, 2018).

Here we show that these cue types which have previously been shown to improve the remembering of episodes can also influence the accessibility of semantic representations, although the effect appeared to be quite subtle. At a behavioural level, the subtle facilitation of cueing could reflect the opposite ways in which the two neurocognitive components of semantic integration contribute to semantic retrieval (Chapter 4). We might imagine that the working memory demands of maintaining cues will slow reaction times down, while the integration of convergent information might speed responses up. In this way, changes associated with the recruitment of MDN and DMN to support the relevant aspects of retrieval might counterbalance each other in terms of observed efficiency on the task.

In Chapter 4, direct comparisons between the two cue types only partially aligned with the expected networks for face and place processing (Epstein and Kanwisher, 1998; Epstein et al., 2007; Haxby et al., 2000; Kanwisher et al., 1997). Although studies of category-specific semantic access have revealed regions that preferentially activate for faces compared to places – such as right occipital face area, bilateral fusiform face area, and superior temporal sulcus (e.g. Fairhall et al., 2014), our contrast of emotions over locations failed to reach statistical significance. In contrast, location cues activated classic sites for spatial processing, including the parahippocampal place area and the retrosplenial cortex.

3. Limitations and future directions

3.1 Chapter 2

As noted in Chapter 2, the different cue types did not appear to be equally effective at priming the meaning of ambiguous words. Visuo-spatial contexts were associated with the strongest cueing effects, perhaps reflecting the highly concrete nature of the information conveyed by a spatial scene. Affect cues were less effective overall than visuo-spatial cues: the effect of emotional prosody only approached significance, while facial expressions influenced behavioural performance only when they primed the irrelevant interpretation (i.e. miscues). This is perhaps not surprising, since the emotional valence associated with a given word is likely to be variable across individuals and it is often influenced by personal experiences. For example, while strawberry JAM is typically associated with positive emotions, it could also trigger unpleasant feelings of disgust if one has accidentally tasted mouldy jam in the recent past. Thus, although some words tend to be more often associated with a given emotion, we should expect a certain degree of individual variability to be always present. In addition, the cues used in this thesis activate the relevant features only indirectly. Unlike mood induction paradigms, our cue manipulation did not alter the emotional state of the participants, and consequently the effects of cues were likely to be more subtle.

Another interesting point to note concerns the way in which emotions are conceptualized. Our experiment used discrete categories of emotions (e.g. fear, happiness, disgust, etc.) to prime the meaning of words, but an alternative way to think about emotional valence in relation to language is that of a "graded" concept, where words rest on a continuum of negative-to-positive valence. By this view, emotional valence might be a more fundamental aspect of meaning for words situated towards the extreme ends of this distribution (e.g. "cancer" or "friendship") compared to more neutral words situated in the middle (e.g. "practice"). Consequently, emotional contexts such as facial expressions and prosody should be more potent cues for concepts that have stronger emotional valence. Future research could explore this idea by manipulating the emotive content of words and measuring the magnitude of cueing effects at different levels of emotiveness. If emotions have a conceptual representation, as suggested by recent theories (Lindquist et al., 2014; for review see Satpute and Lindquist, 2019), stronger cueing effects might be observed when emotions are core aspects of the meaning. This investigation will have to take into account the fact that abstract words tend to be statistically more valenced than neutral word (Kousta et al., 2011; Vigliocco et al., 2014), and therefore concreteness might interact with the effect of valence, if not properly controlled.

