The cognitive and neural basis of semantic control:
A neuropsychological investigation

A thesis submitted to the University of York for the degree of
Doctor of Philosophy in the Department of Psychology

March 2013

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Abstract

This thesis investigated the relationship between semantically-driven behaviour and executive control. Patients with multimodal semantic deficits (referred to here as semantic aphasia or SA) can access detailed semantic information in tasks that provide strong external constraints on processing, suggesting intact semantic representations, but they have poor performance on tasks that require controlled semantic retrieval or inhibition of irrelevant semantic relationships. Additionally, these patients show deficits on non-semantic assessments of executive functioning which correlate with their performance on semantic tasks. In the current study, we explored the hypothesis that semantic control is underpinned by domain-general cognitive control mechanisms. Group of patients with a primary impairment of executive control (referred to here as dysexecutive syndrome or DYS) were compared with SA cases on a range of semantic tasks that differently manipulate semantic control and on non-semantic executive tasks. The results showed that DYS cases exhibit multimodal semantic impairments that are qualitatively similar to the pattern in SA patients (and highly contrasting with the pattern seen in semantic dementia). (1) Both groups were consistent on an item-by-item basis across different modalities (i.e., judgements to the same concepts presented as words and pictures) but inconsistent between different types of semantic tasks, even when these probed the same concepts. (2) There were minimal effects of familiarity and frequency on comprehension across different range of tasks. (3) Performance on semantic tasks was strongly affected by manipulating control demands – DYS and SA cases showed comparable effects of semantic distance between the probe and target, the strength of distracters and semantic ambiguity. (4) Both groups showed ‘refractory’ effects in comprehension, when the same set of semantically related items was presented repeatedly at a fast rate. The DYS group were *more* influenced than SA cases by speed of presentation, and this factor interacted with the semantic relatedness of the items in the set.

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Acknowledgements

I would like to thank my supervisors Dr Beth Jefferies for her consistent and relentless support throughout the last three years, my research committee Professor Andy Ellis and Dr Silvia Gennari for their valuable guidance in shaping this thesis. Also, I am very grateful to the cooperation of the staff in York House and Daniel Yorath House, run by the Brain Injury Rehabilitation Trust (BIRT), in giving me access to their clients, especially, Dr John Freeland, Dr Ohr Barak and Dr Andrew James, James Clarks and Annabel Van Der Knaap and to all the support workers for their massive help. I am indebted to the patients and their carers for their generous assistance throughout the studies.

I would also like to thank number of individuals who have made important contributions to the development of this thesis. Dr Krist Noonan provided data from the SA patients and collected some of the data from the Dyexecutive patients (Chapter 3). Dr Paul Hoffman developed the contextual diversity measure which is used in Chapter 3 and helped through useful discussions about these data in Chapter 2. Thanks are due to Dea Nielsen in collecting some of healthy subjects' data for Chapter 2. I also acknowledge the contribution of Simone Kohler, and four undergraduate project students, Rachel Kirmond, Alison Jane Smith, Jess Hare and Sam Godwyn, for their great help in developing the tDCS task and collecting and analysing data in Chapter 5.

I am grateful Dr. Mahmood Yamani and Dr. Saeed Wahas from from King Fahad Medical City, Saudi Arabia in giving me a scholarship and their unconditional support during the last three years.

Finally, I would like to thank my daughters and my family for their emotional support especially on those days when nothing seemed to go right and all my friends in the Department of Psychology who I thoroughly enjoyed working with.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

CHAPTER 1

Literature review

Impairments of semantic cognition can arise from a number of different causes. Degeneration of amodal conceptual representations, such as in semantic dementia (SD), lead to impaired semantic performance, because knowledge does not remain with sufficient acuity to support detailed semantic decisions (Patterson, Nestore & Rogers, 2007; Rogers et al., 2002). However investigation of multimodal semantic impairment in a group of patients with semantic aphasia (SA) has suggested that impaired regulation of semantic activation also produces multimodal semantic deficits (Jefferies & Lambon Ralph, 2006). In SA, semantic control defects co-occur with impaired executive processing on non-verbal executive tasks; however, this does not necessary imply a causal connection between the two sets of impairments. Investigating this relationship between deficits of semantic control and domain-general executive control is the central focus of this thesis.

The work addresses three research questions:

First, the thesis explores the underlying causes of semantic impairment in SA in a way that complements earlier investigations by adding a comparison with healthy participants performing under conditions of divided attention. In particular, we focus on the absence of word frequency effects in comprehension in SA (and reverse frequency effects – i.e., poorer comprehension of high frequency items) and conclude that deficits in executive control over semantic processing may underlie this pattern. The comprehension task included words of high and low frequency, allowing us to explore the hypothesis that although high frequency words may be processed more efficiently overall, they may also have higher control demands. We examine whether absent and reverse frequency effects can be produced in healthy participants under dual task conditions, when attention is divided.

Secondly, to investigate the relationship between semantic abilities and executive control processes, we examined patients with domain general cognitive control deficits (dysexecutive syndrome; DYS) and assessed in-depth their semantic performance, using a battery of multimodal semantic assessments. This complements previous investigations that have focussed on SA patients with multimodal semantic impairment, and who also have executive dysfunction (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010). A comparison of the relationship between semantic control and executive function in these two case-series helps to establish the extent to which these aspects of cognition are coupled, given that neuroimaging evidence has suggested that the network of brain regions associated with semantic control demands includes multi-demand executive regions plus regions restricted to the semantic domain in anterior prefrontal cortex and left posterior temporal cortex (Noonan et al., submitted; Duncan et al., 2006).

Finally, we evaluate the effects of transcranial direct current stimulation (tDCS) on synonym judgement tasks that vary in semantic control requirement in healthy participants, with the ultimate aim of evaluating whether this technique could be used to improve comprehension, providing a potential rehabilitation tool for patients with semantic aphasia.

Introduction

Whilst the semantic memory store is the part of the long term memory system responsible for our knowledge of facts, concepts and their interrelationships (Tulving, 1983), our ability to retrieve, manipulate and apply this information in a relevant, goal directed manner – e.g. to establish that a panther and a lump of coal are both black when asked to perform a verbal colour judgement task – is thought to depend on the operation of executive processes (Whitney et al, 2011). Jefferies and Lambon Ralph (2006) propose that semantic cognition is underpinned by at least two interacting components: (a) semantic representations and (b) executive processes that direct and control semantic activation. These components of semantic cognition are associated with different neural substrates and can be impaired separately in different groups of brain-injured participants. Patients with semantic dementia (SD) have a degraded store of semantic knowledge following atrophy and hypometabolism focussed on the anterior temporal lobes bilaterally (Galton et al., 2001; Mummery et al., 2000; Nestor et al., 2006). This results in poor performance across the full range of verbal and non-verbal modalities and a high degree of consistency across tasks (Bozeat et al., 2000; Garrard & Carroll, 2006). In contrast, stroke aphasia (SA) patients with multimodal comprehension problems have infarcts affecting left posterior temporal, inferior parietal and inferior frontal regions (Berthier, 2001; Chertkow et al., 1997; Dronkers et al., 2004; Hart & Gordon, 1990; Hillis et al., 2001).These lesions produce semantic impairment that is strongly modulated by task demands; particularly the extent to which executive semantic processes, such as goal-driven attention and selection, are required (Jefferies & Lambon Ralph, 2006).

This thesis explores the neuropsychology of executive semantic processes in patients with SA and dysexecutive syndrome (DYS). It explores the strength of the relationship between executive control over semantic processing and domain-free executive function in these two patient groups, and investigates whether executive impairment in the absence of aphasia is sufficient to produce semantic deficits that resemble those in SA. Semantic control processes are also explored in healthy participants, using dual task methodology to divide attention, and through brain stimulation of left prefrontal cortex to augment semantic control.

The first part of this literature review will consider the dissociation in semantic deficits between SD and SA patients. The areas of brain injury in these two groups will be discussed in terms of the distributed network of brain regions underpinning semantic cognition. Next, the chapter focuses on the relationship between semantic control and executive control in neuropsychological and neuroimaging studies. Finally, the practical implications of this research for speech and language therapy are considered.

Anterior Temporal Lobes and Semantic Dementia

Although not uncontroversial (e.g., Martin, 2007), there is growing evidence of a semantic "hub" in the bilateral anterior temporal lobes (ATLs) (Patterson et al., 2007). Visser et al. (2009) recently examined the sensitivity of ATL structures to semantic judgments in a meta-analysis of 164 PET and fMRI studies. ATL structures were implicated in multimodal semantic decisions for spoken and written words, as well as pictures. The earlier meta-analysis of Binder et al. (2009) also observed reliable activity in ATL in semantic tasks.

The "hub and spokes model" of semantic representation suggests that the bilateral anterior temporal lobes are critical in extracting amodal similarity structure from multimodal experience (Patterson et al., 2007; Rogers et al., 2004). The resulting conceptual representations support performance across all semantic tasks and facilitate appropriate generalisation of shared knowledge to novel tasks and situations (Lambon Ralph & Patterson, 2008). The ATL is proposed to semantic similarities between items even when these share few sensory properties, as well as connecting multimodal features of each item (Mummery et al., 2000; Nestor, Fryer & Hodges, 2006; Williams, Nestor & Hodges, 2005). This view is supported by studies of SD patients, who have profound multimodal comprehension deficits associated with bilateral atrophy of the most anterior portions of the temporal lobes; the pattern of performance in this group suggests degradation of semantic representations (Bozeat et al., 2000; Hodges et al., 1992; Mummery et al., 2000; Nestor et al., 2006). SD is characterized by progressive impairment of semantic ability which affects all modalities of reception and expression, for all kinds of concepts.

The focus of the atrophy in SD contrasts with the pattern of brain damage associated with multimodal semantic impairment in stroke aphasia. In SA patients, the ATL is typically undamaged (Jefferies & Lambon Ralph, 2006); this reflects the low susceptibility of the ATL to damage from stroke. The ATL has two supplies of blood, from the middle and the distal posterior arteries (Visser et al., 2010). In addition, the ATLs store semantic knowledge bilaterally and it is not common to see bilateral strokes (Visser et al., 2010). Given these differences in the focus of the brain damage in SD and SA, we might expect these two groups to show qualitatively different patterns of semantic deficit. Below, we explore the hypothesis that SA patients' semantic memory deficits are not related to semantic storage problems as in SD; instead the executive retrieval mechanisms that access this store are damaged.

Deficits in Semantic Aphasia

Jefferies and Lambon Ralph (2006) compared SA with SD patients and found that both groups showed a similar level of deficits in an array of verbal and non-verbal semantic tasks, yet they had non-overlapping areas of brain damage (bilateral ATL in SD vs. left PFC and temporo-parietal areas in SA). Moreover, SD patients' semantic impairment profile suggested degraded knowledge, while SA patients' performance reflected deregulated semantic control. SD patients were notably consistent in their performance across tasks. In contrast, patients with SA were more inconsistent, particularly when the same concepts were probed using different types of semantic tests (e.g. judgements of semantic association and word-picture matching). SD patients showed a substantial effect of familiarity/frequency while there was a limited effect in the SA patients. In picture naming tasks, the SD group made frequent coordinate and superordinate semantic errors (such as saying "cat" or "animal" for dog), while SA patients made *associative* errors (e.g. "bone" for dog); these responses were almost never found in the SD group. These errors suggest that SA patients retain considerable knowledge about unnamed targets, but their difficulty lies mainly in directing activation towards the target name and inhibiting other associations. Additionally, SA patients exhibited a larger benefit from phonemic cues compared to SD patients in picture naming. Cues help to overcome competition from irrelevant words and concepts in SA, while in SD patients cueing is less beneficial because the store of knowledge is eroded (Jefferies et al., 2008).

Impairments of Semantic Storage vs. Access

This distinction – between degradation of conceptual knowledge in SD and deregulated semantic cognition in SA – resembles the contrast between 'storage' and 'access' semantic impairment drawn previously (Shallice, 1988; Warrington & McCarthy, 1983, 1987); both sets of studies characterise semantic impairments resulting from non-representational damage. Patients with semantic access disorders exhibit profound comprehension problems in the context of relatively preserved conceptual representations (Warrington & Shallice, 1979). Historically, these patients provide the first clear neuropsychological evidence that semantic cognition involves processes beyond the representation of semantic information (Shallice, 1988; Warrington & McCarthy, 1983, 1987). Studies of individuals with refractory access disorder have been important in establishing criteria for distinguishing patients with semantic storage disorders from other forms of impairment where knowledge cannot be accessed or regulated appropriately. However, the distinction between storage and access disorders has been widely debated in the literature. Notably, Rapp and Caramazza (1993) raised two strong criticisms to the proposal of refractory semantic deficits as a syndrome. Firstly, relating to the empirical validity of the distinction, they showed that patients can present with a mixed pattern of access and storage deficits. Secondly, they criticised the absence of a theoretical explanation underpinning the nature of stored representation and access mechanisms (see Rapp & Caramazza, 1993 for a critique of this argument).

Refractory access patients typically present with a number of characteristics which suggest that temporal and contextual factors play an important part in their ability to make accurate semantic judgements (Forde & Humphreys, 1995; Warrington & McCarthy, 1983, 1987). Access to conceptual knowledge is inherently inconsistent – item-specific judgements vary considerably over time, particularly when then the same items are presented repeatedly among semantically similar foils. Serial position effects – worse performance after repeated probes – are more pronounced when the rate of trial presentation is increased. Moreover, patients show minimal or absent effects of lexical frequency and strong effects of cues (Warrington & Shallice, 1979). Although refractory impairments tend to be most commonly reported in the context of verbal tasks (e.g., word-picture matching: Warrington & Crutch, 2004), some evidence suggests that a qualitatively similar pattern can be present on tasks which do not require verbal processing – e.g., sound-picture and picture-picture matching (Crutch & Warrington, 2008b; Forde & Humphreys, 1997; Gardner et al, 2012).

The pattern of semantic impairment in refractory access disorder is distinct from the type of comprehension deficit present in SD (Crutch & Warrington, 2005, 2008a; Warrington & Cipolotti, 1996). In contrast to semantic access disorder, SD patients show minimal effects of temporal factors (e.g., item-repetition, speed of presentation), strong effects of lexical frequency and minimal effects of cueing (Jefferies *et al.*, 2007; Warrington & Cipolotti, 1996). Lesions in refractory access patients typically spare the bilateral ATL and instead disrupt left hemisphere frontal, temporoparietal and subcortical structures (Crutch et al., 2006; Hamilton & Coslett, 2008; McNeil et al., 1994; Warrington & McCarthy, 1983). This strong anatomical division is in keeping with the idea that there are two separate types of semantic disorder and that these latter regions may be involved in regulating access to conceptual knowledge rather than representing semantic information.

A number of different accounts have been proposed to explain patterns of semantic impairment in refractory access cases. Warrington and Cipolotti (1996) proposed that refractoriness reflects abnormalities in the way semantic representations return to a ready state following previous activation. Gotts and Plaut (2002) provided support for this account through a computational implementation of its underlying principles. In their model semantic storage disorders, such as SD, were modelled as lesions affecting the interconnections between large groups of neuron-like units (see also Rogers et al., 2004a). In contrast, semantic access disorders were simulated through damage to neuromodulatory processes which interact with synaptic depression to create a form of neural refractoriness. Patients who show refractory deficits fail to overcome synaptic depression after activation – such effects can be revealed by fMRI studies which find reduced activation with multiple repetitions of an item, known as “repetition suppression”. The neuromodulators acetylcholine and noradrenaline diminish these effects, but in patients with access deficits, the effects are weaker due to damaged white matter tracts that provide these neuromodulatory signals. As a consequence, the system is dominated by synaptic depression and a computational model shows that this could lead to “large effects of presentation rate and repetition, as well as inconsistent responding” (Gotts & Plaut, 2002, p.188). This mechanism might also explain the prevalence of perseveration errors in access patients (Gotts, della Rocchetta, & Cipolotti, 2002; Sandson & Albert, 1987).

An alternative perspective, focussing on the effects of spreading competition in the semantic system, was provided by Jefferies and Lambon Ralph (2006) and Forde and Humphreys (2007). According to this account, repeated probing of semantically related items at fast rates of presentation results in activation spreading across closely related representations. This in turn, leads to poor semantic performance if executive control processes are unable to manage this increased competitive activation. SA patients show declining semantic performance in naming and word-picture matching tasks when they are repeatedly probed at a rapid rate using a small set of semantically-related items (Jefferies et al., 2007). This provides further evidence that semantic impairment in SA is not driven by damage to amodal semantic representations but instead reflects damage to executive-semantic processes. On later cycles, when competition has built up between the items in the set, semantic control deficits might prevent SA patients from selectively focussing on the target concept (Jefferies et al., 2007).

Nevertheless, semantic interference is something that happens in both patients and control groups, Howard et al. (2006) examined the extent to which there are cumulative effects of semantic competitor priming in picture naming task, containing series of five pictures drawn from each of 24 semantic categories. They found a clear effect, where picture-naming latency is slowed by an additional 30 ms for each proceeding semantically related item. This effect is similar to the patients’ studies, although the effect was greater, might be due to their control deficits.

Semantic Control Network

Hart and Gordon (1990) found damage to temporal and parietal areas was associated with comprehension problems in aphasia (i.e. BA 37, 39, 40). Similar findings from five semantically impaired patients, all with damage to posterior inferior temporal areas (i.e. BA 37, 22, 21), were reported by Chertkow et al. (1997). Transcortical sensory aphasia patients suffer from poor comprehension in the context of fluent speech and preserved repetition: studies of these patients reveal that lesions to either the prefrontal cortex (i.e. BA 44, 45, 47) or posterior temporal/inferior parietal areas (i.e. BA 37, 39 etc.) can give rise to selective comprehension deficits, with little difference in the cognitive profiles between these two lesion groups (Berthier, 2001). Similarly, SA patients have damage to prefrontal and temporoparietal regions and damage to either region leads to multimodal semantic deficits and strong effects of executive control demands in comprehension tasks (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010). Gardener et al (2012) explored verbal, visual, and nonverbal auditory refractory effects in SA patients who had pFC +TP cortex or (TP-only) lesions. Through all modalities, patient with pFC + TP showed declined accuracy over repetitions while patients with TP-only lesions did not show the same pattern. These findings support the theory that SA patients have reduced control over multimodal semantic retrieval, suggesting that may be functional specialization within the posterior versus pFC elements of the semantic control network.

Studies have found equivalent impairment of prefrontal and temporoparietal SA patients on semantic tasks such as picture naming, word-picture matching, and judgements of semantic association in the Camel and Cactus Tasks (CCT) in word and picture modalities (Jefferies, Baker, Doran & Lambon Ralph, 2007; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008). Additionally, patients with both types of lesions show improvements in semantic retrieval when provided with external constraints such as phonemic cues in picture naming (Jefferies, et al., 2008).

The combined evidence from patients with SD and stroke aphasia suggests that a large-scale distributed network underpins semantic cognition: this includes ATL and regions in left prefrontal and temporoparietal cortex. Patients with SA suggest that left prefrontal and temporoparietal regions may contribute to executive processes that are involved in controlling semantic access and retrieval. Indeed, a large neuroimaging literature has already established a role for left inferior frontal regions in semantic selection and controlled retrieval (Badre & Wagner, 2002; Demb et al., 1995; Thompson-Schill et al., 1997; Wagner et al., 2001). The role of temporoparietal regions is more controversial; nevertheless, neuroimaging studies frequently observe activation associated with semantic control demands within posterior temporal cortex, inferior parietal regions and intraparietal sulcus (IPS) (Badre et al., 2005; Thompson-Schill et al., 1997; Wagner et al., 2001). Joint activation of PFC and posterior temporal areas has been observed across a range of semantic tasks that require the contextually appropriate activation of specific features of conceptual knowledge. Rodd et al. (2005) suggested that judging whether a word was related to a preceding sentence needed the activation of both frontal and posterior temporal areas only when the sentence contained many ambiguous words with opposite interpretations (e.g. does “battle” go with “the *shell* was *fired* toward the *tank*”). Equally, studies of ambiguity resolutions, employing both homonyms and metaphors, find that PFC and posterior temporal cortex work together to resolve the conflict of accessing the less frequent meaning of a word when presented with more dominant words (Bedny et al., 2008; Gennari et al., 2007; Lee & Dapretto, 2006; Zempleni et al., 2007). Further evidence supporting the function role of these areas in semantic control comes from Cristescu (2006), in which the inferior parietal cortex was found to contribute together with inferior frontal regions and posterior temporal regions in semantic categorization tasks. Also, in tasks requiring high level of control in semantic fluency, where shifting between group of similar items was required, activation was observed in inferior parietal and inferior frontal cortex, suggesting that both areas are contributing to this function (Hirshorn & Thompson-Schill, 2006). In a meta-analysis of neuroimaging studies, Noonan et al. (submitted) found that executive-semantic processing modulated activation in a bilateral network of regions, including ventral and dorsal PFC, posterior temporal cortex, inferior parietal cortex and anterior cingulate regions. The areas that were most consistently activated by executive control, left PFC, pMTG and angular gyrus/IPS, overlapped with the most common areas of damage in semantic aphasia patients with impaired semantic control (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010).

Nagel et al. (2008) investigated the role of the prefrontal and parietal cortex in semantic control in semantic and non-semantic selection tasks. They found activation in IPS and some regions of PFC for both tasks. These regions are part of the ‘multi-demand network’ and are therefore thought to contribute to executive control across multiple tasks and cognitive domains. However, left ventral prefrontal cortex showed a more selective semantic role. This study therefore raises the issue of the extent to which the neural network underpinning semantic control overlaps with that supporting domain-free executive control. This relationship will be discussed in more detail below.

Cognitive Control Network

Patients with SA show deficits on non-verbal executive tasks (e.g., Raven’s coloured progressive matrices, Brixton spatial anticipation), which correlate with the degree of their semantic impairment: these resemble the kinds of deficits seen in patients with dysexcutive syndrome (Stuss & Benson, 1984). To date, semantic performance has not been assessed in dysexecutive patients in sufficient detail to ascertain if this group show a pattern of impairment that is consistent with deregulated semantic processing (as in SA); therefore this is a major aim of this thesis.

The structural and functional organisation of executive processing in the human brain remains contentious; however, there are important similarities across many theories. In particular, the ability to create an attentional set guides the performance of behaviour online, and executive factors are linked to the ability to switch between different cognitive sets when required by the task (Alexander et al., 2005; Dosenbach et al., 2006; Miller, 2000). Performance in the face of competition from distracting information plus the inhibition of task inappropriate information is also frequently ascribed to the operation of core executive processes (Braver et al., 2002; Burgess & Shallice, 1996; Picton et al., 2007). Moreover, processes responsible for the planning and sequencing of behaviour in response to weakly specified environmental circumstances, e.g. where pre-specified structure is not readily available from the task, or the situation is novel in terms of the computations which are required, are a consistent feature of many executive theories (Norman & Shallice, 1986).

In explaining these deficits, a major distinction arises in the executive control literature between theories which attempt to fractionate control processes into component sub-processes (Shallice, 2002; Stuss et al., 1995) and those which argue cognitive control is a unitary system (Braver et al., 2002; Duncan & Owen, 2000). A number of theories have hypothesised highly specific roles for areas in the left and right lateral prefrontal cortex and medial frontal lobes (Shallice, 2004; Stuss & Alexander, 2007). In contrast, Duncan (2001) has proposed that the neural system responsible for executive processing is capable of adaptive coding, allowing the same structures to contribute towards a number of different executive computations across a wide variety of domains. In a meta-analysis of studies requiring executive processing, Duncan and Owen (2000) have shown that processes putatively distinct from executive processing (conflict resolution, working memory load, novelty processing) give rise to broadly equivalent activation patterns in the left and right frontal lobes. Moreover, Duncan (2006) has shown that parietal areas are also critically important to high-level executive processing, and shows the same undifferentiated response to executive processing demands as lateral and medial frontal structures. Damage to a unitary frontoparietal control network might provide an explanation for why SA patients fail numerous non-verbal executive assessments (e.g. Raven's Coloured Progressive Matrices, Wisconsin card sorting test, and the Brixton Spatial Anticipation test) while performing poorly on semantic tasks which required executive regulation. In support of this, a number of articles have found activation in bilateral frontal and posterior parietal cortex in executive tasks using functional neuroimaging. Nee et al. (2007) carried out a meta-analysis of tasks requiring conflict resolution (Stroop, flanker, go-no etc) and found converging activation in bilateral ventral and dorsal PFC, anterior cingulate and inferior parietal cortex. Collette et al. (2006) investigated the neural activation patterns for a range of different executive processes (set-shifting, updating working memory and inhibitory processing) using conjunction analyses, once again parietal cortex, and dorsal ad ventral PFC were shown to be consistently activated by diffuse executive demands. In a neuropsychological study, Peers *et al*. (2005) found similar attention/cognitive control impairment resulting from lesions to PFC or inferior parietal cortex. Moreover, TMS to dorsal PFC and IPS disrupts executive processes for both semantic and non-semantic tasks (Nagel et al., 2008; Whitney et al., 2012), consistent with the finding that anterior and posterior lesions in SA produce comparable deficits of semantic and executive control (Noonan et al., 2010). This fits with the findings from SA patients that non-verbal measures of executive control can predict the performance on semantic tasks (Jefferies & Lambon Ralph, 2006; Luria, 1976). Nevertheless, the large lesions in SA patients may include regions involved in both domain-general and more specific aspects of semantic control.

Cognitive Control vs. Semantic Control

The areas of damage in SA overlap with the neural structures associated with domain general control. Patients with SA present with lesions to the PFC (BA44, 45, 47) and/or temporoparietal cortex (BA21, 37, 39, 40) (Noonan et al., 2010). To explore the semantic control network in more detail, a recent meta-analysis was conducted on functional neuroimaging tasks requiring semantic regulation (Noonan et al. submitted); a number of interesting findings emerged. Firstly, in addition to activation in left hemisphere ventral PFC (BA44, 45, 47), posterior temporal (BA21), and inferior parietal cortex (BA39), which overlap with those areas maximally disrupted in SA, activation was also present in medial frontal structures adjacent to the anterior cingulate (BA32, 24), and the dorsolateral PFC (BA46) bilaterally. This suggests that a large part of the network responsible for executive processing in the semantic domain overlaps with domain general executive processing. A subset of the regions involved in SA, inferior frontal (BA44, 45) and inferior parietal cortex (BA40) were shown to be activated by both semantic and non-semantic executive tasks.

In neuroimaging work, there is also some evidence of categorized specialisation of function within this distributed network underpinning semantic control, while patient studies may be insensitive to these differences because SA patients typically have large lesions. Semantic tasks with high control demands produce higher activation mostly in anterior parts of inferior PFC (BA47), while phonological tasks are associated more with activation in posterior inferior PFC and adjacent parts of premotor cortex (cf. Gough et al., 2005; Vigneau et al., 2006). The posterior parts of left inferior prefrontal cortex may therefore play a role in executive control of linguistic processing in general. Like anterior inferior prefrontal cortex, pMTG seems to be only activated by executively-demanding semantic tasks and does not contribute to domain-general control (Noonan et al., submitted). In contrast, dorsal AG/IPS has been implicated in domain-general executive processes, such as the allocation of attention (Duncan et al., 2009). Noonan et al.'s meta-analysis also found that semantic tasks with high control demands activate ventral AG, while phonological tasks yield more activation of SMG. However, since these contrasts compared semantic/phonological control with low-level baseline or rest trials, they may reflect general semantic and phonological processing rather than the control demands of the tasks. Finally, Noonan et al. noted that the vast majority of the neuroimaging studies included in this meta-analysis considered semantic control processes in the context of verbal semantic tasks. Since most neuroimaging studies manipulate control demands for linguistic stimuli, there is a need for more research to explore whether each site in the network also responds to domain-general executive control requirements for non-verbal stimuli.

Stroke Cognitive Rehabilitation

The findings reviewed above suggest that SA cases have difficulty retrieving conceptual knowledge flexibly in a controlled way. Therefore, one successful rehabilitation strategy in this group might be to provide training on tasks employing semantic control. This approach might also be augmented by the use of transcranial direct current stimulation (tDCS), applied to regions involved in semantic control.

Aphasia treatment typically aims to improve language deficits after stroke by expanding residual language abilities and via compensatory approaches. With regard to treatment focused on the language deficit, the cognitive linguistic approach was recently recommended as standard practice (Cicerone et al., 2000). Cognitive linguistic treatment aims to progress processing at the affected linguistic level, for example semantic (word meaning), implicitly assuming that training of basic language skills will result in improved verbal communication.

There is growing interest in the changes within the brain that reflect aphasia rehabilitation and recovery (Crosson et al, 2007). In a review of functional neuroimaging studies investigating treatment-induced aphasia recovery. There is a large body of research that has employed neuroimaging to detect aphasia recovery in different phases after stroke, starting from acute, subacute and chronic phase (see Kiran Review, 2012).

Studies that focused on stroke aphasia recovery found differences between patients in the pattern of recovery (Kertesz & McCabe, 1977). A neuroimaging study by Saur (2006) used fMRI to scan 14 patients with aphasia in different phases of stroke recovery. It found gradual increase of brain activation from the right hemisphere Broca's area homologue and 320 days post-stroke, the fMRI scan revealed strong left hemisphere activation as a final stage of recovery. This study showed restoration of language function to the left hemisphere over time paralleled with improvements in language function. However, few studies have explored the relationship between early recovery through brain activation and treatment outcome.

Richter et al. (2008) used fMRI in 16 patients with chronic, non-fluent aphasia who suffered from left-hemisphere stroke and examined the relationship between brain activation and the outcome of language therapy. The results showed decreased activations in specific locations in the right hemisphere, which were assumed to be a positive indicator of treatment outcome. However, this study did not explore possible treatment-related activations in the left hemisphere at the same time, which makes it difficult to attribute the decreased of activation in

RH to LH. Support for these predictions can be found in earlier TMS investigations, Naeser et al. (2005) applied TMS to patients with chronic, non-fluent aphasia on the right homologue of Broca's area to improve naming abilities. The findings established that inhibiting the RH may improve language functioning in aphasia. Again, it was not confirmed if inhibiting activations in the RH depends on intact brain areas in the LH.

Strong support for the association between decreased right hemisphere activation and improved language processing came from Fridriksson et al. (2010) which investigated these observations in patients with chronic aphasia and examined brain activation associated with picture-naming task. They found the increase of activation in intact LH was associated with a decrease in the severity of anomia. More supportive findings found in Cornelissen et al. (2003), Meinzer et al. (2008), Postman-Caucheteux et al. (2010) and Rosen et al. (2000) were single – trial fMRI found right frontal activation associated with difficulty in naming in patients with aphasia.

In spite of the important role of preserved LH in aphasia recovery, some studies draw attention to the RH recruitment in some recovery of aphasia cases, considering brain organization differences between patients. There are two important factors to determine the role of RH network in language recovery, lesion size and location. Large lesions in chronic aphasia patients that involved expressive cortex of the LH were found to be associated with greater engagement of the right hemisphere during language processing (Heiss & Thiel, 2006; Kertesz et al., 1979). However, hemispheric involvement was perceived as a changing dynamic process through the phases of recovery based on patient age, time from aphasia onset, and the nature of task demands (Finger et al., 2003; Hillis, 2007).

Another factor that enables the RH to compensate efficiently after left-hemisphere damage is the time of injury. Thiel et al. (2006) used fMRI and TMS with patients with left-hemisphere tumours to detect the transferred representation of language functions to the RH. They found gradual reorganization of language ability in the RH due to the sinister development of left-hemisphere injury in these patients compared to patients after acute stroke. Additionally, the age of left hemisphere stroke onset can be crucial in plasticity. Elkana et al. (2011) found that paediatric patients with left hemisphere strokes showed right hemisphere activation during language tasks, which may refer to the age factor as a better prognosis in language recovery.

Crosson and colleagues (2009) examined the effectiveness of new treatment approach in five patients with chronic aphasia. The treatment encouraged shifting brain activation from the left to the right hemisphere. They examined patients in picture naming task associated with physical movement (opening a box and pressing a button) using their left hand to add more dependency to the RH in picture naming. fMRI results showed great RH activation in four patients who saw improvement in their language processing, while one case showed more activation in LH with no response to the treatment. Similar results were found in Albert et al. (1973) who used Melodic Intonation Therapy (MIT) by pairing speech with melody (i.e. singing) in patients with intact RH with non-fluent aphasia. In sum, these studies suggest that some treatment approaches can compensate for the function of LH, and patients with aphasia are different in their responses to treatment.

Kiran et al. (2012) summarizes the findings of studies exploring language recovery or reorganization in the brain. They established that the recovery process contains several regions, given the explicit observation of the language process in normal individuals where more network regions are involved. (1) The contribution of areas in the brain such as the IFG, MTG, or IPL to language processing indicates collaborations between them, where they are anatomically interconnected with each other and with other regions. (2) Regions that are not functionally connected take part as temporally synchronous units suggesting integrated connectivity between regions involved in language processing and accordingly language recovery.

The important of evaluation of brain damage and brain plasticity for treatment selection leads researchers to use more brain investigations techniques to discover the neurophysiological dynamics of stroke recovery, one brain stimulation methods is tDCS:

Transcranial Direct Current stimulation (tDCS):

tDCS is a brain stimulation technique that utilizes weak electrical currents (1 or 2 milliampere) applied directly to the brain via scalp electrodes. This modulates brain activity by altering the membrane potential of neurons and by influencing the levels of glutamate and gamma-aminobutyric acid (GABA) neurotransmitters (Liebetanz et al., 2002; Stagg et al., 2009). The effects of tDCS on a population of neurons are determined by the polarity of stimulation. Anodal stimulation increases neural excitability and firing rates through depolarisation of resting membrane potentials and reducing the levels of GABA. Conversely, cathodal stimulation causes hyperpolarisation, reduces levels of glutamate and decreases brain excitability.

Recent studies suggest tDCS has potential for enhancing neurorehabilitation following stroke, particularly in combination with motor or cognitive training (Hummel et al., 2006; Schlaug et al., 2008). Although other brain stimulation techniques, e.g., TMS, have also been investigated with this aim, there are several practical advantages of tDCS: it is cheap, portable, has less focal effects on the brain, does not elicit motor twitches or jaw contractions and is thought to be much less likely to induce seizures (and is therefore safer in patients with brain injury).

However, most research employing tDCS to date has focussed on motor functioning. In healthy participants, anodal tDCS over the motor cortex can improve performance for the hand contralateral to the stimulated hemisphere (Boggio et al., 2006; Vines et al., 2006). Moreover, in stroke-affected patients, applying anodal tDCS to the stroke-affected motor cortex has been shown to improve motor functioning – in such studies, the tDCS may have stimulated preserved areas of the motor cortex to enhance synaptic efficiency along the corticospinal tract (Hummel et al., 2006; Schlaug et al., 2008). It may also be possible to improve motor ability by applying cathodal tDCS to the motor cortex *ipsilateral* to the performing hand; in stroke patients, this may help to overcome maladaptive inhibitory projections from the undamaged hemisphere onto the damaged motor cortex (Hummel et al., 2006; Schlaug et al., 2008; Hesse et al., 2007; Nair et al., 2008).

Because tDCS is a flourishing technology, studies on language processes are relatively few compared to motor functions. For example, Fregni et al. (2004) found that anodal tDCS improved performance in a sequential-letter working memory task in healthy volunteers when administered to the dorsolateral prefrontal cortex (DLPFC). This effect was not observed following cathodal or sham stimulation of the same site, nor stimulation of a control site (primary motor cortex). Fertonani et al. (2010) applied anodal, cathodal and sham tDCS to the left dorsolateral prefrontal cortex in healthy volunteers during a picture naming task and found that anodal stimulation allowed participants to respond more quickly, while cathodal stimulation had no effect. In addition, Floel et al. (2008) found that vocabulary learning was enhanced by anodal stimulation of Wernicke's area in healthy volunteers (while there were no effects of cathodal or sham stimulation). Monti et al. (2008) evaluated the effect of tDCS over left frontotemporal areas in post stroke patients. The protocol consisted of the assessment of picture naming (accuracy and response time) before and immediately after anodal or cathodal tDCS (2 mA, 10 minutes) and sham stimulation. Whereas anodal tDCS and sham tDCS failed to induce any changes, cathodal tDCS significantly improved the accuracy of the picture naming task by a mean of 33.6%. Finally, research found that anodal stimulation slightly decreased the response times at the same time as increasing the correct responses in a picture naming task (Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). In contrast, Sela et al (2012) found participants markedly slow in reaction times after tDCS, accompanied by an improved performance on semantic decision tasks that involved idiom comprehension.

The effect of Anodal and cathodal stimulation were thought to be determined by the task used. A few relevant studies have stimulated LIFG, Iyer et al. (2005) found the number of words produced to target letters in verbal fluency tasks in healthy participants increased when the left prefrontal cortex was stimulated by anodal tDCS (Iyer et al., 2005). Similar findings were reported by Gordon et al. (2010) exploring automatic and controlled verbal generation. They found more semantically clustered words during anodal stimulation in letter-cued fluency tasks. Some studies have examined the effects of tDCS on classification learning, employing a weather prediction task (Kincses, Antal, Nitsche, Bártfai, & Paulus, 2004) and a prototype distortion task (Ambrus et al., 2011). Mixed results were found: Kincses et al. (2004) described a minor benefit of anodal stimulation over left prefrontal cortex on implicit learning. Ambrus et al. (2011) reported that when participants were presented with a prototype of a category pattern not seen during training, they tended to reject it following both anodal and cathodal stimulation. Lastly, Cerruti and Schlaug (2009) report positive effects of anodal tDCS over the left dorsolateral prefrontal cortex on the remote associates task (RAT) which loads executive functioning. Subjects are required to find non-obvious associations to solve insight-style problems by ignoring misleading clues (Bowden & Jung-Beeman, 2003). Therefore, a considerable number of studies have reported the effect of tDCS on higher cognitive functions (Holland et al., 2011, Meinzer et al., 2012).

In conclusion, six studies have employed anodal tDCS to examine the involvement of PFC in tasks that require regulation of thought. For example, increasing PFC activity with anodal tDCS lead to improvements in inhibitory control (Hsu et al., 2011), working memory (Boggio et al., 2006), and increased efficiency in task shifting (Leite et al., 2011; see also Dockery et al., 2009;; Gordon et al., 2010 and Iyer et al., 2005), whereas opposing effects of cathodal versus anodal stimulation over left inferior PFC have recently been reported on a feature categorization task (Lupyan et al. 2012) or mix effect of anodal and cathodal effect (Kincses et al., 2004 and Ambrus et al.,2011) .

Although there is a growing literature on the effects of anodal stimulation over LIFG on language, memory and executive measures, few if any directly explore the effect of tDCS on semantic control. Meinzer et al (2012) report that anodal tDCS enhances semantic cognition over LIFG. The task they used to explore semantic cognition involved recalling words from specific categories: however, they did not explore different experimental conditions varying in their reliance automatic and controlled recall. Another recent study by Sela et al. (2012) explores the effect of anodal/cathodal tDCS through alternating stimulation over the prefrontal cortex (LH/RH) during a semantic decision task involving idiom comprehension. They found improvement in performance when the left prefrontal cortex was stimulated.

Finally, in a recent study (Baker, Rorden, & Fridriksson, 2010), compared tDCS with a computerized aphasia treatment (see Fridriksson et al., 2009) to explore the effect of tDCS on anomia treatment outcome in patients with chronic aphasia. Their findings showed that tDCS on the LH significantly improve anomia. fMRI and structural MRI were used to detect that tDCS was applied to brain areas that specialized in picture-naming and to avoid electrodes placement over damaged tissue.

In sum,

As this review of the literature reveals, tDCS may be a useful treatment for patients with aphasia after stroke, but existing research has limitations and is somewhat contradictory. In particular, there is a clear need for further work on the use of tDCS to enhance language, semantic and cognition function, and on its efficacy as a rehabilitation aid post-stroke. Studies in healthy participants can examine potential dissociations between different aspects of semantic and cognitive function by investigating whether tDCS has parallel effects across different tasks that require different types of judgements. Of course, similarities across tasks do not show that the cognitive and neural processes underpinning these tasks are identical, especially given that tDCS uses relatively large electrodes for stimulation and has limited spatial resolution. Diffusion of the current associated with tDCS in the brain depends on electrode size and position (Bikson, Datta, & Elwassif, 2009). In addition, the neurophysiological effects of tDCS are still controversial. For example, recent tDCS studies with aphasia patients saw improvement in language tasks after these individuals received stimulation of opposite polarities, either cathodal (Monti et al., 2008) or anodal (Baker et al., 2010), to the left frontal lobe. Therefore, while it will be important for future research to explore the optimal stimulation parameters for effecting recovery in patients with aphasia and other types of brain injury, there is also a need for studies of the effects of tDCS on cognition, semantics and language in healthy participants.

Thesis structure

The following presents an overview of each chapter, its rationale and findings.

Chapter 2: Provides further exploration of SA patients' performance in comprehension tasks. Patients with multimodal semantic impairment following stroke aphasia fail to show the standard effects of frequency. Instead, they show absent or even *reverse* frequency effects, i.e. better understanding of less common words. In addition, SA is associated with poor regulatory control of semantic processing and executive deficits. We used a synonym judgement task to investigate the possibility that the normal processing advantage for high frequency (HF) words fails to emerge in these patients because HF items place greater demands on executive control. In the first part of this study, SA patients showed better performance on more imageable as opposed to abstract items, but minimal or reverse frequency effects in the same task and these negative effects of word frequency on comprehension were related to the degree of executive impairment. Ratings from healthy subjects indicated that it was easier to establish potential semantic associations between probe and distracter words for HF trials, suggesting that reverse frequency effects might reflect a failure to suppress spurious associations between HF probes and distracters. In a subsequent experiment, the aphasic patients' performance improved when HF probes and targets were presented alongside low frequency distracters, supporting this hypothesis. An additional study with healthy participants used a dual task methodology to examine the impact of divided attention on synonym judgement. Although frequently encountered words were processed more efficiently overall, the secondary task selectively disrupted performance for high but not low frequency trials. Taken together, these results show that positive effects of frequency are counteracted in SA by increases in semantic control requirements for HF words.

Chapter 3: Investigates the relationship between domain-general cognitive control and deregulated semantic cognition, by directly comparing an SA group with patients with a primary impairment of executive functioning (Dysexecutive syndrome; DYS) and assessing their semantic performance in detail. The study was motivated by the findings that SA patients show a strong association between semantic performance and scores on non-verbal assessments of cognitive control, which suggest a causal correlations between the two cognitive domains. The results revealed evidence for a unitary control system underpinning both semantic and non-semantic deficits. All patients showed mildly impaired performance across a range of semantic tasks including, picture naming, word-picture matching and semantic association tasks using words and pictures. Moreover, experimental manipulation of the control requirements of individual semantic tasks on nearest neighbour and synonym judgement tasks performance declined as the distance between probes and targets increased and as distractor items became more strongly associated with the probe items, respectively. These results suggest that cognitive systems which underpin regulation in the semantic domain share neural resources with other non-semantic forms of cognitive control.

Chapter 4: Explores the refractory effect phenomenon in patients who have general executive domain impairment and compares their performance to the SA patients previously studied by Jefferies et al. (2007). The chapter explores the variables associated with the refractory effect, e.g. effects of cycle speed of presentations and semantic blocking within sets, inconsistency, absence of frequency effects and effects of cues in a group of patients who were selected based on impairment in domain-general executive control, as opposed to semantic/linguistic deficits. This reveals whether executive impairment is sufficient to produce the characteristics of access disorder, even in individuals without aphasia.

Chapter 5: Explores the effect of anodal and sham stimulation over LIFG on semantic control, employing two tasks strongly demanding in semantic control (semantic feature and low association tasks). Moreover, these tasks have been used to differentiate different aspects of semantic control, with one task making strong demands on semantic selection (semantic feature task) and the other on controlled retrieval (semantic relatedness judgements for weakly associated words). Two experiments investigated whether modulation of cortical activity using noninvasive transcranial direct current stimulation (tDCS) over LIFG in healthy participants would affect performance in semantic tasks that varied in control demands. Moreover, in the first study we examine whether the effects of tDCS interact with performance gains following training during anodal stimulation; a method which has already been employed by several studies which reported significant improvement in performance of patients with stroke aphasia in picture naming. Since our long term goal is improving semantic control in SA patients, the effects of training during tDCS were evaluated.

CHAPTER 2

Deficits of semantic control produce absent or reverse frequency effects in comprehension: Evidence from neuropsychology and dual task methodology

Note: This chapter has appeared as a publication:

Almaghyuli, A., Lambon Ralph, M.A., Jefferies, E. (2012) Deficits of semantic control produce reverse frequency effects: Evidence from neuropsychology and dual task methodology. Neuropsychologia, 50, 1968-79.

We are grateful to Dea Nielsen, an undergraduate RA, who collected some of the dual-task data. Some of the SA patients were tested in Manchester and York prior to the start of my PhD.

Abstract

Patients with multimodal semantic impairment following stroke (referred to here as 'semantic aphasia' or SA) fail to show the standard effects of frequency in comprehension tasks. Instead, they show absent or even *reverse* frequency effects: i.e., better understanding of less common words. In addition, SA is associated with poor regulatory control of semantic processing and executive deficits. We used a synonym judgement task to investigate the possibility that the normal processing advantage for high frequency (HF) words fails to emerge in these patients because HF items place greater demands on executive control. In the first part of this study, SA patients showed better performance on more imageable as opposed to abstract items, but minimal or reverse frequency effects in the same task and these negative effects of word frequency on comprehension were related to the degree of executive impairment. Ratings from healthy subjects indicated that it was easier to establish potential semantic associations between probe and distracter words for HF trials, suggesting that reverse frequency effects might reflect a failure to suppress spurious associations between HF probes and distracters. In a subsequent experiment, the aphasic patients' performance improved when HF probes and targets were presented alongside low frequency distracters, supporting this hypothesis. An additional study with healthy participants used dual task methodology to examine the impact of divided attention on synonym judgement. Although frequently encountered words were processed more efficiently overall, the secondary task selectively disrupted performance for high but not low frequency trials. Taken together, these results show that positive effects of frequency are counteracted in SA by increases in semantic control requirements for HF words.

Introduction

Semantic cognition – i.e., the selective use of meaning to guide behaviour according to the context or task – is underpinned by at least two interacting components: (a) semantic representations and (b) executive processes which help to direct and control semantic activation in a task-appropriate fashion (Jefferies & Lambon Ralph, 2006). These control processes play a vital role in semantic cognition because only particular aspects of our knowledge are relevant for a specific task or context. For example, we know that pianos are both heavy and played by pressing keys with the fingers: therefore if our task is to move a piano across the room, information about fine motor movements must be disregarded (Saffran, 2000).

These components of semantic cognition are associated with different neural substrates and can be impaired separately in different groups of brain-injured participants. Patients with semantic dementia (SD) have a degraded store of semantic knowledge following atrophy and hypometabolism focussed on the inferior anterior temporal lobes bilaterally (Galton et al., 2001; Mummery et al., 2000; Nestor et al., 2006). This results in poor performance across the full range of verbal and non-verbal modalities and a high degree of consistency across tasks (Bozeat et al., 2000; Garrard & Carroll, 2006). In contrast, stroke aphasia patients with multimodal comprehension problems (referred to below as ‘semantic aphasia’, abbreviated to ‘SA’) have infarcts affecting left posterior temporal, parietal and inferior frontal regions (Berthier, 2001; Chertkow et al., 1997; Dronkers et al., 2004; Hart & Gordon, 1990; Hillis et al., 2001). Stroke rarely produces lesions of the most inferior portion of the ATL (i.e., the focus of brain atrophy in SD) because this is a watershed region which receives a blood supply from multiple arteries; moreover, one of these – the anterior temporal cortical artery – branches off the middle cerebral artery below its major trifurcation, making it less vulnerable to emboli (Borden, 2006).

In a number of previous studies, we have found that SA patients with multimodal comprehension problems have largely intact semantic knowledge but deregulated semantic cognition (Corbett et al., 2009; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008). SA patients are inconsistent across tasks that require different types of semantic processing, even when the same concepts are probed. Unlike patients with SD, individuals with SA show strong benefits of cues that reduce the requirement for internally-driven semantic control (Jefferies et al., 2008; Hoffman et al., 2010; Noonan et al., 2010). Their performance is strongly affected by the executive requirements of semantic tasks: they have difficulty selectively retrieving the task-relevant meanings of items and rejecting highly associated distracters (Corbett et al., 2011; Jefferies et al., 2008; Noonan et al., 2010). Moreover, while SD patients retain good executive skills, semantic deficits in SA are associated with impairments of attention/executive function (Baldo et al., 2005; Jefferies & Lambon Ralph, 2006; Wiener et al., 2004).

These findings suggest that sites within left posterior temporal, parietal and inferior frontal regions form a large-scale distributed system that underpins the executive control of semantic processing. This view is further supported by functional neuroimaging and TMS studies of healthy participants. Although the functional neuroimaging literature has traditionally focussed on the contributions of left inferior frontal cortex (LIFC), many neuroimaging studies have, in fact, observed activation within posterior temporal and parietal cortex which is modulated by semantic control demands (e.g., Badre et al., 2005; Nagel et al., 2008; Thompson-Schill et al., 1997; Wagner et al., 2001). We recently conducted a meta-analysis of functional neuroimaging studies which confirmed that LIFC, posterior middle temporal gyrus (pMTG) and portions of left parietal lobule are all reliably influenced by manipulations of semantic control (Noonan et al., submitted). Moreover, we demonstrated a functional dissociation between ATL and these sites within a single fMRI study utilising ambiguous words in a double-prime paradigm: ATL was sensitive to the number of meanings that were retrieved (consistent with a role for this region in semantic representation), while pMTG, inferior parietal cortex and LIFC showed greater activation when the dominant meanings of words had to be inhibited (suggesting they underpin semantic control; Whitney et al., 2011). This distributed activation was shown to be functionally significant using TMS: stimulation of LIFC, pMTG and IPL disrupted control-demanding comprehension tasks, but not more automatic semantic judgements (Whitney et al., 2011; Whitney et al., in press 2011). The findings of these TMS studies are somewhat similar to studies of patients with SA, which reveal particular difficulties in control-demanding semantic tasks following lesions of either LIFC or temporoparietal regions (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010).

Patients with SD and SA also show striking differences in the effect of frequency on comprehension which have been linked to the differential effects of this variable on representation and control demands (Hoffman et al., 2011a; 2011b). Patients with SD show strong positive effects of frequency in a wide range of semantic tasks: frequently encountered items are better preserved than less frequent stimuli and retained for longer as the disease progresses (Bozeat et al., 2000; Funnell, 1995; Jefferies et al., 2009; Lambon Ralph et al., 1998). Similarly, in healthy participants, high frequency (HF) items have a substantial advantage because the system has a greater opportunity to learn how to process them accurately and efficiently (e.g., Forster & Chambers, 1973; Plaut et al., 1996). Therefore SD patients show an exaggeration of the normal frequency effect, presumably because representations of frequently encountered items are more robust to damage (Rogers et al., 2004). In contrast, frequency effects in SA are either absent (Jefferies et al., 2007; Jefferies & Lambon Ralph, 2006; Warrington & Cipolotti, 1996) or even reversed – i.e., performance can be better for low frequency (LF) items (Hoffman et al., 2011a; 2011b). This is surprising since we might expect higher frequency concepts to show greater resilience to impairment.

What might explain this difference between SD and SA patients in the effects of frequency? A partial explanation is provided by the notion that SA patients do not have a degraded semantic store – consequently, they would not be expected to show disproportionate damage to semantic representations corresponding to less frequent concepts. However, this cannot be a complete explanation because SA patients sometimes show *reverse* frequency effects. This suggests there is a processing cost for HF items, magnified in patients with SA, which overrides the normal processing advantage that frequent items enjoy. Given that SA patients have poor executive control over semantic activation, one possibility is that HF concepts require greater semantic control. HF words and objects are encountered in a wider range of situations and alongside a larger number of other items than LF words because they occur more commonly (Adelman et al., 2006; Hoffman et al., 2011a; 2011b These varied semantic associations are likely to be activated automatically when a HF item is presented, yet many of them will be irrelevant to the task at hand – consequently, semantic processing for HF words might require greater executive control. This difference between HF and LF concepts is likely to be particularly prominent in tasks in which participants are asked to select which of several items is closest in meaning to a probe (i.e., in synonym judgement), because activation could potentially spread from the probe to the distracters as well as to the target. Therefore, although participants will be more efficient at retrieving the meanings of HF items, some of this information will need to be disregarded for the correct response to be made.

In this study, we investigated the hypothesis that absent or reverse frequency effects in SA reflects the greater demands that HF items place on executive control. In particular, patients with SA may fail to suppress spurious associations between HF probes and distracters in synonym judgement due to their deficits in semantic control. We confirmed absent or reverse frequency effects in a synonym judgement task in a sample of SA patients and then collected ratings from healthy participants which established that there were stronger semantic associations between probes and distracters for HF as opposed to LF trials. In a second experiment, we presented HF probes and targets alongside LF distracters, in order to establish whether SA patients would show better performance. This might be expected if these patients have difficulty suppressing irrelevant potential links between HF probes and distracters. Finally, we used dual task methodology with healthy participants to examine the impact of divided attention on synonym judgement for HF and LF words. To anticipate, we obtained convergent findings across these neuropsychological and dual task investigations: both indicated that semantic decisions to HF items are more demanding of executive control than decisions about LF concepts.

Experiment 1: Frequency and synonym judgement in SA patients

Method

Test construction: Participants were asked to select the word closest in meaning to a probe word. There were three choices per trial (the target plus two unrelated distracters). Simultaneous auditory and visual presentation was used and patients indicated their choice by pointing. There were 96 trials split evenly between two non-overlapping frequency bands (mean frequency of probe words (with standard deviations in parentheses) = 128 (102) and 4.6 (4.5) counts per million in the Celex database; Baayen et al., 1993) and three non-overlapping imageability bands (mean imageability of probe words = 275 (17.3), 452 (26.0) and 622 (14.0) respectively, on a scale of 100-700). There were sixteen trials in each of the six frequencies by imageability conditions. Both the targets and distracters were matched to the probe word for frequency and imageability. As a consequence, the trial as a whole (rather than just the probe word) varied frequency and imageability. Full details are provided in Jefferies et al. (2009).

Participants: We examined sixteen SA patients, most of whom participated in our previous investigations of the semantic control deficit in this condition (Corbett et al., 2009; Jefferies et al., 2007; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008; Noonan et al., 2010). The inclusion criteria were as follows: Patients were all native speakers of British English; every case had brain injury and chronic impairment resulting from a cerebrovascular accident (CVA) at least a year previously; moreover, patients were only included if they showed evidence of *multimodal* semantic impairment affecting both words and pictures, for example on the Camel and Cactus test (Adlam et al., 2010; Bozeat et al., 2000). Our previous studies using the same inclusion criteria found that SA patients with multimodal comprehension problems had concomitant executive deficits that were related to the degree of semantic impairment: in this study, we explored the negative effects of word frequency in a similar patient group. Table 1 shows neuroimaging summaries and aphasia classifications for the SA patients. Table 2 and 3 shows neuropsychological test scores on background semantic and non-semantic tasks.

The patients' semantic deficits were sometimes accompanied by additional impairments affecting fluency of speech and/or repetition (see Tables 1, 2 and 3). Seven patients had transcortical sensory aphasia (TSA) – i.e. poor comprehension in the context of fluent speech and good repetition. The remainder had less fluent speech and/or poorer repetition in addition to their multimodal semantic impairment. MR images were available for nine cases (NY, SC, ME, KH, LS, DB, HN, GH, EC) and CT was available for three more (BB, KA, EW). It was not possible to obtain scans for three of the patients due to a lack of consent or contraindications for MRI, although written reports of previous CT scans were available for two of them (PG, JM). In line with the literature on semantic control deficits in stroke aphasia, all of the patients had left temporoparietal and/or prefrontal lesions (see Introduction). Further details of the patients' lesions are available in Jefferies and Lambon Ralph (2006) and Noonan et al. (2010).

Table 1 : Aphasia classifications and neuroimaging summaries for the SA participants

Patient	Age	Edu	Neuroimaging summary	Aphasia Type	BDAE Compreh	BDAE Fluency	BDAE Repetition	Nonword repetition	Word Repetition
HN	80	15	L occipital-temporal	Anomic/TSA	NT	NT	NT	56	86
EW	74	15	L occipital-temporal		NT	NT	NT	NT	80
JD	81	16	Compression of L lateral ventricle & capsular	Mixed Transcortical	NT	NT	NT	73	93
SC	80	16	L occipital-temporal (+ small R frontal infarct)	Anomic/TSA	37	90	60	87	98
ME	40	16	L occipital-temporal	TSA	33	100	100	93	100
GH	56	18	L frontal-parietal	Global	NT	NT	NT	NT	NT
NY	67	15	L frontal-parietal	Conduction	47	37	40	40	81
PG	63	18	L frontal & capsular	TSA	20	40	80	73	91
JM	69	18	L frontal-parietal	TSA	22	63	40	87	95
MS	73	14	No scan	Global	10	0	0	0	0
KH	73	14	L frontal-parietal-occipitotemporal	Mixed Transcortical	30	30	40	43	80
KA	78	14	L frontal-parietal	Global	0	23	0	0	0
BB	59	16	L frontal	Mixed Transcortical	10	17	55	83	96
DB	76	16	L frontal-temporal-parietal	TSA/Wernicke’s	13	90	30	70	85
LS	75	15	L frontal-parietal-occipitotemporal	TSA	13	90	90	90	96
EC	71	16	L frontal-parietal	Global	NT	NT	NT	NT	16

Patients are arranged in order of synonym judgement performance. BDAE = Boston Diagnostic Aphasia Examination (Goodglass, 1983). BDAE Comprehension score is a percentile derived from three subtests (word discrimination, commands, complex ideational material). BDAE Fluency percentile is derived from phrase length, melodic line and grammatical form ratings. BDAE Repetition percentile is average of word and sentence repetition. TSA (transcortical sensory aphasia) was defined as good or intermediate fluency/repetition and poorer comprehension. Word/nonword repetition: Tests 8 and 9 from PALPA (Psycholinguistic Assessments of Language Processing in Aphasia, Kay et al., 1992).

Table 2 : Background semantic test scores for the SA patients

	Synonym judgement												
	Total	HF	LF	HI	LI	CCT words	CCT picture	Picture naming	Word-picture matching	Category fluency	Sound – picture matching	Spoken word – picture matching	Sound-written word matching
Max	96					64	64	64	64	-	48	48	48
Control mean	93.1					60.7	58.9	62.3	63.7	95.7	41.2	47.8	NT
Control SD	2.47					2.06	3.1	1.6	.5	16.5	2.5	0.6	
HN	90	47	43	32	27	*54	54	*50	*50	64	*36	*16	42
EW	*76	38	38	32	19	*48	*45	*45	*57	63	*22	*45	38
JD	*73	33	40	26	20	*38	*38	*49	64	*31	*23	*46	47
SC	*71	36	35	29	14	*56	*47	*48	*59	*17	*32	*41	48
ME	*71	38	33	27	17	*34	*13	*4	*50	*25	*33	*40	40
GH	*71	32	39	29	17	*29	*45	*19	*60	*15	NT	NT	NT
NY	*69	33	36	28	15	*39	*36	*55	*60	*25	*28	*40	47
PG	*69	33	36	29	19	*40	*44	*46	*58	*4	*33	47	44
JM	*69	30	39	26	20	*37	*37	*30	*53	*20	*24	*43	NT
MS	*65	34	31	30	19	*42	*37	*0	*46	*0	NT	NT	NT
KH	*61	34	27	26	14	*41	*46	*29	*54	*21	*30	*44	NT
KA	*60	31	29	25	19	*36	*46	*0	*26	NT	*22	*21	36
BB	*58	27	31	24	15	*30	*38	*10	*54	*13	*26	*33	26
DB	*54	29	25	26	12	*33	*39	*4	*46	*9	*21	*36	NT
LS	*51	23	28	23	15	*16	*16	*5	*37	*11	*27	*35	33
EC	*41	20	21	17	14	*20	*32	*1	*40	NT	NT	NT	NT

Patients are arranged in order of synonym judgement performance. Table shows raw scores. Max = maximum score. * denotes impaired performance (< 2 SD from control mean). Data for controls and many patients taken from Corbett et al. (2009). CCT = Camel and Cactus Test of semantic association (Bozeat et al., 2000). CCT, picture naming, word-picture matching, category and letter fluency taken from Cambridge semantic battery (Adlam et al., 2010). In the sound-picture, spoken word-picture and sound-written word matching tests, patients listened to environmental sounds or spoken words and chose which printed picture or written word (out of 10 options) matched this auditory stimulus (Bozeat et al., 2000).

Table 3 : Background non-semantic test scores for the SA patients

	Digit span (forwards)	Digit span (backwards)	VOSP: dot counting	VOSP: position discrimination	VOSP: number location	VOSP: cube analysis	Letter fluency	Brixton spatial anticipation (correct)	TEA Elevator counting (no distraction)	TEA Elevator counting (distraction)	Raven's coloured matrices
Maximum	-	-	10	20	10	10	-	55	7	10	36
Control mean	-	-	-	-	-	-	44.2	-	-	-	-
Control SD	-	-	-	-	-	-	11.2	-	-	-	-
Normal cut-off	5	2	8	18	7	6	-	28	6	3	-
HN	6	2	*8	19	9	*4	*19	28	7	9	20
EW	*4	2	10	20	10	7	*19	28	7	9	20
JD	5	2	10	20	10	10	* 5	28	7	6	30
SC	6	2	10	*17	10	9	*24	*25	7	*1	22
ME	6	3	*3	*15	*2	*4	*14	*11	7	9	13
GH	*2	*0	10	*4	*0	*0	*2	*18	6	*1	32
NY	*3	2	10	20	10	*5	* 5	34	*3	*2	26
PG	6	2	*5	20	9	10	* 2	*26	*3	*0	23
JM	*3	2	10	19	*5	*3	* 1	NT	*3	*0	14
MS	NT	NT	NT	NT	NT	NT	* 0	*16	NT	NT	12
KH	*4	2	10	*18	9	*3	* 1	*7	6	3	12
KA	0	NT	TA	*14	*6	TA	* 0	*6	NT	NT	12
BB	5	*0	10	*18	8	*2	* 0	*23	*4	*0	24
DB	*4	2	*6	TA	10	*3	*1	*24	*3	*1	31
LS	*4	*1	*6	*16	8	*4	*8	*14	*3	*2	16
EC	NT	NT	*3	*14	10	*6	NT	*24	*1	*1	12

Patients are arranged in order of synonym judgement performance. Table shows raw scores. * denotes impaired performance (< 2 SD from control mean). Data for controls and many patients taken from Corbett et al. (2009). VOSP = Visual Object and Space perception Battery (Warrington & James, 1991). Brixton spatial anticipation test (Burgess & Shallice, 1997). TEA = Test of Everyday Attention (Robertson et al., 1994). Raven’s coloured matrices (Raven, 1962).

Results

The synonym judgement data are shown in Figure 1a. ANOVA was used to examine the effects of frequency and imageability on response accuracy. The SA patients showed a highly significant effect of imageability, F(2,30) = 37.3, $p < 0.0001$, but no effect of frequency overall, F(1,15) < 1. The interaction between frequency and imageability approached significance, F(2,30) = 2.7, $p = .08$. Bonferroni t-tests revealed that there was a reverse frequency effect for highly imageable items (t(15) = 2.7, $p = .05$) but no significant frequency effect for either medium or low imageability items (t(15) < 1). See Figure 1.

Further analyses focused on the relevance of participant variables to synonym judgement performance. Factor analysis was used to extract a single factor score for (i) semantics (based on three comprehension tasks that every patient had completed: CCT words, CCT pictures and the Cambridge word-picture matching test, with the common factor accounting for 63.7% of the variance); (ii) executive function (based on the Brixton, Raven’s Coloured Progressive Matrices and the TEA elevator counting task with distraction, replacing three missing scores with the group average; accounting for 53.7% of the variance); (iii) verbal short-term memory (based on PALPA 9 word repetition and forwards digit span, replacing one missing value with the group average, accounting for 94.2% of the variance) and (iv) visual processing (based on the VOSP dot counting, position discrimination and number location subtests, replacing three missing values with the group average, accounting for 58.5% of the variance).

We then used Pearson’s correlation to examine the association between these factor scores and the synonym task (all *p* values are two-tailed unless otherwise stated). There was no relationship between overall accuracy on the synonym task and the effects of frequency (i.e., the difference in accuracy between HF and LF trials; $r < .1$) or imageability (difference between HI and LI trials; $r = .15$, n.s). Overall performance on the synonym task showed a highly significant correlation with the semantic factor ($r = .74$, $p = .001$), no correlation with the executive factor ($r = .23$, n.s.) or the visual factor ($r < .1$) and a correlation with the verbal short-term memory factor that approached significance ($r = .44$, $p = .09$). This presumably reflected the fact that participants had to hold in mind several words whilst making their decision, especially if their reading was compromised. The effects of word frequency and imageability in synonym judgement did not correlate with any of the factor scores ($r < .36$, n.s.) with one exception: there was a negative correlation between the effect of frequency and the executive factor score ($r = -.46$, $p = .04$, one-tailed *p*). This show, as predicted, that reverse effects of frequency on the synonym judgement task were associated with poorer scores on executive tasks. There was also a near-significant positive correlation between the executive and semantic factor scores ($r = -.41$, $p = .056$, one-tailed *p*), in line with previous findings for SA patients (Baldo et al., 2005; Jefferies & Lambon Ralph, 2006; Wiener et al., 2004), but no significant correlations between the pair-wise combinations of the other factor scores ($r < .39$, $p > .14$).

Figure 1: Effects of frequency, imageability and distracter type on standard synonym judgement accuracy for SA patients (Experiments 1 and 3)

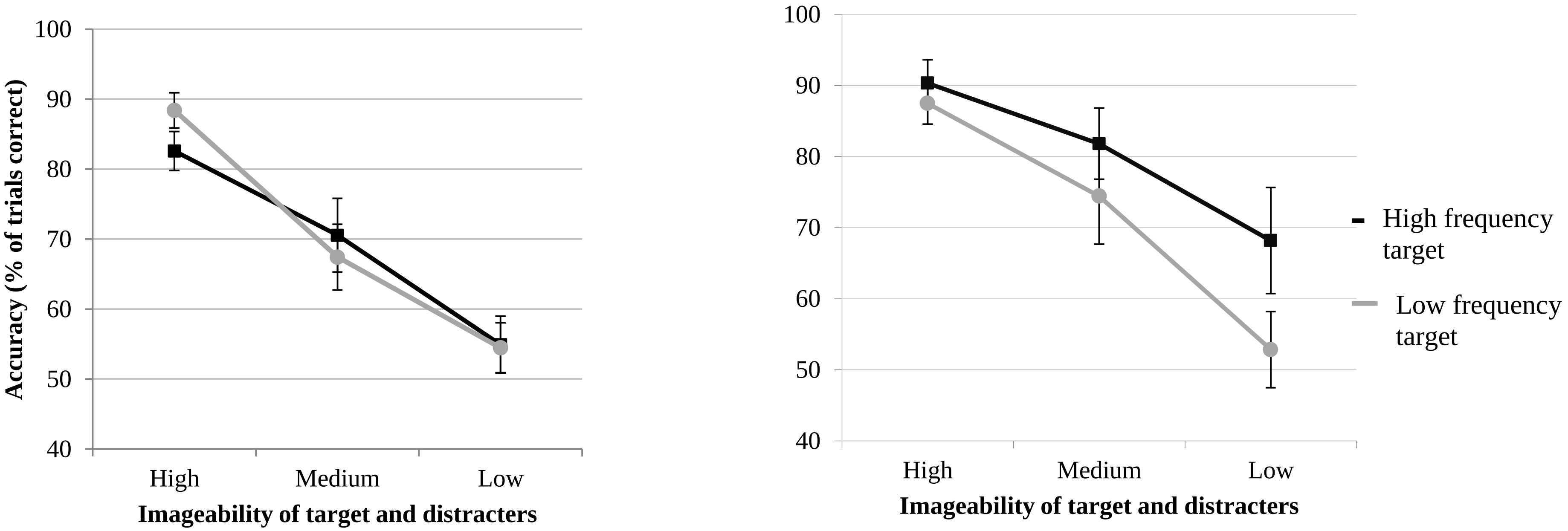


Fig. 1a: Standard synonym judgement (Experiment 1)

Fig. 1b: Reverse frequency distracters (Experiment 3)

Error bars show standard error of mean

Experiment 2: Ratings from healthy participants

In the next study, we explored the possibility that HF trials in the synonym judgement task might place greater demands on executive semantic processing due to the fact that these words appear in more contexts and, as a result, have richer and more variable meanings. Hoffman et al. (2011b) were able to relate a measure of meaning diversity to synonym judgement performance in patients with SA. They found that semantic diversity was higher for words (i) low in imageability and (ii) high in frequency. They proposed, in line with our hypothesis, that the strong correlation between word frequency and semantic diversity explains why the standard frequency effect is not observed in this group. When semantic diversity was taken into account in an item analysis, a small positive effect of frequency emerged.

Here, we extend these ideas to look at the strength of potential links between probe and distracter words. For semantically diverse HF words, task-irrelevant associations between probes and distracters might be more likely to be retrieved than for LF words with less diverse meanings. SA patients with semantic control deficits might have difficulty disregarding these associations as a basis for their decisions, reducing, eliminating or even reversing the standard HF advantage. To look directly at this possibility, we asked healthy participants to rate the ease with which they could generate a semantic link between the HF and LF probes and *distracters* used in Experiment 1.

Method

Participants: The participants consisted of 36 healthy undergraduate students from the University of York. Their ages ranged between 19-22 years old. There were 24 females and 12 males. All were native speakers of British English.

Procedure: Participants were asked to indicate how readily they could form a semantic association between two words. They indicated their answer on a scale from 1 to 5, where 1 corresponded to no clear link between those words and 5 indicated immediate retrieval of a strong link. Participants were presented with 192 pairs of words listed on paper: these corresponded to the 96 probe words from Experiment 1 combined with the two distracters (presented in separate trials). Participants wrote their answer in a box next to each pair of words. The five-point scale was visible at the top of the answering sheet.

Results

Table 4 shows average ratings for each frequency by imageability condition in the synonym judgement experiment. We used simple linear regression to examine the relationship between log frequency and imageability (for the probe words) and probe-distracter association ratings (averaged across the two distracters presented with the same probe). R^2 for the model was .223. Log frequency was the strongest predictor of probe-distracter association strength (β = .46, p < .0001): participants found it easier to identify potential associations for HF probes and their distracters. There was also a weaker negative relationship with imageability (β = -.18, p = .05), reflecting stronger probe-distracter associations for more abstract words. These findings mirror the relationships between semantic diversity and frequency/imageability reported by Hoffman et al. (2011b). HF and abstract words have more diverse meanings, stronger connections with supposedly unrelated distracters, and produce poorer performance in SA patients with impaired semantic control.

Table 4: Ratings from healthy participants of the ease of forming a semantic association between high and low frequency targets and distracters (Experiment 2)

Conditions	Mean	s.d.
High frequency; high imageability	2.21	.77
High frequency; medium imageability	2.30	.68
High frequency; low imageability	2.27	.70
Low frequency; high imageability	1.79	.59
Low frequency; medium imageability	1.95	.59
Low frequency; low imageability	1.97	.58

Ratings are on a scale of 1-5, where 1 represents no clear link between the words and 5 indicates immediate retrieval of a strong link

Experiment 3: Frequency-reversed distracters in SA patients

If stronger associative links between HF probes and distracters are overriding positive effects of frequency in synonym judgement for individuals with SA, patients should show paradoxically better performance on HF trials which incorporate LF distracters (as this should discourage the activation of task-irrelevant associations). LF trials are not expected to show strong effects of reversing the frequency of distracters, because these items are less likely to activate spurious associations in the first place.

Method

The experiment used the same target words and testing format as the test above. The sole difference was that the HF probes/targets were presented with the LF distracters, whereas the LF probes/targets were tested in conjunction with HF distracters. The imageability of the distracters was still matched to the probe/target. Eleven SA patients completed the reverse frequency experiment (MS, KH, JM, EC and GH were not available to take part).

Results

The results are shown in Figure 1b. The data were analysed using a 2x2x3 within-subjects ANOVA incorporating frequency (HF vs. LF), imageability (high, medium and low) and distracter type (standard vs. reversed distracters). There was a significant main effect of imageability, F(2,20) = 43.8, $p < 0.0001$, and distracter type, F(1,10) = 10.0, $p = 0.01$. There was no main effect of frequency (F(1,10) = 2.0, $p = 0.2$). In line with our predictions, there was a highly significant frequency by distracter type interaction (F(1,10) = 11.1, $p = 0.008$). Planned t-tests showed that the SA group performed more accurately for HF items when they were presented with LF distracters, compared with their performance in the standard synonym judgement test used in Experiment 1 ($t(10) = 4.2$, $p = .002$). Reversing the frequency of the distracters did not affect accuracy for the LF items ($t(10) < 1$). No other interactions approached significance (F < 1.8). The SA patients showed significant effect of frequency in the reversed distracter condition overall, F(1,10) = 6.3, $p = 0.03$).

Experiment 4: Synonym judgement under dual task conditions

The findings above are consistent with our hypothesis that semantic judgements to HF words place greater demands on executive control than judgements to LF words – and therefore deficits in semantic control in patients with SA produce absent or reverse frequency effects in this patient group. If this proposal is correct, it might be possible to simulate the performance of SA patients in healthy individuals by using a secondary task to divide attention during synonym judgement. We predict that healthy participants should show a processing advantage for HF words overall (reflecting the language system's substantial experience for these items); however, the secondary task should produce greater disruption to semantic judgements about HF as opposed to LF words.

Method

Participants: 36 healthy undergraduate students aged 19-22 years (24 females) participated for a small cash payment or course credit. All participants were native speakers of British English.

Design: We used a within-subjects design. A computerised version of the synonym judgement task from Experiment 3 was employed, involving written words and key press responses. On some trials, participants made semantic judgements alone, while in other trials they simultaneously performed an auditory-verbal 1-back task. There were four versions of the experiment which presented the same items in four different conditions generated by a 2x2 design (single vs. dual task; frequency-matched vs. frequency-reversed distracters). Every item was presented in each condition across participants (nine subjects per version). Items were not repeated for individual participants.

For each participant, the experiment was presented in 3 blocks: (i) 1-back task under single task conditions; (ii) synonym judgement, with half of the trials requiring simultaneous 1-back performance (dual and single-task trials were presented in a mixed fashion), (iii) a final block of 1-back trials under single task conditions.

Procedure: The experiment was presented using E-prime. All the instructions were delivered via the computer with examples at the beginning of each task. In the blocks involving the 1-back task on its own, a series of random digits from 1-9 were presented through speakers at a rate of 1.5s. Participants listened to the first number without responding, and for each subsequent number, they attempted to say the item that they heard on the previous trial. For example:"9" → listen; "6" → Say 9; "1" → Say 6. A fixation cross was presented on the screen while the participants repeated the numbers and they controlled the presentation of the next trial by pressing a key. In the initial block, there were twelve practice trials followed by a further twelve trials used as a baseline measure of 1-back performance prior to the synonym task.

Next, participants were given practice on the synonym task (with and without a concurrent secondary task). The probe word was presented at the top of the computer screen with three choices beneath. Participants pressed 1, 2 or 3 on the keyboard to respond (where the location of the target on the screen corresponded to the location of the keys on the keyboard). They were asked to respond as quickly and accurately as possible. Participants completed 96 experimental trials, 48 under single task conditions, and 48 requiring simultaneous 1-back performance, presented in a mixed fashion. Participants were unable to antici- pate in advance which synonym trials would be presented under single and dual task conditions; instead, they were instructed to start doing the 1-back task if a number sequence was presented. After a variable interval (3–5 digits in the 1-back sequence), the synonym words were presented while the 1-back task continued; in contrast, in single-task synonym trials, the synonym judgement was presented visually after fixation, in the absence of a number sequence. Again, participants controlled the presentation of each trial by pressing a key on the keyboard.

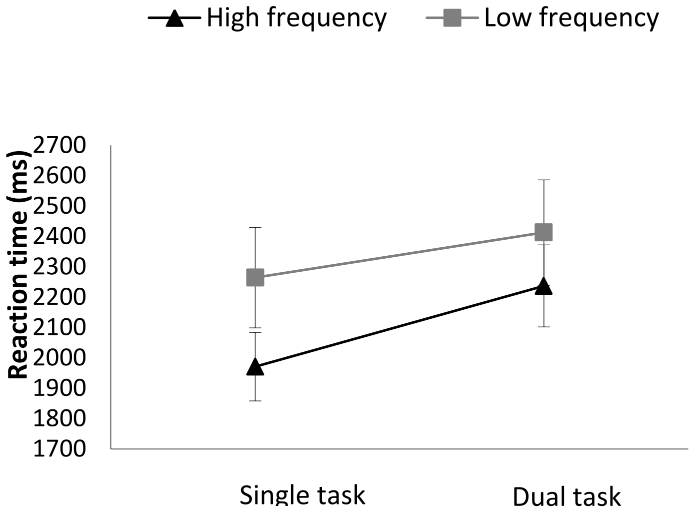
Following the synonym task, participants performed the 1-back task under single task conditions again. Two 'warm-up' trials were followed by twelve assessment trials. The two 1-back only blocks (at the beginning and end of the experiment) were averaged together to provide a measure of 1-back single task performance.

Results

RT for synonym judgement: We used repeated-measures ANOVA to examine the effects of word frequency (high/low), distracter type (standard/reverse) and dual task (single/dual) on response times (RT). The results are shown in Table 5 and Figure 2. The main effect of dual task was significant, F(1,35) = 5.3, *p* = .03, as was the effect of frequency, F(1, 35) = 9.6, *p* = .004) – healthy participants responded more quickly to HF than LF words. There was no main effect of distracter type, F(1,35) = 1.06. The predicted interaction between dual task and frequency reached significance, F(1, 35) = 4.1, *p* = .05 (see Figure 2). There was an effect of the dual task on RT for HF words which approached significance (Bonferroni t(35) = 3.11, *p* = 0.08), but no effect for LF words (t(35) = 1.4). This suggests that semantic decisions to HF words require greater executive control than those to LF words, in line with our findings from SA patients.

In a separate RT analysis, we also examined the effect of imageability and dual task, collapsing across distracter type to boost the number of trials per condition (see Table 5). Decisions about highly imageable words were significantly faster than for more abstract items, F(2,68) = 40.6, *p* < .0001. No other effects or interactions reached significance.

Figure 2: RT for healthy participants in the dual task experiment, showing effects of frequency, distracter type and divided attention (Experiment 4)



Error bars show standard error of mean.

Table 5: Effect of frequency, imageability, distracter type and dual task on RT for healthy participants (Experiment 4)

	Single task	Dual task
HF Standard distracters	1997.34 (666.98)	2234.07 (979.95)
LF Standard distracters	2277.72 (982.78)	2412.75 (937.03)
HF Reverse distracters	1979.67 (695.83)	2346.46 (772.80)
LF Reverse distracters	2369.72 (1218.17)	2482.18 (1177.97)
High imageability	1855.88 (2344.91)	2130.68 (2281.17)
Medium imageability	2053.37 (2748.96)	2251.632 (2754.21)
Low imageability	2545.20 (2751.61)	2678.49 (3026.95)

Figures shows mean (standard deviation in parentheses). HF = High frequency; LF = Low frequency.

Accuracy of synonym judgement: Our primary outcome measure was RT since the accuracy of the healthy participants approached ceiling. Nevertheless, in a repeated-measures ANOVA of response accuracy, including frequency, distracter type and dual task as factors, there were main effects of dual task (F(1,35) = 45.2, *p* < .0001), frequency (F(1,35) = 47.9, *p* < .0001) and distracter type (F(1,35) = 7.01, *p* = .012) but no significant interactions (F(1,35), F < 1). These results are shown in Table 6. Participants were more accurate overall on reverse distracter trials, apparently because they did better on LF trials when these probes and targets were presented with HF distracters (they were close to ceiling on HF synonym judgement).

Following the method above, we also carried out a separate analysis including imageability and dual task as factors: this revealed main effects of both imageability (F(2,70) = 70.4, *p* < .0001) and the secondary task (F(1,35) = 38.4, *p* < .0001), plus a significant interaction between them (F(2,70) = 3.2, *p* = .05). The secondary task reduced accuracy for low imageability (Bonferroni t(35) = 4.2, *p* < .001) and medium imageability words (Bonferroni t(35) = 3.4, *p* = .004), while there was no significant effect of the 1-back task for high imageability items (Bonferroni t(35) = 1.7, n.s.). The more challenging abstract items may have shown the largest influence of the dual task because they were less influenced by ceiling effects.

Table 6: Effect of word frequency, imageability, dual task and distracter type on synonym judgement accuracy for healthy participants (Experiment 4)

	Single task	Dual task
HF Standard distracters	95.13 (6.09)	87.50 (9.86)
LF Standard distracters	81.01 (16.85)	76.15 (15.57)
HF Reverse distracters	95.60 (6.45)	91.43 (9.85)
LF Reverse distracters	84.95 (12.25)	79.62 (14.96)
High imageability	97.32 (1.76)	96.20 (2.02)
Medium imageability	93.08 (3.06)	88.83 (3.36)
Low imageability	81.47 (3.51)	72.76 (3.75)

Table shows mean accuracy on the synonym task, as a percentage of the total trials in each condition (standard deviation in parentheses). HF = high frequency, LF = low frequency.

1-back performance: We analysed the percentage of 1-back responses that were correct for each participant, averaged across all of the trials within each condition. The results are shown in Table 7. Repeated-measures t-tests contrasting single task performance in the initial and final 1-back blocks showed significant improvement across the experiment, t(35) = 3.47, *p* = .001. 1-back performance was significantly more accurate under single task conditions (using an average of the initial and final 1-back blocks) than during synonym judgment overall, t(35) = 7.6, p < .001. We used repeated-measures ANOVA to examine the effect of frequency and distracter type manipulations within the synonym task on 1-back secondary task performance. This confirmed that 1-back performance was worse during LF than HF trials, F(1,35) = 17.49, *p* < .001, presumably because LF items were more difficult overall. There was no effect of distracter type and no frequency by distracter type interaction. In addition, a one-way repeated-measures ANOVA indicated a significant effect of imageability on 1-back performance, F(2,70) = 5.1, *p* = .009. Bonferroni t tests revealed that 1-back performance was better during synonym judgement for high as opposed to low imageability trials, t(35) = 3.0, *p* = .01, presumably because the LI items were also more difficult. No other pairwise comparisons reached significance.

Table 7: 1-back accuracy for healthy participants in the dual task experiment (Experiment 4)

	Mean	s.d.
Baseline 1	91.96	8.14
Baseline 2	96.01	4.01
Baseline average	93.80	5.78
HF Standard distracters	77.26	18.59
HF Reverse distracters	80.14	18.03
LF Standard distracters	72.91	17.37
LF Reverse distracters	73.50	16.27

Baseline = performance on 1-back task performed in isolation. HF = high frequency, LF = low frequency. Table shows accuracy on the 1-back task, expressed as a percentage of items presented.

General Discussion

This study examined the hypothesis that decisions about the meanings of high frequency (HF) words require greater executive control than semantic decisions for low frequency (LF) words. HF words occur in more contexts and have wider and more variable meanings than their LF counterparts. In contrast, LF words are associated with a limited range of linguistic contexts and so similar semantic information is encountered each time (Hoffman et al., 2011b). Greater executive control might be required for HF words in order to selectively focus processing on aspects of meaning that are relevant for a given task or context. This is likely to be particularly evident in a task like synonym judgement, in which it is necessary to select one of several possible targets on the basis of their strength of association with the probe word – high frequency probes might be more likely to activate spurious or irrelevant associations. Patients with semantic aphasia (SA), who have poor executive control over semantic processing, might therefore show a reduction or elimination of the natural processing advantage enjoyed by high frequency items in synonym judgement, or possibly even a reversal of the normal frequency effect.

Over four experiments, we sought convergent evidence for these hypotheses from neuropsychology and healthy participants tested under dual-task conditions. In Experiment 1, SA patients showed minimal or reverse frequency effects, yet better performance for more imageable as opposed to abstract items within the same task, suggesting that our methods were sensitive to the influence of lexical variables on comprehension in SA. The negative effects of comprehension in the SA group were correlated with the degree of executive impairment, in line with our predictions. Moreover, we previously confirmed that the frequency manipulation in this test had a powerful *positive* influence on comprehension in another patient group (semantic dementia) – therefore SD and SA patients show a double dissociation (Jefferies et al., 2009).

In Experiment 2, healthy participants were asked to rate the ease with which they could think of associations between HF and LF probes and their supposedly unrelated distracters. The ratings showed that it was easier to think of a potential relationship between high frequency probes and their distracters: for example, in the HF trial “child with kid, road or university?”, one might imagine a child playing in the road, or a grown-up child at university and consequently miss the synonymous relationship. In contrast, participants found it harder to think of a semantic relationship between low frequency targets and distracters.

Experiment 3 showed that when SA patients were presented with a version of the synonym task with frequency-reversed distracters – i.e., HF probes/targets with LF distracters and LF probes/targets with HF distracters, their performance on HF trials improved. We propose that the SA patients were less likely to respond on the basis of spurious associations when the HF probes were presented with LF distracters because LF words have less varied meanings and occur in fewer contexts (Hoffman et al., 2011b).

Finally, Experiment 4 provides support for our hypotheses in a sample of healthy participants. They carried out the same synonym judgement task as the patients but, on some trials, concurrently performed an auditory-verbal 1-back task. This requirement to perform two tasks simultaneously was designed to divide attention and reduce capacity for executive processing. The results showed that although HF words were less demanding for normal volunteers to process *overall* (resulting in standard frequency effects in response times), dual task conditions produced greater disruption for HF trials. This pattern is similar to that seen in patients with SA and confirms the view that HF words require greater cognitive control. However, the healthy volunteers continued to show near-ceiling accuracy in synonym judgement even under dual task conditions: consequently, the behavioural effects were seen in RT.

Given that the SA patients showed better performance on HF probes/targets when they were presented with LF distracters, it is worth noting that the healthy volunteers in Experiment 4 did not show an effect of frequency-reversed distracters on RT. A possible explanation for this null result is that SA patients are more vulnerable to errors induced by high frequency distracters due to their severely impaired semantic control. In contrast, healthy participants showed near-ceiling performance for HF trials, even under dual task conditions – positive effects of frequency were more prominent for them in both RT and accuracy. Although the secondary task did allow us to see negative effects of frequency in normal individuals *in RT*, any positive impact of the reverse distracter manipulation on HF items may have been swamped by the processing costs associated with presenting LF distracters, which would have taken longer to read and understand.

Taken together, these findings indicate that although HF items normally enjoy a processing advantage – perhaps reflecting more efficient reading processes and/or faster retrieval of associated meanings – they also place greater demands upon executive processes that direct semantic activation in a task-appropriate way. As a consequence, the standard frequency effect is eliminated and, in some cases/trials, even reversed in SA patients. This follows from the fact that (i) SA patients do not have damage to semantic representations in the anterior temporal lobes (unlike patients with semantic dementia; see Introduction) – consequently the resilience of HF representations to damage does not give rise to better preserved comprehension for HF items in SA. (ii) In addition, poor control over semantic activation in SA overrides the normal frequency advantage by disadvantaging HF trials more than LF trials. HF stimuli are observed in a greater variety of contexts/situations and have a greater diversity of meanings (Hoffman et al., 2011): therefore, executive control is required to select the aspects of meaning that are relevant in a specific situation. In addition, executive control is required to ignore spurious links between the probe and distracter words in synonym judgement.

CHAPTER 3

The contribution of executive control to semantic cognition: Insights from a comparison of semantic aphasia and dysexecutive patients

Note: We are grateful to Krist Noonan, who collected data for three out of the thirteen dysexecutive cases reported in this chapter. These data were previously published in his thesis: Noonan, K. A. (2010). *Conceptualising the void: Bridging the gap between semantic cognition and cognitive control*. Ph.D. Thesis. University of Manchester: U.K. All of the remaining DYS data was collected by A. Almaghyuli. SA data appeared in (Almaghyuli et al., 2012; Corbett et al., 2009; Jefferies et al., 2007; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008; Noonan et al., 2010).

Introduction

This chapter explores the relationship between semantic cognition and executive control through a novel case-series comparison of semantic aphasia (SA) and dysexecutive syndrome (DYS). Jefferies and Lambon Ralph (2006) found that SA patients' performance in semantic tasks across modalities was correlated with non-verbal executive measures. The SA group also showed strong effects of semantic control manipulations, such as retrieving the dominant and subordinate meanings of ambiguous words and synonym judgement with strong and weak distracters (Noonan et al., 2010). These findings suggest that, in SA patients, executive processes fail to appropriately control activation in the semantic network, for example by resolving competition and focussing processing on task-relevant features.

Jefferies and Lambon Ralph (2006) envisaged that domain-general control processes interact with the 'hub and spoke' semantic network (i.e., ATL 'hub' interacting with visual, auditory and motor 'spokes'), following the computational model of Rogers et al. (2002). Dysfunction of the semantic control component could explain SA patients' deficits. This architecture provides an explanation of why the semantic control impairment in SA is multimodal, affecting word, picture, sound and object use tasks: the control processes and the semantic representations they operate on are amodal. Studies of SA have observed parallel deficits in the verbal and nonverbal domain when assessed with pictures, environmental sounds and tests of object use (Corbett et al., 2009a; Corbett et al., 2009b; Jefferies & Lambon Ralph, 2006).

Nevertheless, the association between impairment of executive processing and semantic control in SA can be explained in several ways. The executive difficulties of SA patients may be sufficient to explain their marked semantic impairment. This simple view is compatible with Jefferies and Lambon Ralph's (2006) account. Alternatively, the neuropsychological impairment in SA may reflect a more complex combination of deficits. A recent neuroimaging meta-analysis (Noonan et al. submitted) suggested that the brain regions supporting semantic control *partially* overlap with multi-demand executive regions (Duncan et al., 2010): medial/dorsolateral PFC and IPS are components of both networks, while sites in anterior LIFG and pMTG are restricted to the semantic domain. This raises the possibility that SA patients have more severe impairment of semantic control than would be anticipated from dysexecutive patients with a similar level of performance on executive tasks because they have sustained damage to brain regions in inferior PFC and posterior temporal cortex specifically implicated in executive-semantic processes. A case-series comparison of patients with SA and dysexecutive syndrome (referred to here as DYS) provides a means of testing these alternatives. We determine whether executive deficits in DYS are sufficient to produce problems on semantic tasks that resemble those seen in SA cases, and if these impairments are of the same degree and quality in the two groups.

Consideration of the nature of executive functions and how these relate to the deficits in SA suggests there may be some similarities in the way performance breaks down in SA and DYS. Executive processes create an attentional set to guide the performance of behaviour online, and allow switching between different cognitive tasks (Alexander et al., 2005; Dosenbach et al., 2006; Miller, 2000). Performance in the face of competition from distracting information is also frequently ascribed to the operation of core executive processes responsible for inhibition of task-inappropriate information (Braver et al., 2002; Burgess & Shallice, 1996; Picton et al., 2007). Moreover, processes responsible for the planning and sequencing of behaviour in response to weakly specified environmental circumstances are a consistent feature of many executive theories (Norman & Shallice, 1986; Wood & Grafman, 2003). Similarly, SA cases have difficulty discerning which aspects of an item’s meaning are being probed in a specific task or context (Noonan et al., 2010; Corbett et al., 2012). They show strong effects of the strength of distracters in semantic tasks (Noonan et al., 2010) and neuroimaging studies of LIFG reveal effects of the number of distracters in healthy participants (Wagner et al., 2001). SA cases also have difficulty in tasks that are relatively unconstrained, including action sequences such as ‘packing a child’s school bag’ that requires planning (Corbett et al., 2011; 2012). In this study we explore the relationship between semantic regulation and domain-general executive control processes to examine whether they share overlapping cognitive and neural resources.

In the executive control literature, there is little agreement about the structural and functional organisation of executive processing. Different views are expounded in a number of theories. Some theories attempt to divide control processes into component sub-processes (Shallice, 2002; Stuss et al., 1995) while others view cognitive control as a unitary system (Braver et al., 2002; Duncan & Owen, 2000). This debate extends not only to the functional aspects of executive processing, but also to its structural organisation. A number of theories have hypothesised highly specific roles for areas in the left and right lateral prefrontal cortex and medial frontal lobes (Shallice, 2004; Stuss & Alexander, 2007). Lateral prefrontal cortex plays an important role in certain elements of working memory for both spatial and non-spatial domains. Support comes from the study of patients with excisions of the frontal cortex (Petrides and Milner, 1982; Owen et al., 1990, 1995, 1996d). Researchers have also explored functional roles of subdivisions within the lateral prefrontal cortex in working memory. Goldman-Rakic (1987, 1994, 1995) contrasted the roles of dorsolateral (DL) and ventrolateral (VL) prefrontal regions in the organization of information processing based on modality. She argued that DL frontal regions are involved with memory for spatial material, whilst ventrolateral frontal regions serve memory for non-spatial material. A meta-analysis study by Owen (1996) suggests that lateral regions of the frontal lobe are not functionally organized based on information modality, but that specific regions within lateral prefrontal cortex support both spatial and non-spatial working memory. More recently, Badre et al. proposed that the prefrontal cortex is organised hierarchically along the rostro-caudal axis with cognitive control processes requiring greater levels of abstraction supported by more anterior cortical regions (Badre & D'Esposito, 2009; Badre et al., 2009). Evidence from patients with frontal damage and fMRI data established differences in functional activation along the rostro-caudal axis of the lateral frontal cortex, ranging from the lateral frontal polar cortex to the premotor cortex, such that more anterior regions were associated with progressively more abstract action control (Badre et al., 2009, 2010). This idea has also been applied to the semantic domain, where it has been proposed that anterior ventrolateral PFC (BA47) underpins semantic retrieval based on the contextual goals of the task, while more posterior regions (BA45/44) underpin post-retrieval selection processes which resolve competition between already active competitors (Badre & Wagner, 2007).

Duncan (2001) suggests a unitary-function/neutrally-distributed control hypothesis, stating that the neural systems responsible for executive processing utilise adaptive coding, allowing the same structures to contribute toward different executive processing in wide cognitive domains. Adding to that, Duncan and Owen (2000) showed that different forms of executive processing (e.g. problem solving, working memory load, novelty processing) give rise to highly similar bilateral activation patterns in a distributed network, including medial and lateral PFC and IPS. The activation in executive areas was the same regardless of the type of task domain (spatial, semantic or linguistic judgment) or processing modalities (visual, auditory stimuli).

Functional neuroimaging studies support the unitary-function/neurally-distributed control hypothesis; associated activation is commonly found in bilateral frontal and posterior parietal cortex in cognitive control demand tasks. Many studies show joint activation in bilateral ventral and dorsal PFC, anterior cingulate and inferior parietal cortex in tasks needing conflict resolution and different executive processes like stroop, flanker, go-no, set-shifting, updating working memory and inhibitory processing (Nee et al., 2007; Collette et al., 2006). Peers et al. (2005) found similar attention/cognitive control impairment resulting from lesions to PFC or the inferior parietal cortex. Moreover, TMS to dorsal PFC and IPS disrupts executive processes for both semantic and non-semantic tasks (Nagel et al., 2008; Whitney et al., 2012), consistent with the finding that anterior and posterior lesions in SA produce comparable deficits of semantic and executive control (Noonan et al., 2010). This fits with findings from SA patients that non-verbal measures of executive control can predict the performance of semantic tasks (Jefferies & Lambon Ralph, 2006; Luria, 1976). Nevertheless, the large lesions in SA patients and those with acquired brain injury may include regions involved in both domain-general and more specific aspects of semantic control.

A recent activation likelihood estimate (ALE) meta-analysis of neuroimaging studies of semantic control provides further support for the view that executive-semantic processes draw on multi-demand cognitive control sites (Noonan et al., submitted). Parts of LIFG were activated by both semantic control demands and phonological tasks. However, this region still showed some degree of functional specialisation: semantic tasks with high control demands produced higher activation mostly in ventral parts of PFC (BA47), while phonological tasks were associated more with activation in dorsal PFC and adjacent parts of premotor cortex (cf. Gough et al., 2005; Vigneau et al., 2006). pMTG was only activated by executively-demanding semantic tasks and did not contribute to domain-general control, while dorsal AG/IPS was involved in domain-general executive processing. Moreover, semantic tasks with high control demands also activated ventral angular gyrus, while phonological tasks yielded more activation of supramarginal gyrus. Since these contrasts compared semantic/phonological control with low-level baseline or rest trials, they may reflect general semantic and phonological processing in addition to the control demands of the tasks. It is also important to note that the majority of studies that were entered into this meta-analysis used verbal stimuli. Much less is known about how the brain controls retrieval of non-verbal knowledge: this motivates the use of both verbal and non-verbal semantic tasks in both neuroimaging and neuropsychological investigations such as the work presented in this chapter.

In the current study, we take a novel approach to investigating the relationship between semantic cognition and domain-general executive control. Specifically, we ask whether patients with dysexecutive syndrome show features of semantic impairment that are qualitatively similar to those reported in SA patients, and if these deficits occur to the same degree. If the cognitive and neural processes supporting semantic and broader executive control are highly overlapping, and SA patients' deficits reflect their executive problems, DYS and SA cases should show the same difficulties: when their executive difficulties are matched, their semantic deficits should also be matched. Alternatively, if SA patients have damage to control components unique to semantics, reflecting their lesions in LIFG and pMTG, the dysexecutive patients may show milder deficits in the semantic domain.

In this chapter, the semantic performance of DYS patients is contrasted with SA patients, in order to detect similarities and differences in their performance profiles. The following semantic aspects are explored: (1) degree of deficit across different semantic and executive tasks; (2) consistency and correlations between different input modalities (for the same semantic decisions) and across different semantic tasks (for the same items); (3) effects of familiarity and frequency; (4) ratings of semantic control demands and how these relate to task performance; and (5) the effect of experimental manipulations affecting the semantic control demands of tasks – including probe-target overlap, distracter strength, ambiguity and cueing/miscuing. These semantic tasks have varying inhibition and selection demands: SA and DYS patients might be expected to show parallel effects of these manipulations if the deficits in SA arise directly from these patients' domain-general executive impairment.

Participants:

DYS group

A total of 13 DYS patients aged 21-64, mean age = 37.53 (SD = 14.9) took part in the study. On average they had completed 16 years of education (SD = 6.1). They were all native English speakers and all patients had chronic impairment from acquired brain injury at least one year prior to testing. They were recruited from rehabilitation and head injury support units in York, Garforth and Manchester UK. Patients' demographic details are given in Table 8a, with case descriptions in Appendix B.