The results described in Chapter 2 suggest that patients with SA are sensitive to affect cues; however it remains unclear what type of information is being picked up. One possibility is that patients may still recognize different emotional categories (e.g. anger *vs*. fear) despite their semantic deficit. According to the *basic emotion hypothesis* (Ekman et al., 1987; Ekman and Cordaro, 2011; Sauter et al., 2010), the ability to detect discrete emotions in faces relies on innate and psychologically primitive mechanisms – which are largely independent from language systems. As conceptual knowledge about emotions is thought to be irrelevant to the ability to recognize emotional categories (Ekman and Cordaro, 2011), semantic impairment should leave emotional categories intact. However, a growing body of work suggests that it is possible to impair the recognition of discrete emotions by manipulating the accessibility of conceptual knowledge (e.g. Fugate et al., 2010; Gendron et al., 2012; Lindquist et al., 2006). In line with these findings, *constructionist theories* of emotion (Barrett et al., 2007; Lindquist and Gendron, 2013) propose that the perception of discrete emotions relies on different processes: (i) the perception of core valence (i.e. positive vs. negative) and (ii) the ability to access stored meanings about emotional categories in long-term memory. These theories predict that a semantic deficit should impair the recognition of emotional categories, while leaving the ability to extract valence preserved. This pattern of impairment has been documented in patients with semantic dementia (SD) following atrophy of the anterior temporal lobe (Lindquist et al., 2014), raising the question of whether stroke patients with semantic control deficits might show similar behaviour. A follow up study could use a cueing paradigm in which core valence and emotional categories are manipulated orthogonally to address this question. This is an interesting avenue for research, since patients with SA are likely to rely on environmental cues to a greater extent than healthy participants. Being aware of the exact nature of the emotional information that patients can extract from the facial expression of the speaker or from their voice is highly relevant for patient management and rehabilitation.

3.2 Chapter 3

In chapter 3 we examined whether combining affect and location cues would facilitate patients' performance to a greater extent than single cues, since both cue types proved effective in the previous experiment. Against our predictions, we found that patients' performance following two cues was not significantly different than following a single cue. It is important to note that a null result cannot be interpreted as evidence for an impaired mechanism; all we can conclude is that patients did not benefit from multiple cues in these particular circumstances. There are several potential explanations for this result. A first possibility is that providing a conceptually richer environment did not yield any additional benefit on retrieval because patients are not able to integrate the cues. This interpretation seems unlikely, since conceptual combinations have been repeatedly associated with regions in the DMN (Bemis and Pylkkänen, 2013, 2011; Price et al., 2016, 2015; Pylkkänen, 2020), which are largely spared in our patient sample. A more plausible explanation is that the task may not have been sufficiently challenging for patients to benefit from multiple cues. After a single cue, patients' efficiency on subordinate meanings nearly caught up with dominant meanings, suggesting that a second cue may not have been necessary in these circumstances. Additionally, controls had near-ceiling performance across cue conditions – again suggesting that the task did not have sufficient control demands. However, unlike experimental tasks, real-world scenarios contain multiple sources of complexity; semantic ambiguities in real language can co-occur even in the same sentence. A follow up experiment could use a parametric manipulation of task complexity to assess whether additive or supra-additive effects of cues interact with control demands. A third possibility is that the high working memory demands of the task might have prevented patients from effectively using both cues. In this paradigm participants were presented with the cues for two seconds, and then the cue pictures were replaced by the semantic decision task. We know from Chapter 4 that maintaining a single semantic cue vs. scrambled images involves working memory; we can assume that maintaining two cue pictures might pose an even greater working memory load on patients with SA – who already have deficits of semantic control. Perhaps, in situations where both cues are provided, patients tend to rely exclusively on the most constraining rather than processing both. A future experiment could use a different paradigm in which the working memory demands are minimized through the simultaneous presentation of cue pictures and semantic decisions (as in Chapter 2). At present, we are unable to distinguish between these different interpretations for the lack of additive effects of cues in SA and future research is needed. Nevertheless, this question has important implications for patient management: if patients were shown to benefit from multiple cues over and above individual cues, everyday environment could be enriched by affect and spatial information to improve communication.