The DYS patients were selected according to their function in the executive domain. The primary tool for selection was the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson et al., 1996). Patients were referred to us on the basis that their evaluation by a clinical neuropsychologist suggested executive control deficits. We selected patients for inclusion who showed impaired or borderline performance on the BADS test battery. Potential participants were excluded if they sustained brain injury during childhood.

SA group

We examined sixteen SA patients, with mean age = 69.6 (SD = 10.8) most of whom participated in our previous investigations of the semantic control deficit in this condition (Almaghyuli et al., 2012; Corbett et al., 2009; Jefferies et al., 2007; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008; Noonan et al., 2010). More details of these participants can be found in Chapter 2.

Patients were selected on the basis that they showed multimodal semantic impairments that affected their comprehension of words and pictures (see Jefferies et al., 2006 for more details). The SA group did not differ from the DYS patients in age, $t(12) = 1.3$, $p = .21$. However, there were significant differences in the level of education between the two groups, $t(12) = -6.8$, $p > .0001$, with the DYS group having more education (Table 8b).

Control Participants

Data from eight control participants were taken from Noonan et al. (2010). None of the controls had a history of psychiatric or neurological disorders. The control group did not differ from the patients or each other, in terms of age ($t < 1.5$, $p > .1$) and educational level ($t < 1.3$, $p > .2$)

Table 8a: Demographic information for dysexecutive patients (DYS)

Patients	Age	Education	BADS	Neuroimaging summary	PFC	T-P	Aetiology of TBI
MC	28	14	79	White matter damage in L PFC + R parietal contusion	*	ǂ	Alleged attack
TG	25	15	78	Enlargement of R lateral ventricle+ contusions in the cerebellum and cerebrum	ǂ	ǂ	Road traffic accident
JS	64	Dip	78	Hypoxic episode	ǂ	ǂ	Cardiac arrest
GR	59	16	78	L+R frontal-parietal	*	*	Road traffic accident
HM	58	PhD	72	L frontal-parietal	*	*	External insult by sharp object
JYS	21	18	71	Diffuse axonal injury with small intraventracular	ǂ	ǂ	Road traffic accident
AP	25	18	71	No scan	ǂ	ǂ	Road traffic accident
MrL	45	16	70	L temporal lobectomy	ǂ	*	Temporal lobe abscess
JG	22	16	70	L frontal-parietal lobectomy	*	*	Pituitary haemorrhage/Tumour
PG	52	18	65	Bilateral anterior Cerebral Artery (ACA) infracts	ǂ	*	CVA
CR	22	16	65	R frontal + L parietal lobes	*	*	Road traffic accident
MK	38	15	65	Bilateral ischemic encephalopathy of basal ganglia	*	ǂ	Hypoglycaemia attack/encephalopathy
DL	40	14	54	L frontal –temporal	*	*	External insult by sharp object

Patients are arranged in order of Behavioural Assessment of Dysexcutive Syndrome scores (BADS; Wilson et al., 1996). Edu = age of leaving education. Dip= postgraduate diploma. Neuroimaging summaries are based on written reports of clinical scans were available; except in the case of JG, CR and GR they were based on visual inspection of CT scans. PFC = lesion involves left prefrontal cortex; T-P = lesion involves left temporoparietal cortex; * = indicates damage. ǂ = neuroimaging is not sufficient to make a definitive statement regarding the extent of cortical damage or scan not available.

Table 5b: Aphasia classifications and neuroimaging summaries for the SA participants

Patient	Age	Edu	Neuroimaging summary	Aphasia Type	BDAE Compreh	BDAE Fluency	BDAE Repetition	Nonword repetition	Word Repetition
HN	80	15	L occipital-temporal	Anomic/TSA	NT	NT	NT	56	86
EW	74	15	L occipital-temporal		NT	NT	NT	NT	80
JD	81	16	Compression of L lateral ventricle & capsular	Mixed Transcortical	NT	NT	NT	73	93
SC	80	16	L occipital-temporal (+ small R frontal infarct)	Anomic/TSA	37	90	60	87	98
ME	40	16	L occipital-temporal	TSA	33	100	100	93	100
GH	56	18	L frontal-parietal	Global	NT	NT	NT	NT	NT
NY	67	15	L frontal-parietal	Conduction	47	37	40	40	81
PG	63	18	L frontal & capsular	TSA	20	40	80	73	91
JM	69	18	L frontal-parietal	TSA	22	63	40	87	95
MS	73	14	No scan	Global	10	0	0	0	0
KH	73	14	L frontal-parietal-occipitotemporal	Mixed Transcortical	30	30	40	43	80
KA	78	14	L frontal-parietal	Global	0	23	0	0	0
BB	59	16	L frontal	Mixed Transcortical	10	17	55	83	96
DB	76	16	L frontal-temporal-parietal	TSA/Wernicke’s	13	90	30	70	85
LS	75	15	L frontal-parietal-occipitotemporal	TSA	13	90	90	90	96
EC	71	16	L frontal-parietal	Global	NT	NT	NT	NT	16

Patients are arranged in order of synonym judgement performance. BDAE = Boston Diagnostic Aphasia Examination (Goodglass, 1983). BDAE Comprehension score is a percentile derived from three subtests (word discrimination, commands, complex ideational material). BDAE Fluency percentile is derived from phrase length, melodic line and grammatical form ratings. BDAE Repetition percentile is average of word and sentence repetition. TSA (transcortical sensory aphasia) was defined as good or intermediate fluency/repetition and poorer comprehension. Word/non-word repetition: Tests 8 and 9 from PALPA (Psycholinguistic Assessments of Language Processing in Aphasia, Kay et al., 1992).

Background neuropsychological assessment

Executive tests:

The SA and DYS patients were examined on a range of tests to assess executive function/attention:

1. The Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson et al., 1996), which consists of six subtasks (listed in Table 9a) that assess a patient's ability to plan, organize and solve problems.
2. The Brixton Spatial Anticipation task (Burgess & Shallice, 1997), in which the participants need to predict the location of a moving dot in a spatial display. There are 10 circles, one with a dot in it. The dot 'moves' on each page turn, and the participants has to guess which circle the dot will jump to (e.g. moving from circle 1 to 2 to 3 and so on). The rule for the dot's movement is changed several times during the test (e.g. counting backswords from 10 to 9 to 8) without informing the subject, who needs to be able to shift to the new rule and inhibit the old ones to score highly on the task.
3. The Hayling Sentence Completion test (Burgess & Shallice, 1997) requires the participant to produce a nonsense word to end a sentence, suppressing a suitable ending. For example, "It is hard to admit when one is… wrong"). Nonsensical endings require the targeted word to be suppressed (e.g., "Most sharks attack very close to… tables"). It consists of two sets of 15 sentences. Reaction time and responses are recorded.
4. The Raven's Coloured Progressive Matrices (Raven, 1962) is a nonverbal reasoning task in which participants are asked to identify which of six missing elements complete a spatial pattern. Many patterns are presented in colours. This test contains sets A, AB, and B (which get increasingly abstract/difficult), with 12 items per set.
5. Digit-span (forward and backward) is a measure of working memory capacity and sustained attention. Participants are presented with a series of digits (e.g., '8, 3, 4') and must immediately repeat them in the same order. If they do this successfully, they are given a longer list (e.g., '9, 2, 4, 0'). The length of the longest list a person can remember is that person's digit span. In the backward series, participants repeat the same digits in reverse order from the last number heard (e.g., '8, 3, 4' is recalled as '4, 3, 8').
6. The Letter Fluency test requires participants to produce as many words as possible within 1 minute. Participants are asked to produce words that start with a given letter (FAS), excluding numbers, proper names, places or words in different forms.

Semantic tests:

64 items semantic battery

The presence of multimodal semantic impairment was assessed using a battery of semantic tests which tapped different input and output modalities for the same 64 items (Bozeat *et al.*, 2000; Adlam et al., 2010). There were six categories: animals, birds, fruit, household items, vehicles and tools. There were four test components:

1. *Spoken word-picture matching (WPM*): Patients were required to match a verbally presented word to a target picture presented alongside nine semantically related foils. The pictures were black and white line drawings taken from the Snodgrass and Vanderwart (1980) corpus.
2. *Picture naming:* Patients named the individually-presented drawings.
3. *Camel and Cactus Test (CCT)* using the word and the picture versions (Bozeat et al., 2000): The CCT was used to evaluate associative semantic knowledge. Patients had to decide which of four pictures/words was most associated with a probe picture/word (e.g., CAMEL with CACTUS, ROSE, TREE or SUNFLOWER?). In the word version of CCT, the words were presented visually and also read aloud by the experimenter. We also used ratings of (a) the ease of identifying the relevant semantic relationship (e.g., understanding that CAMEL is associated with CACTUS because they are both found in the desert and not because the CAMEL eats CACTUS); (b) the association strength between the probe and the target and (c) the difficulty of rejecting the distractors. These ratings were collected previously by Jefferies and Lambon Ralph (2006).

Jefferies et al. (2006) argue that the executive control demands are different between tasks across this battery of tests. Word-picture matching and naming are most straightforward, in that they involve identify matching – i.e., matching a picture with its own name or identifying and producing the relevant name for a concept. These tasks require semantic competitors to be inhibited, but unlike CCT, they do not require participants to work out the relevant semantic relationship from different possible targets or to flexibly retrieve different aspects of meaning in different contexts. This need to identify what association is being probed makes the CCT potentially more sensitive to impairment of semantic and executive control.

Environmental sound battery

This test contains 48 recorded sounds from six categories: domestic/foreign animals, human sounds, household items, and vehicles and musical instruments (Bozeat et al., 2000).

Participants were tested in three conditions: matching sounds to pictures, sounds to written words and spoken words to pictures. In every trial, the target was presented with 10 within-category distractors. Familiarity ratings for these concepts and sounds were obtained from Bozeat et al. (2000).

Synonym judgment task

There were 96 items in this test, equally split between two bands of frequency (mean frequency of probe words [with standard deviations in parenthesis = 128 (10) and 4.6 (4.5) counts per million in the Celex database (Baayen et al., 1993)] and three imageability bands [mean imageability of probe words = 275 (17.3), 452 (26.0) and 622 (14.0) respectively, on a scale of 100-700, from the MRC Psycholinguistic Database (Coltheart, 1981)]. The test was presented in written form and read aloud by the experimenter. In each trial, the probe word was presented with three potential targets to select from. Full details of this test can be found in Jefferies et al. (2009). A measure of contextual diversity for the probe items was obtained from Hoffman et al. (2010). These values identified the extent to which an item's meaning is consistent across different linguistic contexts, using Latent Semantic Analysis (Landauer & Dumais, 1997). High scores on this factor reflect items with contextually diverse meanings.

Results

Executive tests

To establish the level of impairment in executive and semantic tests in each group, the performance of DYS and SA patients was compared. The SA patients performed poorly on most of the attention/executive measures compared to the DYS patients (see Table 9 and 10). The following differences were significant: Letter fluency: $t(12) = -3.4$, $P = .005$, digit span - backwards: $t(12) = -4.5$, $P = .001$, Raven's coloured progressive matrices: $t(12) = -2.5$, $P = .02$). On the other tests, differences approached significance: Brixton: $t(12) = -1.9$, $P = .08$, digit span forward: $t(12) = -2.1$, $P = .06$). While deficits in digit span and fluency in the SA group might be explained in term of poor speech production, their significant deficits on the Raven's matrices task suggests that the SA group were more impaired even on non-verbal tasks.

Table 6 : Neuropsychological background tests for DYS patients

Tests	Max	Cut off	DYS Mean (S.D)	SA Mean (S.D)	MC	TG	JS	GR	HM	JYS	AP	MrL	JG	PTG	CR	MK	DL
BADS																	
Standardised score					79	78	78	78	72	71	71	70	70	65	65	65	54
(Classification)					Borderlines				Impaired								
1-Rule Shift	4				3	4	4	2	2	4	3	2	4	3	4	4	2
2-Action Program	4				4	4	2	4	3	4	4	3	0	3	3	3	3
3-Key Search	4				2	3	0	2	3	1	1	2	4	1	1	1	1
4-Temporal Judgment	4				2	3	1	3	1	3	3	3	3	2	3	3	2
5-Zoo Map	4				2	3	1	0	3	2	1	1	1	1	0	0	1
6- Six Elements	4				2	3	1	3	1	1	1	2	1	3	1	1	0
RCPM	36	-	26.3(4.7)	19.9(7.2)	29	31	27	26	*24	28	32	*19	30	27	31	*20	*18
Brixton	54	28	29.2(13.5)	20.8(8.3)	46	41	43	6	30	39	31	28	30	*26	41	*13	*6
Letter Fluency	-	18	31.5 (14.0)	6.7(8.1)	38	41	38	29	21	*9	35	*4	21	37	*5	24	*5
Digit span																	
Forward	-	5	5.4(1.1)	4.1(1.7)	6	6	7	6	6	*4	7	*4	5	5	6	*4	*4
Backward	-	2	3.3(0.6)	1.7(0.9)	4	4	4	4	3	3	4	3	3	3	3	3	2

Table shows raw scores. DYS are arranged by severity of performance on BADS (Wilson et al., 1996). A profile score, ranging from 0–4, is calculated for each test and an overall profile score produced as a sum of individual test scores. Profile scores converted to standard scores with a mean of 100 and a standard deviation of 15 with the use of age as a covariate, RCM= Raven's coloured progressive matrices (Raven, 1962); Brixton spatial anticipation task (Burgess & Shallice, 1997). Letter fluency refers to the combined scores from the letters F, A and S. Subtest scores on the BADS are presented on scale ranging from severely impaired (0) to normal performance (4). * denotes impaired performance (< 2 SD below mean).

Table 7: Background non-semantic test scores for the SA patients

Tests	**Max**	**Mean (S.D)**	**HN**	**EW**	**JD**	**SC**	**ME**	**GH**	**NY**	**PG**	**JM**	**MS**	**KH**	**KA**	**BB**	**DB**	**LS**	**EC**
Digit Span (forwards)	5	-	6	*4	5	6	6	*2	*3	6	*3	NT	*4	0	5	*4	*4	NT
Digit Span (backwards)	2	-	2	2	2	2	3	*0	2	2	2	NT	2	NT	*0	2	*1	NT
Letter fluency	-	44.2 (11.2)	*19	*19	* 5	24	*14	*2	* 5	* 2	* 1	* 0	* 1	* 0	* 0	*1	*8	NT
Brixton	28	-	28	28	28	*25	*11	*18	34	*26	NT	*16	*7	*6	*23	*24	*14	*24
RCM	-	-	*20	*20	30	22	*13	32	26	23	*14	*12	*12	*12	24	31	*16	*12

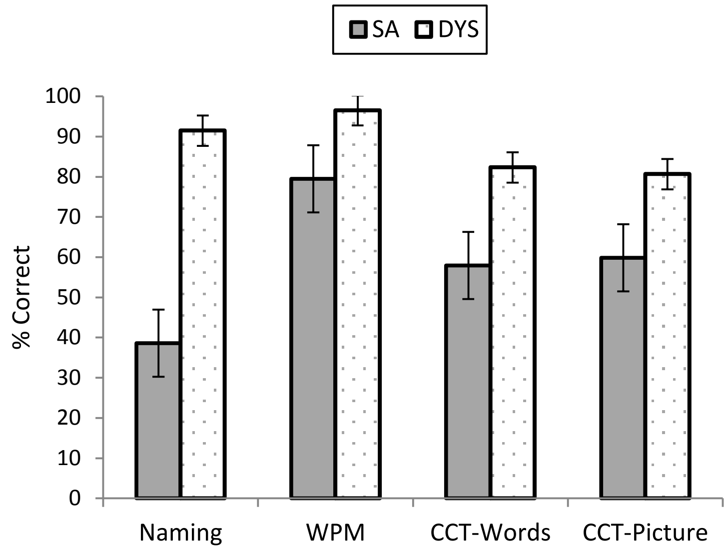
Table shows raw scores. Patients are arranged in order of synonym judgement performance. RCM = Raven's coloured matrices (Raven, 1962); Brixton spatial anticipation task (Burgess & Shallice, 1997). Letter fluency refers to the combined scores from the letters F, A and S. * denotes impaired performance (< 2 SD below mean or below normalised score provided in test manual).

Semantic tests

Group comparisons: Table 11 and 12 summarises both groups' scores in the 64–item Cambridge battery and the environmental sounds test. Both groups showed multimodal semantic impairments in most of the tests. A 4x2 ANOVA of the factors in the semantic task (naming, word-picture matching, CCT-words and CCT-pictures) and the groups (SA vs. DYS) showed a main effect of semantic task, *F*(3, 36) = 15.40, *P* > .001 and a main effect of group, *F*(1,12) = 34.8, *P* > .001, and an interaction between group and task, *F*(3, 36) = 8.09, *P* > .001.

A further set of 2x2 ANOVAs were used to compare pairs of tasks in turn. A significant interaction was found between patient group and task when word-picture matching and naming were compared, *F*(1, 12) = 15.9, *P* = .002, reflecting the poorer language production of the SA group. No significant interaction was found between CCT-word and CCT-picture: *F*(1, 12) = .72, *P* = .68, indicating that the two groups showed comparable deficits in the verbal and non-verbal domains. There was also no interaction between CCT-word and word-picture matching: *F*(1, 12) = 1.23, *P* = .28. These tasks differ in their control demands and the absence of the interaction is compatible with the suggestion that SA and DYS patients have similar problems on more control-demanding tasks. Both groups of patients showed better performance in word-picture matching, which only required identity matching across modalities, than association matching tasks such as CCT, which required participants to work out the relevant semantic relationship being probed on each trial (Kemmerer et al., 2012). In SA, there was significant differences between WPM and CCT-word, *t*(15) = -4.9, two-tailed *p* = .000 and between WPM and CCT-picture, *t*(15) = 3.9, two-tailed *p* = .001. In DYS group, the same significant differences were found between WPM and CCT-word, *t*(12) = 8.3, two-tailed *p* = .000 and between WPM and CCT-picture, *t*(12) = 6.2, two-tailed *p* = .000.

Figure 3: SA and DYS patient’s 64-semantic battery performance comparisons



Error bars show SE of the mean.

There were significant differences between the groups. Performance was poorer for the SA patients in all measures: Picture naming *t*(12) = -4.68, two-tailed *p* = .001; word-picture matching *t*(12) = -3.12, *p* =.009, CCT-words *t*(12) = -5.14, *p* = .001 and CCT-pictures *t*(12) = -4.24, *p* = .001).

In the environmental sounds battery, data were only available from 10 SA patients. Again, the SA group were more impaired in sound- picture matching *t*(10)= 3.45, two-tailed *p* = .006, and word-picture matching *t*(10) = 2.48, two-tailed *p = .032* but there was no difference between groups in sound-word matching *t*(10) < 1.

Compared to the healthy controls, all the dysexecutive patients were outside the normal range on at least two of the semantic tasks. We used the modified t-test procedures outlined in Crawford and Garthwaite (2002) to establish which tests were significantly impaired for each patient taking into account the mean, standard deviation and sample size for the control group. The findings for each individual case are given in Table 13. Every patient showed impairment on at least one semantic task. Three cases showed deficits on all three tasks examined in Table 4, seven cases had impaired performance on between 4 and 6 tasks, and the remaining three cases showed deficits on 1 or 2 tasks.

Table 8: Semantic battery for DYS patients

Mean/ SD				**DYS**	**cases**											
Test	DYS	SA	Controls	**MC**	**TG**	**JS**	**GR**	**HM**	**JYS**	**AP**	**MrL**	**JG**	**PG**	**CR**	**MK**	**DL**
Word to Picture Matching	61.7 (1.8)	50.8 (9.9)	63.8 (0.4)	63*	60*	64	63*	*61	63*	63*	*62	63*	63*	60*	60*	*58
CCT Pictures	51.6 (5.3)	38.3 (10.7)	58.9 (3.07)	51*	48*	45*	53	42*	59	48*	59	55	51*	55	57	*46
CCT Words	52.6 (4.1)	37 (10.6)	60.7 (2.06)	55*	50*	56*	58	54*	59	48*	*51	50*	50*	52*	57	*48
Sound to picture matching	34.7 (2.4)	27.4 (4.9)	41.2 (2.5)	35*	35*	34*	*33	35*	35*	36*	*33	36*	41	30*	34*	*35
Sound to word matching	36.3 (3.5)	40.1 (7.0)	41.2 (2.7)	36*	35*	36	31*	33*	38	39	37	39	45	35*	36	*33
Word to picture	46 (1.1)	37.4 (9.40)	47.7 (0.5)	47*	45*	48	46*	45*	47	46*	*45	47	47	46*	46*	*44
Picture Naming	58.5 (4.8)	24.6 (21.4)	62.3 (1.6)	62	55*	64	58*	49	63	63	*56	61	60	56*	64	*52
Synonym judgment	78.5 (5.7)	65.5 (11)	93.1 2.4	79*	78*	93	83*	82*	74*	72*	71*	77*	82*	79*	74*	77*

Table 9: Semantic battery for SA patients

	Mean/ SD			SA cases														
Test	DYS	SA	Controls	**HN**	**EW**	**JD**	**SC**	**ME**	**GH**	**NY**	**PG**	**JM**	**MS**	**KH**	**KA**	**BB**	**DB**	**LS**
Word to Picture Matching	61.7 (1.8)	50.8 (9.9)	63.8 (0.4)	*50	*57	64	*59	*50	*60	*60	*58	*53	*46	*54	*26	*54	*46	*37
CCT Pictures	51.6 (5.3)	38.3 (10.7)	58.9 (3.07)	*54	*45	*38	*47	*13	*45	*36	*44	*37	*37	*46	*46	*38	*39	*16
CCT Words	52.6 (4.1)	37 (10.6)	60.7 (2.06)	*54	*48	*38	*56	*34	*29	*39	*40	*37	*42	*41	*36	*30	*33	*16
Sound to picture matching	34.7 2.4	27.4 (4.9)	41.2 (2.5)	*36	*22	*23	*32	*33	NT	*28	*33	*24	*NT	*30	*22	*26	*21	*27
Sound to word matching	36.3 3.5	40.1 (7.0)	41.2 (2.7)	42	38	47	48	40	NT	47	44	NT	NT	NT	36	*26	NT	*33
Word to picture	46 1.1	37.4 (9.40	47.7 (0.5)	*16	*45	*46	*41	*40	NT	*40	*47	*43	NT	*44	*21	*33	*36	*35
Picture Naming	58.5 (4.8)	24.6 (21.4)	62.3 (1.6)	*50	*45	*49	*48	4*	*19	*55	*46	*30	*0	*29	*0	*10	*4	*5
Synonym judgment	78.5 (5.7)	65.5 (11)	93.1 2.4	89	*76	*73	*71	*71	*71	*69	*69	*65	*61	*61	*60	*58	*54	*51

Dysexecutive patients are arranged in order of Behavioural Assessment of Dysexcutive Syndrome (BADS); SA patients are arranged in order of synonym judgement performance. Table shows raw scores. * denotes impaired performance (< 2 SD from control mean). Data for controls and many SA patients taken from Corbett et al. (2009). CCT = Camel and Cactus Test of semantic association (Bozeat et al., 2000). CCT, picture naming and word-picture matching tasks taken from Cambridge semantic battery (Adlam et al., 2010). In the sound-picture, spoken word-picture and sound-written word matching tests, patients listened to environmental sounds or spoken words and chose which printed picture or written word (out of 10 options) matched this auditory stimulus (Bozeat et al., 2000). Synonym judgment test (Jefferies et al., 2009)

Table 10: DYS patient impairment on semantic battery compared to healthy controls

	64- item Cambridge battery				**Environmental sounds battery**		
DYS Patients	**Picture Naming**	**Word-picture matching**	**CCT-picture**	**CCT-word**	**Sound-picture matching**	**Sound-word matching**	**Word-picture matching**
MC	*t*(30) < 1	*t*(26) = 1.9, p =.061	*t*(19) = 2.5, p = .022	*t*(19) = 2.6, p =.015*	t(19)= 2.4, p = .026*	t(19) = 1.8, p =.007*	*t*(19) < 1
TG	*t*(30) = 4.4, p =.000*	*t*(26)= 9.3, p =.000*	*t*(19) = 3.4, p = .003*	*t*(19) = 5.0, p =.000*	t(19)= 2.4, p = .026*	t(19) = 2.2, p =.038*	t(19) = 4.6, p =.000*
JS	*t*(30) =1.0, p =.305	*t*(26)= 0.4, p =.628	*t*(19) = 4.4, p = .000*	*t*(19) = 2.2, p =.039*	t(19)= 2.8, p = .012*	t(19) = 1.8, p =.007*	*t*(19) < 1
GR	*t*(30) =3.8, p =.001*	*t*(26)= 0.4, p =.628	*t*(19) =1.8, p = .077	*t*(19) < 1	t(19)= 3.2, p = .005*	t(19) = 3.6, p =.002*	t(19) = 2.9, p =.009*
HM	*t*(30) = 8.1, p =.000*	*t*(26)= 6.8, p =.000*	*t*(19) =5.3, p = .000*	*t*(19) = 3.1, p =.005*	t(19)= 2.4, p = .026*	t(19) = 2.9, p =.008*	t(19) = 4.6, p =.000*
JYS	*t*(30) < 1	*t*(26)= 1.9, p =.061	*t*(19) < 1	*t*(19) < 1	t(19) = 2.4, p = .026*	*t*(19) < 1	*t*(19) < 1
AP	*t*(30) < 1	*t*(26)= 1.9, p =.061	*t*(19)= 3.4, p = .003*	*t*(19) = 6.0, p =.000*	t(19) = 3.2, p = .005*	*t*(19) < 1	t(19) = 2.9, p =.009*
MrL	*t*(30) = 3.8, p =.001*	*t*(26)= 4.4, p =.000*	*t*(19) < 1	*t*(19) = 4.5, p =.000*	t(19) = 3.2, p = .005*	*t*(19) < 1	t(19) = 4.6, p =.000*
JG	*t*(30) = 0.7, p =.431	*t*(26) = 1.9, p =.061	*t*(19) < 1	*t*(19) = 5.5, p =.000*	t(19) = 2.0, p = .058	*t*(19) < 1	*t*(19) < 1
PG	*t*(30) < 1	*t*(26) = 1.9, p =.061	*t*(19)=2.5, p = .022*	*t*(19) = 5.1, p =.000*	*t*(19) < 1	*t*(19) < 1	*t*(19) < 1
CR	*t*(30) = 3.8, p =.001*	*t*(26) = 9.3, p =.000*	*t*(19) < 1	*t*(19) = 4.1, p =.001*	t(19) = 4.3, p = .000*	t(19)= 2.2, p =.038*	t(19) = 2.9, p =.009*
MK	*t*(30) < 1	*t*(26) = 9.3, p =.000*	*t*(19) < 1	*t*(19) = 1.7, p =.097	t(19) = 2.8, p= .012*	t(19)= 1.8, p =.071	t(19) = 2.9, p =.009*
DL	*t*(30) = 6.3, p =.000*	*t*(26) = 14.2, p =.000*	*t*(19)= 4.1, p = .001*	*t*(19) = 6.0, p=.000*	t(19)= 2.4, p= .026*	t(19)= 2.9, p =.008*	t(19) = 6.3, p =.000*
Total	**6/13**	**6/13**	**6/13**	**10/13**	**11/13**	**7/13**	**8/18**

Dysexecutive patients are arranged in order of Behavioural Assessment of Dysexcutive Syndrome scores from mildest to most severe. Table shows degree of impairment for each patient, established using the modified t-test procedure outlined in Crawford and Garthwaite (2002). The singlims.exe program was used to compare individual DYS patients' scores with healthy controls taking into account the control mean and SD plus sample size of the control group. Data for controls taken from Corbett et al. (2009). CCT = Camel and Cactus Test of semantic association for concepts presented as pictures and written words (Bozeat et al., 2000). * Significantly below control performance.

Effect of familiarity/frequency on 64-items battery

Degradation of concepts in SD is associated with large effects of frequency/familiarity contrast (Jefferies et al., 2006). In contrast, SA patients fail to show the standard effects of frequency in comprehension tasks. Instead, they show absent or even *reverse* frequency effects, i.e., better understanding of less common words (Almaghyuli et al., 2012). In addition, SA is associated with poor regulatory control of semantic processing and executive deficits (Almaghyuli et al., 2012; Jefferies et al., 2006; Noonan et al., 2010)**.** Decisions about the meanings of high frequency (HF) words are thought to require greater executive control than semantic decisions for low frequency (LF) words. HF words occur in more contexts and have wider and more variable meanings than their LF counterparts which are associated with a limited range of linguistic contexts and so similar semantic information is encountered each time (Hoffman et al., 2011). Greater executive control might be required for HF words in order to selectively focus processing on aspects of meaning that are relevant for a given task or context. Evidence for this proposal is provided in Chapter 2, which shows that divided attention in the context of a dual task paradigm disrupts HF judgment more than LF trials, even in healthy participants.

The 64 items from the battery were divided into two sets based on familiarity ratings (20 items in each set, with the highest and lowest familiarity ratings) following the methods adopted by Jefferies et al. (2006). A 2x2 ANOVA was used to compare the two groups (SA, DYS) and the influence of familiarity (high, low) for each task. The results revealed no main effect of familiarity for either SA or DYS patients in the word-CCT or the picture-CCT. No interaction between familiarity and group was found for these two tasks. In other words, in semantic association tasks, irrespective of modality, neither SA nor DYS patients showed strong effects of the familiarity of the items, contrasting sharply with the pattern seen in SD cases. There was a main effect of familiarity in word-picture matching and picture naming (see Table 14), and this interacted with group. However, the effects of familiarity were in opposite directions on these two tasks.

T-tests revealed an influence of familiarity for both naming and word-picture matching in the SA patients but these effects went in opposite directions: in word-picture matching, high familiarity items were less accurate $t(10) = 5.7$, P = .001, Bonferroni correction = .002while in picture naming, they were more accurate, $t(10) = -4.2$, P = .002, Bonferroni correction = .004. For the DYS cases, there were only reverse familiarity effects for word-picture matching, $t(12) = -2.2$, P = .04. The positive effects of familiarity in picture naming found for SA and not DYS cases might reflect the processing advantage of high frequency items in speech production. The DYS patients did not have severe language/phonological problems, so did not have the same difficulty in naming less familiar concepts.

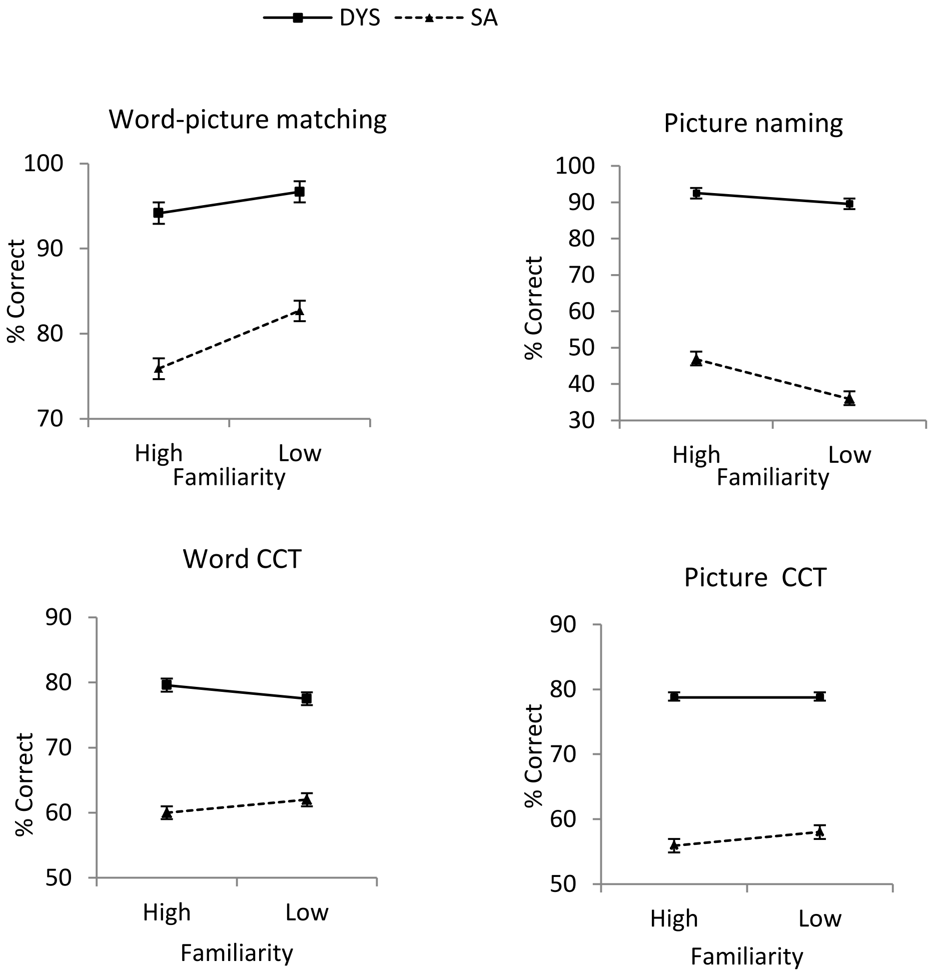
Moreover, although both groups showed negative effects of familiarity in word-picture matching, the group interaction reported above shows that this effect was stronger in SA.

Table 11 : Effect of familiarity/frequency in SA and DYS performance in 64-semantic items

Semantic tasks	Familiarity	Group	Familiarity by Group
WPM	F(1,10) = 22.4, P = .001	F(1,10) =37.2, P > .001	F(1,10) = 45.4, P > .001
Naming	F(1,10) = 18.5, P = .002	F(1,10) = 9.61, P = .012	F(1,10) = 15.2, P = .003
CCT-Word	F(1,10) = .015, P = .90	F(1,10) = 14.5, P = .003	F(1,10) = .348, P = .568
CCT-Picture	F(1,10) = 1.06, P = .36	F(1,10) = 8.91, P = .041	F(1,10) = .0951, P = .82

Table shows 2x2 ANOVA, examining the factors of familiarity and group for each task.

Figure 4: Effect of familiarity on different semantic tasks from the 64- items battery



Error bars show standard error of the mean.

Correlations between semantic tests

SA patients previously showed significant item correlation across tasks requiring similar types of semantic judgment (e.g. CCT-W versus CCT-P) but not across semantic tasks with different control demands (e.g. CCT-word vs. word-picture matching) (Jefferies et al., 2006). We predict that DYS cases will show a similar pattern as SA patients: there will be no correlation between tasks within the 64-items battery when executive control requirements are varied.

a. Correlation across modalities (within the same task):

   For the SA group, correlations between the CCT-word and the CCT-picture tasks were significant $r = .658$, $p < 0.01$ (see Fig. 5). Similarly, a strong correlation was found between the three versions of the environmental sounds test: ($r = .74$, $p > 0.01$, $r = .68$, $p > 0.05$, $r = .51$, $p > 0.05$) and between word-picture matching and picture naming: $r = .733$, $p > 0.01$.

   For the DYS group, accuracy was not always correlated across the different versions of semantic tests that involved different input modalities. The word and the picture versions of CCT were not correlated; $r = .272$, $p = .18$. However, scores on two versions of the environmental sounds test showed a strong correlation ($r = .730$, $p < 0.01$, $r = .59$, $p < 0.05$, $r = .23$, $p = 0.20$) as did word-picture matching and picture naming $r = .542$, $p < 0.05$. This suggests that DYS cases may show somewhat less consistent/predictable semantic impairment compared with the SA group, but that both groups can show significant predictability when the type of judgment required does not change between versions of tests.

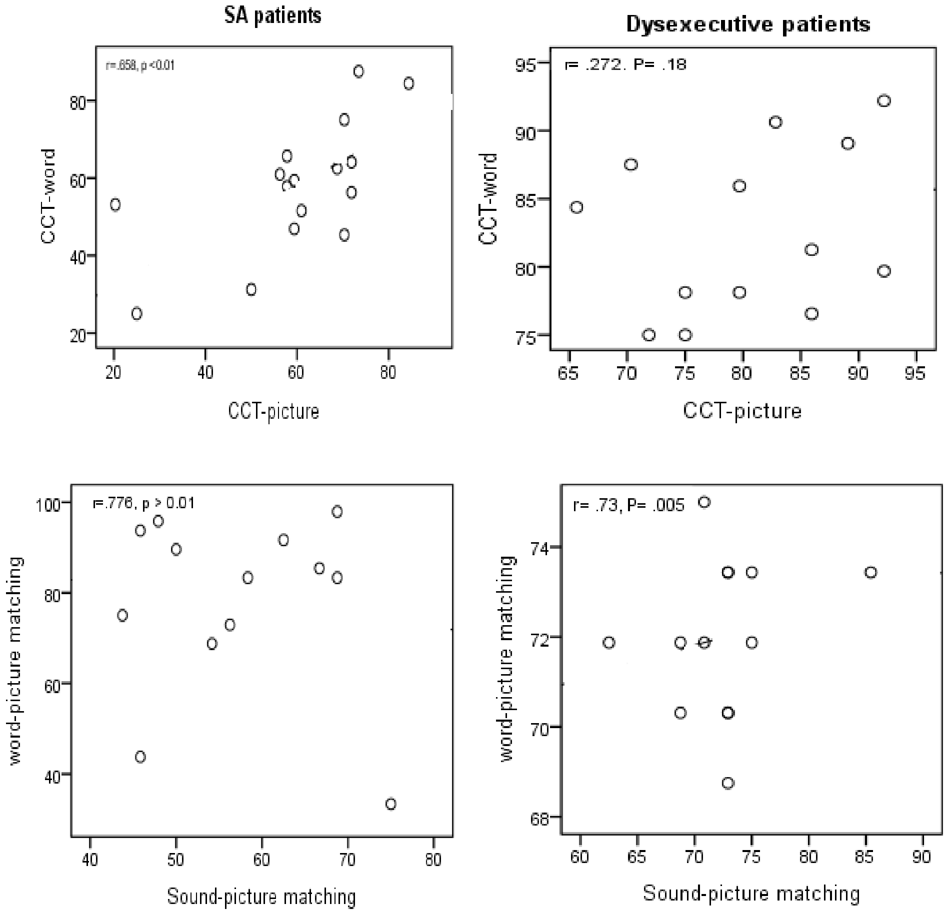
b. Correlation across different types of semantic tasks, with differing control demands:

   The SA and DYS groups did not show correlation across tasks requiring different types of semantic judgment, for example, CCT-picture and word-picture matching tasks (see Table 15 and 16).

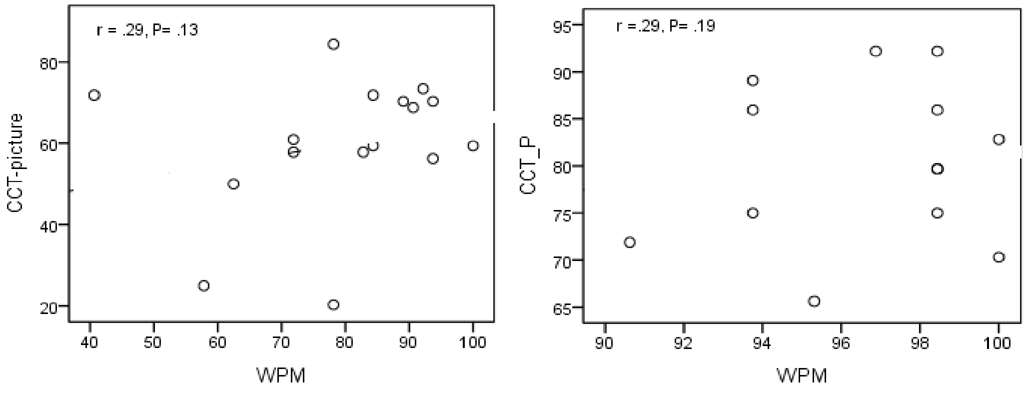
   In summary, both patient groups showed some correlations across a variety of verbal and non-verbal semantic tasks. Correlations across sets that tapped different input modalities were somewhat stronger in the SA patients, while both groups showed a correlation between picture naming and word–picture matching. However, neither patient group showed a correlation between simple selection tasks, such as word/sound–picture matching and tests that tapped semantic associations. Both the SA and DYS groups were strongly influenced by the type of semantic judgement that was required.

Figure 5: Correlation across different input modalities and semantic tasks

A) Across modalities (within task correlations):



B) Between task correlations



All graphs show % correct in each task

Table 12: Correlations between executive and semantic tests in SA and DYS groups

Tests	**Group**	**Executive tests**						**64-Semantic tests**				**Environmental sounds**			
		BADS	Ravens	Brixton	L-fluency	Forward	Backward	Pic-naming	WPM	CCT_W	CCT_P	Sound-pic	Sound_word	Word-pic	Syn-judg
BADS	DYS		.29	.61*	.55*	.65*	.76**	.24	.69**	-.31	.49	-.14	-.16	.58*	.69**
Ravens	DYS			.61*	.36	.65*	.54*	.39	.55*	-.01	-.05	.07	.35	.63*	.17
	SA			**.59***	**-.08**	**.10**	**-.41**	**.34**	**.59***	**.10**	**.28**	**-.32**	**.58***	**.19**	**.26**
Brixton	DYS		.		.08	.39	.27	.32	.36	.03	.05	-.09	.38	.57*	.19
	SA				**.29**	**.39**	**.06**	**.66***	**.58***	**.32**	**.27**	**.07**	**.58**	**.19**	**.33**
L-fluency	DYS					.62*	.75**	.39	.65*	-.38	.16	.46	.25	.55*	.54*
	SA					**.53***	**.38**	**.42**	**.19**	**.59***	**.07**	**.38**	**.52**	**-.09**	**.53***
Forward	DYS			.			.77**	.08	.45	-.58*	-.04	-.09	-.11	.35	.57*
	SA						**.42**	**.37**	**.47**	**.33**	**-.13**	**.59***	**.35**	**.26**	**.29**
Backward	DYS							.46	.79**	-.10	.34	-.09	-.04	.56*	.37
	SA							**.244**	**-.036**	**.388**	**-.144**	**.260**	**.356**	**.250**	**.200**

Table 13: Correlations between executive and semantic tests in SA and DYS groups (continued)

Tests	Group	Executive tests						64-Semantic tests				Environmental sounds			
		BADS	Ravens	Brixton	L-fluency	Forward	Backward	Pic-naming	WPM	CCT_W	CCT_P	Sound-pic	Sound_word	Word-pic	Syn-judg
Pic-naming	DYS								.49	.39	.23	.21	.54*	.77**	-.04
	SA								**.711****	**.652****	**.477**	**.098**	**.471**	**.327**	**.724****
WPM	DYS	.								.09	.29	.27	.34	.74**	.33
	SA									**.448**	**.246**	**.096**	**.574***	**.672***	**.543***
CCT-W	DYS										.26	-.24	.23	.16	-.57*
	SA										**.657****	**-.32**	**-.36**	**.35**	**.29**
CCT-P	DYS											-.311	-.321	.409	.288
	SA												**.067**	**-.233**	**.433**
Sound-pic	DYS												.73**	.23	.04
	SA												**.74****	**.68***	**.136**
Sound-word	DYS													.59*	-.16
	SA													**.48***	**.502**
Word-pic	DYS														.47
	SA														**-.119**

Numbers represent person correlation coefficient, * means significant ($p < 0.05$). number in bold text are for SA group. BADS = Behavioural Assessment of Dysexcutive Syndrome (Wilson et al., 1996); RCM= Raven's coloured progressive matrices (Raven, 1962); Brixton spatial anticipation task (Burgess & Shallice, 1997). Letter fluency refers to the combined scores from the letters F, A and S. CCT = Camel and Cactus Test of semantic association (Bozeat et al., 2000). CCT, picture naming, word-picture matching, and letter fluency taken from Cambridge semantic battery (Adlam et al., 2010). In the sound-picture, spoken word-picture and sound-written word matching tests, patients listened to environmental sounds or spoken words and chose which printed picture or written word (out of 10 options) matched this auditory stimulus (Bozeat et al., 2000). Synonym judgment test (Jefferies et al. 2009)

Correlation with executive impairment

In the previous section, SA and DYS patients showed sensitivity to the nature of the semantic task: performance did not correlate across tasks with differing executive control demands. We now examine the strength of the relationship between semantic performance and executive function in these two groups of patients since they showed impairments in semantic and executive control.

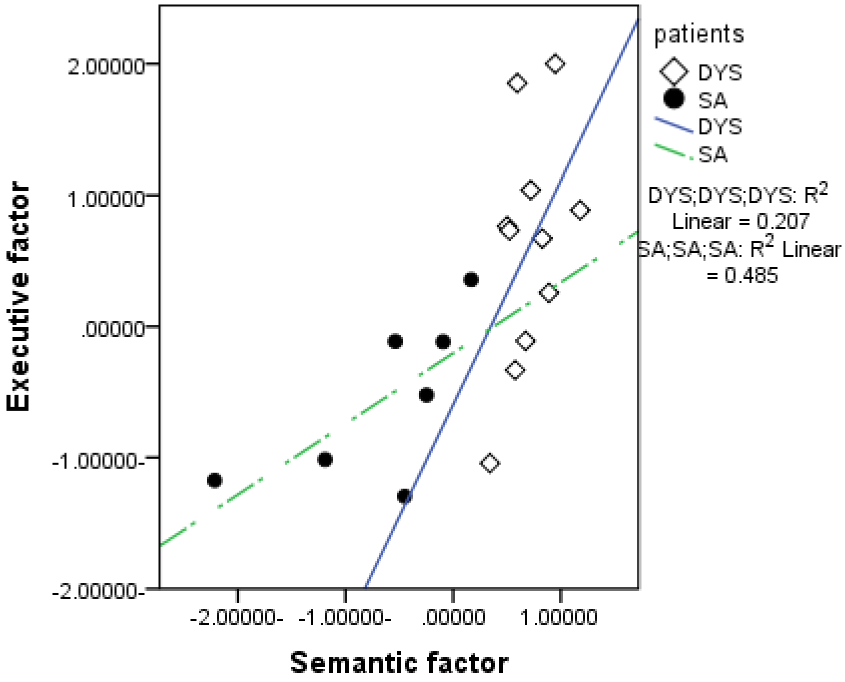
The SA patients showed a correlation between Raven's Matrices and the word-picture matching test from the 64 item battery and sound-word matching from the environmental sounds battery (see Table 15 and 16 for statistics). However, in the DYS group, there was no correlation between Raven's Matrices and any of the semantic tests, perhaps because DYS patients were not severely impaired on this test.

A single 'executive factor' score was extracted from the Raven's Coloured Progressive Matrices and Brixton spatial anticipation test using factor analysis and saved as a variable. This executive score correlated with two of the semantic tasks in the SA group: the 64 items naming task (r = 0.71, p = 0.03) and the 64 items word-picture matching task (r = 0.68, P = 0.04). A semantic factor was extracted from the semantic tests (WPM, CCT-word, CCT-picture, Environmental sounds battery and Synonym judgment) and this also significantly correlated with the executive factor in SA (r = 0.58, p = 0.04). This analysis included the seven SA patients who had completed the relevant assessments.

DYS patients showed impairment in three executive tests that 11 patients were tested on; these were the Behavioural Assessment of Dysexecutive Syndrome (BADS), Raven's Coloured Progressive Matrices and Brixton tests. The executive factor derived from these tests was significantly correlated with the 64 items word-picture matching task (r = 0.77, p < 0.01), and the correlation approached significance for the 64 items naming task (r = 0.50, p = 0.09). A semantic factor extracted from the semantic tests (WPM, CCT-word, CCT-picture, Environmental sounds battery and Synonym judgment) significantly correlated with the executive factor (r = 0.56, p = 0.03). Two patients with ceiling-level performance were excluded from this analysis.

Figure 6 summarises the global correlation between semantic tasks and executive tasks in the two groups. To produce this figure, all patients from both groups were entered into the factor analysis to derive semantic and executive scores that are directly comparable across the two groups. The graph shows that for the same degree of executive impairment, the SA group had more severe deficits of semantic processing compared to the DYS group.

Figure 6: Executive and semantic tasks correlation in SA and DYS patients



Item consistency

SD patients with degraded knowledge show high a degree of item-consistency when the same items are presented in different tasks (Bozeat et al., 2000), presumably because the degree of degradation of each concept determines performance for that item irrespective of the task. In contrast, patients with SA are much less consistent because the executive demands fluctuate from trial to trial depending on exactly which items have been selected as the target and the distracters. Jefferies and Lambon Ralph (2006) found that item-by-item consistency in SA reproduced the pattern of correlations across tasks (see previous section): SA cases were consistent across different input modalities but not across different tasks (with differing requirements for top-down control).

To explore item-by-item consistency in individual DYS patients, the contingency coefficients across semantic tasks were calculated for each combination of tasks from the 64-items semantic battery and the environmental sounds battery, producing 9 scores (see Table 17). Excluding the comparison of picture naming and word-picture matching, where the output demands are very different, 4 of these comparisons are ‘within task’ (i.e., look at consistency across different modality versions of the same task) and 4 are ‘between task’ (i.e., examine different kinds of semantic tasks, such as word-picture matching and associative judgements, for the same items). 10/13 DYS patients showed significant within-task consistency on at least one of the four comparisons. Of the 3 exceptions, patient TG showed near-significant consistency and patient JS showed no evidence of consistency but showed near ceiling-level performance on several tasks. Patient HM showed a lack of consistency on all 4 within-task comparisons: we consider these individual differences in the general discussion.