In Chapter 3 we focused our investigation on SA, since the pattern of brain damage allowed us to make specific predictions about their potentially spared ability to integrate cues. An alternative way to study the neurocognitive bases of semantic cue integration would be to compare patient groups with similar levels of semantic impairment but opposite brain damage. Future research could contrast the performance of patients with SA and patients with damage in ATL or other regions within DMN on the same task. Ideal candidates would be patients who had herpes simplex encephalitis resulting in lesions focused on the anteromedial temporal lobes, who are impaired at tasks that require multimodal (i.e. visual and auditory) information integration (Taylor et al., 2006). By directly contrasting two patients groups with opposite behavioural patterns, this research could overcome the issue of near-ceiling performance in healthy controls. This experimental design would allow us to examine whether one group is more impaired at cue combinations than the other – despite having an equivalent semantic impairment. This question has important theoretical implications, as it would allow more definitive conclusions about the causal role of DMN regions in conceptual integration.

3.3 Chapter 4

In line with literature indicating a role of DMN in conceptual combinations (Price et al., 2016, 2015; Pylkkänen, 2020), our fMRI study found recruitment in several DMN nodes when participants performed semantic decisions following multiple convergent cues, compared to when a single cue type was provided. The observation that combining affect and spatial cues elicited a specific pattern of neural activity partly aligns with the Hub and Spoke model of semantic cognition (Jefferies, 2013; Lambon Ralph et al., 2016), which anticipates that modality-specific features are integrated to form more complex and abstract representations. However, our results are not perfectly consistent with the predictions raised by this model. Against the idea that conceptual representations are formed in the heteromodal hub in ATL, the present study failed to recover this region for cue combinations. This could be due to the nature of the task, which required participants to create "temporary" combinations of the cues to guide retrieval in a specific trial. The lack of ATL activation could also be due to the type of stimuli adopted in the experimental paradigm; these were complex and contained multiple features. For example, the trial FALL - GRAVITY was cued by a *facial expression of fear* and by an *indoor bouldering* location (Figure 6.3.), but it remains unclear the extent to which the information contained in these cues is "core" to the concept FALL. Perhaps more concrete concepts (e.g. DOG) which are more straightforwardly defined by their sensory-features (e.g. furry coat, wagging tail, bark sound) would have shown increased ATL activation when preceded by these well-defined features; in this context, it would also be easier to test the effects of cue combinations. Future experiments could therefore explore whether BOLD activity increases in ATL when concrete concepts are cued using their basic features (Chiou and Lambon Ralph, 2019). Another possibility is that information integration may occur across distributed semantic regions rather than in a single location. A similar proposal has been advanced by semantic theories which suggest abstract representations are formed in several "convergence zones" (Binder et al., 2009; Binder and Desai, 2011; Tranel et al., 1997). Our findings that cue combinations unfold along the Principal Gradient (Margulies et al., 2016) suggest that a 'distributed' view of conceptual integration might provide a more accurate description of how different sources of information are brought together. In this view, large areas of cortex will work in concert to reach increasingly higher level of abstraction.

Figure 6.3. Example of a trial in the two-cues condition - from Lanzoni et al., 2020.

Although our paradigm allowed us to recover a set of regions within DMN that support cue combinations, it should be noted that both affect and location cues are multimodal contexts which are known to be relevant for the DMN (Chanes and Barrett, 2016; Greicius et al., 2003; Raichle et al., 2001; Satpute and Lindquist, 2019; Simpson et al., 2000; Bellmund et al., 2016; Burgess, 2002; Burgess et al., 2002; Robin et al., 2018). Future research could examine the effect of unimodal features that are more readily associated with the systems responsible for perception and action (e.g. sound, smell, motion). If the DMN activation following multiple cues reflects information integration, we would expect a similar pattern of neural activity when classic "spoke" representations are used instead of complex contexts.