In contrast to the consistency seen *within* semantic tasks, only one case, MC, showed evidence of consistency *between* different types of semantic tasks that probed the same concepts, and two others (AD and AP) showed near-significant effects. In total, there were 13 significant contingency coefficients for the DYS group and 12/13 were from ‘within-task comparisons’. Thus, there was evidence of consistency across modalities (in parallel versions of tests which held the control requirements constant) but not when the control demands of the semantic tasks changed. In SA group, there were significant consistency across different input modalities within the same semantic task; they showed significant consistency between CCT-picture and words. A similar pattern was observed for the environmental sounds battery. Again, they showed significant consistency between all of the word–picture, sound–picture and sound–word matching tests. However, SA patients did not show strong consistency across any semantic tasks. Consistency approached significance for word–picture matching/word CCT (n = 6, Wald > 3.7, $P < 0.06$) and naming/word–picture matching (n = 3, Wald > 3.1, $P < 0.08$) (see Jefferies and Lambon Ralph , 2006).

Table 14: Item consistency within task comparisons across task

Within task comparisons			Between task comparisons				Within task comparisons		
DYS patients	**WPM/naming**	**CCT-W/CCT-P**	**WPM/CCT-W**	**WPM/CCT-P**	**Naming/CCT-W**	**Naming/CCT-P**	**Sound-P/Sound-W**	**Sound-W/W-P**	**Sound-P/W-P**
MC	C < .1, n.s	C = .33, p = .00*	C < .1, n.s	C = .24, p = .04*	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .23, p = .09
TG	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .21, p = .08
JS	-	C < .1, n.s	-	-	-	C < .1, n.s	C < .1, n.s	-	-
GR	C = .31, p = .00*	C = .26, p = .02*	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .23, p = .09	C < .1, n.s	C < .1, n.s
HM	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s
JYS	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .44, p = .001*	C < .1, n.s	C = .23, p = .09
AP	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .21, p = .08	C = .21, p = .08	C = .21, p = .08	C = .50, p = .001*	C < .1, n.s	C < .1, n.s
MrL	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .43, p = .001*	C= .26, p = .06	C < .1, n.s
JG	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C= .22, p = .07	C < .1, n.s	C = .50, p = .001*	C < .1, n.s	C < .1, n.s
PG	C < .1, n.s	C = .28, p = .01*	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s
CR	C < .1, n.s	C = .44, p = .00*	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .29, p = .04*	C < .1, n.s	C = .29, p = .03*
MK	C < .1, n.s	C < .1, n.s	-	C < .1, n.s	C < .1, n.s	-	C = .34, p = .01*	C < .1, n.s	C < .1, n.s
DL	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C < .1, n.s	C = .28, p = .04*	C < .1, n.s	C < .1, n.s
Total	1	2	0	1	2	1	8	1	4

Dysexecutive patients are arranged in order of Behavioural Assessment of Dysexcutive Syndrome. Table shows contingency coefficients that calculated across the 64-item battery. CCT = Camel and Cactus Test of semantic association (Bozeat et al., 2000). CCT-W= CCT for written words and CCT-P= CCT for picture, WPM= word-picture matching. In the sound-picture, spoken word- picture and sound-written word matching tests, patients listened to environmental sounds or spoken words and chose which printed picture or written word (out of 10 options) matched this auditory stimulus (Bozeat et al., 2000). * Contingency coefficient significant, C coefficients were computed only for cases where accuracy below 90% on both conditions. Analyses missing for this reason are marked.

Factors affecting associative decisions

In this analysis, we investigate several ratings previously found to predict associative semantic judgements within the CCT task in SA patients (Jefferies & Lambon Ralph, 2006). The ratings listed below were obtained from healthy participants for each trial on the CCT in this earlier investigation. We used logistic regression to examine the extent to which the average ratings for each trial would predict performance on the picture and word versions of the CCT. Concept familiarity and lexical frequency were also included to control for these possible confounds. In the SD patient group, performance was better for trials high in frequency and familiarity but a similar effect was not observed in the SA group (see Jefferies & Lambon Ralph, 2006 for SA analysis).

We examined the following:

1. The ease with which the relevant associative dimension could be identified; for example, working out that "Camel" goes with "Cactus" because they are both associated with deserts, and that the other plant choices are not relevant even though "Camel" might prefer to eat them;
2. The extent to which the probes and targets occur together in the environment; and
3. The ease of rejecting the distracters in each trial.

These ratings are clearly not independent. For example, the association between pencil and paper might be straightforward to discern because these objects are commonly found and used together and this also makes the distraction objects easier to reject. However, Jefferies and Lambon Ralph (2006) found that while all three factors predicted performance in the SA group, only factor 2 – related to frequency/familiarity – was relevant in the SD group.

In the DYS group, all three executive factors correlated with accuracy on the CCT combining words and pictures (r =.18-20, $p < .001$). Logistic regression models included frequency/familiarity, modality of presentation (words/pictures), patient identity and each of the ratings above in turn (in separate analyses), to predict CCT performance. Factors 3 (Wald = 10.9, $p < .01$) and 2 (Wald = 6.3, $p < .01$) predicted accuracy on the CCT, while the effect of Factor 1 was not significant (Wald = .24, $p = .61$). DYS patients did not show any effects of familiarity or frequency in any analysis (Wald < 1). In addition, there were no effects of modality of presentation (Wald < 1) but patient identity effects were detected (Wald = 31.0, $p = .002$).

Next, we conducted parallel analyses comparing SA and DYS directly. All three executive factors correlated with accuracy on the CCT (combining words and pictures) in both groups (DYS: $r = .18\text{-}.20$, $p < .001$, SA: $r = .16\text{-}.21$, $p < .001$). Patient group was added to the logistic regression model above (and only group interactions are reported below). Factor 2 had a greater effect on SA than DYS patients (Factor 2 by group: Wald = 5.1, p < .001). The interaction with group for Factors 3 and 1 approached significance (Wald = 7.2, p = .007; Wald= 7.2, p = .006). SA patients were more sensitive to inter-item frequency, but both groups were strongly influenced by selection/executive demands.

Environmental sounds battery

The aim of this test was to explore the deficits that might occur in DYS patients in accessing semantic knowledge from environmental sounds and spoken words (Table 18). A 3x2 ANOVA was used, with task (sound-picture, sound-word, word-picture matching) and group (SA, DYS). The results showed significant main effect of task: F(2,20) = 13.74, p < .000, a main effect of group: F(1,10) = 5.21, p = .04, and the interaction between task and group was significant: F(2,20) = 5.35, p = .04. The SA group were more impaired than DYS cases in the sound-picture matching task *t*(10)= 3.4, p = .006, Bonferroni p = .01,. There were no significant differences between groups in word-picture matching *t*(10) = 2.4, p = .04, Bonferroni p = .12 or in sound-word matching *t*(10) < 1. Compared to the controls, 6/13 patients were impaired in all components of the environmental sounds battery. Individually, 12/13 of the patients were impaired in the sound-picture matching task.

This battery gave us the chance to explore the effect of concept familiarity and sound familiarity using ratings from Bozeat et al. (2000). We used logistic regression to predict individual item accuracy using the following variables: patient identity, task, concept familiarity and sound familiarity. Task was the only factor that predicted performance in the DYS group (Wald = 101.94, p < .05). Conceptual familiarity (Wald < 1) and sound familiarity did not influence performance in the DYS group (Wald = .796, p = .3). Again, like SA patients and unlike the SD cases, neither conceptual familiarity nor sound familiarity influenced performance in dysexecutive syndrome.

Table : Dysexecutive patients' performance on the environmental sounds battery compared to the controls

Patients	Sound-picture matching	Sound-word matching	Word-picture matching
MC	t(19)=2.4, p=.02*	t(19)=1.8, p=.007	t(19)=1.1, p=.24
TG	t(19)=2.4, p=.02*	t(19)=2.2, p=.038*	t(19)=4.6, p=.000*
JS	t(19)=2.8, p=.01*	t(19)=1.8, p=.007	t(19)< 1
GR	t(19)=3.2, p=.005*	t(19)=3.6, p=.002*	t(19)=2.9, p=.009
HM	t(19)=2.4, p=.02*	t(19)=2.9, p=.008	t(19)=4.6, p=.000*
JYS	t(19)=2.4, p=.02*	t(19)< 1	t(19)=1.1, p=.24
AP	t(19)=3.2, p=.005*	t(19)< 1	t(19)=2.9, p=.009
MrL	t(19)=3.2, p=.005*	t(19)=1.5, p=.147	t(19)=4.6, p=.000*
JG	t(19)=2.02, p=.05*	t(19)< 1	t(19)=1.1, p=.24
PG	t(19) < 1	t(19)< 1	t(19)=1.1, p=.24
CR	t(19)=4.3, p= .000*	t(19)=2.2, p=.03*	t(19)=2.9, p=.009
MK	t(19)=2.8, p=.01*	t(19)=1.8, p=.007	t(19)=2.9, p=.009
DL	t(19)=2.4, p=.026*	t(19)=2.9, p=.008	t(19)=6.3, p=.000*
Total	12/13	3/13	4/13

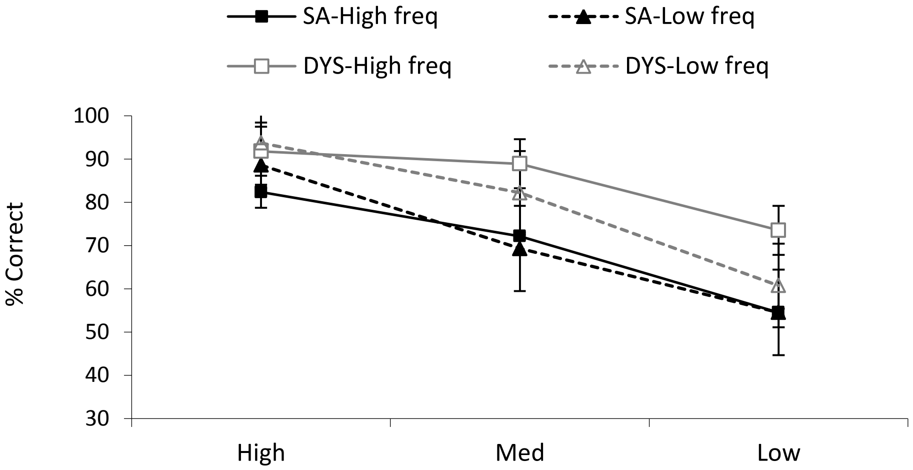
*Indicates impairment compared to the control using McNamar two- tailed

Frequency and imageability effects in synonym judgment

A 2x2x3 repeated measures ANOVA was used to explore the effects of frequency (high, low), imageability (high, medium, low) and group (SA, DYS) on synonym judgment performance, using the task that was the focus of Chapter 2. Our results showed no main effect of frequency, $F(1,7) = 1.56$, $p = .251$. There was a significant main effect of imageability, $F(2, 14) = 18.4$, $p < .001$ and a main effect of group F(1,7) = 14.00, $p = .007$. There was no significant interaction between group and frequency (i.e., both groups showed a similar lack of frequency effects in synonym judgement, $p > .1$). There was also no interaction between imageability and group: both groups showed parallel effects of imageability, with better comprehension of more imageable concepts, $p > .1$.

Both SA and DYS groups showed no difference in their performance on high and low frequency items: SA, $t(7) = 1.25$, $p = .25$; DYS, $t(12) = 1.37$, $p = .19$. Both groups were significantly poorer on low compared with high imageability items, SA: t(7) = 8.7, p = .001 Bonferroni, p = .003 DYS: t(12) = 5.5, p = .001 Bonferroni, p = .003, while there were no significant differences between low and medium imageability items in both groups, SA: $t(7) =$ 1.72, p > .1, DYS: t(12) = 1.9, p > .1

Figure 7: Frequency by imageability in SA and DYS groups



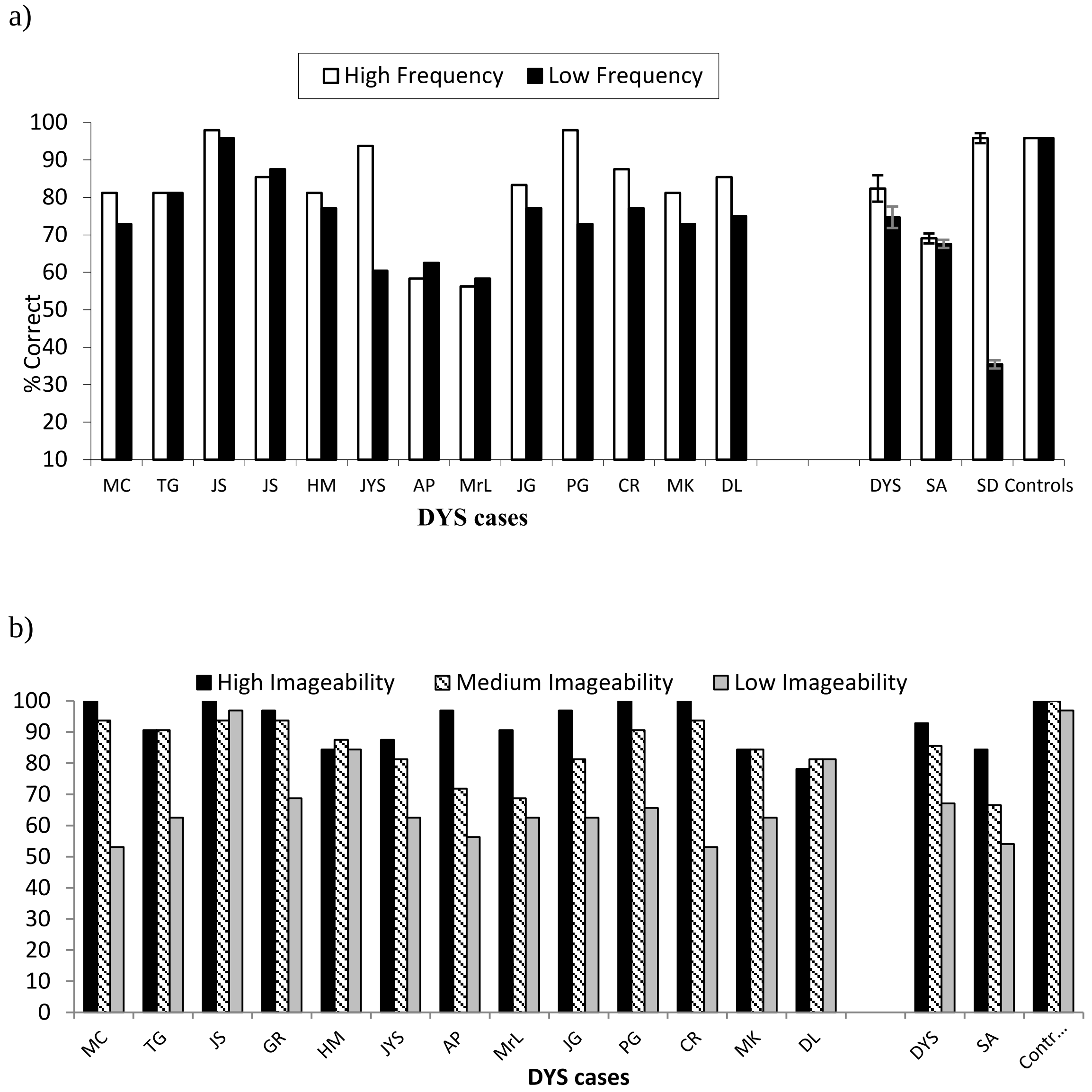
Error bars represent the standard error of the mean

Compared to the control group, using the modified t-test procedures outlined in Crawford and Garthwaite (2002), 12 DYS patients showed significant impairment in the task as a whole, with the exception of JS ($t(19) = .77$, $p =.22$). Regarding the frequency effect, overall, DYS cases were largely insensitive to this manipulation ($X^2 =1.2$, two-tailed $p > .11$). Only two patients showed frequency effects: PG ($X^2 = 12.04$, two tailed $p < .001$) and JYS ($X^2 = 15.09$, two tailed $p < .001$). On imageability effect, patients showed strong effect of imageability ($X^2 (2) =78.8$, two tailed $p < .001$). Nine out of 13 DYS patients showed better performance on high compared to low imageability items (Figure 8). Ten out of 13 patients were significantly poorer on low than medium imageability items.

Generally, there was no effect of frequency but a strong effect of imageability in DYS. These results reflect the same pattern of impairment that was seen in SA patients (Jefferies et al., 2007). This suggests there is a processing cost for high frequency (HF) items, magnified in patients with SA, which overrides the normal processing advantage that frequent items enjoy. A similar processing cost was found for more familiar targets in the word-picture matching test from the Cambridge semantic battery above. HF words and objects are encountered in a wider range of situations and alongside a larger number of other items than LF words, because they occur more commonly (Adelman et al., 2006; Hoffman et al., 2011a; 2011b). These varied semantic associations are likely to be activated automatically when an HF item is presented, yet many of them will be irrelevant to the task at hand. Consequently, semantic processing for HF words might require greater executive control. This difference between HF and LF concepts is likely to be particularly prominent in tasks in which participants are asked to select which of several items is closest in meaning to a probe (i.e., in synonym judgement), because activation could potentially spread from the probe to the distractors as well as to the target. Therefore, although participants will be more efficient at retrieving the meanings of HF items, some of this information will need to be disregarded for the correct response to be made.

Logistic regression was conducted on the synonym judgment data from the DYS patients including the following variables as predications: patient identity, lexical frequency and contextual diversity (utilising data from Hoffman et al., 2011). First, we used lexical frequency to predict patient performance: the results were consistent with the previous conclusions because there was no relationship between accuracy and frequency (Wald < 1). However, positive effects of frequency appeared when contextual diversity was taken into account (frequency: Wald = 28.1, p < .001; contextual diversity: Wald = 32.9, P < .001). The same pattern was seen previously in SA (Hoffman et al., 2012), suggesting that in both of these patient groups, deficient executive and semantic control impaired the ability to focus selectively on a relevant context for HF items. When the contextual diversity of HF items was accounted for in the analysis, it was possible to reveal the processing advantage that HF items enjoy by virtue of the fact that these items are processed more often. Patient identity also predicted performance (Wald = 23.2, p = .025).

Figure 8: Frequency and imageability effects in the synonym judgment task



Frequency effects in synonym judgment (Jefferies et al., 2009). (B) Imageability effects in synonym judgment. DYS patients are ordered according to Behavioural Assessment of Dysexexcusive Syndrome (BADS) scores. Error bars represent the standard error of the mean.

Experimental tasks manipulating semantic control demands

The previous analysis suggests that executive dysfunction in DYS patients is associated with impairments in multimodal semantic tasks that resemble those in SA. In the following experiments, we explored the effect of increasing demands on executive semantic control in several ways: 1) using targets that were highly similar or more distant from the probe word; 2) comparing weakly and strongly related distractions; 3) comparing the dominant and less frequent meanings of ambiguous words and 4) examining the effects of cues designed to reduce the requirement for internal semantic control.

SA patients previously showed strong effects of all these manipulations (Noonan et al., 2010). Our prediction is: if executive dysfunction underpins the pattern of impairment in SA, DYS patients will also show poorer performance on executively-demanding semantic tasks and the effect of the manipulations will be comparable in DYS and SA groups.

Experiment 1: Distant and close semantic associations

Rationale: We aimed to explore the patients' ability to manipulate and search semantic knowledge online. A 'Nearest Neighbour' semantic judgment task was used in which participants had to specify which of three options was the closest in meaning to the probe item (task from Noonan et al., 2010). Unlike synonym judgment in which participants' match probe and target words based on their highly similar meanings, this task required comparisons of the semantic distances of multiple probes and target pairs. The semantic distance between probe and targets was manipulated within each trial, leaving the probe and distractors the same. The probe and the target could have a close semantic relationship (e.g., SHIP and YACHT), such that they shared a lot of semantic features, making the correct target easy to detect. In high control trials, in contrast, the probe and the target shared fewer features (e.g., SHIP and VAN) making it more difficult to identify which potential target was closest in meaning to the probe.

We predicted that DYS patients with a cognitive control deficit would show a similar pattern to SA performance in this task; they would struggle when the probe-target distance was greater (Noonan et al., 2010).

Method: The Nearest Neighbour test contained 64 concrete nouns drawn from eight semantic categories (animals, birds, plants, fruit/vegetables, tools, clothes, vehicles and household objects) and two domains (natural and man-made things). The semantic relation between target and probe was either close or distant. Participants were presented with a probe word and had to judge which of three accompanying words was closest in meaning. The words were presented as written stimuli and were also read aloud by the experimenter. Participants were instructed to respond as quickly and accurately as possible.

Noonan et al. (2010) manipulated the semantic distance between the probe and the target to create two conditions. In half the trials (64/128), the probe and the target were distantly related while sharing membership of the same broad semantic category (e.g., chipmunk and bee are both animals). In the remaining closely related trials, probe and target shared membership of a more specific subcategory in addition to their broader categorical similarities (e.g., chipmunk and squirrel = rodents/animals). Target words in the distant condition also served as closely related targets in other trials (e.g., wasp and bee), allowing the same words to be presented in the two conditions. Distractor items were drawn from different semantic categories from the probe/target (e.g. chipmunk presented with wheat and cherry). Testing was completed over two sessions such that the close and distant versions of items did not occur within the same session

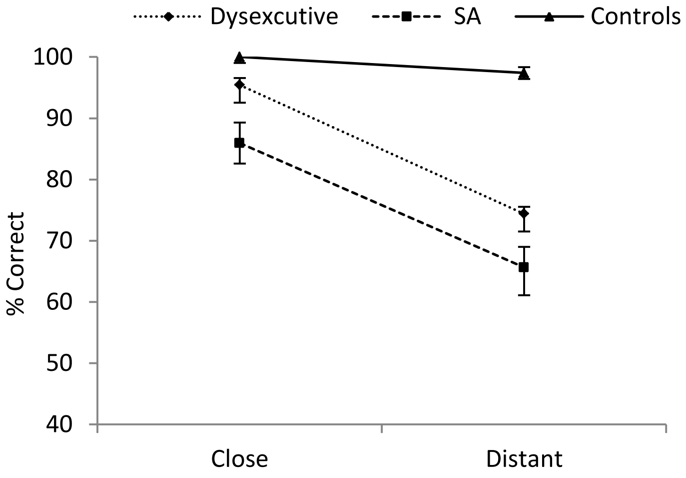
(Noonan et al., 2010). Data were available for six SA patients' (from Noonan et al., 2010) and 13 DYS patients.

Results: A two-way ANOVA revealed main effects of group (SA, DYS): *F*(1,10) = 12.5, p < .001, and semantic distance (close, distant): *F*(1,10) = 183.6, p < .001. No significant interaction was found, *F*(1,10) = 1.37, p = .268. We used the revised standardised difference test (RSDT) to directly compare the effect of semantic distance across SA and DYS patients: this test compares the size of the effect in one group with the size of the effect in other (Crawford & Garthwaite, 2005). All 13 DYS patients were not significantly different from the SA group in terms of the effect of semantic distance, t(7)< 1, confirming the ANOVA results but on a case-by-case basis.

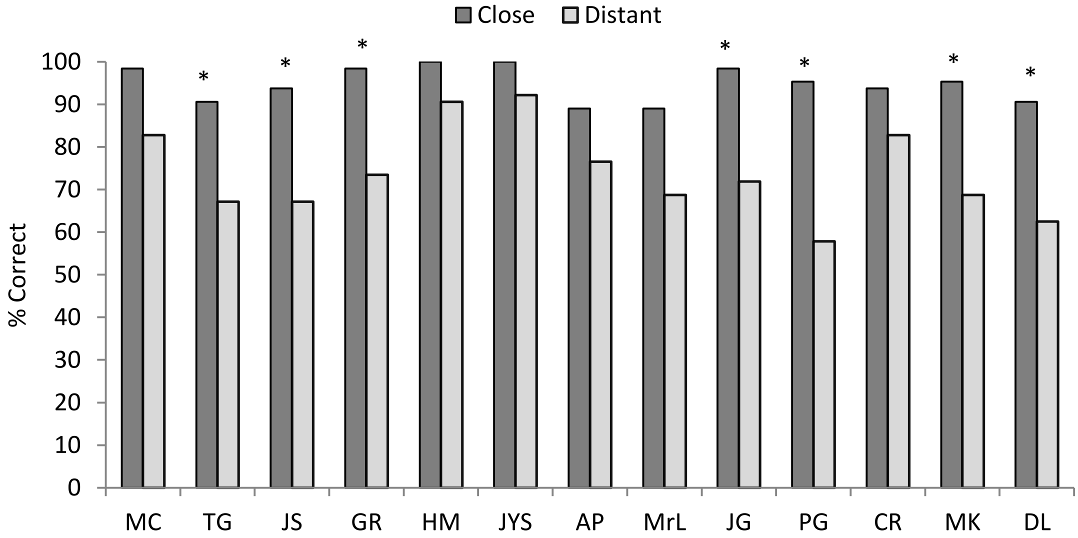
On an individual level, 7/13 DYS patients showed significantly better performance for semantically close targets (χ_2 = 6.2 to 23.5, one-tailed *p* < .005). The other 6 patients showed no difference between conditions (χ_2< 1), see Figure 9b.

Figure 9: Semantic distance effects on the nearest neighbour task

a)



Error bars represent the standard error of the mean b)



Dysexecutive patients are ordered according to overall performance on the Behavioural Assessment of Dysexecutive Syndrome (BADS) from mild to severe impairment. Nearest neighbour task and SA patients' data is taken from Noonan et al. (2010). Distant trials required selection of targets with fewer overlapping features, sharing only general category information, * indicates significant difference.

Experiment 2: Antonym/synonym judgment with highly associated distractors

Rationale: The ability to inhibit irrelevant distractors when judging which of several words are related in meaning depends on intact semantic control. When two concepts are strongly related, their relationship becomes hard to ignore even when they relate to a task-irrelevant dimension (Badre et al., 2005; Samson et al., 2007; Wagner et al., 2001). A previous study found that SA patients performed more poorly on synonym/antonym judgment when the distractor words were highly associated with the probe (Noonan et al., 2010). These findings are consistent with the view that poor executive control prevents SA patients from overcoming interference from activated but irrelevant concepts in semantic tasks.

In this experiment we examined the degree to which the performance of DYS patients is similarly disrupted by the use of highly associated distractors (using a task taken from Samson et al., 2007). We predicted that like SA cases, DYS patients may have difficulty selecting the target in trials containing strongly associated distractors because executive control is required to overcome competition and increase activation of the target.

Method:

Synonym/Antonym judgment with high associated distractors - This task contained 144 trials in one block. Patients were presented with a probe word accompanied by three choices and asked to judge which of the choices had either the same meaning (synonym condition) in one session or the opposite meaning in a different block (antonym condition) in another session. The stimuli were presented as written words and also read aloud by the experimenter. On every trial, the three choices were a synonym, an antonym and a word unrelated to the probe. There were two types of distractors, which either had a strong association or weak association with the probe. The probe and the three choice words always had the same grammatical class. The order of each type of choice word was balanced across trials. The strength of the associative words was manipulated.

For half of the trials (n = 72), the synonym (distractor) was highly associated with the probe, whereas the antonym was weakly associated with the probe. For example, the probe word “neat” was presented with the options tidy (synonym), messy (antonym) and lucky (unrelated). For the other half of the trials (n = 72), the antonym (distractor) was highly associated with the probe, but the synonym was weakly associated. For example, the probe “happy” was presented with cheerful (synonym), sad (antonym) and conscious (unrelated) word. For the synonym condition, executive demands were high when the antonym was highly associated to the probe and lower when this association was weaker. Similarly, in the antonym condition, executive demands were high when the synonym was strongly associated with the probe. Data from 12 DYS patients were available, since MK withdrew from the study. Data from 6 SA cases were also available for this task.

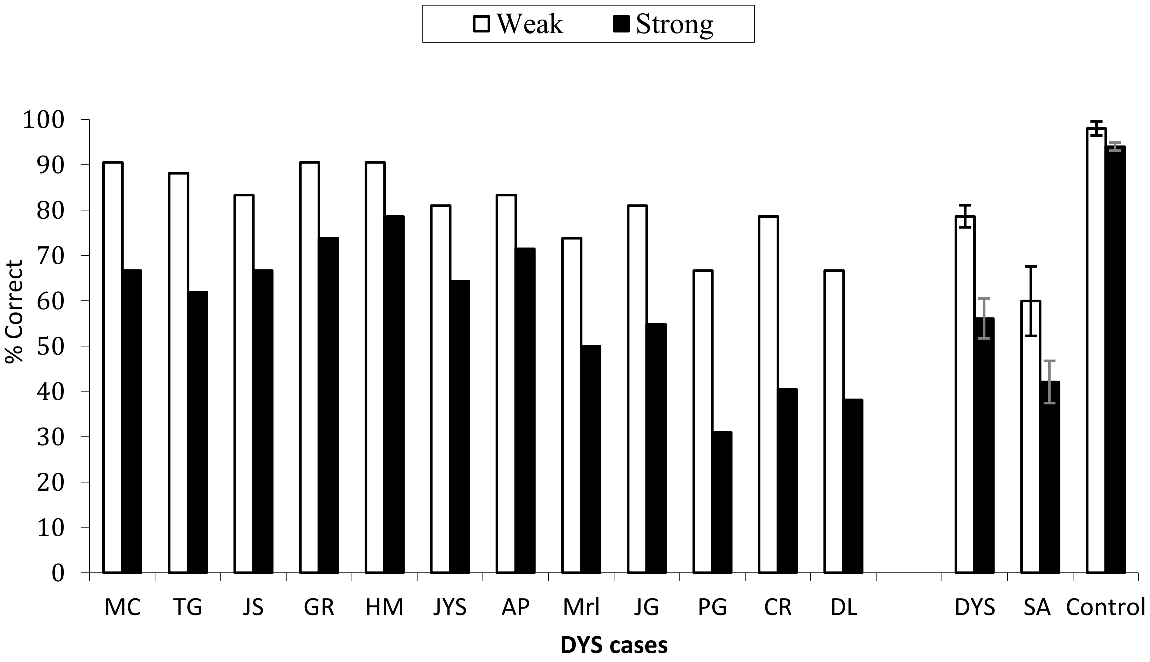
Results*:* A three-way ANOVA examined the effects of group (SA, DYS) distractor strength (weak, strong) and judgment task (synonym, antonym). The results show a main effect of distractor strength, *F*(1,5) = 24.3, p < .005, and group, F(1,5) = 10.5, p = .02, but no influence of judgment type (antonym or synonym), F(1,5) = 4.97, p = .076. There was no significant interaction between group, distractor type and judgment task because DYS and SA patients showed the same pattern of impairment: both were less accurate on judgments accompanied by strongly associated distractors (see Figure 10).

On an individual level, the DYS patients were more reliably influenced by the strength of the distractor than the SA cases (Table 19). Every case showed an effect of distracter strength for at least one of the judgement types (synonym/antonym judgment) in McNemar analyses. In contrast, only 3 out of 6 SA cases showed a significant effect across these two tasks.

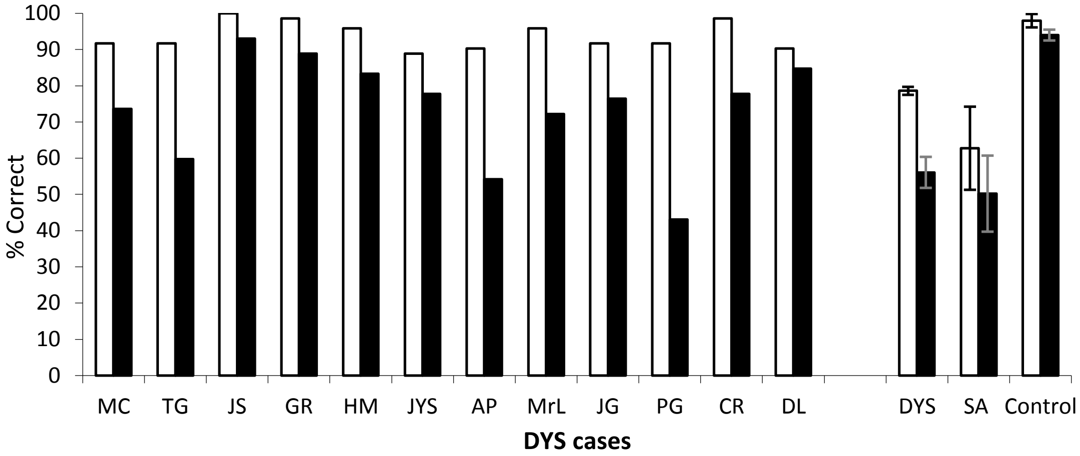
In summary, both SA and DYS patients performed poorly on synonym/antonym judgment tasks when the distractors were strongly associated with the probe.

Figure 10: Impact of distractor associative strength on synonym and antonym judgment

a) Synonym judgment



b) Antonym judgment



Dysexecutive patients are ordered according to overall performance on the Behavioural Assessment of Dysexecutive Syndrome (BADS) from mild to severe impairment. SA patients' data is taken from Noonan et al. (2010). Error bars show the standard error of the mean.

Table 15: Individual effects of distractor association on Synonym/Antonym judgment

Patients	Group	Antonym judgment	Synonym judgment
MC	DYS	X^2=8.1, p= .004*	X^2=7.1, p= .008*
TG	DYS	X^2=19.9, p= .000*	X^2=7.6, p= .005*
JS	DYS	X^2=5.1, p= .02*	X^2=3.2, p= .06
GR	DYS	X^2=5.8, p= .01*	X^2=3.9, p= .04*
HM	DYS	X^2=6.0, p= .01*	X^2=2.2, p= .13
JYS	DYS	X^2=3.2, p= .05*	X^2=2.9, p= .07
AP	DYS	X^2=23.4, p= .000*	X^2= 1.7, p= .14
MrL	DYS	X^2=1.1, p= .23	X^2= 5.1, p= .02*
JG	DYS	X^2=6.2, p= .01*	X^2= 6.6, p= .009*
PAG	DYS	X^2=38.6, p= .000*	X^2= 10.7, p= .001*
CR	DYS	X^2=15.1, p= .000*	X^2= 12.6, p= .000*
DL	DYS	X^2=1.1, p= .23	X^2= 6.8, p= .008*
Total		10/12	8/12
PG	SA	X^2=15.5, p= .000*	X^2= 2.1, p= .12
SC	SA	X^2=15.1, p= .000*	X^2=17.3, p= .000*
LS	SA	X^2=1.28, p= .17	X^2=.34, p= .65
NY	SA	X^2=.773, p= .25	X^2= 1.2, p= .39
KA	SA	X^2=13.6, p= .000*	X^2=.83, p= .49
BB	SA	X^2=1.1, p= .23	X^2=3.9, p= .07
Total		3/6	1/6

Table showed McNemar's test results comparing distractor type (weak, strong) in two tasks (synonym and antonym).

Experiment 3: Semantic ambiguity and the influence of cueing

Previous research has suggested that when ambiguous items are encountered, their multiple meanings are activated at same time (Rodd, Gaskell, & Marslen-Wilson, 2004; Simpson & Burgess, 1984; Onifer & Swinney, 1981). The competition between these alternative interpretations is determined by the frequency of each meaning; in this case, less frequent meanings are more difficult to process and experience strong competition (Simpson, 1985). Semantic control processes in healthy people are essential in selecting the less common meaning of homonyms and ignoring the dominant meaning when it presents an incorrect interpretation (Noonan et al., 2010). SA patients with impaired semantic control have damage to the left inferior frontal gyrus and posterior temporal cortex, which have been found to be sensitive to semantic ambiguity decisions according to neuroimaging studies (Zempleni et al., 2007; Rodd et al., 2005; Hoffman et al., 2011).

Rationale: This task explores the ability of DYS patients to process dominant and less frequent meanings of homonyms and examines how cueing might benefit this group given that, like SA cases, they are thought to have a problem with control processing, not with semantic representation (Noonan et al., 2010).

SA patients have difficulty retrieving less frequent meanings of ambiguous words (Netal, 2010). Noonan et al. (2010) examined the hypothesis that this impairment does not reflect loss of the less frequent interpretations, but instead control processes, by giving a sentence context that either correctly cued or miscued the relevant meaning of the homonyms. They found that cueing helped patients to retrieve the less frequent meanings of homonyms, reflecting their intact semantic representations, while miscuing led to increased activation of competing meanings and poor performance. We predict that DYS patients will have a similar pattern of performance to SA patients because they have primary executive control impairments.

Method: Patients chose one word from four choices that had a similar meaning to a probe word. Apart from the target word, the other 3 words were not related to the probe words. The experimenter read out the words, which were also written down. Thirty ambiguous words were chosen as probes, based on Twilley, Dixon, Taylor, and Clark (1994). The relative frequency of the two meanings of the words – based on how often they were picked in a free association task – was used to select dominant and non-dominant alternatives. Target words for the more frequent and less frequent meanings were matched for lexical frequency and imageability and the distractors were matched to the average lexical frequency/imageability of the target words. The same distractors were used in both the trials that tested the two meanings of the probe word (Noonan et al., 2010).

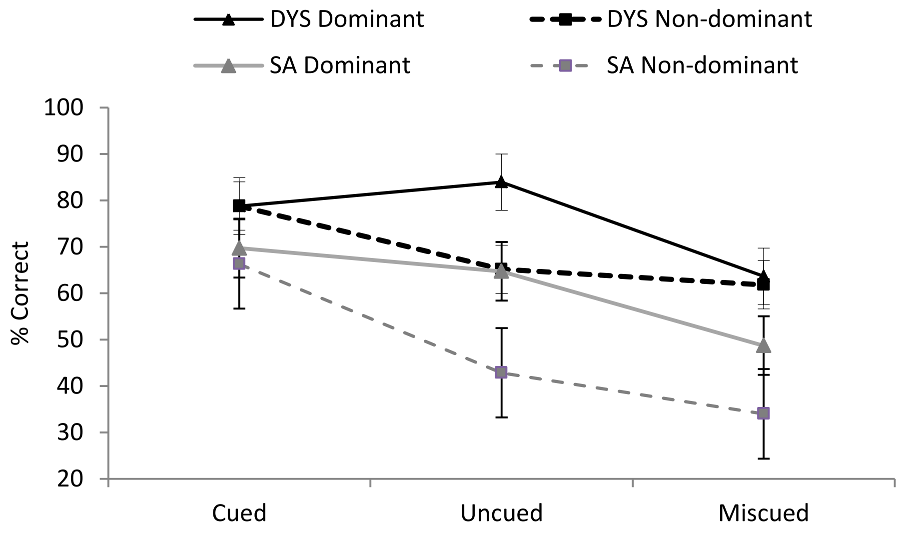
There were three cueing conditions in each task: no cue, correct cues and miscues. In the cue/miscue trials, a written sentence was read out immediately before each trial, which either primed the appropriate semantic meaning or the opposing meaning. The task instructions were the same, with the sentence reading/listening added. Patients were asked to select the word related in meaning to the probe word as quickly and accurately as possible. They were told that the sentences that were read out/seen beforehand would be helpful on some trials but not others.

Testing was carried out over four sessions, with the uncued condition tested in the first two sessions. The alternative meanings of the same word were not given in the same session. Cued and miscued conditions were then tested in two later sessions.

Results: The results are shown in Figure 11. A three-way ANOVA, using group (SA, DYS), target meaning (dominant, less dominant) and cueing condition (cued, miscued, no cue) revealed a main effect of group, $F(1,6) = 6.7$, $p = .04$, dominance of the target meaning, $F(1,6) = 35.8$, $p = .001$, and cueing, $F(2,12) = 74.0$, $p < .001$. The group by cueing interaction did not quite reach significance, F(2,12) = 2.86, p = .09, and both groups showed significant cueing effects. There was no interaction between group and dominance, F(1,6) = 4.54, p =.48, indicating that both groups showed comparable effects of this manipulation. The three-way interaction also approached significance F(2,12) = 3.08, p < .08. This reflected the fact that SA patients were more accurate in accessing the less frequent meaning of items when they were cued, and that this benefit of cueing was greater than in the DYS patients. Planned comparisons revealed significant differences in accuracy for less frequent meaning for cued vs. uncued trials, t(6) = 7.5, p < .001. There was no significant benefit of cueing for the dominant meaning of items for the SA group, t(6) = 1.2, p = .273.

Individual patient's data are shown in Table 20. Seven DYS patients showed better a performance on trials involving dominant as opposed to less frequent meanings (JG, JS, HM, MC, MK, MrL and AP) (X^2 >.45, one-tailed p < .05, using data from the uncued condition). Four SA patients also showed an effect of dominance (SC, NY, KA and ME) (χ_2 > 3.35, one-tailed *p* = .03 to *p* < .001).Nine DYS and six SA patients were more accurate in the cued than the miscued trials (DYS: McNemar one-tailed exact p = .05-.007, (SA:McNemar one-tailed exact *p* = .007 to < .001) combining the dominant and less frequent meanings).

Figure 11: Influence of cueing context on access to dominant and non-dominant meanings of homonyms in DYS and SA



Error bars show standard error of the mean

Table 16: Influence of cueing context on access to dominant and less frequent meaning of homonyms in SA and DYS

		SA Patients							DYS Patients										
		SC	PG	NY	BB	KA	ME	LS	JG	JS	MC	HM	MK	MrL	AP	TG	PAG	DL	JYS
Dominant	*Cue*	83	90	73	56	66	80	40	87	87	87	83	93	43	90	83	83	47	83
	Miscue	76	46	60	40	40	63	16	60	73	77	57	67	40	67	63	67	60	70
	No cue	86	63	76	46	70	76	36	97	93	90	87	90	57	90	80	93	57	90
Less Frequent	*Cue*	80	86	73	63	60	56	46	80	87	90	70	80	60	80	80	80	70	90
	Miscue	73	33	33	26	20	30	23	60	67	67	60	70	40	70	60	70	53	63
	No cue	66	56	43	43	26	33	33	80	73	70	60	73	33	57	67	80	47	77

Scores represent percentage correct.

Experiment 4: Effect of cues and miscues on picture naming

Studies have established stronger benefits of phonemic cues in picture naming tasks for SA patients compared to SD cases (Jefferies *et al.*, 2008, Noonan et al., 2010). Phonemic cues act to increase activation of target words relative to semantically related competitors and help SA patients overcome their difficulties in regulating semantic activation. In SD, cueing is less beneficial because these patients do not have difficulties directing their residual semantic activation correctly; instead their semantic knowledge is impaired.

Noonan et al. (2010) found that miscues, which increased competition with the target response, impaired SA patients' ability to correctly name a picture and led to additional semantic errors. This implies that SA patients found it difficult to direct activation towards the correct targets and away from semantic competitors.

Rationale: Since cueing effects in SA are thought to follow from these patients' deregulated semantic cognition, we examined the same effects in the DYS group. We predicted that this group would show similar effects of both cues and miscues that modulate the extent to which executive processes are required to direct activation towards the target away from any competition.

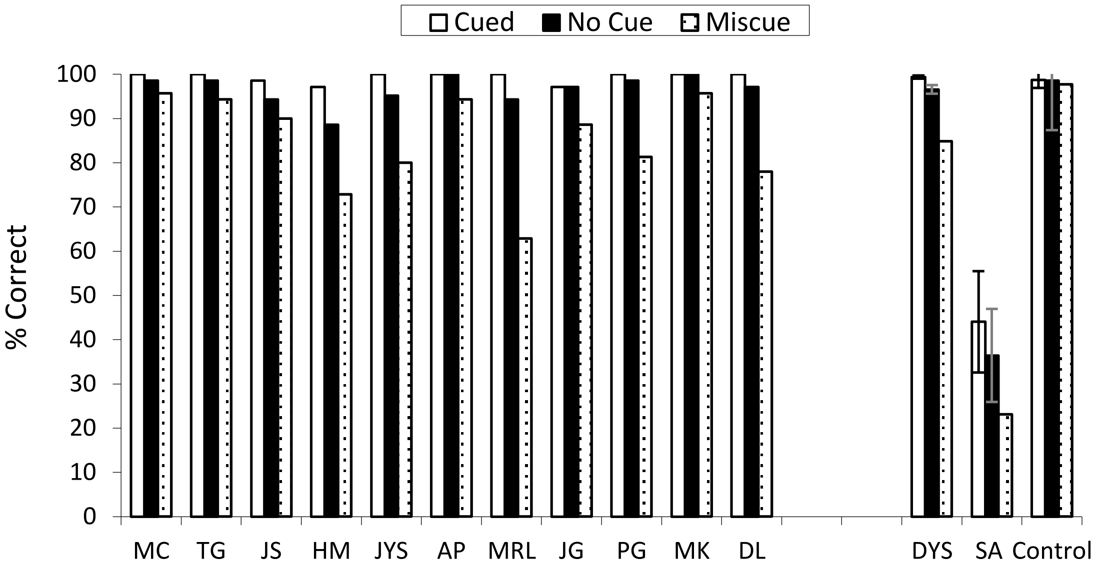
Method: This test was taken from the study of Lambon Ralph et al. (2000). Originally, a total of 140 black and white line drawings were used with the SA group (Noonan et al., 2010), however, in this study only 70 items were used with the DYS group, due to the poor tolerance of those patients. They were tested in three conditions: (a) uncued picture naming, (b) correct cue – the experimenter gave the first phoneme of the picture presented; and (c) miscued naming – the experimenter provided the first phoneme of an item semantically related to the target picture (e.g. web + /s/ from spider). In each session, one third of the items were assigned to each condition. Items were assigned to conditions using a latin-square design across three testing sessions such that, at the end of the experiment, all items appeared in all three conditions. In each session different types of cue were mixed together across the items. Patients were informed that the initial phoneme cue may be helpful on some trials but not others (Noonan et al., 2009). Participants were asked to name the pictures as quickly and accurately as possible.

Results: Figure 12 shows picture naming accuracy for the two groups (SA, DYS) in three conditions: cue, no cue and miscue. A 2x3 repeated ANOVA revealed a main effect of cueing, (F(2, 10) = 11.9, p = .002) and group (F(1, 5) = 23.1, p = .005). The DYS group had better naming overall. The interaction between group and cueing was not significant (F(2, 10) = 2.51, p = .13), suggesting that the SA and DYS groups were equally sensitive to cues and miscues in picture naming.

At an individual level, almost all SA patients showed more success in picture naming with appropriate cues than with no cues (McNemar one-tailed exact p = .01 to < .0001; Noonan et al., 2010). Cues improved naming accuracy relative to no cues for NY, PG, ME and LS (McNemar one-tailed exact p = .04 to < .0001) and the cueing effect approached significance for BB (p = .09). SC did not show a significant cueing effect (p = .18), although he showed an effect with longer phonemic cues in a previous study (Jefferies et al., 2008). The effect of correct cueing could not be readily assessed for the DYS patients as their baseline naming was at or near ceiling. One case (MrL) showed a significant effect (McNemar one-tailed exact p = .05). In the miscued condition, 6/11 DYS patients (DL, PAG, MrL, HM, JYS and JG) and 5/6 of the SA group (SC, NY, KA, PG and MA) were significantly poorer in their accuracy compared to the no cue condition (McNemar one-tailed exact *p* = .06 to < .0001).

These findings suggest that the SA and DYS patients had difficulty directing activation towards appropriate targets and away from semantic competitors. Although uncued picture naming was largely preserved in the DYS cases, making it difficult to assess the effect of correct phonological cues, the group did show miscuing effects which were equivalent in size to the SA group. It is also possible that phonological deficits, particularly in the SA group, may have influenced performance on this task. Phonemic cues may have strengthened deficient phonological processing in SA and aided name retrieval. Nevertheless, SA cases show similar patterns in object use tasks without a phonemic component: they are better able to retrieve an appropriate action for an object when given a more constrained task, such as a picture of the recipient of the object, or the object itself (Corbett et al., 2011).

Figure 12: Effects of phonemic cueing and miscuing on accuracy of picture naming



Dysexecutive patients are ordered according to overall performance on Behavioural Assessment of Dysexecutive Syndrome (BADS) from mild to severe impairment. SA data is taken from Noonan et al. (2010). Error bars show standard error of the mean.

Error analysis

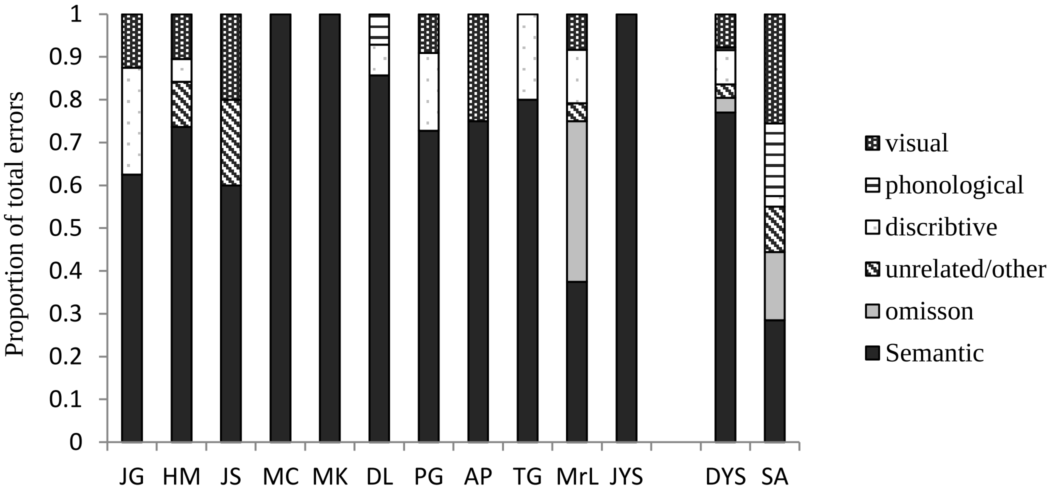
Errors from SA and DYS patients were classified into sixerror types as follows: *Semantic:* these responses were either superordinate (e.g., Apple named as 'fruit') or coordinate (e.g., a member of the same semantic category – cat named as 'dog' or orange as 'banana') or a response that is functionally or associatively related to the target (e.g., rabbit → 'carrot'). *Omission*: no response given. Other error: naming part of the target (e.g. hand → 'finger'). *Visual:* a response with a visual relationship to the target (e.g., egg → 'ball'). *Phonological:* a real word or non-word response bearing a phonological and non-semantic relation to the target. *Discriptive*: a response that discibe the use of the object (e.g., chair → 'we sit on it'). *Unrelated*: a response that not liked or related to the object (e.g., door → 'bag).