The lack of a behavioural facilitation effect from multiple cues in this experiment suggests that semantic decisions following two cues were not easier than trials with less contextual support, at least in this sample. Consequently, this allowed us to rule out "task-negative" interpretations of the DMN involvement, which would predict activation when an easy task is contrasted with a hard task (Humphreys et al., 2019, 2015; Humphreys and Lambon Ralph, 2015). However, the behavioural advantage for two cues vs. uncued decisions observed with a larger sample in Chapter 5 raises the question of whether a similar difference would have emerged here with more participants, and suggests a (subtle) facilitation of cue combinations. Nevertheless, a task-negative account is unlikely to provide an adequate explanation of the DMN pattern of activation - since a growing body of work suggests that DMN is involved in cognitively demanding tasks (Crittenden et al., 2015; Murphy et al., 2018; Turnbull et al., 2019a; Vatansever et al., 2017b, 2015a). The highly heterogeneous nature of DMN (Andrews-Hanna et al., 2010; Braga and Buckner, 2017; Yeo et al., 2011) suggests an alternative possibility, whereby task-difficulty may interact with long-term knowledge differently in different DMN subsystems. For example, a recent meta-analysis revealed task-dependent dissociations between the dorsal medial PFC subsystem and the "core" (Humphreys et al., 2015): while ATL is activated for semantic tasks regardless of difficulty, AG deactivates for all tasks and this effect is related to task difficulty. Consequently, we might expect that semantic integration interacts with the easiness of the semantic decisions in the "core" but not in the lateral temporal cortex. Our study does not allow us to come to a conclusion regarding the contribution of task difficulty to our results, but future experiments could include a control condition where difficulty is manipulated experimentally and could examine the response across DMN components. A parametric manipulation of the number of cues could also provide further evidence for a role of DMN in semantic integration (over and above task difficulty): if BOLD signal in DMN increased parametrically with the number cues, while behavioural efficiency remained constant, this would establish with greater precision the relationship between semantic integration and DMN.

In terms of the cognitive interpretation of the principal gradient, the heteromodal end of the gradient appears to support several aspects of cognition (see Section 2.3.2). Patterns of increased neural activity at the DMN end of the gradient have been observed during perceptually decoupled working memory tasks (Murphy et al., 2019, 2018), retrieval of long-term semantic knowledge (Wang et al., 2020), and integration of multimodal information in the present thesis (Lanzoni et al., 2020). These findings raise the question of whether the description of the top of the gradient in terms of a single cognitive function may be possible with further research, or whether we should instead accept an explanation based on the need to separate cognition from perceptual systems. Future studies could aim to explore commonalities and differences between the types of cognition that have been linked to the principal gradient to establish whether they recruit similar portions of heteromodal cortex and whether they follow similar transitions along the gradient. Moreover, future work should explore interactions between these functions in a more systematic fashion. For example, does integration interact with the meaningfulness of the items? To answer this question, a follow up study could explore the gradient recruitment during tasks which require to integrate meaningful stimuli compared to tasks probing simple perceptual features (e.g. lines that can be perceived as shapes, or discrete dots that elicit a conscious experience of motion). Future research could also examine interactions between the memory demands of the task and the strength of integration effects. For instance, would we see more activation at the top end of the gradient if the stimuli to integrate unfolded over time in a succession of events? Despite these open questions, the novel findings in this thesis emphasize the explanatory power of the principal gradient – which is able to explain the computations underpinning memory-guided cognition, as well as semantic retrieval and integration.