The majority of picture naming errors for both groups were semantic errors and omissions (see Figure 13). There were significant differences in the frequency of semantic errors between the SA and DYS group, $t(5)= 4.7$, $p = .005$; data presented as proportion of total errors. This is because while the DYS patients made almost exclusively semantic errors, the SA group showed a more mixed pattern, including more omissions and unrelated responses.

There were no clear difference between the both groups in the type of semantic errors, coordinate and associative response were present in all conditions in the SA group, and were more frequent in the miscued condition in DYS group.

Given that the DYS patients made a low number of errors overall and the SA patients' errors have already been analysed in full by Noonan et al., (2010), we will not consider the effect of cues and miscues on picture naming errors further.

Figure 13: Picture naming errors in the miscueing condition



Data presented as proportion of total errors in the miscueing condtion. Semantic errors = superordinate, coordinate and associative responses. SA data is taken from Noonan et al. (2010).

General discussion

This study directly compared the nature of semantic impairment in two patient groups: semantic aphasia (SA) and dysexecutive syndrome (DYS). The investigation addresses the question of whether dysexecutive syndrome in the absence of aphasia is sufficient to produce severe multimodal semantic impairment, given that SA patients show deficits of semantic cognition which are associated with impairment in non-semantic executive tasks (Jefferies & Lambon Ralph, 2006). We asked whether the SA and DYS groups would show a qualitatively similar pattern of semantic impairment, consistent with damage to executive-semantic control processes, as opposed to loss of conceptual knowledge per se, as in semantic dementia (SD). We also asked whether executive deficits at a particular level would produce the same degree of semantic difficulties in the two groups. In this way, we can investigate the relationship between domain-general executive functions and semantic control, and establish the extent to which these facets of cognition may draw on shared, partially overlapping or more distinct cognitive and neural architectures. We predicted that the DYS cases would reproduce the deficits seen in SA not SD. Therefore, the DYS group were directly compared with SA patients in analyses of modality, consistency, cross-task correlations, familiarity/frequency, task demands and experimental manipulations of semantic control requirements – including probe-target distance, distractor strength, ambiguity and cueing/miscuing – that have proved useful in understanding the nature of semantic deficits in SA.

There are few studies of DYS patients focused on semantic cognition and to our knowledge none have compared this group to patients with stroke aphasia with multimodal semantic impairment who have been shown to have deficits of semantic control. This study is also unique in the way it utilises a semantic battery that can detect the hallmarks of semantic control deficits (see Table 21 for results summary).

Table 17: Summary of performance in SA and DYS cases

Patients	**Group**	**Cueing in naming**	**Miscueing in naming**	**Frequency**	**Ambiguity**	**Synonym judgment: distractor strength**	**Nearest neighbour**
		Effects of cueing	*Effects of miscueing*	*Effects of frequency*	*Effects of non-dominant meaning*	*Effects of strong associated distractor*	*Effects of distant relation*
MC	DYS	Ceiling	x	x	√	√	x
TG	DYS	Ceiling	x	x	x	√	√
JS	DYS	Ceiling	x	x	√	√	√
GR	DYS	Ceiling	x	x	√	√	√
HM	DYS	Ceiling	√	√	x	x	√
JYS	DYS	Ceiling	√	x	x	x	*x*
AP	DYS	Ceiling	x	x	√	x	*x*
MrL	DYS	√	√	√	√	√	x
JG	DYS	Ceiling	√	x	√	√	√
PAG	DYS	Ceiling	√	√	√	√	√
CR	DYS	Ceiling	x	x	√	√	x
DL	DYS	√	√	X	√	√	√
Total		2/12	6/12	2/12	9/12	9/12	7/12
PG	SA	√	√	x	√	x	*x*
SC	SA	√	√	x	√	√	√
LS	SA	√	√	x	x	x	√
NY	SA	√	√	x	√	x	√
KA	SA	√	√	x	√	x	√
BB	SA	√	X	X	X	X	√
Total		6/6	5/6	0/6	4/6	1/6	5/6

Dysexecutive patients are ordered according to overall performance on the Behavioural Assessment of Dysexecutive Syndrome (BADS) from mild to severe impairment. SA patients' data is taken from Noonan et al. (2010). Cueing = performance in naming test taken from Lambon Ralph et al. (2000). Frequency = performance in synonym judgment test (Jefferies et al., 2006), Antonym/synonym judgment = performance on task taken from Samson et al. (2007) and Noonan et al. (2010). Nearest neighbour = performance in task taken from Noonan et al. (2010). Ceiling = 80-100%, Ticks indicate significant effect for each individual.

The results can be summarized as follows:

1. *Semantic/executive performance:* All the DYS patients showed evidence of impaired semantic performance on a range of semantic tasks including words, pictures and environmental sounds. They were less impaired than the SA patients, but semantic impairment was associated with executive control deficits regardless of the modality of presentation (i.e., word, picture and environmental sounds tasks showed a similar degree of impairment). In statistical comparisons of performance on different types of semantic tasks, both patient groups showed equivalent effects of task demands: they performed more poorly in less-constrained tasks such as judgments of semantic association (which required participants to establish which association was being probed on each trial) than in simple identity matching tasks such as word-picture matching. In addition, both groups showed a strong correlation between executive and semantic tasks. However, the SA group showed greater impairment of the semantic tasks than the DYS cases, relative to the degree of

executive deficits they displayed. This might be because the SA patients had additional (subtle) damage to multi-modal semantic or language representations, which interacted with their control impairment, or because they had sustained damage to both domain-general executive regions (e.g., medial PFC, dorsolateral PFC; IPS – see Introduction) and cortical areas specifically implicated in semantic control (anterior LIFG; pMTG).

2. *Familiarity/frequency*: The DYS and SA cases showed little effect of concept familiarity and lexical frequency across a range of tasks (i.e., synonym judgement; CCT which taps associative judgements with words and pictures; sound to picture/word matching in the environmental sounds battery and Cambridge semantic battery). In contrast, these variables have a strong positive effect on comprehension in SD patients, who show degradation of core semantic representations (Bozeat et al., 2000; Funnell, 1995; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 1998). In addition, the DYS patients showed a strong effect of imageability in synonym judgment: they performed better on high compared to low imageability items. These results reflect the same pattern of impairment that was seen in SA patients (Jefferies et al., 2007). This suggests there is a processing cost for less imageable and high frequency (HF) items, magnified in patients with SA and DYS. Given that both SA and DYS patients have poor executive control over semantic activation, one possibility is that abstract and HF concepts require greater semantic control. HF words and objects are encountered in a wider range of situations and alongside a larger number of other items than LF words, because they occur more commonly (Adelman et al., 2006; Hoffman et al., 2011a; 2011b). These varied semantic associations are likely to be activated automatically when an HF item is presented, yet many of them will be irrelevant to the task at hand. Similarly, the meanings of abstract words are less constrained by concrete features. Consequently, semantic processing for abstract and HF words might require greater executive control. Although participants will be more efficient at retrieving the meanings of frequently-presented items, some of this information will need to be disregarded for the correct response to be made. In support of this hypothesis, positive frequency effects appeared in DYS and SA patients when assessments of contextual diversity were included in the analysis of their synonym judgement performance (see also Hoffman et al., 2011a). However the absence of a frequency effect was not seen in the entire DYS group: HM, MrL and PAG continued to show substantial effects of word frequency on comprehension.

3. *Correlations within and across semantic tasks:* Both patient groups were impaired to a similar degree across a variety of different verbal and non-verbal semantic tasks.

Correlations were found between different versions of the same test that tapped different input modalities (the picture versus word versions of the CCT) and these were stronger in the SA patients. This suggests the DYS cases could have been more inconsistent in general when the same items were retrieved in similar task contexts, perhaps reflecting the tendency of DYS patients to respond impulsively. Both groups also showed a correlation between tasks that tapped different output modalities – picture naming and word–picture matching. Although on the surface these tasks make very different demands, they have similar cognitive control requirements (choosing what to point to versus selecting a name to say aloud). In contrast, neither patient group showed correlations between simple selection tasks, such as word/sound–picture matching, and tests that tapped semantic associations (CCT), even when these employed the same items. Therefore, both the SA and DYS groups were strongly influenced by the type of semantic judgement that was required.

4. *Consistency*: The DYS group showed a similar pattern as the SA group in analyses of item-by-item consistency for individual patients: both groups showed evidence of consistency across different modalities within the same task, but were less consistent between different semantic tasks that probed the same items. However, the DYS group appeared to be less consistent overall. In addition, there were some individual differences: HM and perhaps patient JS showed an unexpected and unusual level of *inconsistency* between semantic tasks that tapped the same kinds of semantic decisions across modalities, while patient MC showed an unusual level of consistency even between tasks with different executive demands.

5. *Experimental manipulation of control demands*: DYS and SA showed parallel effects of manipulations of semantic control. Both groups were impaired in tasks that loaded heavily on semantic control of semantic knowledge: there were very few interactions between group and manipulations of semantic control, suggesting that although the SA patients performed more poorly overall, executive semantic processes were disrupted in a similar way in the two groups (specific exceptions are discussed below).
    - In the Nearest Neighbour task, the SA and DYS patients showed equivalent effects of probe-target strength: they both showed greater difficulty in making an association between probe and target when they were further apart in semantic space (e.g. SHIP and VAN) than when they were semantically similar (SHIP and YACHT). More distant pairs are harder to match because they have fewer overlapping features: this suggests that both groups may have had similar impairment in the establishment of distant categorical relationships, based on more abstract forms of conceptual overlap.

- Both groups showed poor inhibition of strongly associated distractors in synonym/antonym judgments. The ability to inhibit irrelevant distractors when judging which of several words are related in meaning depends on intact semantic control. When two concepts are strongly related, their relationship becomes hard to ignore even when they relate to a task-irrelevant dimension (Badre et al., 2005; Samson et al., 2007; Wagner et al., 2001). This finding of poor performance with strong distractors suggests both patient groups have difficulty controlling activation so that it is channelled away from directed irrelevant items. Only two cases (HM and AP) showed similar level of impairments in the two conditions employing strong and weak distractors.
- The DYS group had difficulties retrieving less frequent meanings of ambiguous words, reproducing the pattern found in the SA group (Noonan et al., 2010). The dominant meanings of ambiguous words are thought to be retrieved relatively automatically; therefore, when semantic judgements tap the less frequent interpretation, semantic control processes may be needed to inhibit irrelevant aspects of meaning and focus processing on task-relevant semantic features. Moreover, both groups benefited from sentence contexts that cued the relevant as opposed to the irrelevant meanings of ambiguous probe words. This suggests both groups showed poor internally-generated control over semantic activation, yet retained the lower frequency meanings that they could not always access. Both patient groups also showed miscuing effects; i.e., poorer semantic performance following a sentence context that was designed to strengthen the irrelevant interpretation of the word, compared with a no cue condition where no sentence was presented. However, despite the similarities in the effects of ambiguity and cueing/miscuing in this experiment, there was a three-way interaction between ambiguity, cueing and group: this reflected a stronger miscuing effect for non-dominant interpretations of ambiguous words in the SA group.
- The DYS patients made similar types of errors to those found in SA patients in picture naming tasks (Jefferies et al., 2006; Noonan et al., 2010). Both groups produced some responses that were associatively rather than categorically related to the target (unlike cases with SD), supporting the view that failure of controlled semantic retrieval, not impairment in knowledge, produces deficits in picture naming. Similar naming errors have been reported from a single semantically and executively impaired CVA patient (Humphreys and Forde, 2005). However, the total number of errors in the SA group was substantially larger; moreover, this group made more diverse errors, including unrelated responses and omissions, which might have reflected their aphasia symptoms beyond their semantic deficit. The benefit of phonemic cueing had a

> smaller impact on DYS compared to SA because their largely intact speech production resulted in ceiling-level performance. However, one individual case (MrL) showed significant improvement with cueing, because he had poor expressive ability compared to the other DYS patients. In contrast, in SA patients, phonemic cues strongly helped in picture naming, showing that such patients had knowledge that they could not access dependably without external support (Jefferies et al., 2007). The phonemic cues were argued to activate the target word over any semantically related competitors, thereby directing attention to relevant aspects of conceptual knowledge. In the miscuing condition, which was designed to strengthen the activation of a close semantic competitor, the DYS group showed a similar increase in errors relative to the no-cue condition as the SA group.

Patients who were recruited in this study were shown to be impaired in tasks requiring executive function across verbal and non-verbal assessment. The patients did not show any clear comprehension problems, but their performance in the semantic assessments exhibited a qualitatively similar pattern of semantic performance, typical of patients with SA, especially when control demands were manipulated. However, there were three DYS cases (HM, MrL and PAG) who did not consistently show the same pattern as the SA patients. All three continued to show positive effects of frequency/familiarity on their comprehension. Patient HM also failed to show the expected effects of distractor strength. All of these cases had somewhat unusual patterns of brain injury, which were potentially more SD-like. HM was diagnosed with vascular dementia a year after the current study: he was therefore likely to have had a complex pattern of older injury and on-going neurodegeneration, which could conceivably have effected more anterior portions of the temporal lobe, that is, regions atrophied in SD. In subsequent analyses, it will be appropriate to exclude this case. MrL has speech production problems due to left temporal lobectomy. PAG is a case of bilateral anterior cerebral artery infracts.

Although this study was not designed to evaluate different theories of executive control per se, our results are highly compatible with the multi-demand theory. Duncan (2001) considers high-level control as a unitary system, underpinned by a bilateral network located in prefrontal and parietal regions, which is responsible for domain-general executive demands and not cognitive control only within certain domains (Duncan, 2006; Hon et al., 2006). According to this view, neural and cognitive resources are shared across all aspects of executive control, including verbal and non-verbal semantic and non-semantic domains (Duncan, 2006; Duncan & Owen, 2000; Nagel et al., 2008). Many studies show joint activation in bilateral PFC, anterior cingulate and intraparietal sulcus in dealing with tasks needing conflict resolution or different executive processes like stroop, flanker, go-no, set-shifting, updating working memory and inhibitory processing (Nee *et al.*, 2007; Collette *et al.*, 2006). Peers *et al*. (2005) found similar attention/cognitive control impairment resulting from lesions to PFC or inferior parietal cortex. Moreover, TMS to dorsal PFC and IPS disrupts executive processes for both semantic and non-semantic tasks (Nagel et al., 2008; Whitney et al., 2012), consistent with the finding that anterior and posterior lesions in SA produce comparable deficits of semantic and executive control (Noonan et al., 2010). This shared cognitive and neural architecture for executive-semantic processing and domain-general control is compatible with many of our current results. This view would predict an association between impairment in multimodal semantic control and executive control difficulties in non-semantic tasks, which was seen in both the SA and DYS patients.

Nevertheless, aspects of the data reported in this chapter suggest some differentiation of semantic and non-semantic control. The SA patients had more severe semantic deficits than would be predicted from their executive performance, compared with DYS patients. The SA patients also showed somewhat larger cueing/miscuing effects (although some of these differences could be explained in terms of ceiling-level performance in picture naming tasks in the DYS patients). Finally, the DYS patients showed more inconsistency across multiple versions of the same task that had broadly similar executive control requirements – an effect which we suggest above might be linked to impulsive responding in participants with DYS. Cases with SA may have more severe semantic impairment, relative to the degree of executive deficit, as their lesions encompass areas associated with semantic control specifically (e.g., anterior LIFG; pMTG). Semantic tasks with high control demands produce higher activation, mostly in ventral parts of PFC (BA47), while phonological tasks are associated more with activation in dorsal PFC and adjacent parts of premotor cortex (cf. Gough et al., 2005; Vigneau et al., 2006). A recent meta-analysis of neuroimaging studies of semantic control also revealed that pMTG was only activated by executively-demanding semantic tasks and did not contribute to domain-general control (Noonan et al. submitted).

In conclusion, our findings reveal that primary impairment of executive control in patients with DYS is sufficient to reproduce many of the features of the semantic deficit seen in SA.

CHAPTER 4

Refractory effects in Dysexecutive (DYS) patients

Note: The DYS data was collected by Azizah Almaghyuli and compared with SA data from Jefferies et al. (2007).

Introduction

This chapter explores the possibility that DYS cases show refractory effects, similar to those seen in semantic aphasia cases, when concepts are presented repeatedly and rapidly. This chapter therefore provides a test of the theory that refractory effects arise from increasing competition within a small set of semantically related items, as a result of an executive semantic control. It provides an additional point of comparison with SA, to establish if these two patient groups show qualitatively similar patterns of semantic impairment.

A refractory deficit is found when patients show declining performance when stimuli are repeatedly presented at a rapid rate. Early theories suggested that refractory behaviour reflects a deficit in access to semantic knowledge rather than in its storage (Warrington and Shallice, 1979). An important classic distinction in the literature on semantic disorders contrasts “storage” impairments (i.e., degradation of semantic representation) with “access” disorders, where concepts are still available but enter a refractory state and become inaccessible when the same items are presented repeatedly and rapidly in cyclical word-picture matching tasks. Warrington and Shallice (1979) described the characteristics of storage disorder as consistency over time, relative preservation of familiar, frequent and superordinate information and no effect from cueing. In contrast, access disorders show the reverse pattern. Patients are inconsistent in comprehension tasks, insensitive to frequency and show “refractory” effects in cyclical tasks, especially when sets of semantically related items are presented at a rapid rate (Warrington and Shallice, 1979).

The distinction between storage and access disorders has been widely debated in the literature. Notably, Rapp and Caramazza (1993) raised two strong criticisms to the proposal of refractory semantic deficits as a syndrome. Firstly, relating to the empirical validity of the distinction, they showed that patients can present with a mixed pattern of access and storage deficits. Secondly, they criticised the absence of a theoretical explanation underpinning the nature of stored representation and access mechanisms. Warrington and Cipolotti (1996) partially addressed these concerns by proposing a neurophysiological basis for the two different types of impairment. They suggested firstly, that the refractory effect might result from vascular lesions and tumours, which increase the neural refractory period, and secondly, that degraded-store deficits can result from cell death and damage to neurons, such as in semantic dementia.

The mechanisms underpinning refractory effects are unclear and remain the focus of substantial research efforts. In the refractory task, a small group of semantically related items are repeatedly presented in cycles, with targets becoming distractors and vice versa. Therefore, in this task, it is necessary to dampen down activity that is no longer-task relevant, and then re-activate these representations a short while later. According to the neuromodulation model proposed by Gotts and Plaut (2002), patients who show refractory deficits fail to overcome synaptic depression after activation – such effects can be revealed by fMRI studies which find reduced activation with multiple repetitions of an item, known as “repetition suppression”. The neuromodulators acetylcholine and noradrenaline diminish these effects, but in patients with access deficits, the effects are weaker due to damaged white matter tracts that provide these neuromodulatory signals. As a consequence, the system is dominated by synaptic depression and a computational model shows that this could lead to “large effects of presentation rate and repetition, as well as inconsistent responding” (Gotts & Plaut, 2002, p.188). This mechanism might also explain the prevalence of perseveration errors in access patients (Gotts, della Rocchetta, & Cipolotti, 2002; Sandson & Albert, 1987).

Another potentially related account is that refractory effects reflect a failure to resolve competition following disruption to executive-semantic or language selection mechanisms (since neuromodulators play an important role in cognitive control). In this paradigm, the targets become distracters and vice versa; therefore competition for selection is likely to increase across cycles and some patients with aphasia may have difficulty resolving this competition (Jefferies et al., 2007; Schnur et al., 2006). Schnur et al. (2006) suggest that refractory deficits result from impairment of *verbal* selection mechanisms which produce an increase in lexical competition across cycles in picture naming when semantically related sets are presented repeatedly. They linked this pattern in aphasia to damage to LIFG. However, patients with SA – who have multimodal comprehension problems in the context of largely intact semantic knowledge but deregulated semantic cognition (Corbett et al., 2009; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008) – have refractory effects in both verbal and pictorial semantic tasks (Gardner et al., 2012). Their performance is strongly affected by the executive requirements of semantic tasks: they have difficulty selectively retrieving the task-relevant meanings of items and rejecting highly associated distractors (Corbett et al., 2011; Jefferies et al., 2008; Noonan et al., 2010) and their semantic deficits are associated with impairments of attention/executive function (Baldo et al., 2005; Jefferies & Lambon Ralph, 2006; Wiener et al., 2004). This “executive control” hypothesis makes an important prediction for the current study: if refractory phenomena reflect a failure to resolve competition between related concepts, patients with dysexecutive syndrome should show substantial impairments for semantically-related sets at fast speeds and as items are repeated. The effects should be seen in comprehension as well as naming tasks, given that executive resources are thought to play an important role in comprehension.

“Access” patients, described by Warrington et al. and “semantic aphasia” patients, described by Jefferies et al. (2006), share several characteristics. (1) “Access” patients are inconsistent: their performance on one trial does not correlate with a later performance on the same items (Warrington & McCarthy, 1987). This suggests that the items are not “degraded” but inaccessible in certain conditions. Similarly, Jefferies and Lambon Ralph (2006) established that SA patients do not show item consistency across semantic tests which vary in control demands. (2) Low frequency items produce more errors for those with degeneration of semantic knowledge (e.g., patients with SD), but “access” patients do not show this effect of progressive deterioration of knowledge. This is also true for SA patients, who may even show reverse frequency effects, i.e. comprehension of low frequency words is less impaired than high frequency words (Hoffman, Jefferies, & Lambon Ralph, 2011). This is thought to be related to the competition demands which high frequency words face (see Chapter 2). (3) In contrast to patients with SD, “access” patients show lower performance on spoken-word-picture matching tasks when the picture is probed using the superordinate name (e.g. bird, insect) compared to the item name (e.g. peacock, beetle), known as the inverse hierarchy effect (Crutch & Warrington, 2008a). Similarly, Humphreys and Forde (2005) described patient FK who presented with a significant impairment in accessing semantic knowledge about objects when tested across a range of input and output modalities. He was weakest at discriminating superordinate categories in a picture naming task and matching superordinate-level labels to items. They suggest that superordinate classification requires the drawing together of disparate information, which is particularly taxing without constraints from item-based associations; therefore this task requires greater executive control. (4) Priming effects have been shown in “access” patients which are not predicted in those with permanent loss of semantic representations (Warrington & Shallice, 1979). Spoken prompts for word reading (e.g. ice prompting cold) improve performance. Similarly, SA patients have been found to greatly improve after being given a phonological cue in picture naming tasks, while cueing effects in SD were more modest (Jefferies, Patterson, & Lambon Ralph, 2007). (5) The possibility that “semantic access” disorder overlaps with the semantic control deficits in patients with SA was specifically examined by Jefferies, Baker, Doran, and Lambon Ralph (2007). They found that SA patients showed classic signs of access disorder, including the effects of item repetition and speed of presentation and that these refractory symptoms were associated with deficits in executive control over semantic activation.

In spite of these similarities between “access” patients and SA cases with executive-semantic impairment, there is a critical difference in terms of modality. Firstly, according to the Warrington group, access deficits happen only in the auditory/verbal domain (Warrington and Crutch, 2004). Accordingly, access to the visual domain remains intact (Warrington & Shallice, 1979). Warrington and Crutch (2004) argue that the contrast in performance between word and picture tasks supports the view that semantic systems are modality-specific. In subsequent work, one of their well-studied access cases was found to show refractory effects in non-verbal environmental sounds matching tasks, as well as for words, suggesting that there may be a processing distinction between visual and auditory semantic systems (Warrington and Crutch, 2004; Crutch & Warrington, 2008). In contrast, Jefferies and Lambon Ralph suggested that the refractory impairment in SA is related to difficulty accessing the amodal semantic store following damage to domain-general executive control processes that modulate semantic activation across modalities. Support for this view is provided by SA patients' consistent performance for the same concepts presented in different modalities (Jefferies & Lambon Ralph, 2006) and the presence of refractory effects in word, picture and environmental sounds tasks (Gardner et al., 2012).

Beyond the association between executive and refractory effects in SA, further support for the executive hypothesis comes from lesion location. Schnur, Schwartz, Brechr, Rossi, and Hodgson (2006) studied semantic blocking effects in picture naming in eighteen aphasic patients. They were required to name pictures in semantically related and unrelated arrays, presented at both slow and fast rates and repeated as sets across several cycles. They found greater build-up of competition (indexed by increased error rates over cycles) in patients with damage to left inferior frontal gyrus (LIFG) compared to patients with posterior brain damage. Schnur and colleagues suggest these effects were specific to overcoming competition in lexical retrieval in a naming task, but a similar pattern has been observed for cyclical *comprehension* tasks in SA (Jefferies et al., 2007). SA patients have infarcts affecting left posterior temporal, parietal and inferior frontal regions (Berthier, 2001; Chertkow et al., 1997; Dronkers et al., 2004; Hart & Gordon, 1990; Hillis et al., 2001). While both PFC and posterior temporal/interior parietal regions may contribute to aspects of semantic control, SA cases with prefrontal cortex (PFC) lesions appear to show stronger refractory effects while patients with left temporoparietal (TP) cortex lesions are less sensitive to refractory variables (Jefferies et al., 2007; Gardner et al., 2012; Campanella et al., 2009). Specifically, patients with left PFC lesions appear to be more affected by stimulus set repetition compared to TP patients, suggesting that although temporoparietal lesions can elicit failures of semantic control in SA patients, PFC may be specialised for selection. Jefferies et al. (2007) examined whether refractory effects resulting from left PFC lesions were specific to picture naming by directly comparing cyclical naming and word-picture matching: refractory effects were found in both tasks, supporting the view that these effects can be attributed to a decrease in semantic control as opposed to lexical selection. In support of this view, Campanella et al. (2009) studied 20 patients with tumours who had damage to temporoparietal cortex and found that there was a weak effect of repetition and speed of presentation on comprehension. Finally, Gardner et al. (2011) confirmed that lesion location influences the strength of multimodal refractory deficits, by comparing a group of SA patients across different modalities (cyclical visual, verbal and non-verbal auditory tasks). They found greater reduction in accuracy in the left PFC group compared to TP lesion patients across these tasks. This result fits with the theory that impaired executive control over multimodal semantic retrieval in SA patients can reflect a degree of functional specialization within anterior and posterior regions that form part of the semantic control network.

The current study explores refractory effects in patients who have general executive impairment and compares their performance to the SA patients previously studied by Jefferies et al. (2007). The patients were selected on the basis of impairment of non-verbal executive control, as opposed to semantic/linguistic deficits. This will reveal whether executive impairment is sufficient to produce the characteristics of access disorder, even in individuals without aphasia, and therefore provides an important test of the proposal that difficulty resolving competition on later cycles of refractory tasks can reflect executive dysfunction (although of course not all patients with ‘semantic access disorders’ may be explained in this way – there may be multiple potential causes of the same phenomenon). Additionally, this study provides another point of comparison between the SA and DYS groups: it might be that although there are some similarities between these patients in the nature of their semantic deficits, there are also some differences in the effects of specific ‘refractory’ variables. Therefore, the main aims of this study are to explore variables associated with the refractory effect, e.g. effects of cycle, speed of presentation and semantic blocking within word-picture matching in a direct comparison of the two groups. We also consider whether DYS patients show all of the classic characteristics of semantic access disorder; namely, inconsistency, the absence of frequency effects and strong effects of cueing. As in Chapter 3, we adopt a case-series approach, providing a comparison at the group level but also analysis of each individual within the group.

Participants:

Dysexecutive syndrome (DYS):

Seven patients, six males and one female, with Acquired Brain Injury were recruited from rehabilitation centres in the UK. All cases had experienced chronic brain injury at least one year previously. The patients were selected to show dysexecutive syndrome. The primary tool for selection was the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson et al., 1996), following initial referral based on a clinical neuropsychologist evaluation which suggested executive deficits. Patients were selected if they showed impaired/borderline performance on the BADS test battery (more details in Chapter 3). Some exclusion criteria were also applied: the brain injury should not have occurred during childhood, the patients should not be suffering from any psychotic symptoms and they should not be on any medication which might affect their performance (see Table 22). (MC, AP, PAG, HM, MrL, JS and TG) were also tested in Chapter 3.

Semantic aphasia (SA):

The SA group comprised eight aphasic stroke patients from Jefferies et al. (2007), consisting of six males and two females, aged between 36 and 76. They were recruited from stroke clubs and speech and language therapy services in Manchester, UK. All cases showed chronic impairment, and were selected to show comprehension deficits in both picture and word tasks. However, patients were not selected specifically on the basis that they showed refractory effects. Four cases had transcortical sensory aphasia, and the others had less fluent speech and/or poorer repetition. Table 23 shows biographical/neuroimaging details and aphasia classifications grounded on the Boston Diagnostic Aphasia Examination (Goodglass, 1983) and repetition tests from the PALPA battery (Kay, Lesser, & Coltheart, 1992). Imaging reported injury in the left inferior prefrontal cortex (LIPC) in 5/6 cases who had a left frontal lesion (only a previous scan report was available for the sixth patient due to contraindication for MRI). An additional two patients had temporoparietal infarcts that did not encompass left prefrontal regions. As noted in the Introduction, these two cases were found to show weaker refractory effects by Jefferies et al. (2007).

Table 18: Demographic information for dysexecutive patients (DYS)

Patients	Age	Education	Neuroimaging summary	PFC	T-P	Aetiology of ABI
MC	28	14	White matter damage in L PFC+ R parietal contusion	*		Alleged attack
TG	25	15	Enlargement of R lateral ventricle+contusions in the cerebellum and cerebrum	-	-	Road traffic accident
JS	64	Dip	Hypoxic episode	-	-	Cardiac arrest
HM	47	PhD	L frontal-parietal	*	*	External insult by sharp object
AP	25	18	No scan	-	-	Road traffic accident
MrL	45	16	L temporal		*	Temporal lobe abscess
PG	52	18	Bilateral anterior cerebral artery (ACA) infarcts		*	CVA

Patients are arranged in order of Behavioural Assessment of Dysexecutive Syndrome scores (BADS; Wilson et al., 1996). Edu = age of leaving education. Dip = Postgraduate Diploma. Neuroimaging summaries are based on written reports of clinical scans where available, except in the case of MC, MRI scan was available PFC = lesion involves left prefrontal cortex; T-P = lesion involves left temporoparietal cortex; * = indicates damage to specific area, - = neuroimaging is not sufficient to make a definitive statement regarding the extent of cortical damage, ABI = acquired brain injury.

Table 19: Aphasia classifications and neuroimaging summaries for the SA participants

Patient	Age	Sex	Education	Neuroimaging summary	Aphasia Type	BDAE Compreh	BDAE Fluency	BDAE Repetition	Nonword repetition	Word Repetition
NY	63	M	15	L frontal-temporal-parietal	Conduction	47	37	40	40	81
SC	78	M	16	L occipital-temporal (+ R frontal-parietal)	Anomic/TSA	37	90	60	87	98
PG	59	M	18	L frontal & capsular	TSA	20	40	80	73	91
KH	73	M	14	L frontal-occipital-temporal	Mixed Transcortical	30	30	40	43	80
BB	55	F	16	L frontal and capsular	Mixed Transcortical	10	17	55	83	96
ME	36	F	16	L occipital-temporal	TSA	33	100	100	93	100
LS	71	M	15	L frontal-parietal-temporal	TSA	13	90	90	90	96
KA	74	M	14	L frontal-parietal	Global	0	23	0	0	0

Patients are arranged in order of word-picture matching scores. BDAE = Boston Diagnostic Aphasia Examination (Goodglass, 1983). BDAE Comprehension score is a percentile derived from three subtests (word discrimination, commands, complex ideational material). BDAE Fluency percentile is derived from phrase length, melodic line and grammatical form ratings. BDAE Repetition percentile is average of word and sentence repetition. TSA (transcortical sensory aphasia) was defined as good or intermediate fluency/repetition and poorer comprehension. Word/nonword repetition: Tests 8 and 9 from PALPA (Psycholinguistic Assessments of Language Processing in Aphasia, Kay et al., 1992).

Background neuropsychological and semantic tests:

The patients were examined on a series of general neuropsychological assessments and completed a semantic battery (see Chapter 3). Both groups showed multimodal semantic impairments in most of the tests. Performance was poorer for the SA patients in all measures: picture naming, word-picture matching, CCT-Word, CCT-Picture and in the environmental sounds battery.

Experimental investigation of cyclical word-picture matching:

Method

The experiment explored three factors that classically affect “semantic access” patients, speed of presentation, where the response-stimulus interval (RSI) could be fast (RSI=0s) or slow (RSI=5s); semantic relatedness contrasting related and unrelated sets; and repetition of trials across 4 cycles. Items were chosen from six categories, fruit, birds, tools, vehicles, musical instruments and foreign animals. Each category contained six items. On each trial, the patient was asked to indicate items that matched a spoken-word from six pictures. For the semantically related condition, the six items were drawn from the same category. In the unrelated condition, the items were drawn from six different categories. To avoid testing items twice in a row, all the items in the semantically related and unrelated conditions were shown once and repeated three more times in a pseudorandom order. Items were presented in different conditions, semantically related/unrelated arrays and at both fast and slow speeds. In the fast presentation condition (RSI=0s), the next trial was presented immediately after the selection of an item, whereas in the slow presentation (RSI=5s), a blank screen appeared for 5s after each response before the new trial was presented. Therefore this manipulation did not alter the length of time participants had to respond, but rather the time between trials. Participants had to respond within 10s or an error was recorded and experiment progressed to the next trial. At the beginning of each session, participants had four practice trials. The order of items across these conditions was counterbalanced. There were 576 trials in total (36 items x 4 repetition or cycles x 2 speeds x 2 relatedness conditions).

The experiment was presented on a computer using E-prime software. The patient listened to the name of a target object and indicated the response by pointing to the matching item on the computer screen as quickly as possible. The researcher then progressed the experiment to the next trial. To complete the whole task, 3-6 sessions were needed, depending on the tolerance of the participants

Results

Accuracy in DYS

Figure 14a shows the means and standard errors for the DYS patients on the word-picture matching task. A 2x2x4 ANOVA (slow/fast, related/unrelated, 4 cycles) revealed a main effect of relatedness (F(1,6) =11.9, p = .01). The DYS patients performed more poorly on the semantically related versus the unrelated blocks. There was a main effect of speed (F(1,6) = 22.7, p = .003) and cycle/repetition (F(3,18) = 3.14, p = .05). There were also interactions between relatedness and speed of presentation (F(1,6) = 11.22, p = .01) and relatedness and cycle (F(3,18) = 3.8, p = .02). The ANOVA is summarised in Table 24.

To explore the relatedness by speed interaction, t-tests were used to compare the effect of speed for related and unrelated sets. There was an effect of speed for related sets (t(6) =-3.7 , p = .01 corrected = .04) but not unrelated sets (t(6) = -2.5, p = .03 corrected = .12), which showed near-ceiling comprehension. To explore the relatedness by cycle interaction, t-tests were used to compare comprehension of related and unrelated sets at cycles 1, 2, 3 and 4. There was a non-significant difference between related and unrelated sets at cycle 1(t(6) = -2.1, p = .08), and better comprehension of unrelated than related sets at cycle 2 (t(6) = -3.2, p = .01 corrected = .04), cycle 3 (t(6) = -2.8, p = .02 corrected = .08) and cycle 4 (t(6) = -2.2, p = .06), indicating that the related sets showed larger effects of speed.

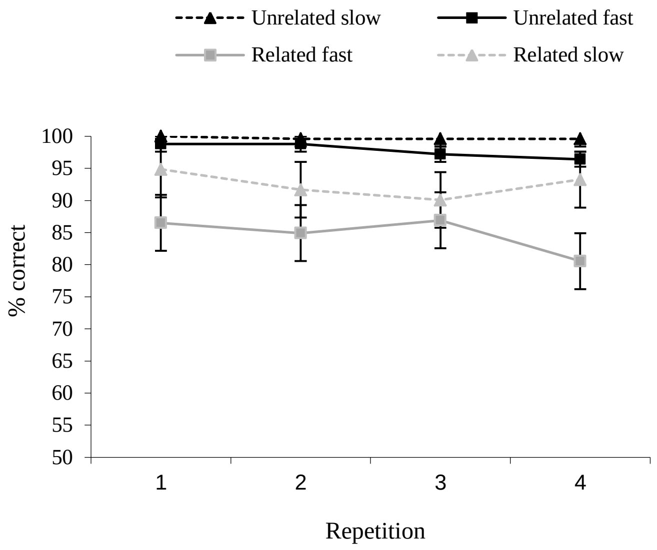
Accuracy in SA

This data was previously reported in Jefferies et al. (2007) and is reproduced here to allow comparison with the DYS group.

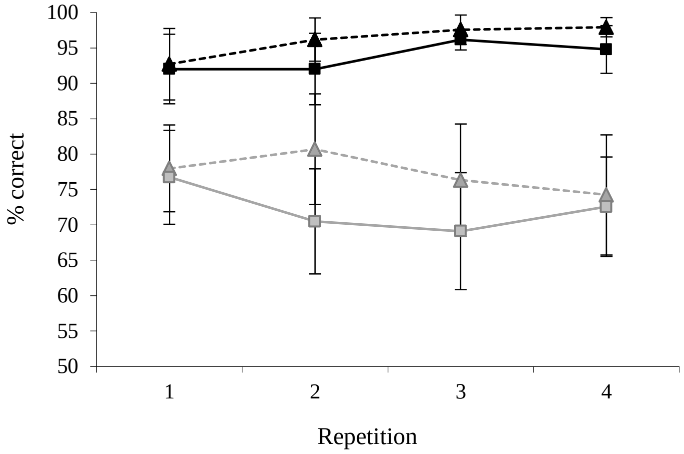
Figure 14b shows the means and standard errors for the SA patients on the word-picture matching task. Table 20 shows a 2x2x4 ANOVA which revealed a main effect of relatedness (*F*(1,7) = 17.7, p = .004). Patients performed more poorly on the semantically related versus the unrelated blocks. The main effects of speed and cycle were not significant, although the interaction between relatedness and cycle approached significance (*F*(3,21) = 2.9, p = .06). For semantically related items, the decrease in accuracy between the first and fourth presentations approached significance (t(7) = 2.0, uncorrected p = .08) but there was no change in cycle for the unrelated sets. Cycle also interacted with speed (*F*(3, 21) = 5.1, p = .008). There was an increase in accuracy between the first and second presentation at the slow speed (t(7) = -2.8, uncorrected p = .03) and a decrease at the fast speed (t(7) = 2.2, uncorrected p = .06).

Figure 14: Refractory effects in word-picture matching accuracy for DYS and SA patients

a) Dysexecutive patients



b) Semantic aphasia



Error bars show standard error of mean

Table 20: Accuracy in cyclical word-picture matching

Condition	SA	DYS	Group interaction
Speed	F(1,7) = .514, *p* = .068	F(1,6) = 22.7, *p* = .003	F(1,6) = 4.46, *p* = .079
Relatedness	F(1,7) = 17.6, *p* = .004	F(1,6) = 11.9, *p* = .013	F(1,6) = 17.6, *p* = .006
Cycle	F(3,21) = .004, *p* = .001	F(3,18) = 3.14, *p* = .05	F(3,18) = 1.11, *p* = .369
Speed x Relatedness	F(1,7) = 1.25, n.s.	F(1,6) = 11.2, *p* = .015	F(1,6) = 12.5, *p* = .012
Relatedness x Cycle	F(3,21) = 2.9, *p* = .058	F(3,18) < 1	F(3,18) = 3.67, *p* = .032
Speed x Cycle	F(3,21) = 5.09, *p* = .008	F(3,18) = 3.89, *p* = .02	F(3,18) = 1.98, n.s.
Speed x Cycle x Relatedness	F(3,21) = 1.53, n.s.	F(3,18) = 1.42, n.s.	F(3,18) < 1

Table shows repeated measures ANOVA results.

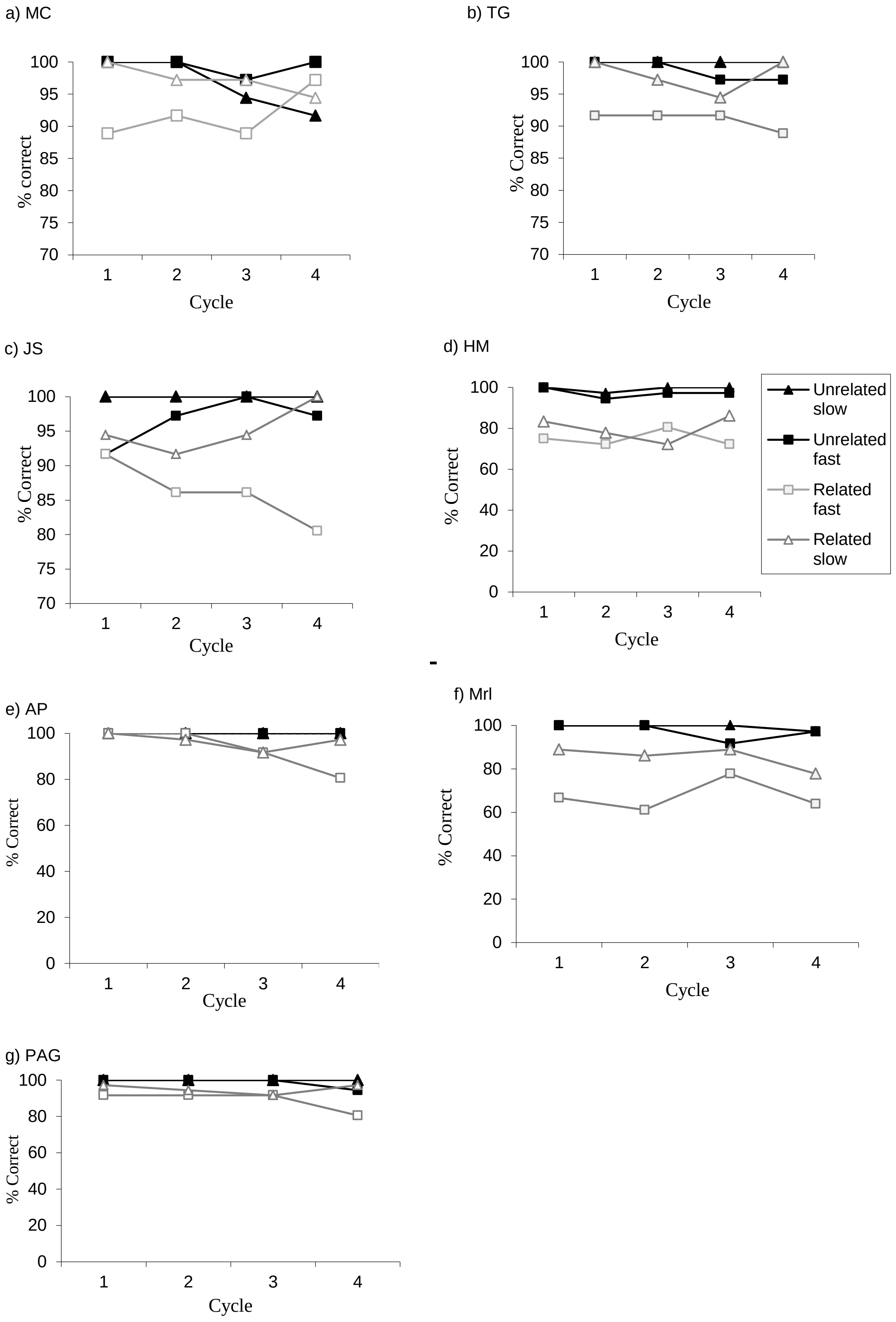
Group comparison: Accuracy

A 2x2x2x4 ANOVA revealed a significant main effect of group (*F*(1,6) = 4.7, *p* = .07): performance was more impaired in the SA group. There was a near significant interaction between group and speed. The overall effect of speed only reached significance for the DYS group (see Table 20). There was a significant interaction between group and relatedness. Both groups showed a significant effect of this variable, but the difference between related and unrelated sets was more marked in the SA patients. There were two three-way interactions: DYS patients showed a larger interaction between speed and relatedness while SA cases showed a large interaction between relatedness and cycle (see Table 24). These results suggest that although both groups show effects of refractory variables, the exact pattern of effects is influenced by the degree of impairment to executive and semantic processing.

Individual accuracy:

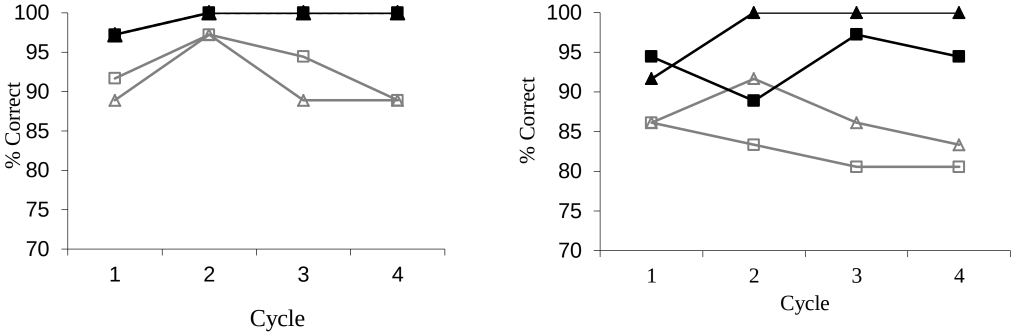
Figures 15a and 15b show the performance of each individual SA and DYS patient. Logistic regression was employed for each case individually to determine the main effects of relatedness, speed and repetition and the interaction between these factors (see Table 21). Almost all cases across both groups showed a strong effect of relatedness. 5/7 DYS patients were strongly influenced by speed in their performance and the two DYS cases who did not show effects of speed (HM and AP) reached ceiling in their performance. As revealed by the group comparison above, the effects of speed were somewhat weaker in SA: 3/8 cases in this group showed effects of speed. Two SA cases did not show any effect of cycle or speed (ME and SC) and those two were the only cases that had temporoparietal lesions that spared the left prefrontal cortex (see Table 25 for a full breakdown of the effects in the logistic regressions).

Figure 15a: Refractory effects in word-picture matching for individual DYS patients

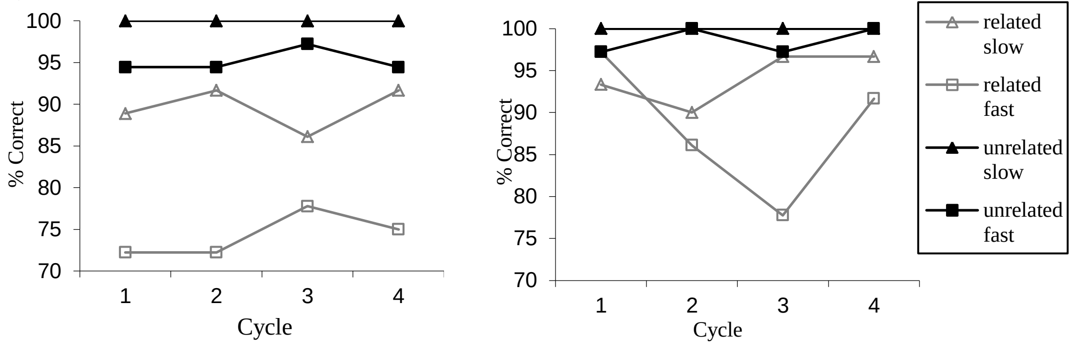


Patients are arranged in order of Behavioural Assessment of Dysexcutive Syndrome scores (BADS; Wilson et al., 1996) from mild to severe.

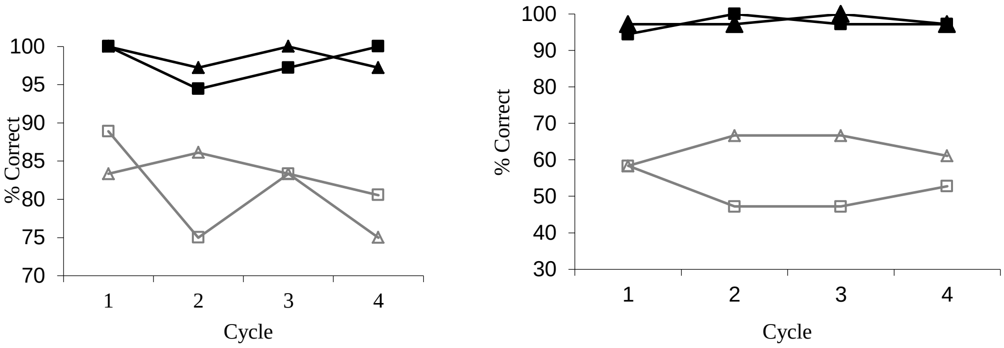
Figure 15b: Refractory effects in word-picture matching for individual SA patients


a) SC

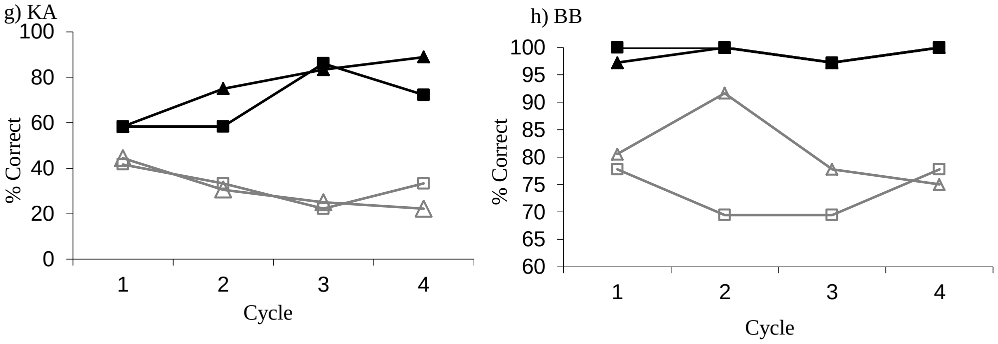
b) KH


c) PG

d) NY


e) ME

f) LS


g) KA

h) BB

Patients are arranged in order of word–picture matching scores, data taking from Jefferies et al. (2007)

Table 21: Word-picture matching accuracy for individual patients

Condition	**SA patients**								**DYS patients**						
	KH	ME	NY	PG	SC	KA	LS	BB	MC	TG	JS	HM	AP	Mrl	PG
Related %	85	82	91	82	92	32	57	77	94	94	91	77	95	76	92
Unrelated %	96	98	99	98	99	73	98	99	98	99	98	98	100	98	99
Relatedness (Wald)	17.9**	28.7**	12.2**	28.9**	11.5**	91.0**	72.5**	32.1**	6.1**	8.1**	12.4**	35.3**	0	32.0**	11.8**
Slow %	92	90	97	95	95	53	81	90	97	99	98	90	98	92	98
Fast %	88	90	93	85	96	51	74	86	94	95	91	86	97	82	94
Speed (Wald)	2.9*	n.s	3.7*	15.6**	n.s	n.s	4.2*	n.s	4.4*	6.8**	10.7**	1.8	1.7	11.5**	5.5**
Related items Trial 1 (%)	86	86	88	81	90	43	58	79	94	96	93	79	100	78	94
Related items Trial 2 (%)	88	81	81	82	97	32	57	81	94	94	89	75	99	74	93
Related items Trial 3 (%)	83	83	79	82	92	24	57	74	93	93	90	76	92	83	92
Related items Trial 4 (%)	82	78	86	83	89	28	57	76	96	94	90	79	89	71	89
Relatedness by repetition (Wald)	3.2*	n.s	n.s	n.s	n.s	16.7**	n.s	8.4**	n.s	n.s	n.s	n.s	n.s	n.s	n.s
Fast speed Trial 1	90	94	97	83	94	50	76	88	47	47	45	43	50	41	47
Fast speed Trial 2	86	84	93	83	98	45	73	84	47	47	45	41	50	40	47
Fast speed Trail 3	88	90	87	87	97	54	72	83	45	47	46	44	47	42	47
Fast speed Trial 4	87	90	95	84	94	52	75	88	47	46	44	42	45	40	43
Speed by repetition (Wald)	4.2*	3.1*	n.s	n.s	n.s	n.s	n.s	n.s	3.1*	4.2*	8.2**	n.s	n.s	8.6**	n.s

Figure indicates percentage of items correct. Wald values derived from logistic regressions computed for individual patients. Wald values for relatedness and speed were derived from an analysis that also included cycle/repetition. Interaction terms were entered in addition to main effects one at a time. All effects that reached p<.1 are shown. * = p<.05; ** = p <.01. SA Patients are arranged in order of word-picture matching scores obtained in baseline testing and DYS group arranged in order of Behavioural Assessment of Dysexecutive Syndrome scores (BADS; Wilson et al., 1996) from mild to severe

Reaction times:

Response times for each patient are shown in Table 26. Only correct responses were considered and the outlying values above or below 2 standard deviations from the mean for each participant were removed separately in each condition (see Table 26). Since RT can only be examined for correct responses, we focussed only on patients that had an accuracy of at least 50% in every individual condition, and at least 85% correct overall. Word-picture matching accuracy was sufficient to allow RT to be analysed for six SA patients (KH, ME, NY, PG, SC, BB). There were too few correct trials to analyse for two SA patients (KA and LS). The DYS patients all achieved scores above 70% in every condition, leaving sufficient correct responses to examine the effects of relatedness, speed and repetition on reaction time.

RT in DYS

Figure 16a shows the means and standard errors for the DYS patients. A 2x2x4 ANOVA (slow/fast, related/unrelated, 4 cycles) revealed a main effect of relatedness ($F(1,6) = 59.99$, $p < .0001$): DYS patients responded more slowly on the semantically related versus the unrelated blocks. The effect of speed approached significance ($F(1,6) = 5.414$, $p = .059$) but there was no effect of repetition (see Table 23).

The interaction between the relatedness of items and the speed of presentation was significant ($F(1,6) = 25.108$, $p = .002$). There was a somewhat larger effect of relatedness for the fast condition, t(6) = -2.3, = .04, Bonferroni p = .08, compared to the slow condition, t(6) = .24, = .13. Also, a near-significant interaction was found between speed and cycle ($F(3,18) = 2.80$, $p = .07$). There was an effect of speed at each cycle but this was largest on cycle 3, t(6)= -2.2, = .05, Bonferroni p = .1.

RT in SA

Figure 16b shows that the patients as a group showed a main effect of relatedness, $F(1, 5) = 203.61$, $p < .0001$, and an interaction between relatedness and repetition, $F(3,15) = 4.92$, $p = .014$, but no effect of speed. This group showed little change with cycle for unrelated items and became slower for related items as they were repeated, suggesting a refractory effect. The difference between cycles 1-4 for related items compared to unrelated items approached significance, t(6) = 3.4, p = .02, Bonferroni p = .08.

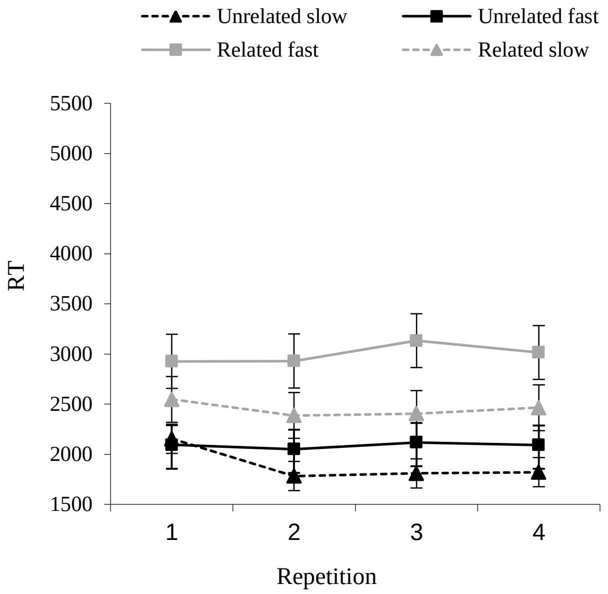
Table 22: Mean word-picture matching RT

	SA patients							**DYS patients**							
	NY	SC	PG	KH	ME	BB	Average	HM	JS	MC	TG	AP	Mrl	PG	Average
Related	3524	3910	4053	4483	4785	5121	4313	3391	2465	2208	2549	2372	3784	2204	2711
Unrelated	2700	2981	3180	3622	3684	3879	3341	2586	1981	1615	1732	1606	2662	1745	1990
Fast	3086	3424	3544	4005	4245	4482	3798	3122	2148	1876	2247	2362	3659	2119	2505
Slow	3096	3427	3604	4053	4124	4377	3780	2767	2275	1934	2019	1602	2698	1817	2159
Unrelated Time 1	2787	3168	3095	3873	3566	3846	3389	2598	2436	1800	2018	1548	2554	1915	2124
Unrelated Time 2	2668	2933	3149	3631	3635	3800	3303	2552	1862	1532	1584	1569	2613	1702	1916
Unrelated Time 3	2635	2936	3200	3559	3801	3951	3347	2738	1866	1535	1636	1743	2552	1673	1963
Unrelated Time 4	2717	2885	3277	3443	3730	3913	3328	2464	1755	1586	1693	1564	2944	1690	1956
Related Time 1	3442	3998	3460	4494	4476	4876	4124	3249	2737	2370	2579	2043	3816	2364	2737
Related Time 2	3385	3774	4275	4515	4495	5409	4309	3419	2286	2139	2357	2272	3874	2258	2658
Related Time 3	3577	3952	4226	4677	5297	5274	4501	3596	2508	2148	2653	2603	3868	2006	2769
Related Time 4	3678	3919	4215	4225	4850	4902	4298	3312	2332	2172	2624	2667	3867	2202	2739

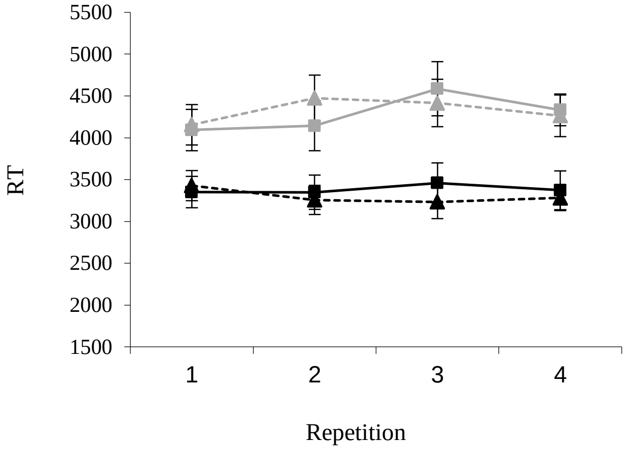
Table shows averages RT for each condition in milliseconds.

Figure 16a-b: Refractory effects in word-picture matching response times for DYS and SA

a) Dysexecutive patients



b) Semantic aphasia



Error bars show standard errors.

Group comparison: RT

Table 27 shows the results of an omnibus ANOVA comparing both groups. In RT, both SA and DYS patients showed an effect of relatedness and this was bigger in the SA group. Neither group showed a significant effect of cycle or speed, though there was a substantial speed by relatedness interaction for the DYS group, reflecting a larger effect of relatedness for the fast condition, and this interaction was larger in the DYS than in the SA group**.** There was also a 3-way interaction between speed and cycle, as the speed by cycle interaction was larger in the DYS group, and finally a 3-way interaction between group, relatedness and cycle, because this interaction was larger in the SA group.

Table 23: Reaction time effects in cyclical word-picture matching

Condition	**SA**	**DYS**	**Group interaction**
Speed	F(1,5) < 1	F(1,6) = 5.414 , *p* = .059	F(1,5) = 4.22, *p* = .095
Relatedness	F(1,5) = 203.61, *p* < .0001	F(1,6) = 59.99, *p* < .0001	F(1,5) = 148.7, *p* < .0001
Cycle	F(3,15) =1.11 , n.s.	F(3,18) =1.03, n.s.	F(3,15) = 1.76, n.s.
Speed x Relatedness	F(1,5) = 2.05, n.s.	F(1,6) = 25.108, *p* = .002	F(1,5) = 12.12, *p* = .017
Relatedness x Cycle	F(3,15) = 4.92 , *p* =.014	F(3,18) = 2.38, *p* =.103	F(3,15) = 5.54, *p* = .009
Speed x Cycle	F(3,15) = 2.52 , *p* = .097	F(3,18) = 2.80, *p* = .070	F(3,15) = 17.3, *p* < .0001
Speed x Cycle x Relatedness	F(3,15) = 1.16 , n.s.	F(3,18) < 1	F(3,15) = 2.35, *p* = .113

Table shows repeated measures ANOVA results.

Individual reaction time analysis:

Response times for individual cases in both groups were analysed using ANOVA, treating items as cases. Reaction times were slower for related items compared to unrelated items for every patient in both groups (see Table 28). DYS patients were more influenced by the speed of presentation: of the 7 patients, 5 responded faster in slow trials compared to fast ones. In addition, 4 DYS cases showed significant or near-significant effects of repetition including AP, who did not show refractory effects in word-picture matching accuracy, yet did show this pattern in reaction time (See Figure 17a).

None of the SA patients showed any effect of speed of presentation. Three SA cases became significantly slower in their response with the repetition of cycles, while the other three maintained the same speed of response (See Figure 17b).

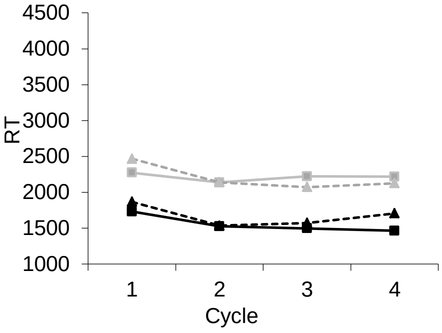
Table 24: Repeated measures ANOVAs for reaction time data for individual cases

Patient	Group	Relatedness	Speed	Repetition
MC	DYS	F(1, 554) = 90.17, p <.000*	F(1, 554) < 1	F(3,554) = 3.181, p= .024*
TG	DYS	F(1, 557) = 85.02, p < .000*	F(1, 557)=5.77, P = .017*	F(3,557) = 2.13, p = .095
JS	DYS	F(1, 544) = 28.43, p < .000*	F(1, 544) = 1.86, n.s.	F(3,544) = 8.14, p < .000*
HM	DYS	F(1, 505) = 46.05, p < .000*	F(1, 505) = 8.467, p = .004*	F(3,505) = 1.04, n.s.
AP	DYS	F(1, 560) = 67.10, p < .000*	F(1, 560) =66.03, p<001*	F(3,560) = 2.53, p= .056*
MrL	DYS	F(1, 504) = 48.05, p < .000*	F(1, 504) =34.87, p <001 *	F(3,504) < 1
PG	DYS	F(1, 549) = 35.10, p <. 000*	F(1, 549) =14.64, p <001*	F(3,549) = 2.40, p= .067*
KH	SA	F(1, 491) = 80.05, p < .000*	F(1, 491) < 1	F(3,491) = 2.54, p= .055*
ME	SA	F(1, 494) = 139.9, p < .000*	F(1, 494) =1.32, n.s.	F(3,494) = 4.95, p = .002*
NY	SA	F(1, 476) = 144.04, p < .000*	F(1, 476) < 1	F(3,476) = 1.03, n.s.
PG	SA	F(1, 489) = 104.13, p < .000*	F(1, 489) < 1	F(3,489) =5.06, p = .002*
SC	SA	F(1, 524) = 129.5, p < .000*	F(1, 525) < 1	F(3, 522) = 1.05, n.s.
BB	SA	F(1, 485) = 178.76, p < .000*	F(1, 485) <1	F(3,485) = 1.17, n.s.

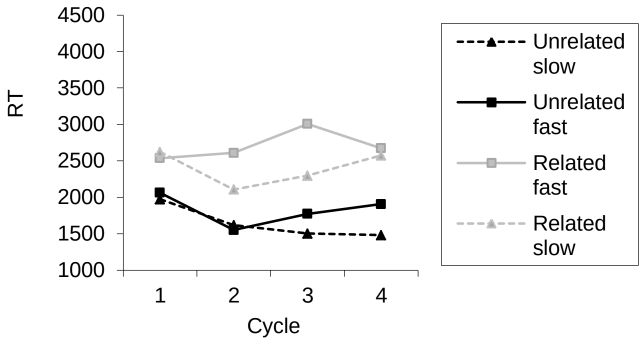
Table shows repeated measures ANOVA results, treating items as cases for individual patients, * = significant effect. SA patients are arranged in order of word-picture matching scores obtained in baseline testing and DYS group arranged in order of Behavioural Assessment of Dysexecutive Syndrome scores (BADS; Wilson et al., 1996) from mild to severe.

Figure 17a: <u>Reaction times for DYS patients</u>

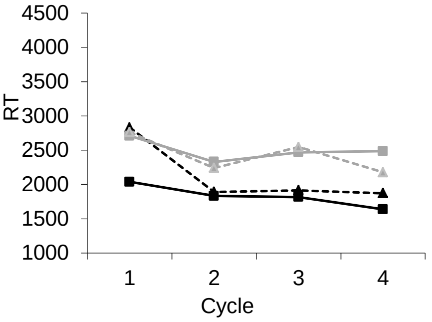
a) MC



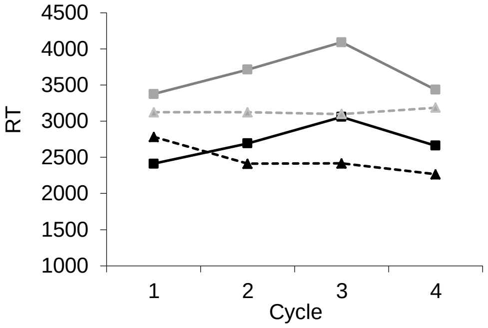
b) TG



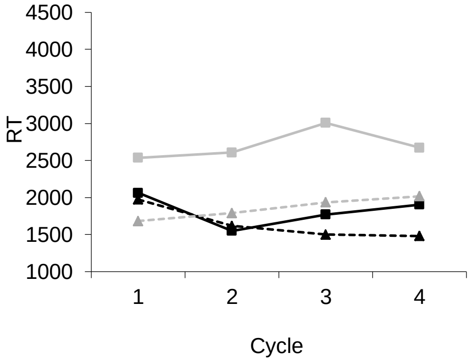
c) JS



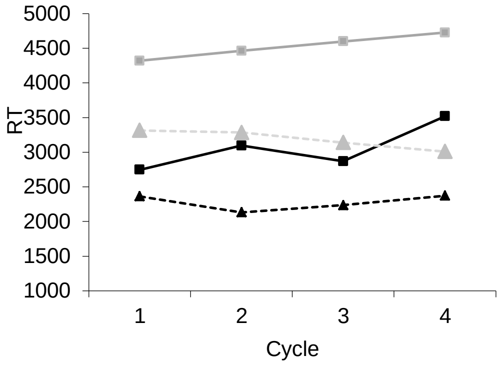
d) HM



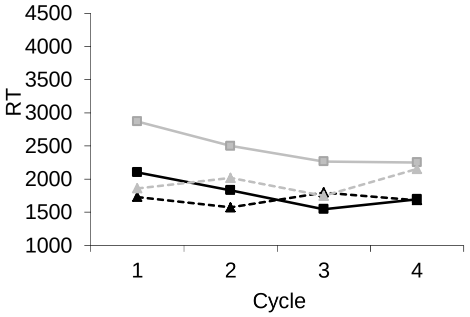
e) AP



f) MrI

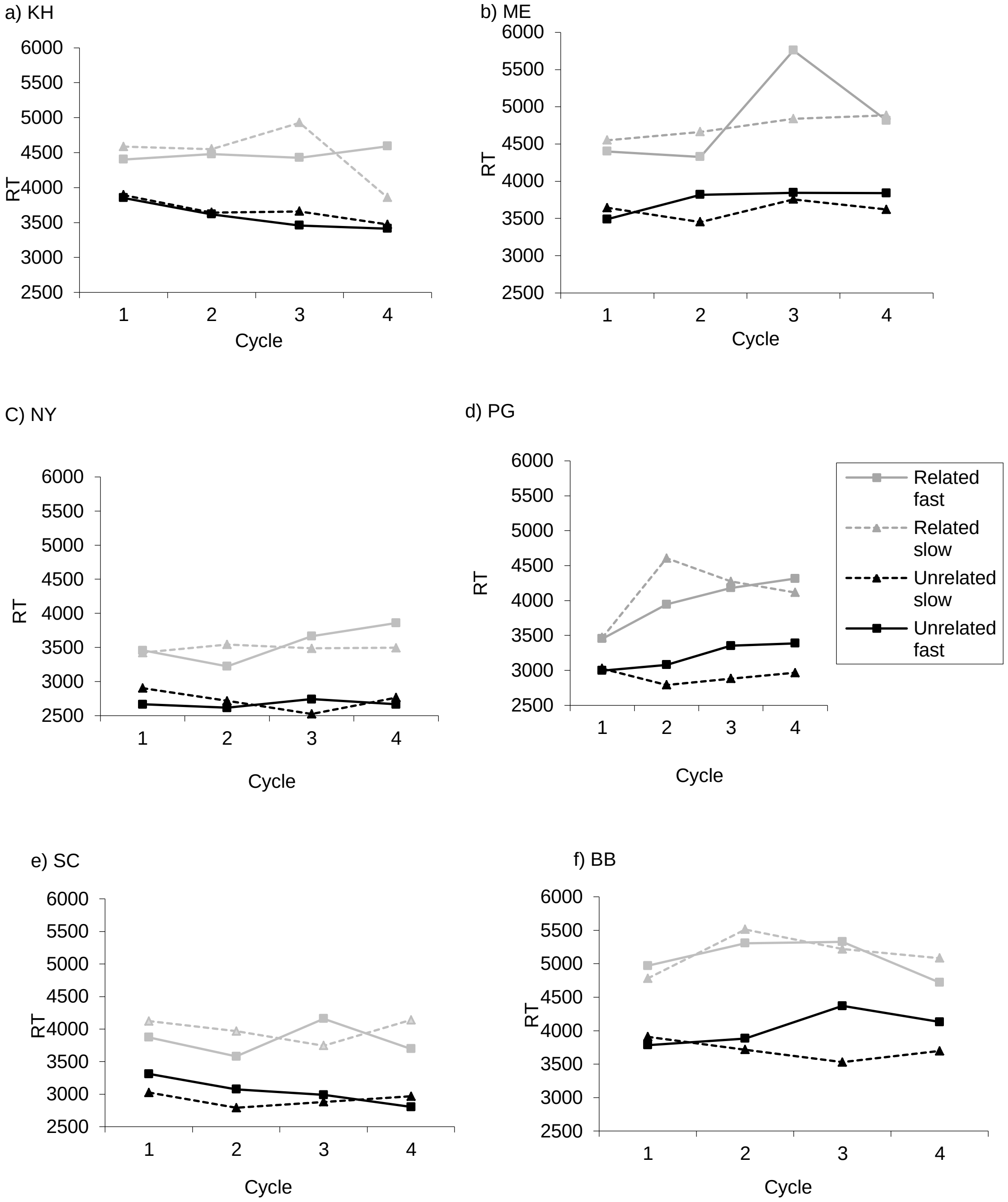


g) PG



DYS group arranged in order of Behavioural Assessment of Dysexecutive Syndrome scores (BADS; Wilson et al., 1996) from mild to severe.

Figure 17b: Reaction times for SA patients



Summary of refractory effects in word-picture matching accuracy and RT:

On a cyclical word-picture matching task, both SA and DYS cases showed effects associated with "semantic access disorder", including relatedness, cycle and speed of presentation, and interactions between these variables, consistent with the hypothesis that as semantically-related sets of items are presented repeatedly at a fast rate, there is increasing competition between the target and the distractors (which were targets on previous trials). Patients with executive deficits, and poor semantic control, have difficulty resolving this competition. However, Chapter 3 shows these groups have differing degrees of semantic and executive impairments and perhaps as a consequence, they showed somewhat divergent patterns on this paradigm. While the two groups showed broadly equivalent effects of cycle overall, the DYS group showed greater effects of speed of presentation, and a larger interaction between speed and relatedness. In other words, these cases had particular difficulty on the related fast condition. In contrast, the SA group showed larger effects of relatedness, and a stronger interaction between relatedness and cycle. Therefore, more severe semantic impairment might be associated with strong effects of relatedness (in SA), while dysexecutive syndrome plus mild semantic deficit is associated with a refractory period following semantic retrieval, generating strong effects of speed which interact with semantic relatedness. It is important to note that the post-hoc t-tests used to explore the interactions between relatedness, cycle, and speed were often non-significant, especially with Bonferroni correction; however, the significant interactions between group and 'refractory' variables confirm that SA and DYS patients do show some differing effects.

Other hallmarks of "access" semantic impairment: In the following sections, we consider whether DYS cases show the other effects associated with "access" semantic impairment, according to Warrington et al (1979), in addition to effects of cycle, speed and semantic blocking/relatedness. Some of these effects were discussed in the previous chapter, but the two sets of patients utilised in Chapters 3 and 4 are only partially overlapping – therefore, these analyses are reproduced here for the appropriate patient group.

Consistency across repetitions

Rationale:

"Access" cases classically show inconsistency in their performance, suggesting that rather than a loss of knowledge per se, they may have difficulty retrieving this knowledge in certain trials (Warrington & McCarthy, 1987). SA cases are also inconsistent across different semantic tasks probing the same items when control demands change (e.g., between semantic association and word-picture matching tests), but can be consistent when there is no change in the task requirements, for example, for the same semantic associations tested for words and pictures (Jefferies et al., 2006). They are less consistent than classic "storage" patients with SD (Jefferies et al., 2007), suggesting that SA cases show this characteristics of semantic access deficits to some degree. In this section, we consider whether DYS patients also show inconsistent performance on word-picture matching.

Method:

The contingency coefficients between adjacent presentations of items in the same speed/relatedness conditions for each patient were calculated, obtaining three scores: first-second, second-third, and third-fourth presentations (see Table 29). This establishes the extent to which success or failure on each item in each cycle predicts performance on other cycles.

Results:

In the DYS group, all three contingency coefficients were significant for 2 cases (HM and MC) and 2/3 were significant for MrL, PAG and TG, while JS and AP showed inconsistency across all repetitions of items.

In the SA group, all three contingency coefficients were significant for 4 cases (KH, KA, LS and BB). Two out of three were significant for ME and PG. One out of three was significant for NY and SC.

Table 25: Consistency across item repetitions

Patients	**Group**	**R1*R2**	**R2*R3**	**R3*R4**
MC	DYS	C=.22, P < .001*	C=.14, P =.08*	C=.24, P < .001*
TG	DYS	C=.02, P =.76	C=.17, P =.03*	C=.14, P =.07
JS	DYS	C=.06, P =.45	C=.07, P =.36	C=.08, P =.30
HM	DYS	C=.40, P <.001*	C=.40, P < .001*	C=.37, P < .001*
AP	DYS	-	C=.01, P =.83	C=.05, P =.54
MrL	DYS	C=.18, P =.02*	C=. 00, P =.98	C=.16, P =.05*
PAG	DYS	C=.39, P < .001*	C=.04, P =.63	C=.05, P =.49
KH	SA	C=.31, P =.00*	C=.44, P < .001*	C=.47, P < .001*
KA	SA	C=.29, P =.00*	C=.31, P < .001*	C=.45, P < .001*
LS	SA	C=.27, P < .002*	C=.40, P <.002*	C=.42, P < .002*
BB	SA	C=.19, P < .01*	C=.24, P. < .002*	C=.32, P < .002*
ME	SA	C=.15, P < .01*	C= .23, P< .01*	C=.30, P = .41
PG	SA	C=.04, P < .001*	C=.15, P< .001*	C=.34, P =.62
NY	SA	C=.02, P =.43	C=.17, P =.62	C=.27, P < .002*
SC	SA	C=.08, P =.62	C=.07, P =.83	C=.25, P < .001*

Table shows repeated measures ANOVA results, *significant effect, - AP at ceiling on cycle 1
R1, R2, R3, R4: performance on cycles 1, 2, 3 and 4.

Frequency effect in synonym judgment:

Rationale:

Sematic "access" cases and SA patients fail to show the standard positive effects of frequency in comprehension tasks, unlike storage cases with SD (Warrington, 1975). SA cases show absent or even *reverse* frequency effects (Almaghyuli et al., 2012), that is, better understanding of less common words (see Chapter 2 for a fuller discussion). Decisions about the meanings of high frequency (HF) words might require greater executive control than semantic decisions for low frequency (LF) words. HF words occur in more contexts and have wider and more variable meanings than their LF counterparts which are associated with a limited range of linguistic contexts and so similar semantic information is encountered each time (Hoffman et al., 2011). Greater executive control might be required for HF words in order to selectively focus processing on aspects of meaning that are relevant for a given task or context. If executive dysfunction underpins both refractory effects on cyclical comprehension tasks and absent/reverse frequency effects, DYS cases who show refractory effects should also fail to show the normal processing advantages for HF items in synonym judgement.

Method:

The effect of word frequency in comprehension was explored using a synonym judgment test (see Chapter 2). Participants were asked to select the word closest in meaning to a probe word. There were three choices per trial (the target plus two unrelated distracters). Simultaneous auditory and visual presentation was used and patients indicated their choice by pointing. There were 96 trials split evenly between two frequency bands (mean frequency of probe words (with standard deviations in parentheses) = 128 (102) and 4.6 (4.5) counts per million in the Celex database) (Baayen et al., 1993) and three imageability bands (mean imageability of probe words = 275 (17.3), 452 (26.0) and 622 (14.0) respectively, on a scale of 100-700). There were sixteen trials in each of the six frequencies by imageability conditions. Both the targets and distracters were matched to the probe word for frequency and imageability. As a consequence, the trial as a whole (rather than just the probe word) varied frequency and imageability. Full details are provided in Chapter 3.

Results:

The results from this task are also reported in Chapter 3 but the relevant analyses of frequency are reproduced here to allow assessment of the full range of refractory phenomena in the same patients.

A 2 (group) x 2 (frequency) ANOVA revealed no main effect of frequency (*F*(1,6) < 1, but a main effect of patient group (*F*(1,6) = 8.2, *p* = .03), with milder impairment in the DYS group. There was no interaction between patient group and frequency (*F*(1,6) < 1), suggesting both groups showed the same pattern.

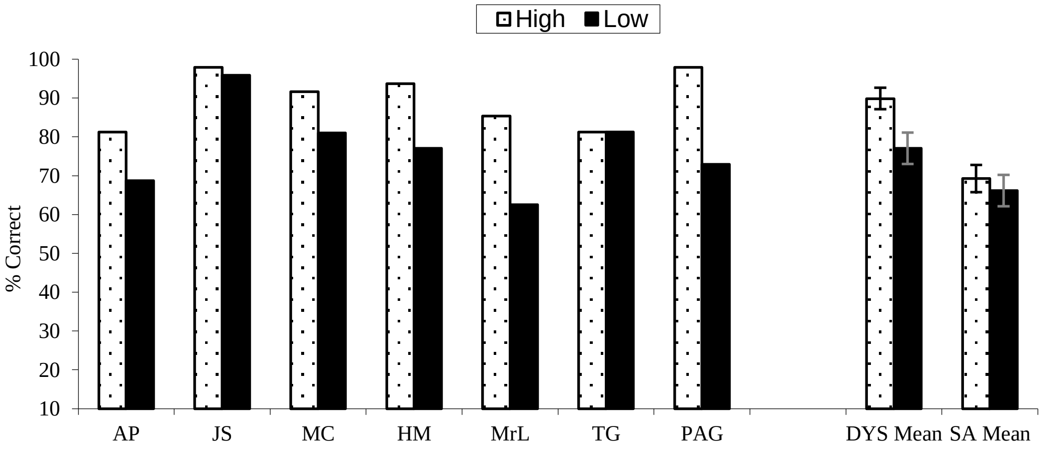
At the individual level, none of the SA patients showed significance for high over low frequency words, while 3 DYS patients (HM, MrL, PAG) showed substantial effects of word frequency on comprehension (Fisher's exact test: 2–tailed *p* < .05). Four cases (MC, TG, JS and AP) were not affected by this variable (see Figure 18).

Summary:

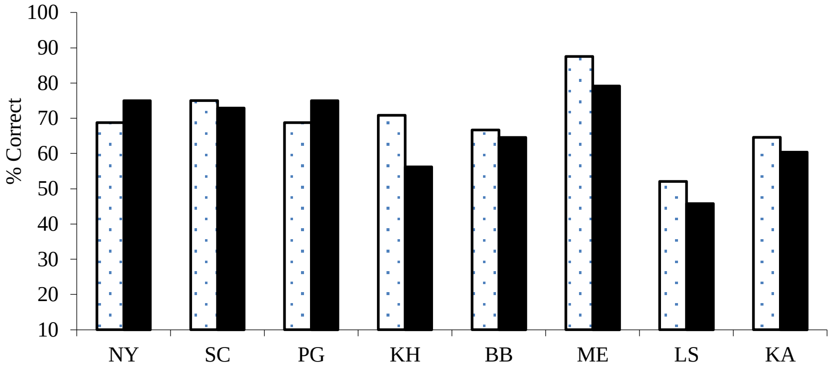
Lexical frequency positively influenced the performance of three DYS patients, HM, MrL and PAG, but in SA this beneficial effect of lexical frequency may have been cancelled out by the executive control requirements of high frequency items.

Figure 18: Effect of word frequency in synonym judgment

a) Dysexecutive patients



b) Semantic aphasia



Error bars showed error of mean

Table 26: Fisher's exact test for frequency effects in DYS and SA

Patients	**Group**	**Frequency**
MC	DYS	P = 1.00
TG	DYS	P = 1.00
JS	DYS	P = 1.00
HM	DYS	P = .04*
AP	DYS	P = .23
MrL	DYS	P = .01*
PAG	DYS	P = .001*
KH	SA	P = .83
ME	SA	P = .41
NY	SA	P = .65
PG	SA	P = .65
SC	SA	P = 1.00
BB	SA	P = 1.00
LS	SA	P = .68

Table shows significance of Fisher's exact test: 2–tailed.

Effect of phonemic cues on picture naming:

Rationale: SA patients and access cases have previously shown benefit from cueing. This suggests their semantic knowledge is intact, but they have difficulty generating internal constraints on knowledge retrieval and therefore benefit greatly from the provision of external cues for recall (Jefferies et al., 2009). We examine the same effect in the DYS group. We predict that this group will benefit from cueing because they have primary impairment of control processes that direct semantic activation. However, phonemic *miscues* on picture naming might lead to more errors in their performance, because these are designed to strengthen the activation of a close semantic competitor.

Method: Data reported in Chapter 3 is summarised for the DYS/SA cases who both took part in the cyclical word-picture matching experiment. Details are provided in Chapter 3.

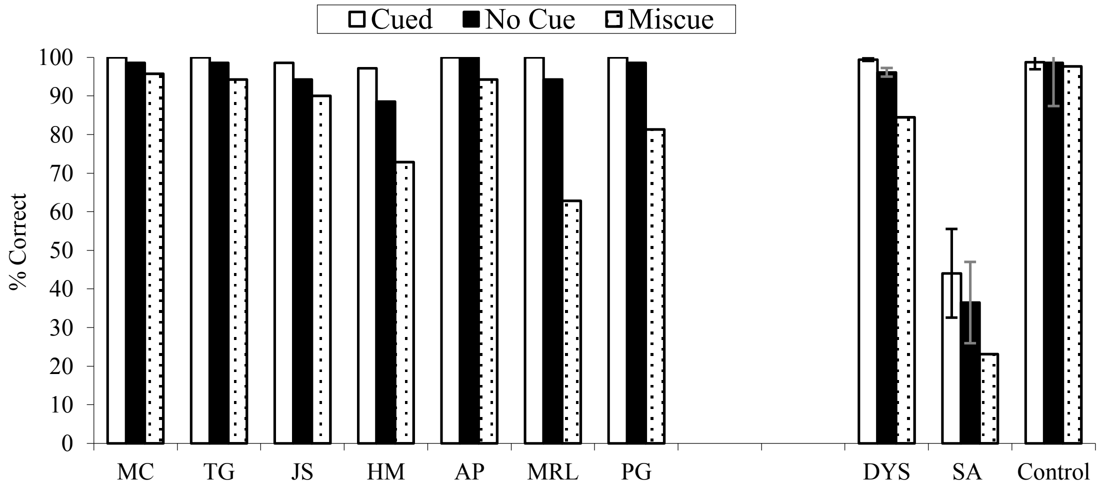
Only six of the SA patients were tested. KA, who had very poor spoken output, was not tested on this task.

Results:

Figure 19 shows picture naming accuracy for the two groups (SA, DYS) in two conditions: cued and without cues. A 2x2 repeated measures ANOVA revealed a main effect of cueing (F(1, 5) = 7.28, p = .04) and group (F(1, 5) = 19.4, p = .007). DYS patients had better naming overall. The interaction between group and cueing was not significant (F(1, 5) < 1.

At an individual level, cues enhanced naming accuracy comparing to no cues for 4/6 SA cases: NY, PG, ME and LS (McNemar one-tailed exact p =.04 to <.0001) and the cueing effect approached significance for BB (p = .09). The final SA case, SC, did not show a significant cueing effect (p = .18), although he showed an effect with longer phonemic cues in a previous study (Jefferies et al., 2008). DYS patients individually showed no cueing effects on their naming accuracy because their performance was close to ceiling in both conditions. Only one case, MrL, showed effects that were significant (McNemar one-tailed exact p = .05). In the miscued condition, 3/7 DYS patients (PAG, MrL and HM) and 5/6 of the SA group (SC, NY, KA, PG and MA) were significantly poorer in their accuracy compared to the no cue condition (McNemar one-tailed exact *p* = .06 to < .0001). DYS group did show miscuing effects which were equivalent in size to the SA group (see Chapter 3).

Figure 19: Effects of phonemic cueing on picture naming in DYS



Dysexecutive patients are ordered according to overall performance on Behavioural Assessment of Dysexecutive Syndrome (BADS) from mild to severe impairment. SA patients' data from Noonan et al. 2010). Error bars show standard error of the mean.

Table 27: Summary of the results

Patients	Group	Speed	Relatedness	Repetition	Consistency	Cueing	Frequency
MC	DYS	√	√	√	√	x	x
TG	DYS	√	√	x	x	x	x
JS	DYS	√	√	√	x	x	x
HM	DYS	x	√	x	√	x	√
AP	DYS	x	√	√	x	x	x
MrL	DYS	√	√	x	√	√	√
PAG	DYS	√	√	√	X	X	√
Total		5/7	7/7	4/7	3/7	1/7	3/7
KH	SA	√	√	√	√	√	x
ME	SA	x	√	√	√	√	x
NY	SA	√	√	x	√	√	x
PG	SA	√	√	√	√	√	x
SC	SA	x	√	x	√	√	x
BB	SA	x	√	x	√	√	x
LS	SA	√	√	X	√	√	X
Total		4/7	7/7	3/7	7/7	7/7	0/7

Dysexecutive patients are ordered according to overall performance on Behavioural Assessment of Dysexecutive Syndrome (BADS) from mild to severe impairment. SA data was reported previously by Jefferies et al. (2007). √ = significant effect, x = no effect.

General discussion

This study explores for the first time the full range of effects associated with "semantic access disorder" – namely, refractory variables (item repetition in cycles, speed of presentation and semantic relatedness), the absence of frequency effects, facilitation by cueing, and consistency in a group of patients with dysexecutive syndrome (DYS). This provides a means of testing the hypothesis that refractory effects follow executive impairment which prevents the efficient resolution of competition between the target and distractors on each trial. Jefferies et al. (2007) examined the existence of these symptoms in a group of eight patients with semantic aphasia (SA) and a single patient with semantic dementia (SD). They found that most of these symptoms were common in patients with SA, even though these cases were not specifically selected to show access impairment. In contrast, the case with SD did not show such effects.

This same dissociation between SD and stroke/acquired brain injury was reported by (Warrington et al., 1979; Warrington & Cipolotti, 1996).

Table 31 summarizes our findings as following:

1. *Refractory effects in word-picture matching*: DYS patients were similar to the SA group in their performance in the cyclical word-picture matching task, taking into consideration that those patients were not selected based on any refractory/access phenomena, but were included in the study if they showed executive dysfunction (see Chapter 3). Both groups showed effects of speed, cycle and relatedness. However, these variables did not have an identical influence on the two groups. In contrast to SA patients, those with dysexecutive syndrome as a group were more sensitive to the speed of presentation. They made more errors and become slower when items were repeated at a fast rate, particularly when they were semantically related. This is likely to reflect the fact that when these items are presented repeatedly at a fast rate, activation spreads between the items and does not return to baseline between trials. Accordingly, the whole set of items will remain active due to the build-up of competition with the target. At an individual level, HM and AP from the DYS group showed a weak refractory effect in accuracy for word-picture matching tasks, but they were not affected by the speed of presentation as were all the other DYS cases. However, refractory effects were shown again in reaction time for the same task. AP and HM did not show refractory effects in accuracy due to the ceiling effect.

2. *Frequency effects*: The DYS patients mirrored those with SA in that many cases showed little effect of frequency manipulated in the synonym judgement task, but it was not totally absent in all patients, as in the SA group. HM, MrL and PAG showed substantial effects of word frequency on comprehension. However, the standard positive effect of frequency may have been masked by the fact that frequently encountered items typically occur in a wider range of contexts than low frequency items. This may increase the executive requirements of semantic tasks, as it is necessary to direct activation towards the relevant aspects of meaning for frequently occurring concepts (Hoffman et al., 2011 and see Chapter 2). In support of this hypothesis, positive frequency effects emerged in our patients when estimates of contextual diversity were included in the analysis of their synonym judgement performance (see Chapter 3).

3. *Item consistency*: DYS patients were more inconsistent than SA patients, who all showed considerable levels of consistency when the same items were represented in an identical task context. However, both groups showed inconsistency across different semantic tasks which required different levels of control (see Chapter 3). HM and MC showed consistency throughout the repetition.

4. *Phonemic cueing*: DYS patients as a group did not show an effect of cueing, which could be related to their intact naming ability compared to SA patients who have speech production impairment (which varied between cases). However, two individual cases (HM and MrL) showed improvement with cueing, because they had poor expressive ability compared to the other DYS patients.

Overall summary: DYS patients show refractory effects, supporting the idea that these effects can arise from impaired executive control, and more generally supporting the view that semantic impairment could be related to executive control (Jefferies et al., 2006).

The current study was motivated by the theory which breaks down semantic cognition into conceptual representations and semantic control processes that interact together to direct activation toward task-relevant aspects of meaning. In this view, the nature of semantic impairment in SD patients is attributed to degraded semantic representations, while in SA patients it is associated with executive function impairment (Jefferies & Lambon Ralph, 2006). A similar distinction has been drawn between "storage" and "access" semantic impairments (Warrington & McCarthy, 1983; Warrington & Cipolotti, 1996; Gotts & Plaut, 2002). Storage disorders show strong frequency effects, highly consistent performance, no impact of cueing and no refractory effects, whereas access deficits produce an absence of frequency effects, inconsistent responses, strong effects of cueing and strong refractory effects. Our findings partly support this distinction and uniquely suggest that refractory effects can result from executive deficits, even in the absence of aphasia and severe semantic impairment. Some characteristics of access impairment were shown in the DYS patients. Firstly, strong refractory effects and speed of presentation were crucial evidence that executive control deficits co-occur with refractory effects. In the word-picture matching task, they made more errors and became slower when items were repeated at a fast rate, especially when they were semantically related, because activation spreads between related items and does not fully decline between trials. Accordingly, the whole set of items will remain active and produce build-up of competition with the target. Their ability to regulate and control this activation will be diminished by executive impairment. Our findings support predications in Jeffries et al. (2007) that deficits in semantic control should produce a strong refractory effect.

Refractory effects were relatively weak in one case (HM). This patient was not affected by speed and repetition and showed strong consistency in his performance. At the same time, this patient benefited from cueing and was influenced by lexical frequency. This mixed pattern of "access" and "storage" deficits was noted by Rapp and Caramazza (1993) who suggested that patients do not always show a clear dissociation between access/storage impairments, undermining the empirical validity of this distinction. It is hard to distinguish between the two deficits in all patients. In the case of HM, he may have shown a generally mixed profile with damage to semantic representations as well as to control mechanisms, as he was diagnosed with vascular dementia a year after the current study was completed.

However, while access patients were expected be essentially inconsistent, our DYS patients were to some extent inconsistent on the test-retest task compared to the SA patients who all showed a considerable level of consistency. Both groups showed inconsistency across different semantic tasks which required different levels of control, but unlike SA cases, the DYS group did not show consistency across different versions of the same semantic test, for example between the picture and word versions of Camel and Cactus (CCT) (see Chapter 3). HM and MC showed consistency throughout the repetitions of word-picture matching task presented in this chapter, while JS and AP were inconsistent across item repetitions, which again raises the point that “access” and “storage” can be a mixture and not exclusive syndromes as Rapp & Caramazz (1993) argue.

In conclusion, we have revealed that many of the symptoms of semantic access/refractory impairment were exhibited in our sample of patients with primary executive control problems, which is strong evidence that refractory variables are associated with difficulties in controlling activation within the semantic system. Furthermore, patients with executive control deficits can show a mixture of “storage” and “access” disorders.

CHAPTER 5

Enhancing semantic control in healthy participants by stimulating the left inferior frontal gyrus with anodal tDCS

Note: We are thankful to Simone Kohler, an Erasmus exchange student who collaborated on Experiment 1, and four undergraduate project students (Rachel Kirmond, Alison Jane Smith, Jess Hare and Sam Godwyn) who assisted with Experiment 2. These students were supervised by A. Almaghyuli and E. Jefferies and helped to develop the behavioural tasks. They also assisted with the collection of data and performed prelimnary analyses.

Introduction:

This thesis so far has explored the way in which semantic cognition requires interaction between semantic representation and executive control; intact semantic cognition needs good functioning in both of these components to allow us to comprehend a vast array of multisensory stimuli and to express our knowledge through both verbal and non-verbal domains (Jefferies & Lambon Ralph, 2006). Neuropsychology, functional neuroimaging and transcranial magnetic stimulation studies have highlighted the importance of the LIFG in semantic control. In this chapter, we determine whether modulation of cortical activity using noninvasive transcranial direct current stimulation (tDCS) over LIFG in healthy participants affects performance in semantic tasks that vary in control demands. This type of research, whilst still in its infancy, has the potential to provide more effective therapy for people with chronic brain injury who have semantic impairment related to semantic control difficulties, such as those with semantic aphasia (Chapters 2 and 3) and dysexecutive syndrome (Chapters 3 and 4).

Semantic cognition allows us to retrieve task-appropriate information by activating the relevant parts of the semantic network. This process can be automatic or require executive semantic control. Activation in the semantic network spreads automatically to closely related ideas, allowing them to be easily retrieved (Neely & Khan, 2001: Posner & Synder, 1975). However this automatic retrieval does not always meet the required demands, it can be activated too little, or give too much information. Too little information is retrieved automatically when the most relevant information is weakly related to the cue. Retrieving this knowledge requires a targeted expansion of activation, which is a type of semantic control known as controlled retrieval. In other situations the activated semantic network may contain irrelevant information, at that time, another type of semantic control known as semantic selection is required to select the relevant information and inhibit the activated alternatives (Thompson-Schill et al., 1997; Badre et al., 2005; Wagner et al., 2001). Damage to any part of the semantic system can lead to impairment in the ability to access and/or retrieve information, as seen in semantic aphasia (SA). These patients have multimodal comprehension problems following infarcts in the left inferior frontal gyrus (LIFG) or temporoparietal regions, causing deregulated semantic cognition (Corbett et al., 2009; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2008).

Neuroimaging studies of healthy individuals and patients draw attention to the involvement of the LIFG in semantic control. For instance, activation in the LIFG of healthy participants increases when non-dominant or subordinate meanings of ambiguous words are retrieved (Gennari et al. 2007; Zempleni et al. 2007; Bedny et al. 2008). Although most fMRI studies have reported activation in the LIFG as a whole, Badre et al (2005) propose possible subdivisions within this area: they suggest anterior regions (BA 47) are involved in 'controlled semantic retrieval' while more posterior regions (BA 44/45) allow selection between competing representations. Further support comes from a recent transcranial magnetic stimulation (TMS) study by Whitney et al (2011), which found that temporary infarcts to the LIFG impaired performance in a task requiring executively demanding semantic judgments, without affecting a non-semantic task requiring similar executive control; a noteworthy result, since the contribution of LIFG in executive control generally (i.e. including the non-semantic field) has been speculated by several authors, not least because of its location within prefrontal cortex (e.g. Jacobson et al, 2011).

While TMS studies provide an insight into the nature of cognitive deficits through the production of temporary focal lesions, a recently developed brain stimulation technique called of transcranial direct current stimulation (tDCS) provides a means by which cortical activation in focal areas can be enhanced (Nitsche et al, 2008; Stagg & Nitsche, 2011) by utilizing weak electrical currents (1 or 2 milliampere) applied directly to the brain via scalp electrodes. This modulates brain activity by altering the membrane potential of neurons and by influencing the levels of glutamate and gamma-aminobutyric acid (GABA) neurotransmitters (Liebetanz et al., 2002; Stagg et al., 2009). The effects of tDCS on a population of neurons are determined by the polarity of stimulation. Anodal stimulation increases neural excitability and firing rates through depolarisation of resting membrane potentials and reducing the levels of GABA. Conversely, cathodal stimulation causes hyperpolarisation, reduces levels of glutamate and decreases brain excitability.

There is a substantial literature supporting the use of tDCS to enhance motor functioning. In healthy participants, anodal tDCS over the motor cortex can improve performance for the hand contralateral to the stimulated hemisphere (Boggio et al., 2006 ; Vines et al., 2006). Moreover, in stroke-affected patients, applying anodal tDCS to the stroke-affected motor cortex has been shown to improve motor functioning. In such studies, the tDCS may have stimulated preserved areas of the motor cortex to enhance synaptic efficiency along the corticospinal tract (Hummel et al., 2006; Schlaug et al., 2008). It may also be possible to improve motor ability by applying cathodal tDCS to the motor cortex *ipsilateral* to the performing hand; in stroke patients, this may help to overcome maladaptive inhibitory projections from the undamaged hemisphere onto the damaged motor cortex (Hummel et al., 2006; Schlaug et al., 2008; Hesse et al., 2007; Nair et al., 2008).