3.4 Chapter 5

This study did not recover an association between the connectivity of the brain at rest and efficiency in semantic decisions following multiple cues relative to a single cue, even though this effect might be expected. Chapter 4 linked cue integration with a specific neural substrate encompassing regions of the DMN, including bilateral angular gyrus, medial prefrontal cortex, posterior cingulate, and middle temporal gyrus. Additionally, Chapter 5 found behavioural facilitation following multiple cues, suggesting that this behavioural pattern might be reflected in the intrinsic architecture of the brain. Thus, we hypothesized that specific patterns of coupling from DMN regions might be associated with better performance on coherent cue combinations. Increased coupling between regions of the same network has been linked to improved performance in tasks which rely on the network (Baird et al., 2013; Gonzalez Alam et al., 2019; Smallwood et al., 2013a; Zhang et al., 2019). For example, a recent study by Gonzalez Alam et al. (2019) showed that stronger coupling between left hemisphere semantic control regions and other language-relevant regions in the left hemisphere was associated with more efficient semantic retrieval. Alternatively, we expected to find associations between efficiency in the 2 cues vs. 1 cue condition and greater coupling between regions functionally relevant for the task (e.g. DMN and occipito-temporal cortex for processing visual cues). This pattern of brain-behaviour association has been seen in tasks probing semantic associations (Krieger-Redwood et al., 2016), response inhibition (Gonzalez Alam et al., 2018), and semantic summation (Evans et al., 2020). Our analysis did not reveal associations between intrinsic connectivity and efficiency at cue combinations; however this could be due to the small sample size in chapter 5 and the consequent lack of power (but see Mollo et al., 2016 for a similar sample size). Our choice of using network-based seeds could also have influenced the pattern of results, therefore a follow up study could use more circumscribed seeds placed in regions known to be important for conceptual combinations, such as ATL and AG (Bemis and Pylkkänen, 2013; Price et al., 2016, 2015).

While this study shows that separation between different components of DMN at rest is predictive of behavioural efficiency in the 1 cue vs. 0 cues trials, we only recovered a single cluster in rAG. It remains unclear whether efficiency in contextually guided semantic decisions compared to uncued decisions is related to (i) the separation of DMN to rAG specifically, or (ii) whether it is attributable to more general segregation within the DMN. This could be explored using multivariate techniques such as canonical correlation analysis (CCA) which test the relationship between resting-state connectivity of multiple seed regions and behavioural variables simultaneously. Recently, this approach has been implemented by Vatansever et al. (2017a) to examine how several DMN and semantic control regions contribute to different "varieties" or components of semantic cognition. Nevertheless, findings that rAG had opposite patterns of connectivity at rest with (i) DMN regions involved in cue combinations and (ii) MDN regions supporting cue maintenance, is consistent with the complex functional role of parietal cortex, which is thought to be a nexus between different large scale networks (Braga and Buckner, 2017; Bzdok et al., 2013). This is because greater separation between rAG and other regions within DMN might enable this site to couple more strongly with regions relevant for maintaining cues in a goal-driven fashion.

4. Conclusion

This thesis sought to investigate the psychological and neural bases of cued semantic retrieval using a combination of neuropsychology, task-based fMRI and functional connectivity methods. The empirical work in this thesis was motivated by recent accounts of cortical organization (Lambon Ralph et al., 2016; Margulies et al., 2016) which suggest that high-order conceptual representations are formed through the progressive integration of information from unimodal to heteromodal brain regions. This view anticipates an alternative way in which flexible patterns of semantic retrieval can be achieved, beyond the top-down application of semantic control; different patterns of retrieval that suit the changing circumstances can also emerge from the context, which might configure representations at the top end of the principal gradient to suit the task. The thesis provides evidence consistent with this view by showing that affect and location contexts constrain retrieval in people with deficient semantic control, and generate specific patterns of neural activation - which reflect the interplay of multiple demand and default mode cortex in a way that supports flexible retrieval. In line with the idea of a gradient of abstraction spanning unimodal to heteromodal regions (Margulies et al., 2016), we described a systematic shift along the cortical surface when multiple sources of information could drive access to the relevant representations in long-term memory. Collectively, these findings improve our understanding of the mechanisms underpinning flexible semantic retrieval and elucidate the role of default mode cortex in cognition. Furthermore, this thesis has important practical implications for patient management and rehabilitation, since affect and location contexts can be controlled in everyday situations for the benefit of patients with SA.

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