Because tDCS is a flourishing technology, studies on language processes are relatively few compared to motor functions. For example, Fregni et al. (2004) found that anodal tDCS improved performance in a sequential-letter working memory task in healthy volunteers when administered to the dorsolateral prefrontal cortex (DLPFC). This effect was not observed following cathodal or sham stimulation of the same site, nor stimulation of a control site (primary motor cortex). Fertonani et al. (2010) applied anodal, cathodal and sham tDCS to the left dorsolateral prefrontal cortex in healthy volunteers during a picture naming task and found that anodal stimulation allowed participants to respond more quickly, while cathodal stimulation had no effect. In addition, Floel et al. (2008) found that vocabulary learning was enhanced by anodal stimulation of Wernicke's area in healthy volunteers (while there were no effects of cathodal or sham stimulation). Monti et al. (2008) evaluated the effect of tDCS over left frontotemporal areas in post stroke patients. The protocol consisted of the assessment of picture naming (accuracy and response time) before and immediately after anodal or cathodal tDCS (2 mA, 10 minutes) and sham stimulation. Whereas anodal tDCS and sham tDCS failed to induce any changes, cathodal tDCS significantly improved the accuracy of the picture naming task by a mean of 33.6%. Finally, research found that Anodal stimulation slightly decreased the response times at the same time as increasing the correct responses in a picture naming task (Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). In contrast, Sela et al (2012) found participants markedly slow in reaction times after tDCS, accompanied by an improved performance on semantic decision tasks that involved idiom comprehension.

A few relevant studies have stimulated LIFG, as in the present chapter. Iyer et al. (2005) found the number of words produced to target letters in verbal fluency tasks in healthy participants increased when the left prefrontal cortex was stimulated by anodal tDCS (Iyer et al., 2005). Similar findings were reported by Gordon et al. (2010) exploring automatic and controlled verbal generation. They found more semantically clustered words during anodal stimulation in letter-cued fluency tasks. Some studies have examined the effects of tDCS on classification learning, employing a weather prediction task (Kincses, Antal, Nitsche, Bártfai, & Paulus, 2004) and a prototype distortion task (Ambrus et al., 2011). Mixed results were found: Kincses et al. (2004) described a minor benefit of anodal stimulation over left prefrontal cortex on implicit learning. Ambrus et al. (2011) reported that when participants were presented with a prototype of a category pattern not seen during training, they tended to reject it following both anodal and cathodal stimulation. Lastly, Cerruti and Schlaug (2009) report positive effects of anodal tDCS over the left dorsolateral prefrontal cortex on the remote associates task (RAT) which loads executive functioning. Subjects are required to find non-obvious associations to solve insight-style problems by ignoring misleading clues (Bowden & Jung-Beeman, 2003). Therefore, a considerable number of studies have reported the effect of tDCS on higher cognitive functions (Holland et al., 2011, Meinzer et al., 2012).

Although there is a growing literature on the effects of anodal stimulation over LIFG on language, memory and executive measures, few if any directly explore the effect of tDCS on semantic control. However, two recent studies greatly motivated our predictions about the current study. Meinzer et al (2012) report that anodal tDCS enhances semantic cognition over LIFG. The task they used to explore semantic cognition involved recalling words from specific categories: however, they did not explore different experimental conditions varying in their reliance on automatic and controlled recall. Another recent study by Sela et al. (2012) explores the effect of anodal/cathodal tDCS through alternating stimulation over the prefrontal cortex (LH/RH) during a semantic decision task involving idiom comprehension. They found improvement in performance when the left prefrontal cortex was stimulated.

In conclusion, six studies have employed anodal tDCS to examine the involvement of PFC in tasks that require regulation of thought. For example, increasing PFC activity with anodal tDCS lead to improvements in inhibitory control (Hsu et al., 2011), working memory (Boggio et al., 2006), and increased efficiency in task shifting (Leite et al., 2011; see also Dockery et al., 2009;; Gordon et al., 2010 and Iyer et al., 2005), whereas opposing effects of cathodal versus anodal stimulation over left inferior PFC have recently been reported on a feature categorization task (Lupyan et al. 2012) or mix effect of anodal and cathodal effect (Kincses et al., 2004 and Ambrus et al.,2011) .

In this study, we explore the effect of anodal and sham stimulation over LIFG on semantic control, employing two tasks strongly demanding in semantic control (semantic feature and low association tasks). Both tasks have previously been shown to produce activation in LIFG (Thompson-Schill et al., 1997; Badre et al., 2005; Wagner et al., 2001). Moreover, these tasks have been used to differentiate different aspects of semantic control, with one task making strong demands on semantic selection (semantic feature task) and the other on controlled retrieval (semantic relatedness judgements for weakly associated words).
This chaper reports two experiments:

1. Experiment 1 compared the effect of anodal and sham tDCS on behavioural gains following training on a task with high executive-semantic demands. A between-subjects design was used (i.e., random allocation of participants to anodal and sham conditions), since participants can only be trained once on a given task. In the baseline and post-tDCS testing, several semantic tasks varying in their semantic control requirements and one non-semantic executive task were administered. The tDCS effects were evaluated for both the trained task (semantic feature selection: i.e., matching a tomato with a London bus since these are both red) and untrained tasks that (i) had parallel executive requirements but involved visual decisions; (ii) tapped semantic control in a different way.(identifying word pairs with weak but global semantic associations); and (iii) involved making judgements about strongly-associated words (requiring little semantic control).

2. Experiment 2 employed the same tasks but in a within-subjects design to increase statistical power. We used individual session baselines, unique stimuli sets per session and counterbalancing to overcome some effects of repeated testing. Since we opted for a

comparison of different stimulation conditions (anodal vs. sham) in the same participants, this study did not employ task training.

In summary, the two experiments reported here investigated whether modulation of cortical activity using noninvasive transcranial direct current stimulation (tDCS) over LIFG in healthy participants would affect performance in semantic tasks that varied in control demands. Moreover, in the first study below, we examined whether the effects of tDCS would interact with performance gains following training during anodal stimulation which has already been employed by several studies which established significant improvement in performance of patients with stroke aphasia in picture naming training (Floel et al., 2011; Baker et al., 2010; Monti et al., 2008). Since our long term goal is improving semantic control in SA patients, the effects of training during tDCS were evaluated.

Experiment 1: Anodal/sham tDCS accompanied by task training

Participants:

The experiment took place in the Department of Psychology, at the University of York. The sample consisted of 40 undergraduate students, 32 females and 8 males, aged 18-21 (Mean age = 19.8, *SD* = 1.26). They were all native English speakers, right-handed and not colour-blind. They were recruited through the department's electronic experiment booking system, adverts and word-of-mouth. The participants gave informed consent under a protocol approved by the Research Ethics Committee of the York Neuroimaging Centre. Participants were given detailed information about the study one day prior to the stimulation. Written consent and a safety screening checklist were completed by the participants: general exclusion criteria regarding neurostimulation applications were considered (e.g., neurological diseases or metallic implants. A copy of this information sheet and checklist are provided in the Appendix C. All participants received payment of either £10 cash or 2 hours course credits.

Experimental tasks:

There were three semantic tasks and one non-semantic task.

1) **Semantic tasks**: We used a set of semantic judgement tasks adapted from the fMRI literature (Badre et al., 2005) and re-employed in the TMS study of Whitney et al. (2011). On every trial, participants were shown a probe word at the top of the screen with three word choices below and were asked to select the word related in meaning to the top word. A fixation point appeared on the screen to signal the start of each trial. Participants indicated their response by pressing

one of three designated keys on a keyboard with their left hand (i.e., the key that matched the position of the target). There were three tasks:

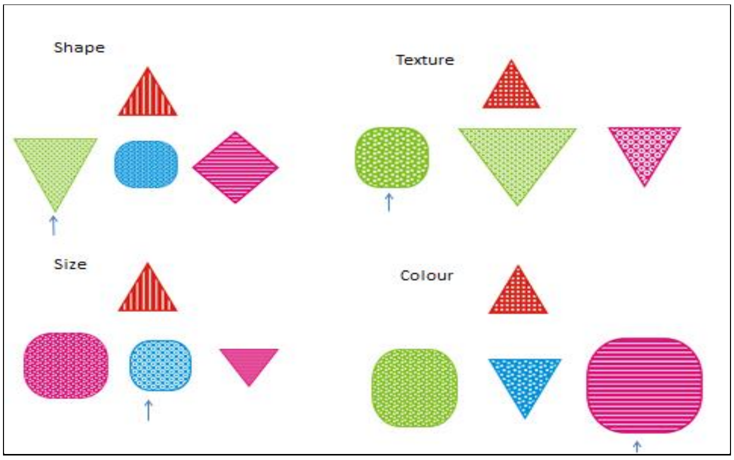
a) *Matching words with strong semantic associations*: This task involved identifying a strong semantic associate of a probe word from amongst three choices (e.g., salt-pepper, slug, coin). In this case, semantic retrieval is thought to take place relatively automatically via spreading activation (Badre et al., 2005; Whitney et al., 2011). This task therefore makes minimal demands on semantic control.

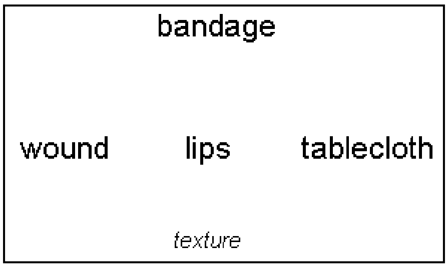
b) *Matching words with weak semantic association*s: This task was identical to (a) except that the associative strength between the probe and target words was weak (e.g. salt-grain). Under these conditions, identifying the target relies to a greater extent on *controlled retrieval* (Badre et al., 2005; Whitney et al., 2011)

c) *Matching words on the basis of specific semantic features*: In this task, participants made a decision based on a specific semantic feature (e.g., matching asprin with dove because both objects are white). This task is thought to make strong demands on *semantic selection*. Each trial also included a strong globally-related distracter (e.g., sick), increasing the demands on conceptual inhibition. There were four possible feature dimensions for items to be matched on: size, colour, texture or shape

2) Non-semantic figure feature task: A visual decision task also required feature selection but employed non-semantic stimuli (simple shapes not words). The stimuli varied in four dimensions: shape (triangle, circle and square), colour (blue, red and green), size (small, medium and large) and texture (lines, squares and dots). Participants had to make a selection according to a specific visual feature (e.g., find a shape matching in texture), whilst avoiding a strong distracter (e.g. an item similar in most other dimensions, including colour, size and shape). This task was therefore designed to resemble the feature-selection semantic task above (see Figure 20 for an example).

Figure 20: Example of the figure feature task, semantic feature task





Stimuli

Three of the four task stimulus sets were taken from existing (published) neuropsychological experiments. Stimuli from the high and low association tasks were taken from those used by Whitney et al (2011), where probe and target pairs in the high association task had a mean free association strength of 0.240 (i.e. 24% of respondents named the target in response to the probe in a free association paradigm; SD = 0.182), whilst pairs in the low association task had a significantly lower mean association strength of 0.035 (SD = 0.095, P <0.001). Probe distractors were words which were not recalled in response to the probe in a free association paradigm, and stimuli between the two conditions showed comparable word length and frequency (as determined by software program N-Watch). The semantic feature stimulus set was taken from Badre (2005), where the frequency and length of probe and target words was comparable between different feature subsets. In the semantic feature trials, one of the distractors was semantically related on an irrelevant dimension, and one was not semantically related. The figure feature stimuli consisted of simple two dimensional geometric shapes, varying in size, colour, texture (pattern) and shape (number of angles). In line with the word probe tasks, no two figure feature trials contained the same combination of figures, and one of the distractors was related on an irrelevant dimension.

Design

We used a between-subject design. Participants were randomly assigned to two different stimulation conditions: half received anodal stimulation for 10 minutes, the other half received sham stimulation, in which the current was rapidly ramped down and stopped after 30 seconds. In previous studies participants were not able to distinguish between real or sham stimulation using this protocol (Paulus, 2003) and we examined if this was also true for our participants using ratings scales. As dependent variables we recorded reaction time and accuracy.

There were three different phases for the experiment:
1- Baseline testing phase (around 5 minutes)
2 -Training phase simultaneously with the stimulation (10 minutes)
3 - Post-tDCS testing phase (around 5 minutes)

For the pre- and post-testing phases, we used the four different tasks described above. There were 32 self-paced trials per task (with 8 of each feature in the two feature selection tasks using mini-blocks). The order of the blocks randomly varied across subjects, but remained the same for pre- and post-testing. In the training phase, participants were asked to practise the semantic feature task, and received feedback after each trial regarding accuracy and reaction time.

Different stimuli sets were used for the three different phases such that trials were not repeated. The training set was identical for all subjects, whereas the order of the pre- and post-set alternated between participants.

Apparatus

The experiment was carried out in the tDCS lab. The experimental tasks were presented using e-prime 2.0 software (2004). Participants viewed the experiment on a desktop computer, and used the arrow keys on the keyboard (using the left hand to avoid any effects of left-hemisphere stimulation) to record responses. All participants were required to fill in a sensation rating questionnaire adapted from Fertonani et al (2010) (see Appendix D).

Transcranial direct current stimulation was delivered by a DC stimulator PLUS by neuroConn GmbH and a pair of sterile saline-soaked sponge-electrodes with a diameter of 35 cm^2. The stimulation parameters were 2 mA for 10 minutes with 3 seconds of each fade-in and fade-out for the anodal stimulation condition and the same for the sham condition but with duration of only 30 seconds. This protocol is regarded as being safe according to previous studies (Been et al., 2007).

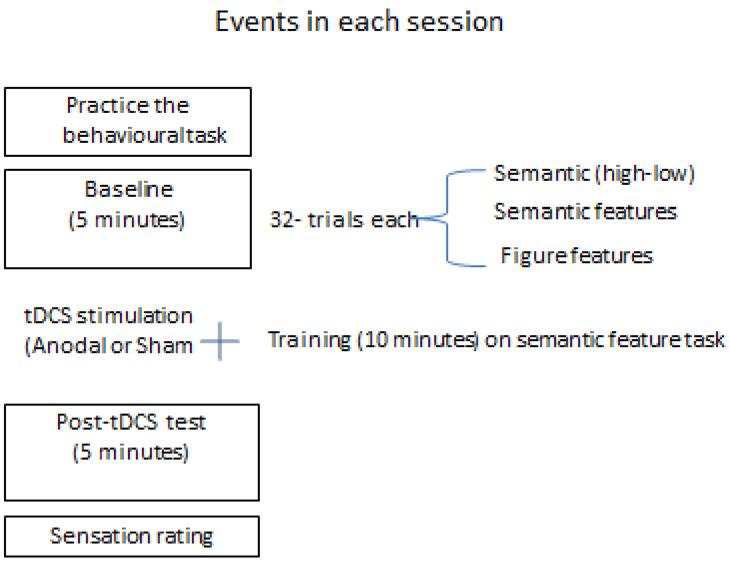
Procedure

First the purpose and nature of the experiment were explained to the participants. After that they were asked to sign a consent form and complete the safety screening form mentioned above. To fix the electrodes we identified our target site on the participant’s scalp. In line with other studies (Hsu et al., 2011; Fertonani et al., 2010) we used the international 10-20 system and some special anatomical landmarks at the inion and nasion. In line with an anatomical study by Koessler et al. (2009) we considered site F7 as the projection of the left IFG. After placing the anode over the F7 site, the reference electrode was placed on the contralateral supraorbital region used in many previous studies (Flöel et al., 2008; Nitsche et al., 2004). All participants then had the chance to familiarise themselves with the sensation of tDCS, before the behavioural testing started.

In order to become acquainted with the task, participants were asked to do some practise trials. All tasks were explained via instructions on the computer screen, with a couple of example trials for each task. Participants were reminded to respond as quickly and accurately as possible. During the actual testing only short instructions at the beginning of each block were needed.

The first behavioural test was conducted without any stimulation, followed by the training phase with simultaneous stimulation (anodal or sham), finishing with another testing directly after the stimulation. Afterwards, the electrodes were detached and the participants asked to complete rating scales of the intensity of heat/itch/pain sensations they may have experienced during the stimulation. The experiment ended with giving the money and debriefing (see Figure 21).

Figure 21: Experiment procedures for every participants in anodal and sham groups



Rationale and predictions: tDCS is thought to modulate brain plasticity (Nitsche et al., 2004); consequently, positive effects of anodal tDCS on the performance of a behavioural task might be dependent on task training *during* tDCS. This will allow us to evaluate the transfer of tDCS effects both within the training domain (e.g., for semantic decisions) and between domains (e.g., from semantic selection to visual selection). Training during anodal stimulation has already been employed by several studies which established significant improvement in performance of patients with stroke aphasia in picture naming training (Floel et al., 2011; Baker et al., 2010; Monti et al., 2008). Since our long term goal is improving semantic control in SA patients, the effects of training during tDCS were evaluated.

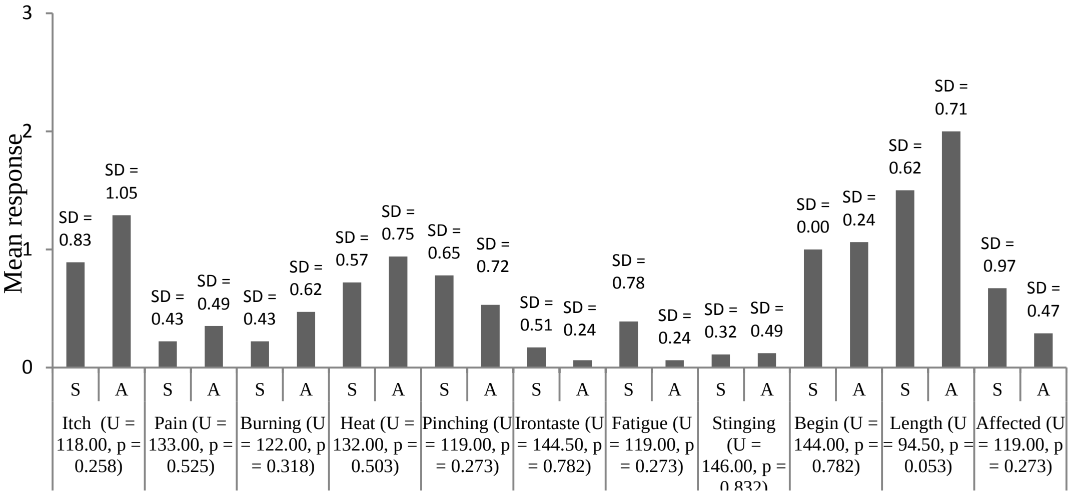
We anticipate that anodal tDCS over LIFG will facilitate performance in the low association semantic condition, given the strong evidence that LIFG is crucial for semantic control (e.g., Thompson-Schill et al., 1997; Badre et al., 2005). In contrast, sham tDCS over LIFG should have no effect on the semantic judgement task. Additionally, this experiment provides a means of exploring the specificity of the mechanisms contributing to semantic control. We can investigate whether positive effects of training on the semantic feature task, which loads heavily on semantic selection, transfer to other semantic tasks that do and do not load this aspect of semantic control. We can also establish whether semantic training improves performance on the non-semantic figure feature task. Such a finding would suggest overlap between the brain networks that support semantic and domain-free executive control, and therefore provide further evidence for one of the research questions in Chapters 2 and 3.

Results:

Sensations

In the sensation rating questionnaire, participants indicated their experience of sensations associated with stimulation. Intensities for these sensations were rated (with none, mild, moderate, considerable, and strong ratings translating to 0-5 ordinal data points). Participants also indicated when the sensations began (with beginning, middle or end of stimulation allotting 1-3 points), how long sensations lasted (with stopped soon, some minutes, throughout stimulation allotting 1-3 points) and how much they affected performance (with not at all, a little, quite a lot, a lot, a huge amount allotting 0-4 points; see appendix D for sensation rating frequencies). A series of Mann-Whitney U tests revealed no significant differences between intensity, onset time, duration or effect on performance of tDCS between stimulation types (see Figure 22). Additionally, sensation ratings were generally low, and participants did not feel their performance was affected by the stimulation. Consequently, sham stimulation constituted a good control condition for anodal stimulation and the sensations produced by tDCS did not interfere with individual performance.

Figure 22: <u>Modal responses for sensation ratings for the two stimulation type (S = Sham, A = Anodal)</u>



The raw data used for the between-subjects analyses were the accuracy scores and response reaction times (RTs) for each trial. Trials with outlying RTs ±2 SDs of the task mean were removed for each participant. RT analysis was based on the average RT for each task. Ceiling effects were particularly apparent in the tasks that did not strongly tap semantic control (figure feature and high association), with mean accuracy ratings of around 80% for both baseline and post-stimulation blocks. Four participants were identified as extreme outliers (two from the anodal group and one from the sham group) using the boxplots function in SPSS and were excluded from further analysis. One participant's data was removed due to a technical problem.

Reaction times*:*

The mean reaction time for each participant was entered into 2x2 repeated measures ANOVA with the following factors: time (baseline, post: within-subjects variable), and stimulation type (anodal, sham: between-subjects variable). The reaction times were analysed for each task separately. There were significant main effects of time for both the semantic feature selection task (F(1,35) = 6.7, p < .05), and the non-semantic figure feature task: (F(1,35) = 23.3, p < .001). However, the interactions between time and stimulation type for both tasks were not significant, suggesting that these main effects of time reflected generic fatigue or task learning effects. No effects of time or tDCS stimulation were found for the other two tasks requiring judgements of global semantic relatedness (high and low association strength; see Table 32). These results suggest there were no difference between the anodal and sham groups in the effect of training on RT: training improved both groups of participants for the semantic and figure feature tasks. Responses in the anodal group were either equivalent to or slightly faster than the sham group (see Figure 23).

Table 28: Effects of stimulation type on performance reaction time in all tasks

Tasks	**Time (pre vs. post-stimulation)**	**Interaction: time by stimulation (anodal vs. sham)**
High association	F(1,35) =.34, p = .56	F(1,35) =.06, p = .79
Low association	F(1,35) = .58, p = .45	F(1,35) = .12, p = .72
Semantic features	F(1,35) = 6.7, p = .01*	F(1,35) = .70, p = .40
Figure features	(F(1,35) = 23.3, p = .000*	F(1,35) = .04, p = .83

*significant effects, ANOVA results for each task separately.

Accuracy:

As in the reaction time analysis we used a 2x2 repeated measures ANOVA with the following factors: time (baseline/post) and stimulation type (anodal/sham). Again, each task was examined separately. On the low semantic association task, there was no significant main effect of time (F(1,53) = 1.3, p = .26) but the critical interaction between time and stimulation type was significant (F(1,35) = 4.8, p < .05). While performance in the anodal group was equivalent at baseline and post-tDCS testing, t(20)= .258, p = .79, the sham group showed a significant increase in errors with time, t(19)= -2.5, p = .01, post-hoc Bonferroni = .02, suggesting that tDCS may have overcome errors through sustaining attention and/or reducing mental fatigue. There was a significant effect of time in the task tapping strong global associations (F(1,35) = 7.3, p = .01) but no significant interaction between time and stimulation type. Both groups improved in their performance. In contrast, for other tasks (semantic feature and figure feature), none of the effects were significant (see Figure 23).

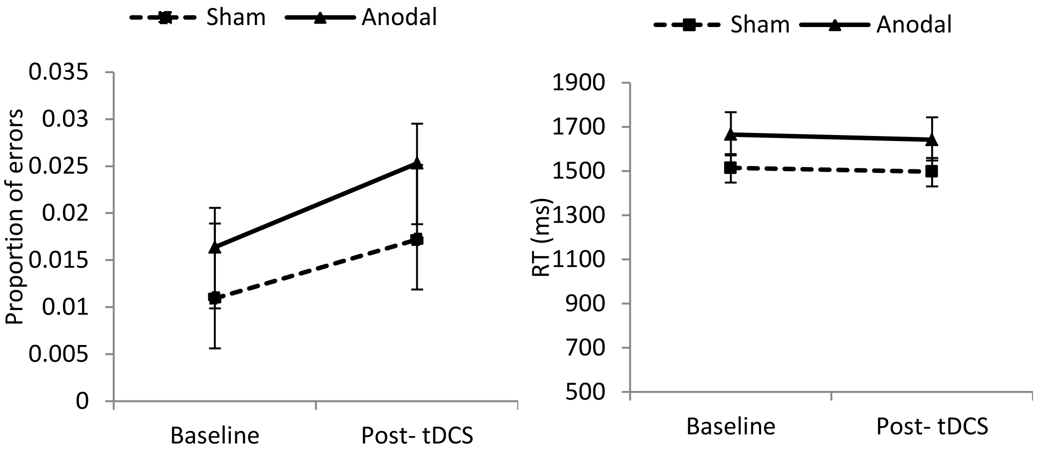
Table 29: Effects of stimulation type on performance accuracy in all tasks

Tasks	**Time**	**Interaction**
High association	(F(1,35) = 7.3, p = .01*	F(1,35) =.06, p = .64
Low association	F(1,53) = 1.3, p = .26	(F(1,35) = 4.8, p = .02*
Semantic features	F(1,35) = .42, p = .52	F(1,35) = .91, p = .34
Figure features	(F(1,35) = .03, p = .84	F(1,35) = .15, p = .13

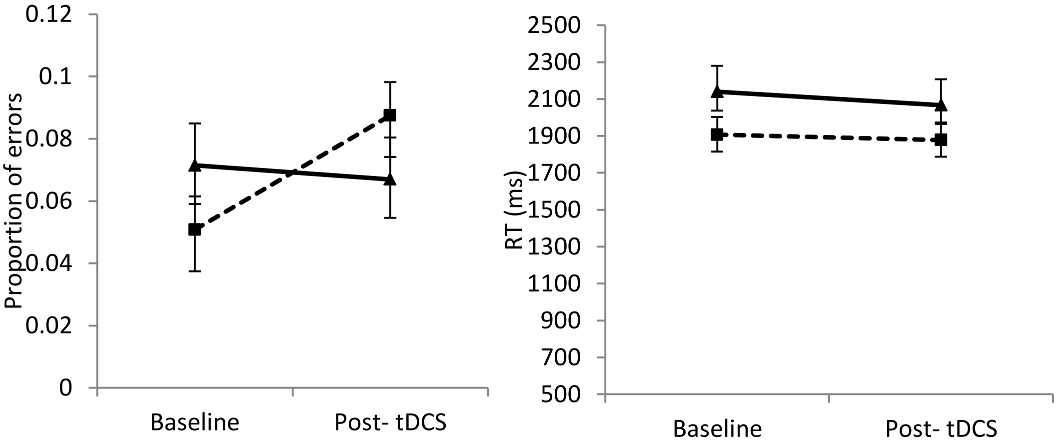
*significant effects, ANOVA results for each task separately

Figure 23: Performance on Experiment 1, split by task

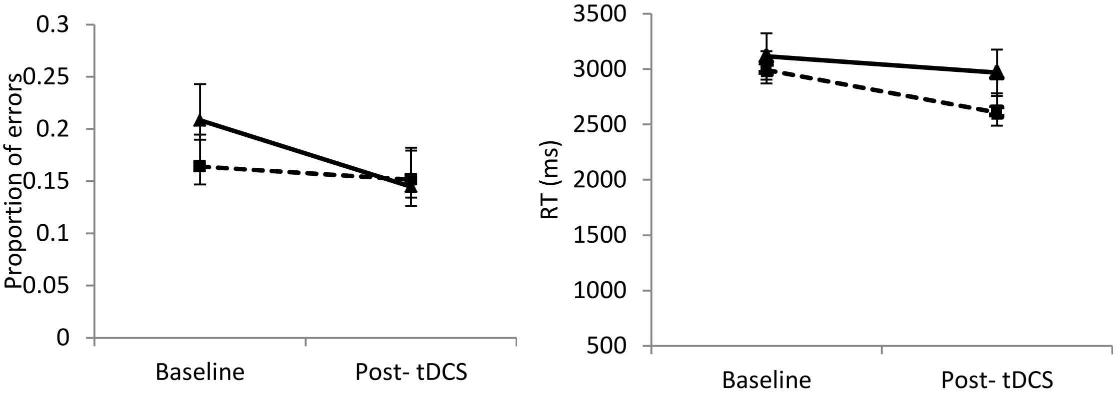
a) Global semantic task: high-strength associations



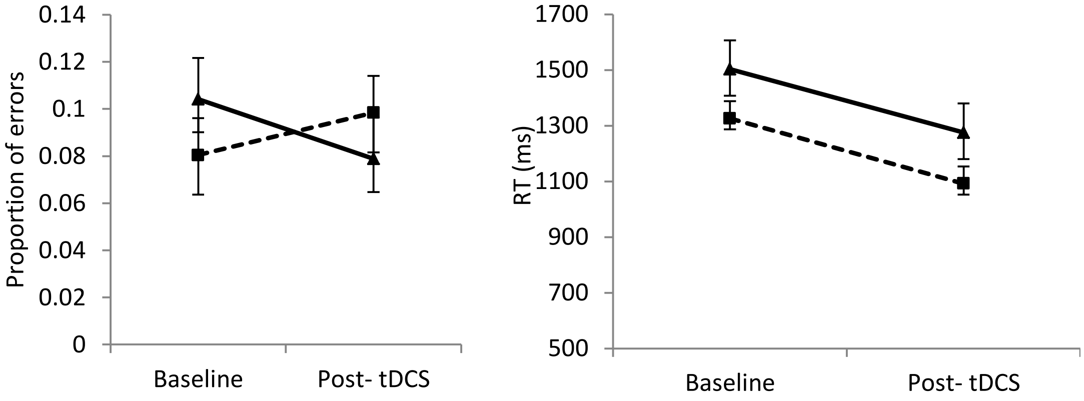
b) Global semantic task: low-strength associations



c) Semantic feature selection



d) Non-semantic task (figure feature selection)



Error bars show SE of mean

Summary: The results do not point to very strong effects of tDCS overall, but are nevertheless encouraging in that a significant interaction between time and stimulation was found on a semantic task with strong control demands, which required participants to determine that weakly associated word pairs were related. This tDCS effect was restricted to errors (did not affect response times). The effect on error rate was not seen for the semantic feature selection task, which was trained during the stimulation period, possibly because the task training itself resulted in a very substantial reduction in errors. At the same time, no transfer training effect was found on the executively-demanding non-semantic figure feature task. However, it is important to note that the (non-significant) interaction for the figure feature task nevertheless replicated the pattern for the weakly associated word pairs; with a different task design or more participants, this interaction may have been significant.

Some possible explanations were considered in interpreting the current results:

Reaction time task: Participants were asked to respond as fast and as accurately as possible but there was no deadline for responses. Consequently, error rates were very low. Since the effects we observed were in accuracy, it might be that a different paradigm that prevents participants from making slower responses in demanding situations would be more sensitive.

Training effect: In spite of the positive effects of tDCS that have been observed for trained tasks in several patient studies (Floel et al., 2011; Baker et al., 2010; Monti et al., 2008), it seems that healthy participants who have intact semantic control are not necessarily more likely to show tDCS effects when brain stimulation is combined with behavioural/cognitive training. We found tDCS effects for an untrained but not a trained task which maximised semantic control demands. Task training markedly improved task performance for the trained task within both anodal and sham sessions and therefore potentially masked differences between them.

Electrode position: We elected to use a reference electrode in the right supraorbital region, in line with other studies. However, the reference electrode was relatively close to the anode in some participants, which might have resulted in the transfer of some of the current through the scalp and not through the brain (Wagner et al., 2007a). This could be another reason why the tDCS effects we observed were relatively weak.

Confounding variables in between-subject design: There were difficulties in controlling individual differences between subjects in the anodal and sham groups, particularly in their performance at baseline on the various tasks. This may have reduced the power within this experiment to reveal effects of tDCS on semantic cognition.

We considered these aspects of the design in a second experiment.

Experiment 2: Effects of anodal/ sham stimulation over LIFG without task training

Rationale:

This experiment attempted to replicate the findings above using a design that addressed the methodological issues discussed above.

Participants:

Forty-seven participants (16 male and 31 female) with a mean age of 19.89 years (SD = 1.20) took part in the study. All participants were undergraduate students from the University of York.

The same recruitment procedures and eligibility for stimulation was applied as in Experiment 1. They were paid £10 per hour for taking part.

Experimental tasks:

The same four tasks as in Experiment 1 were re-employed in this experiment, except this time there was no task training phase.

Design:

The experiment employed a within-subjects design, with each participant experiencing both anodal and sham conditions in two different sessions. To control for stimulation order effects, the design was counterbalanced, with 24 participants experiencing the sham condition first and 23 participants experiencing the anodal condition first. In order to ensure that any task improvements post-stimulation did not result from item practise effects within a session, there were two sets of items: participants who received the first in the baseline went on to receive the second set post-stimulation (and vice versa). Whilst this set order was retained for the second stimulation session (meaning that comparison between baseline/post-stimulation scores for the two types of stimulation did not result from a difference in the item set), the items within each set appeared in a different order over the two presentations. Items in the first stimulus set were arranged into “blocks” A and C (containing the same items but in a different order), with both task and within-task item order pseudo-randomised between the two. Items within the second set were similarly pseudo-randomised into blocks B and D. As such, participants in each condition experienced one of four stimuli block combinations: A-D (sets A and D, containing different items, at baseline and post-stimulation in Session 1)/C-B (sets C and B, at baseline and post-stimulation in Session 2, containing different items to each other but the same items as in Session 1), B-C/D-A, C-B/D-A, or D-A/B-C. This was a single blind study, with participants naïve to the stimulation type received in each session, but experimenters informed of it.

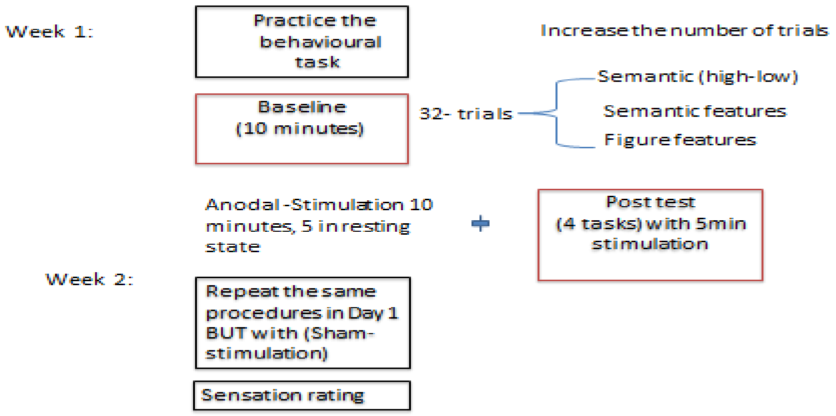
Transcranial Direct Current Stimulation

Anodal tDCS (2mA) was delivered for 10 minutes by a direct current stimulator (PLUS by neuroConn GmbH), via saline-soaked sponge covered electrodes (35cm²). The anodal electrode was placed over area F7 of the International 10-20 System for EEG electrode placement, a site corresponding to the LIFG. The reference electrode was placed on the right upper arm, following the procedures detailed in previous papers. (Accornero et al., 2007; Galea et al., 2009; Koenigs et al., 2009; Monti et al., 2008; Vandermeeren et al., 2010). Both anodal and sham stimulation conditions began with a fade-in of 3 seconds, and a fade-out of 3 seconds. In the sham stimulation, the stimulator was turned off after 30 seconds, since the perceived effects of true stimulation have been reported to fade out 30 seconds after administration (Baker et al, 2010).

Procedure:

The experiment was divided into two sessions, taking place one week apart. In the first session, once health screening and consent had been obtained, participants were instructed on the nature of the tasks they would be presented with. They then completed a practise task containing 2 high associations, 2 low associations, 8 semantic feature tasks and 8 figure feature tasks (using stimuli separate from those in the experimental set). The baseline block of trials was then administered. Following completion of the baseline block, the experimenter determined the placement of the electrodes, and began the stimulation procedure (either sham or anodal). After 5 minutes of stimulation, the post-stimulation test block was administered. Anodal tDCS continued for 5 minutes into this block, with block duration typically ranging between 5-10 minutes. Once the post-stimulation block had finished, the electrodes were removed, and a random sample of 25 participants filled in the sensation rating questionnaire. The second session was identical to the first (minus the screening/consent processes and the questionnaire administration) except that the sham/anodal stimulation condition was switched. Participants received payment following completion of the second session (see Figure 24).

Figure 24: <u>Experiment 2 stimulation event for each subject</u>



Results:

Subject analysis

The data were accuracy scores and response times (RTs) for each trial. Trials with outlying RTs, more than two s.d. from the task mean, were removed (for each task/session and subject separately). RT analysis was based on the average RT for each task. Participants who were identified as extreme outliers in accuracy and RT were removed from the data, using the boxplots function in SPSS fallowing the same procedures in Experiment 1, four participants were excluded from further analysis and replaced by new participants.

Accuracy:

A 2-way within subjects ANOVA was employed to examine the effects of stimulation type (sham, anodal) and time (baseline, post). A significant effect of stimulation type was observed for accuracy in the high association task, F(1,46) = 4.9, *p* = .03, with sham stimulation being associated with higher accuracy scores than anodal stimulation across both baseline and post-stimulation blocks (see Table 34 and 35). There were no other significant effects of stimulation type or time, and critically, no interactions between these factors.

Table 30: Accuracy for all participants

Tasks	Stimulation type	Time	Interaction
High association	F(1,46) = 4.9, *p* = .03*	F(1,46) =1.6, *p* = .20	F(1,46) = .03, *p* = .85
Low association	F(1,46) = 2.0, *p* = .16	F(1,46) = .36, *p* = .56	F(1,46) = 1.6, *p* = .21
Semantic features	F(1,46) = .15, *p* = .69	F(1,46) = .14, *p* = .70	F(1,46) = .34, *p* = .56
Figure features	F(1,46) = .027, *p* = .87	F(1,46) = .04, *p* =.84	F(1,46) = .005, *p* =.94

*significant effects, ANOVA results for each task separately

Table 31: Mean accuracy and RT scores across stimulation types before and after stimulation

		Baseline Acc.		Post-stim. Acc.		Baseline RT		Post-stim. RT	
Task	Stim.	Mean %	SD	Mean %	SD	Mean	SD	Mean	SD
Aggregate	Anodal	64.46	12.77	64.09	12.68	1138.39	95.66	1127.39	80.69
	Sham	66.26	10.70	65.94	11.55	1140.47	104.96	1130.30	81.88
FF	Anodal	80.63	9.81	79.52	9.72	938.97	120.16	907.31	110.78
	Sham	80.06	11.06	81.25	9.81	917.39	113.71	919.02	142.16
SF	Anodal	34.78	24.40	31.66	21.72	1339.97	144.84	1341.54	130.79
	Sham	34.44	21.75	34.36	21.63	1348.88	130.02	1350.57	109.06
HA	Anodal	82.44	13.13	80.84	13.31	1145.10	114.03	1123.92	88.24
	Sham	85.56	11.56	83.38	12.28	1137.81	96.71	1126.91	94.45
LA	Anodal	62.56	19.13	65.91	17.06	1221.14	132.68	1225.37	109.07
	Sham	67.88	15.00	66.86	15.56	1254.07	146.86	1241.94	110.22

NB. FF = figure feature, SF = semantic feature, HA = high association, LA = low association task

Reaction times:

There were no significant main effects of stimulation type or time on reaction time when data was examined by subjects (see Table 36).

Table 32: RT for all participants

Tasks	**Stimulation type**	**Time**	**Interaction**
High association	F(1,46) = .03, p = .85	F(1,46) = 2.1, p= .15	F(1,46) = .36, p = .55
Low association	F(1,46) = 2.0, p = .15	F(1,46)= .06, p = .80	F(1,46) = .48, p = .54
Semantic features	F(1,46) = .23, p =.61	F(1,46)= .03, p = .86	F(1,46) = .10, p = .75
Figure features	F(1,46) = .44, p =.83	F(1,46)= 3.0, p = .08	F(1,46) = 1.8, p = .18

Baseline/difference correlations

The relation between baseline performance and change post-stimulation in each task was explored using bivariate correlations (see Table 37). Strong correlations were obtained in almost every task, irrespective of stimulation condition. Participants who performed relatively poorly at baseline showed a greater relative improvement post-stimulation to those obtaining high baseline scores. In the case of accuracy, high baseline scores were associated with a decrease in performance which can be related to a failure to sustain attention in the high accuracy performers. Participants performing at ceiling at baseline (specifically, those demonstrating over 70% or so accuracy or markedly low reaction times) are unable to improve on their already high performance and thus post-stimulation performance will more probably decrease rather than increase. Interestingly, those showing moderate or poor baseline performance (less than 70%) demonstrate a more equal division of positive and negative performance change post-stimulation, irrespective of the type of stimulation used.

Table 33: Pearson correlation coefficients for correlations between baseline accuracy/RT and change in performance post-stimulation

Stimulation type	Anodal accuracy	Sham accuracy	Anodal RT	Sham RT
Aggregate	-0.53*	-0.67*	-0.65*	-0.66*
Figure features	-0.68*	-0.71*	-0.12	-0.02
Semantic features	-0.74*	-0.83*	-0.73*	-0.76*
High association	-0.50*	-0.69*	-0.50*	-0.44*
Low association	-0.62*	-0.47*	-0.66*	-0.73*

*Significant p= .001, RT = reaction time. Baseline accuracy/RT was the performance in the initial baseline test in each session, prior to the application of tDCS, in each task separately. Change in performance was calculated by subtracting post-tDCS performance from the baseline performance, for each task and stimulation condition separately.

Effect of stimulation on poorly-perfoming participants:

Since we would not expect significant effects of anodal tDCS on participants with high accuracy at baseline, we took steps to eliminate ceiling effects in the data. A repeated-measures ANOVA was re-calculated examining stimulation type (sham, anodal) and time (baseline, post-tDCS), including only participants who scored less than 75% on all tasks with a relatively matched average mean between them. Only 35 participants were included, 72% of the whole sample.

Accuracy:

Table 38 provides the results of ANOVA for the poor performers on each task. The results showed a significant main effect of time in the *high association* condition. Accuracy decreased over time in the sham condition, while there was no change in performance after anodal stimulation; however, the interaction between time and stimulation type did not reach significance for this comparatively easy task.

Table 34: ANOVA showing effects of tDCS on task accuracy for participants who scored less than 75% on all tasks

Tasks	Stimulation type	Time	Interaction
High association	F(1,34) = 6.5, P = .01*	F(1,34) = .56, n.s.	F(1,34) =.66, n.s.
Low association	F(1,34) = 6.8, P = .01*	F(1,34) = .35, n.s.	F(1,34) = 4.6, P = .03*
Semantic feature	F(1,34) =5.6, P = .02*	F(1,34) = 46.3, P = .000*	F(1,34) = 2.1, n.s
Figure feature	F(1,34) = .19, n.s.	F(1,34) = .38, n.s.	F(1,34) = 1.2, n.s.

* = significant; ANOVAs were performed for each task separately

In line with the results of the previous study, anodal stimulation produced a significant beneficial effect on performance on the *low association* task. A significant interaction between stimulation type and time was detected (see Table 38). A t-test was used to compare the level of improvement after stimulation between baseline and post-tDCS: the increase in accuracy after anodal stimulation approached significance (t(34) = 1.8, uncorrected p = .06). However, when the Bonferroni correction was applied this was clearly not significant (p =.12). There was no significant increase in accuracy after the sham stimulation, (t(34) = .80, uncorrected p = .42; p = .84 with Bonferroni correction).

On the *figure feature* task, there was no main effect of stimulation or time and no interaction.

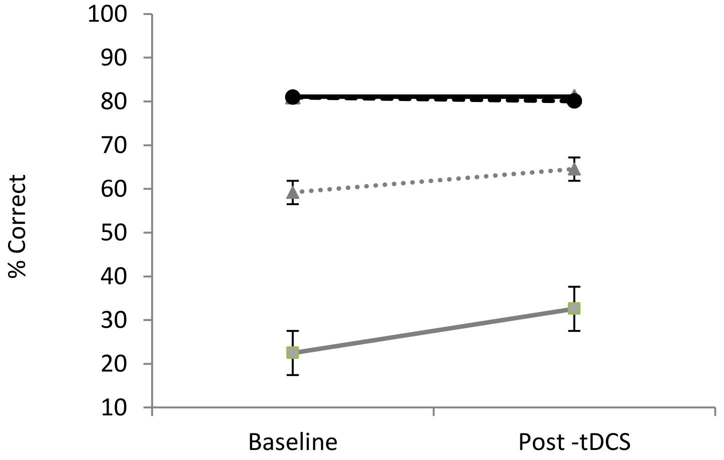
Significant main effects of stimulation and time were found in the *semantic feature selection* task: participants showed significant improvement after anodal stimulation compared to sham stimulation and there was a significant difference between baseline and post-tDCS stimulation, but the interaction between these factors did not reach significance (see Figure 25).

To explore if there was a 3-way interaction, we used a repeated-measures ANOVA incorporating the following factors: stimulation type (Anodal, Sham), time (Baseline, Post tDCS), task (semantic high, low, semantic features, figure features). This revealed a significant main effect of task, F(3, 138) = 462.2, *p* = .000. There was no significant 3-way interaction, F(3, 138) < 1.

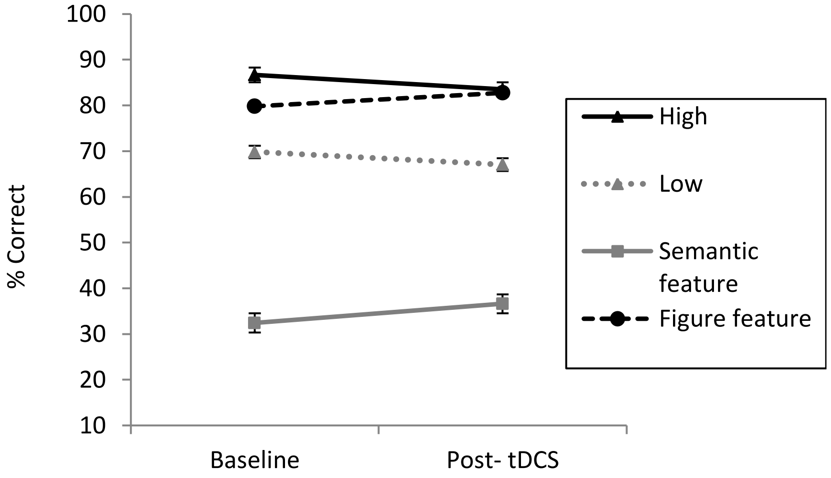
Figure 25: Accuracy performance for participants who scored less than 75% on all tasks

Tasks split by stimulation type

a) Anodal



b) b) Sham



Error bars show standard errors

In sum, as predicted, anodal tDCS improved performance in one task with strong semantic control demands (low association task), replicating the key interaction in Experiment 1. We did not find an interaction between stimulation and time in the semantic feature task, even though this experiment did not involve concurrent task training (and therefore stimulation-induced improvements in performance might not be masked by strong task training effects as in Experiment 1: despite this methodological change, performance in both the anodal and sham sessions improved over time as the task was repeated. In addition, although we did not expect an effect of anodal stimulation on judging strong semantic associations (and indeed the critical interaction was not significant), there was a decline in accuracy seen in the sham session, which may have resulted from a decline in sustained attention and/or mental fatigue, and this was not seen following anodal stimulation.

Reaction times:

The ANOVA results for reaction times (provided in Table 39) and mean and SD (see Table 40) show that on the semantic feature task, there was no significant main effect of stimulation, but a significant effect of time and an interaction between stimulation type and time. Paired-samples Bonferrroni-adjusted t tests compared baseline/post-stimulation sessions following anodal and sham stimulation. Participants became significantly faster in the sham condition *t*(34) = 3.1, *p* = .004, while there was no significant change in the anodal condition *t*(34) = -.19, *p* = .84. The form of this interaction is not consistent with behavioural facilitation following tDCS.

Table 35 : ANOVA showing effects of tDCS on RT for participants who scored less than 75% correct on all tasks

Tasks	Stimulation type	Time	Interaction
High association	F(1,34)=9.0, *p*=.005*	F(1,34)< 1	F(1,34)= 18.2, *p*=.000*
Low association	F(1,34)=6.7, *p*=.01*	F(1,34)< 1	F(1,34)=.09, n.s.
Semantic feature	F(1,34)=.12, n.s.	F(1,34)=4.8, *p*=.03*	F(1,34)= 8.7, *p*=.006*
Figure feature	F(1,34)=6.4, *p*=.01*	F(1,34)=1.8, n.s.	F(1,34)=4.5, p=.03*

*Significant, ANOVA was performed for each task separately

Table 36: Mean RT scores across stimulation types before and after stimulation

		Baseline RT		**Post-stim. RT**	
Task	Stim.	Mean	SD	Mean	SD
HA	Anodal	1147.791	95.26224	1067.142	136.4774
	Sham	1136.602	86.22726	1237.702	178.6307
LA	Anodal	1202.218	99.89862	1212.007	117.6409
	Sham	1254.824	157.7843	1262.489	111.8105
SF	Anodal	1307.856	138.0796	1322.782	154.4075
	Sham	1352.719	187.957	1247.028	128.8508
FF	Anodal	959.2861	114.1377	1013.674	182.7029
	Sham	940.5294	110.3256	925.0045	103.7695

FF = figure feature, SF = semantic feature, HA = high association, LA = low association task.

In the low association task, there was significant main effect of stimulation type. Participants were significantly slower in the sham condition than in the anodal condition, although neither type of stimulation significantly reduced RT from baseline to post-test. However, a significant main effect of stimulation was found in the figure feature task. Anodal stimulation made participants significantly slower, while sham made them slightly faster. Therefore, a significant interaction between stimulation type and time was found. Paired-samples t tests comparing baseline/post-test anodal to sham stimulation showed significant increase in reaction times after anodal stimulation, *t* (34) = -2.1, *p* =.04 (Bonferrroni-adjusted) =.02, compared to baseline and sham stimulation, *t* (34) = 2.5, *p* =.017 (Bonferrroni-adjusted) = .005. While there was no significant change in reaction time in the sham condition compared to the baseline, *t* (34) = .70, *p* = .48 (Bonferrroni-adjusted) =.08

In the high association task, there was a significant main effect of anodal stimulation and significant interaction with time. Response times decreased significantly after anodal stimulation and increased after sham stimulation, *t* (34) = -3.7, *p* =.001.

To explore if there was a 3-way interaction, we examined the following factors in a repeated-measures ANOVA: stimulation type (Anodal, Sham) x time (Baseline, Post tDCS) x task (semantic high, low, semantic feature selection, figure feature selection). A repeated measures ANOVA revealed significant main effects of task, F(3, 129) = 497.2, *p* = .000. There was no significant 3-way interaction (stimulation x time x task), F(3, 129) = .693, *p* = .56.

In summary, anodal stimulation produced faster reaction times in the high association task and slightly faster reaction times in the low semantic association task, while interestingly; participants were significantly slower after anodal stimulation in the semantic feature and figure feature tasks. Both of these tasks load on feature selecting ability and follow the same mechanism of decision making. A possible explanation could be that neural modulation to F7 produced general involvement of the control process which may consequently have made participant slow in deciding the correct response (Cerruti et al., 2009).The improvement in speed in the high association task is again related to the spread effects of anodal tDCS as it was found in the accuracy of the same task.

Order effects:

Participants' performance improved over the experimental sessions, since the tasks were repeated. To explore this phenomenon, we used a series of ANOVAs, in which the stimulation type that participants received in their first session was included as a between-subjects factor, along with stimulation type (anodal vs. sham) and time (baseline, post-tDCS) as within-subjects factors (see Table 41a - b and 42 a-b-Figure A and B).

Figure A: Aggregate accuracy scores for anodal and sham stimulation according to first session stimulation type (with standard error bars).

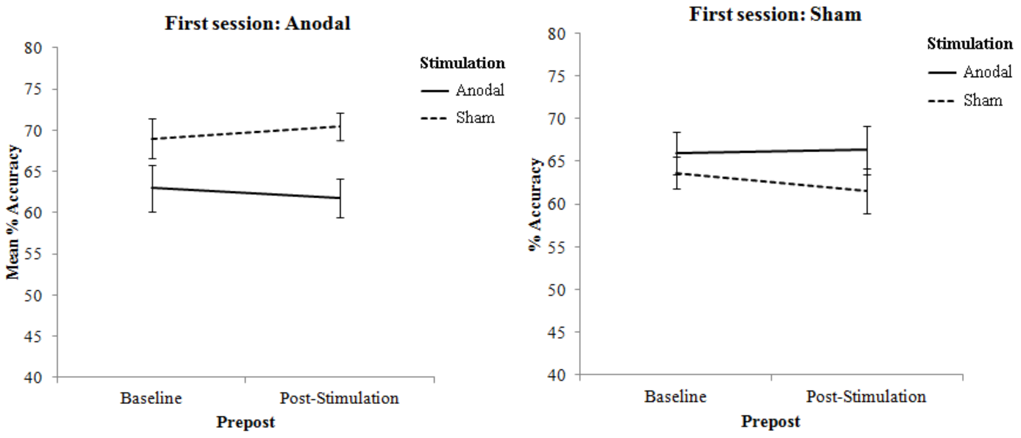


Figure B: Aggregate RT scores for anodal and sham stimulation according to first session stimulation type (with standard error bars).

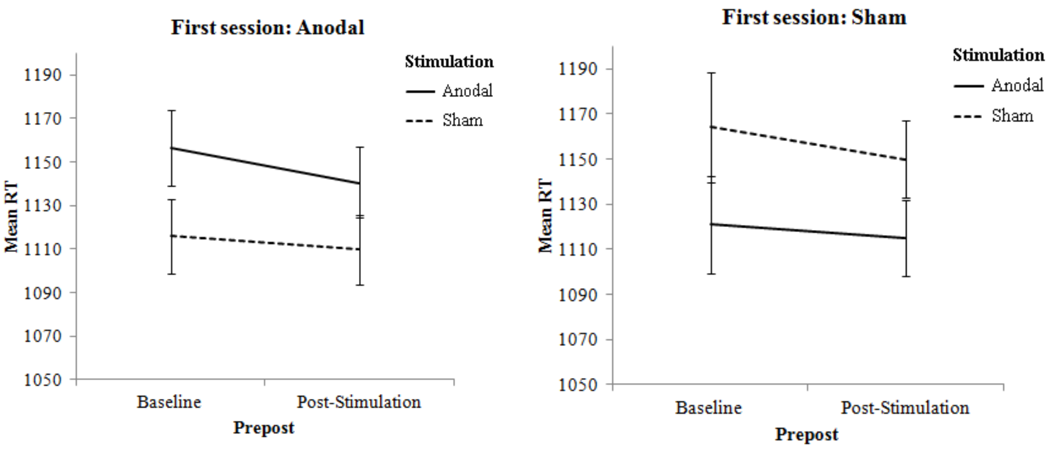


Table 37: 38Order effects in accuracy and RT

41a: Accuracy

Task	Stimulation type	Time	Order	Time x Stimulation	Stimulation X Order	Time x Order	3-way interaction
HA	F(1,22)=4.8, p= .03*	F(1,22)< 1	F(1,22)=7.5, p= .01*	F(1,22)< 1	F(1,22)= 1.9, p= .17	F(1,22)< 1	F(1,22)< 1
LA	F(1,22)=4.1, p= .05*	F(1,22)=1.1, p= .31	F(1,22)=15.3, p= .001*	F(1,22)< 1	F(1,22)= 1.5, p= .31	F(1,22)< 1	F(1,22)< 1
SF	F(1,22)=18.8, p= .000*	F(1,22)=2.1, p= .15	F(1,22)=.91, p= .35	F(1,22)< 1	F(1,22)= 8.1, p= .009*	F(1,22)< 1	F(1,22)< 1
FF	F(1,22)< 1	F(1,22)< 1	F(1,22)=.89, p= .35	F(1,22)< 1	F(1,22)< 1	F(1,22)< 1	F(1,22)< 1

41b: Reaction time

Task	Stimulation type	Time	Order	Time x Stimulation	Stimulation X Order	Time x Order	3-way interaction
HA	F(1,22)=7.9, p= .01*	F(1,22)< 1	F(1,22)=5.5, p= .02*	F(1,22)=15.5, p= .001*	F(1,22)< 1	F(1,22)< 1	F(1,22)< 1
LA	F(1,22)=1.9, p= .17	F(1,22)< 1	F(1,22)=10.2, p= .004*	F(1,22)< 1	F(1,22)< 1	F(1,22)< 1	F(1,22)< 1
SF	F(1,22)=1.1, p= .32	F(1,22)=7.1, p= .01*	F(1,22)=3.3, p= .08*	F(1,22)=2.7, p= .12	F(1,22)=6.9, p= .01*	F(1,22)< 1	F(1,22)< 1
FF	F(1,22)=6.9, p= .01*	F(1,22)=1.2, p= .27	F(1,22)=1.7, p= .21	F(1,22)< 1	F(1,22)=2.1, p= .15	F(1,22)< 1	F(1,22)< 1

FF = figure feature task, SF = semantic feature task, HA = high association task, LA = low association task.

Table 42a: Mean accuracy and RT scores across stimulation types before and after stimulation on the1^{St} day

	1^{st} Day	Baseline Acc.		Post-stim. Acc.		Baseline RT		Post-stim. RT	
Tasks	Stim.	Mean	SD %	Mean	SD %	Mean	SD	Mean	SD
FF	Anodal	26.43	3.96	26.08	2.90	955.17	113.4	968.2	149.9
	Sham	25.13	3.97	26.01	5.82	955.07	118.7	951.24	150.5
SF	Anodal	15.39	9.37	21.73	19.86	1377.4	1343.3	1343.3	165.3
	Sham	8.91	6.83	11.04	7.57	1380.7	206.9	1236.4	131.65
HA	Anodal	26.86	4.54	26.13	4.21	1157.1	78.59	1100.9	106.4
	Sham	27.5	3.45	26.2	4.65	1161.5	78.60	1229.7	187.61
LA	Anodal	19.60	5.54	21.3	5.66	1251.2	119.7	1222.3	92.33
	Sham	21.34	4.51	20.91	4.81	1250.0	115.78	1278.6	159.88

Table 42b: Mean accuracy and RT scores across stimulation types before and after stimulation on the 2^{nd} day

	2^{nd} Day	Baseline Acc.		Post-stim. Acc.		Baseline RT		Post-stim. RT	
Tasks	Stim.	Mean	SD %	Mean	SD %	Mean	SD	Mean	SD
FF	Anodal	26.29	3.73	26.04	3.39	956.6	143.4	995.6	197.7
	Sham	26.69	4.46	26.73	3.03	902.1	98.9	995.6	197.7
SF	Anodal	13.04	10.8	13.25	8.15	1298.9	150.6	1307.7	124.75
	Sham	13.04	6.83	12.86	3.03	1317.4	130.7	1307.7	124.7
HA	Anodal	27.00	4.41	26.58	4.77	1134.53	140.7	1051.7	139.9
	Sham	28.39	4.12	28.4	2.96	1100.39	75.00	1051.7	139.9
LA	Anodal	22.2	5.32	21.50	5.67	1180.0	134.3	1180.4	127.7
	Sham	23.17	4.95	24.52	2.60	1226.0	120.66	1180.4	127.70

FF = figure feature, SF = semantic feature, HA = high association, LA = low association task.

Accuracy for individual tasks:

On the figure feature task, there was no significant effect of stimulation type, time and order in the performance accuracy and no interactions were detected.

On the high association task, there was a significant main effect of stimulation type and order. Participants showed poorer performance in both stimulation conditions in the first day relative to the second day of testing. They also showed slight improvement within the sham condition between baseline and post-tDCS sessions, which could be related to practice, while there was no difference in accuracy in the anodal condition.

On the low association task, there was a significant effect of stimulation and order, for the anodal condition. There was a significant improvement in accuracy when anodal stimulation was applied in the first session and a decrease in accuracy in the sham condition. In the second session, participants in the sham condition improved, but not the anodal participants. No interaction between stimulation type and order was reported.

On the semantic feature task, there was significant effect of stimulation type and a nearly significant interaction between order and stimulation type. The anodal tDCS significantly improved participants' performance in the second session, while there was a decrease in accuracy in the sham condition in the second session (see Table 42 a-b).

In summary, a strong order effect was found in most sessions when anodal stimulation was the first session, while an improvement in the second session was associated with sham stimulation. One explanation could be related to the practice effect, which might reduce the effect of anodal stimulation, as subjects who completed the anodal session first performed better than participants who completed the anodal session second, because they had less practice, which again might be supported by the findings of Meinzer et al. (2011).

Item analysis:

Considering the substantial ceiling effects in the subject analysis, we explored possible weaknesses within the item set which could have further desensitised our tasks to the effects of tDCS. Item accuracy scores were represented in terms of the percentage of participants who answered an item correctly in a given condition (i.e., sham baseline, sham post-stimulation, anodal baseline, anodal post-stimulation), whilst item RT scores were the average RT for that item across participants in each condition.

In a first by-items analysis, we considered accuracy/RT for all items: The same 2 x 2 ANOVAs used in the by-subjects analyses were run to compare the effects of stimulation on all items. As in the by-subjects analysis examining poor performers, the critical time by stimulation interaction was significant for the task tapping distant associations (in both accuracy and RT). Anodal, t(63) = -1.30, p= .19, Sham, t(63)= 1.08, p = .28, both group showed improvement in their performance but, anodal stimulation slightly improve performance comparing to sham. RT, Anodal were group approach significant, they were faster than sham stimulation group, t(63) = -2.1, p = .03, Bonferroni correction = .06. This interaction of time and stimulation was also significant for the semantic feature task (RT only) Anodal group were significantly slower, Anodal t(55)= -3.8, p = .000, sham t(57)= -.96, p = .33

The results showed a significant main effect of anodal stimulation on the low association task, higher accuracy after stimulation and faster RT compared to the sham condition, significant interaction between stimulation and time in both accuracy and reaction time. Another significant main effect of anodal stimulation was also found on figure feature RT and high association task accuracy, but no significant interaction was found. Surprisingly, performance on the semantic feature task was not improved by anodal stimulation, but was significantly slower than the RT from the interaction detected (See Table 43 and Figure 26).

Table 43: Accuracy/RT all items analysis

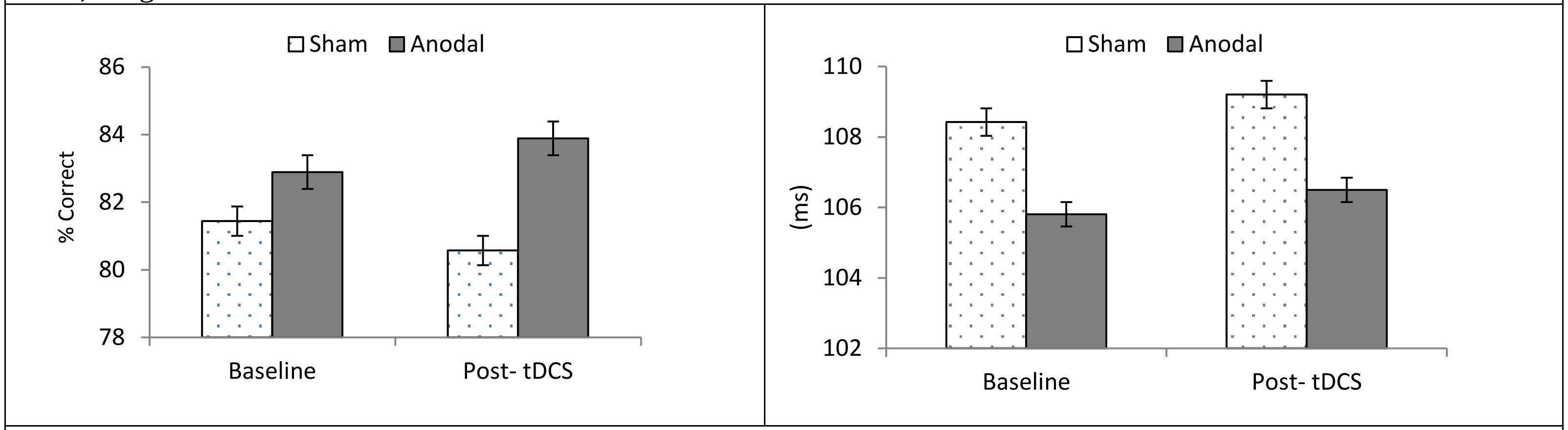
		Stimulation type		Time		Stimulation x Time	
Tasks	Measure	F	P	F	P	F	P
Figure feature	Acc	1.92	.18	1.63	.21	0.14	.71
	RT	10.5	.002*	1.72	.62	3.63	.06
Semantic feature	Acc	1.07	.31	1.63	.02*	3.40	.07
	RT	72.9	.001*	1.6	.135	8.60	.005*
High association	Acc	38.1	.001*	1.63	.009*	49	.22
	RT	3.23	.08	1.63	.03*	.46	.46
Low association	Acc	9.3	.003	1.63	.96	5.22	.02*
	RT	2.1	.15	1.63	.75	13.1	.001*

*Significant. ANOVA was demonstrated for each task separately

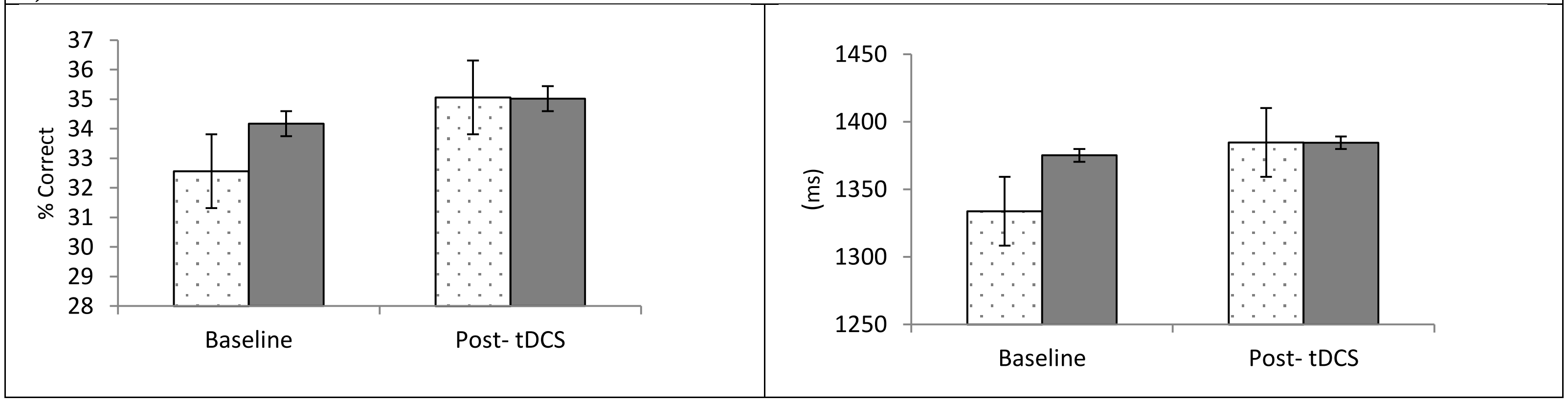
Figure 26: Items analysis

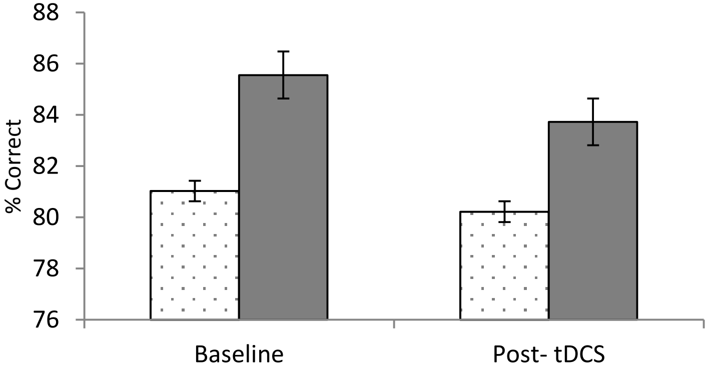
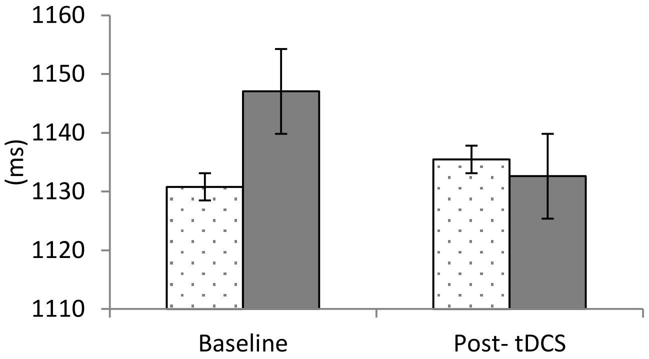
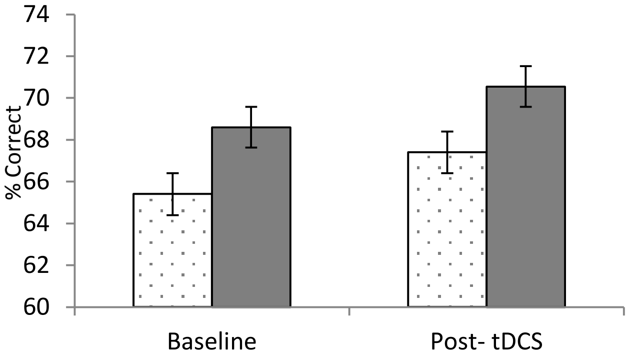
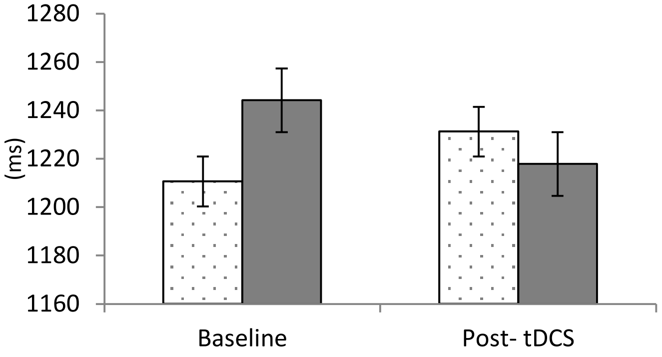
Accuracy **Reaction times**

a) Figure feature



b) Semantic feature



Accuracy	**Reaction times**
c) High association	
	
d) Low association	
	

Error bars show standard errors

In a final by-items analysis, we considered only those more difficult items that are less likely to produce ceiling-level performance, since the previous analyses have suggested that participants with poorer performance show stronger effects of anodal stimulation. Items answered correctly by fewer than 70% of the participants at baseline (i.e., in the absence of stimulation) were selected for analysis from each block for each of the four tasks. For low semantic association= 27 item, high association= 23, figure features = 24 and semantic features= 58.

Accuracy:

2 x 2 ANOVA was used (stimulation x time) with each task separately. The results showed significant improvement in accuracy after anodal stimulation on the low association task, F(1,36) = 5.2, *p* = .02 and a greater speeding of response times compared to the sham condition, F(1,36) = 11.8, *p* = .01, but no significant interaction was detected. Another main effect of anodal was found on the high association task accuracy F(1,22) = 13.2, *p* = .001. Significant main effect of time in semantic feature task F(1,57) = 4.4, *p* = .04, both group became more accurate regardless the stimulation type.

General discussion

The current chapter compared the effects of anodal and sham tDCS over LIFG on four different semantic and non-semantic tasks, varying in their control requirements. First, the high association task involved identifying a match between words with a strong linguistic and semantic relationship, such as salt-pepper: this is thought to be achieved primarily by the automatic spread of activation between related concepts and therefore requires relatively little semantic control. Two additional semantic tasks were designed to tap different aspects of semantic control: the low association task involved detecting relationships between more distantly associated words, such as salt-grain: this is thought to load the controlled retrieval of semantic information (Badre et al., 2005). In contrast, the semantic feature selection task required participants to match words according to a specific semantic feature, such as colour or size: this is thought to load semantic selection. The final task provided a non-verbal and non-semantic analogue of the semantic feature selection task: rather than identifying a match based on the semantic features of words, participants were asked to match specific features of visual figures, while ignoring non-relevant features that might also match with the distracters. By exploring the effect of excitatory brain stimulation of these diverse tasks, we can explore the cognitive and neural architecture underpinning different aspects of semantic and executive cognition and the relationship between them.

We report two experiments with largely convergent results. In Experiment 1, anodal tDCS was delivered during task-training, necessitating a between-subjects design (since task-training effects are likely to strongly carry over across sessions). In Experiment 2, we employed a within-subjects design in which participants completed two tDCS sessions – involving anodal and sham applications – in a counterbalanced order.

Results from the first experiment, in which tDCS was accompanied by task training in a between-subjects design, showed the effect of anodal stimulation on a task with strong control demands, without exactly training this type of task (a few errors and overcoming the fatigue effect). In the second experiment, task training was avoided and anodal tDCS was delivered whilst resting and during task performance. To establish the effect, subjects analysis results were driven by the ceiling effect at baseline (specifically, those demonstrating over 70% or so accuracy or markedly low reaction times) as tDCS did not make their performance any better and accordingly no effect of tDCS was found. Results completely reflected enhancement in performance when tDCS effect was investigated in subjects with poor performance at the baseline. Anodal tDCS over LIFG increased accuracy performance on tasks requiring a strong level of semantic control, as was found in experiment 1 (semantic feature and low association tasks). This result accords with Meinzer et al. (2012) who found anodal tDCS of LIFG improved controlled recall. Our findings build on this research by demonstrating improvements in semantic selection as well.

Additional activation in left inferior frontal gyrus (LIFG) was augmented by anodal tDCS enhance semantic control. Several studies showed similar findings of anodal tDCS over left prefrontal cortex improving tasks associated with high level cognitive control (Lyer et al., 2005; Gordon et al., 2010). This finding accords with the growing evidence that established the crucial role of LIFG in semantic control (Thompson-Schill et al., 1997; Badre et al., 2005; Wagner et al., 2001; Jefferies & Lambon Ralph, 2006; Whitney et al., 2011).

Inconsistent with our prediction, no transfer training effect on the two feature selection tasks after tDCS was found. We expected tDCS effects on semantic feature selection (since LIFG is strongly implicated in semantic selection), but extension to non-verbal/non-semantic task depends on expectations about overlap of general executive and semantic control systems.

A few possible explanations for this were established:

The open reaction time element increased accuracy in all tasks

Participants were less challenged by task demands because they had enough time to make mostly the correct decision. Low error proportions in both sham and anodal made tDCS stimulation effects not sufficient between groups.

Task-training masked tDCS effect

In spite of the observed positive effect of task training during tDCS stimulation in patient studies (Floel et al., 2011; Baker et al., 2010; Monti et al., 2008), in healthy participants who have intact semantic control, training boosted their performance to become even better, and masked stimulation effects. Separate analysis of the training task during tDCS stimulation showed that the performance of subjects who received anodal stimulation reduced when compared to the sham group. This decrease in performance during tDCS was supported by the findings of Meinzer et al (2011), where fMRI revealed specific task-related activity reductions during tDCS versus sham tDCS. Due to the difference in the number of trials in the semantic feature task in the baseline and the training phase, it is difficult to confirm statistically if there was reduction in the performance in the same task with and without stimulation. However, no effect of practice was observed in the same task under stimulation.

Items analysis revealed facilitating effect of anodal on semantic selection tasks more than on controlled retrieval tasks, which suggests that anodal tDCS varied more between subjects. However, finding that tDCS is effective in enhancing poor performance in tasks that required control gives great potential for tDCS as a tool of neurorehablitation for patients with semantic aphasia, who showed similar pattern of performance or even worse.

Additionally, a strong order effect was found in most sessions when anodal stimulation was the first session, while an improvement in the second session was associated with sham stimulation. One explanation could be related to the practice effect, which might reduce the effect of anodal stimulation, as subjects who completed the anodal session first performed better than participants who completed the anodal session second, because they had less practice, which again might be supported by the findings of Meinzer et al (2011).

One interesting findings of the current study was the increase in reaction time in the semantic feature task during anodal stimulation compared to the sham state. Improved accuracy was associated with slow reaction times. These findings were reported in Sela et al. (2012) on the effect of tDCS during semantic decision tasks that involved idiom comprehension and tap semantic control when the prefrontal cortex was stimulated. Attribution was giving to the general engagement of the control process of PFC when neural modulation was produced. Accordingly, subjects may take time deciding on the correct decision. Taking into consideration the complexity of semantic feature selection tasks used in this study, which required subjects to inhibit a strong globally-related distracter, this explanation might be consistent with our findings. Further support for this explanation came from the findings of rTMS over PFC. Rizzo et al. (2007) recognized a reverse rTMS effect on left and right sites RTs were faster and errors were higher when participants were required to choose the proper meaning for both figurative and literal sentences, which again made selection challenging.

The neural enhancement by tDCS over LIFG in this study was not restricted to performance on semantic selection and controlled retrieval. Improvement was detected on the high association task where semantic control demands were assumed to be minimal because the correct response could be competently recognized through automatic spreading activation between associated representations in the semantic network (Wagner et al. 2001; Badre et al. 2005; Whitney et al., 2011). Although a single location was stimulated in this study, we cannot be assertive regarding the specificity of the results' supportive evidence for the focal effect of tDCS (e.g., Antal et al., 2003; Kincses et al., 2004). But, it might be that other areas involved in cognitive control or anodal stimulation could increase language network connectivity (Meinzer et al., 2011; Polanía et al., 2011). This observation can be very encouraging for the neurorehabilitation of patients with multi-focal lesions, because targeting one site could spread facilitation to a larger network, which could facilitate recovery in those patients.

In conclusion, there was some evidence that anodal tDCS over LIFG improved semantic control in participants with poor performance on tasks requiring strong semantic control but, not in all tasks as predicted, not in all participants, problems with floor /celling effect which needs more research. Anodal tDCS can improve network connectivity in stimulated brain sites, which could add advantages to this technique to be used in neurorehablitation.

Finally, even though tDCS has substantial potential for making a great impact on cognitive neuroscience research and has implications for neurorehabilitation, studies that explore the neural correlates associated with beneficial behavioural effects of atDCS remain very few. As far as we are aware, only a few studies assess the effects of tDCS on brain activity in the language domain (Holland et al., 2011) or the motor domain (Antal et al., 2011; Polaníaet al., 2011, 2012; Zheng et al., 2011; Meinzer et al., 2011). Further research is needed to explain the neural underpinnings of the behavioural effects that were observed here.

CHAPTER 6

Discussion

Overview

This thesis explores the relationship between semantic cognition and executive processing using three complementary methodologies: (1) a dual-task study of semantic processing in healthy participants with and without a demanding secondary task to divide attention; (2) two groups of semantically impaired patients, who both show a relationship between semantic and executive deficits (although the nature of this relationship differs across groups) and (3) tDCS studies employing electrical stimulation to LIFG and examining the impact on semantic and non-semantic tasks with similar executive demands. This chapter will start by outlining the four primary research themes. We will then review the main findings from each empirical chapter and relate them to these four themes. In addition, this chapter will link the findings with the existing theories of semantic and executive control and discuss the potential applications of the results in a clinical setting. Along the way, suggestions for future studies will be outlined.

Research Themes

Theme 1: Exploring the nature of the semantic impairment in semantic aphasia and dysexecutive syndrome

Semantic cognition is composed of two interactive primary components: amodal conceptual representations and semantic control processes which channel semantic activation in a task-sensitive manner, such that only task-critical elements of conceptual structure are brought to the fore. Jefferies and Lambon Ralph (2006) found that SA patients' performance in semantic tasks across modalities was correlated with non-verbal executive measures. The SA group also showed strong effects of semantic control manipulations, such as retrieving the dominant and subordinate meanings of ambiguous words and synonym judgement with strong and weak distracters (Noonan et al., 2010). These findings suggest that, in SA patients, executive processes fail to appropriately control activation in the semantic network, for example by resolving competition and focussing processing on task-relevant features.

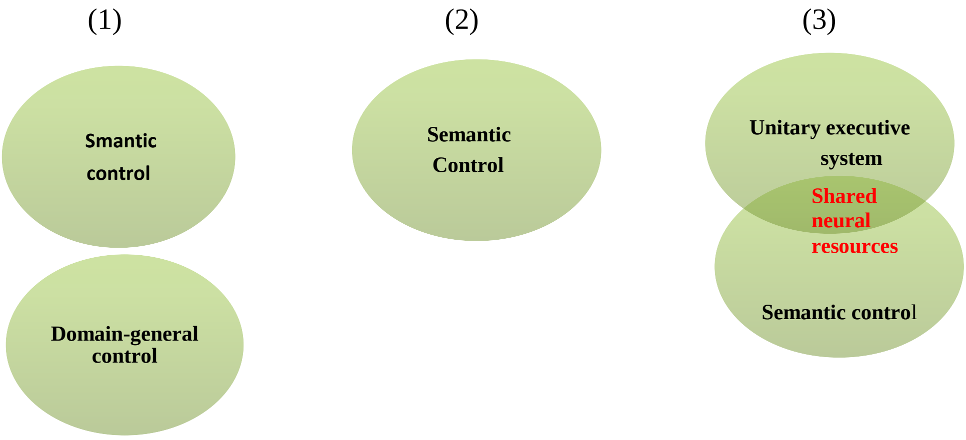
The association between impairment of executive processing and semantic control in SA can be explained in several ways. The executive difficulties of SA patients may be sufficient to explain their marked semantic impairment. This simple view is compatible with Jefferies and Lambon Ralph's (2006) account. Alternatively, the neuropsychological impairment in SA may reflect a more complex combination of deficits. A recent neuroimaging meta-analysis (Noonan et al. submitted) suggested that the brain regions supporting semantic control *partially* overlap with multi-demand executive regions (Duncan et al., 2010): medial/dorsolateral PFC and IPS are components of both networks, while sites in anterior LIFG and pMTG are restricted to the semantic domain. This raises the possibility that SA patients have more severe impairment of semantic control than would be anticipated from dysexecutive patients with a similar level of performance on executive tasks because they have sustained damage to brain regions in inferior PFC and posterior temporal cortex specifically implicated in executive-semantic processes. This thesis provides a means of testing these alternatives by providing a case-series comparison of patients with SA and dysexecutive syndrome (referred to here as DYS) to determine whether executive deficits in DYS are sufficient to produce problems on semantic tasks that resemble those seen in SA cases, and if these impairments are of the same degree and quality in the two groups.

Consideration of the nature of executive functions and how these relate to the deficits in SA suggests there may be some similarities in the way performance breaks down in SA and DYS. Executive processes create an attentional set to guide the performance of behaviour online, and allow switching between different cognitive tasks (Alexander et al., 2005; Dosenbach et al., 2006; Miller, 2000). Performance in the face of competition from distracting information is also frequently ascribed to the operation of core executive processes responsible for inhibition of task-inappropriate information (Braver et al., 2002; Burgess & Shallice, 1996; Picton et al., 2007). Moreover, processes responsible for the planning and sequencing of behaviour in response to weakly specified environmental circumstances are a consistent feature of many executive theories (Norman & Shallice, 1986; Wood & Grafman, 2003). Similarly, SA cases have difficulty discerning which aspects of an item's meaning are being probed in a specific task or context (Noonan et al., 2010; Corbett et al., 2012). They show strong effects of the strength of distracters in semantic tasks (Noonan et al., 2010) and neuroimaging studies of LIFG reveal effects of the number of distracters in healthy participants (Wagner et al., 2001). SA cases also have difficulty in tasks that are relatively unconstrained, including action sequences such as 'packing a child's school bag' that requires planning (Corbett et al., 2011; 2012).

Theme 2: Is semantic control domain-specific or domain-general?

There are well established studies which address the strong association between performance on verbal/non-verbal semantic tasks and assessment on non-verbal executive tasks (Corbett *et al.*, 2009a; Corbett *et al.*, 2009b; Jefferies & Lambon Ralph, 2006). The relationship between semantic control and domain-general executive functions in SA implies that a unitary control structure could give rise to deficits in semantic and non-semantic tasks. There are three different views: (1) semantic and domain-general control could be completely separate systems, from a functional and anatomical perspective. The acquired brain damage in SA patients might reflect the combined damage to those two systems. This might give rise to more severe semantic deficits in SA than would be expected from the degree of impairment to non-verbal executive tasks (given that these two components of mental control operate cooperatively in the context of semantic tasks). (2) Another view suggests that semantic and domain-general control might be underpinned by a unitary executive system (Jefferies & Lambon Ralph, 2006). By this simple account, the semantic deficits in SA would be entirely predicted by their degree of deficits on non-verbal executive measures. (3) Finally, we might envisage the neural resources for executive and semantic control are partially overlapping: the two large-scale distributed networks that underpin executive processes in a semantic and non-semantic context might draw on some shared cortical regions, as well as some regions which are distinct (Noonan et al., submitted). These alternatives are depicted graphically in Figure 28.

Figure 28: Semantic/executive control – functional and neural overlap



Theme 3: The neural substrate of semantic control

Previous investigations have revealed semantic control deficits in SA patients following either temporoparietal or PFC lesions with minimal differences in semantic profile across the two lesion subgroups (Corbett *et al.*, 2009a; Corbett *et al.*, 2009b; Jefferies *et al.*, 2007; Jefferies & Lambon Ralph, 2006; Jefferies *et al.*, 2008).

SA patients showed poor performance on verbal and non-verbal semantic processing tasks that involved pictures, environmental sounds and tests of object use (Corbett *et al*., 2009a; Corbett *et al*., 2009b; Jefferies & Lambon Ralph, 2006). Moreover, consistent associations were found between the level of semantic regulation and domain-general control deficit (Jefferies & Lambon Ralph, 2006; Luria, 1976). This association suggests that the neural and the cognitive resources are shared to some extend for both verbal and nonverbal semantic processing (Duncan, 2006; Duncan & Owen, 2000; Nagel *et al*., 2008). Supporting evidence that neural resources are shared across different domains of executive processing is provided by a recent meta-analysis investigating the neural activation in functional neuroimaging tasks that required different degrees of cognitive control (Noonan *et al.*, 2010; see below).

Functional neuroimaging studies support the unitary-function/neurally-distributed control hypothesis; associated activation is commonly found in bilateral frontal and posterior parietal cortex in tasks with high cognitive control demand, irrespective of modality or the nature of the decision. Many studies show joint activation in bilateral ventral and dorsal PFC, anterior cingulate and inferior parietal cortex in tasks needing conflict resolution and different executive processes like Stroop, flanker, go-no, set-shifting, updating working memory and inhibitory processing (Nee et al., 2007; Collette et al., 2006). Peers et al. (2005) found similar attention/cognitive control impairment resulting from lesions to PFC or the inferior parietal cortex. Moreover, TMS to dorsal PFC and IPS disrupts executive processes for both semantic and non-semantic tasks (Nagel et al., 2008; Whitney et al., 2012), consistent with the finding that anterior and posterior lesions in SA produce comparable deficits of semantic and executive control (Noonan et al., 2010). A recent activation likelihood estimate (ALE) meta-analysis of neuroimaging studies of semantic control provides further support for the view that executive-semantic processes draw on multi-demand cognitive control sites (Noonan et al., submitted). Parts of LIFG were activated by both semantic control demands and phonological tasks. However, this region still showed some degree of functional specialisation: semantic tasks with high control demands produced higher activation mostly in ventral parts of PFC (BA47), while phonological tasks were associated more with activation in dorsal PFC and adjacent parts of premotor cortex (cf. Gough et al., 2005; Vigneau et al., 2006). pMTG was only activated by executively-demanding semantic tasks and did not contribute to domain-general control, while dorsal AG/IPS was involved in domain-general executive processing. Moreover, semantic tasks with high control demands also activated ventral angular gyrus, while phonological tasks yielded more activation of supramarginal gyrus. Since these contrasts compared semantic/phonological control with low-level baseline or rest trials, they may reflect general semantic and phonological processing in addition to the control demands of the tasks. It is also important to note that the majority of studies that were entered into this meta-analysis used verbal stimuli. Much less is known about how the brain controls retrieval of non-verbal knowledge: this motivates the use of both verbal and non-verbal semantic tasks in both neuroimaging and neuropsychological investigations such as the work presented in this thesis.

Theme 4: tDCS application in semantic control neurorehabilitation:

Given that the neuropsychological investigations suggest patients with SA retain a great deal of conceptual processing but have difficulty accessing it in a task- and context-appropriate fashion, rehabilitation strategies should focus on retaining executive control over semantic activation, as opposed to the relearning of semantic information per se. DYS patients might benefit from similar rehabilitation strategies since they also have problems accessing relevant aspects of conceptual knowledge.

Anodal transcranial direct current stimulation (tDCS) provides a means by which cortical activation in focal areas can be enhanced (Nitsche *et al*., 2008; Stagg & Nitsche, 2011). By applying weak electrical currents (around 1-2 milliampere (mA) to underlying cortical regions via scalp electrodes, anodal tDCS alters the membrane potential of neurons leading to depolarisation, and reduces levels of the neurotransmitter gamma-aminobutyric acid (GABA); in some cases resulting in behavioural facilitation (Liebetanz *et al*., 2002). Not only does this technique allow for investigation of the functioning of neural networks, but repeated use of tDCS has been implicated in long term improvement of cognitive/behavioural functioning, even in participants with neurological disorders (see Nitsche *et al*., 2008 for a review). This method is being used increasingly in the context of rehabilitation, although much of the existing work focuses on motor functions (Boggio et al., 2006; Vines et al., 2006)

Consequently, tDCS could potentially benefit those with SA in two ways. Firstly, understanding of the semantic control network could be enhanced via the selective excitation of key components (such as the LIFG) in healthy controls, and observing the effects on semantic control tasks. Secondly, should such stimulation produce favourable results (i.e. facilitate semantic control), repeated application to these areas could be investigated as a neurorehabilitative aid for patients with SA. Patients with stroke have responded well to tDCS previously in non-semantic executive control tasks, and may show particular improvement when tDCS is combined with motor or cognitive training (Hummel & Cohen, 2006; Flöel *et al*, 2008; Schlaug *et al.*, 2008; Baker *et al.*, 2010; Fiori *et al.*, 2011). Existing tDCS studies have successfully applied anodal stimulation to prefrontal areas including the LIFG in healthy participants, suggesting the area’s responsiveness to the technique (i.e. Iyer *et al.*, 2005; Cattaneo *et al.*, 2011; Jacobson *et al.*, 2011; Fertonani *et al.*, 2010; Meinzer *et al.*, 2012). Until recently, however, no studies had investigated the behavioural effects of stimulation to this area in relation to high versus low or non-semantic control tasks, and those doing so in the last few years have reported only small effect sizes (Lupyan *et al.*, 2012). This research area is likely to expand significantly over the next few years.

Results and discussion

The results of a case-series comparison of patients with SA and dysexecutive syndrome (DYS), which (Chapter 2, 3 and 4) showed the following:

Chapter 3 investigated in depth the relationship between domain-general cognitive control and deregulated semantic cognition, by directly comparing semantic aphasia patients with multimodal semantic impairment (SA) with patients with a primary impairment of executive functioning (dysexecutive syndrome; DYS). This study aimed to determine whether executive deficits in DYS are sufficient to produce problems on semantic tasks that resemble those seen in SA cases, by providing a case-series comparison. The study was motivated by the findings that SA patients show a strong association between semantic performance and scores on non-verbal assessments of cognitive control, which suggest a causal correlation between the two cognitive domains.

For the most part, the data suggest considerable overlap between executive control and executive-semantic functions. The primary impairment of executive control in patients with dysexecutive syndrome led to patterns of semantic performance qualitatively similar to semantic performance pattern that seen in SA. Both groups failed to show better comprehension of items high in frequency and familiarity (unlike cases with semantic dementia), and showed parallel effects of executive control manipulations in semantic tasks. **Chapter 3** used a number of different executive-semantic manipulations to induce high and low semantic control conditions within four different types of semantic task (utilising both expressive and receptive measures). Critically, both DYS and SA patients performed poorly across all of these assessments when the requirement for self-induced executive control was increased. The nature of the regulatory manipulations varied considerably across tasks suggesting impairment to a unitary control system may have been responsible for impaired performance on all tasks (Theme 2). On the nearest neighbour task, executive control was manipulated by varying the distance between probes and targets such that patients had to explore and manipulate semantic structure flexibly and online in order to identify the task-appropriate semantic dimensions. There was no interaction between semantic distance and patient group. Synonym judgement and picture naming tasks were used to explore patients' ability to engage in inhibitory processing of task-irrelevant stimuli. When distracter foils were strongly associated with the target on a synonym judgement task, or phonemic miscues were provided on a picture naming test, DYS patients' accuracy declined significantly suggesting they were unable to override competition within the semantic system. Finally, the ability to augment less salient aspects of semantic structure was probed using an associative judgement task with ambiguous words. SA patients were poorer at activating the less common meanings of homonyms, relative to the more frequently encountered, prepotent connotations. The finding that all of these different executive manipulations led to the same qualitative pattern of impairment in SA and DYS patients suggests that a single cognitive control system – responsible for biasing semantic activation in a task, time and context sensitive fashion – may underpin all aspects of multimodal semantic impairment in both groups (Theme 2).

Although this thesis was not designed to evaluate different theories of executive control per se, our results in **Chapter 3** are highly compatible with the multi-demand theory (view 2, Theme 2). Duncan (2001) considers high-level control as a unitary system, underpinned by a bilateral network located in prefrontal and parietal regions, which is responsible for domain-general executive demands and not cognitive control only within certain domains (Duncan, 2006; Hon et al., 2006). According to this view, neural and cognitive resources are shared across all aspects of executive control, including verbal and non-verbal semantic and non-semantic domains (Duncan, 2006; Duncan & Owen, 2000; Nagel et al., 2008). This shared cognitive and neural architecture for executive-semantic processing and domain-general control would predict an association between impairment in multimodal semantic control and executive control difficulties in non-semantic tasks, which was seen in both the SA and DYS patients (Theme 1). This fits with findings from SA patients that non-verbal measures of executive control can predict the performance of semantic tasks (Jefferies & Lambon Ralph, 2006; Luria, 1976).

Nevertheless, aspects of the data reported in **Chapter 3** suggested some differentiation of semantic and non-semantic control. As noted above (Theme 3), a recent meta-analysis of neuroimaging studies of semantic control revealed that although executive-semantic processing draws on ‘multi-demand’ regions such as medial and lateral PFC and IPS (Duncan, 2006), anterior parts of LIFG and pMTG had a more selective semantic role (Noonan et al. submitted). This meta-analysis is therefore consistent with view 3 above, that the brain networks supporting executive control and semantic control are only partially overlapping. The SA patients had more severe semantic deficits than would be predicted from their executive performance, compared with DYS patients. The SA patients also showed somewhat larger cueing/miscuing effects (although some of these differences could be explained in terms of ceiling-level performance in picture naming tasks in the DYS patients). Finally, the DYS patients showed more inconsistency across multiple versions of the same task that had broadly similar executive control requirements – an effect which we suggest above might be linked to impulsive responding in participants with DYS (Theme 1). Cases with SA may have more severe semantic impairment, relative to the degree of executive deficit, as their lesions encompass areas associated with semantic control specifically (e.g., anterior LIFG; pMTG). However, the large lesions in SA patients and those with acquired brain injury may include regions involved in both domain-general and more specific aspects of semantic control. Moreover, for the DYS group, the CT/MRI reports about the brain injury were not available for all the patients and some of the patients in the sample were unable to give consent to be scanned. Due to these limitations, our focus was on the pattern of neuropsychological impairment and not on the pattern of brain injury in the SA and DYS groups (which in SA cases can involve much of the frontal, temporal and parietal cortex in the left hemisphere, and in DYS cases is likely to be quite diffuse). However, the similarities and differences in the pattern of semantic impairment in these two groups support the view that the cognitive and neural systems underpinning semantic and domain-general executive control are largely but not completely overlapping (Theme 3).

Chapter 2 discussed a task synonym judgement, in which it was necessary to select one of several possible targets on the basis of its strength of association with the probe word; this established that high frequency probes might be more likely to activate spurious or irrelevant associations. Patients with semantic aphasia (SA), who had poor executive control over semantic processing, showed a reduction or elimination of the natural processing advantage enjoyed by high frequency items in synonym judgement, or even a reversal of the normal frequency effect (Theme 1). This chapter therefore adds to existing knowledge of the nature of the semantic impairment in SA. We interpreted this pattern of findings in terms of the stronger executive control demands of high frequency words: these items occur frequently in a wide variety of contexts, and therefore additional control may be required to focus processing on the relevant associations. DYS patients showed a similar pattern – i.e., no advantage in comprehension for more frequent or familiar concepts **Chapter 3**. Additionally, a dual-task study of semantic processing in healthy participants, who were tested with and without a demanding secondary task designed to divide attention, supported this view: there was greater disruption for HF trials when executive resources were reduced (Theme 2). The secondary task involved n-back judgements on strings of numbers and had little semantic content. The absence of a processing advantage for HF words in patients with domain-general executive deficits and in healthy volunteers under conditions of divided attention is consistent with the view that multi-demand executive resources are employed under normal circumstances to overcome the selection/inhibition demands of HF items.

Chapter 4 explored the issues of similarities and differences between DYS and SA cases in greater detail, in the context of ‘cyclical’ word-picture matching tasks, in which the same small sets of items were presented repeatedly, such that distracters on one trial became the target on subsequent trials. This adds to the evidence obtained in **Chapter 3**, since patients with SA previously showed ‘refractory’ effects under these conditions for verbal, picture and sounds-based tasks, which were linked to their inability to resolve semantic competition. We explored performance in the two groups investigating three factors: presentation speed in which the response-stimulus interval was manipulated (RSI = 0 s versus 5 s), semantic relatedness, and repetition of trials. Deficits of semantic control in both groups produced strong refractory effects, perhaps because when semantically related items were presented repeatedly at a fast rate, spreading activation between items did not fully decay between trials. As a result, the entire set of items may have become highly active giving rise to strong competition with the target. This competition would be expected to become more intense as the experiment progressed and consequently both patient groups struggled to make accurate and rapid semantic judgements. These effects have been explained in terms of top-down control over semantic processing. Semantically related concepts are the target on one trial and then become distracters, so this paradigm generates strong competition and high selection/inhibitory demands; in particular, participants are required to inhibit items they have just selected, and then re-select these items when they become the target again (Jefferies et al., 2007).

Although both groups showed effects of speed, cycle and relatedness, these variables did not have an identical influence on the two groups. In contrast to SA patients, those with dysexecutive syndrome were more sensitive to the speed of presentation as a group. They made more errors and become slower when items were repeated at a fast rate, particularly when they were semantically related, while SA patients tended to respond more slowly and therefore they could have been relatively insensitive to this manipulation (Theme 1 and 2). This difference might reflect the fact that DYS patients are highly impulsive – this can be seen in their performance in the executive tests that require responding fast, e.g., Rule shift and Zoo map components from BADS (Chapter 3; Theme 2). The demand to process concepts at a fast pace might interact with this impairment, so DYS cases become more impulsive in the fast condition. The role of impulsive responding in explaining differences in the semantic impairment of SA and DYS cases requires further investigation.

The DYS patients mirrored those with SA in that many cases showed little effect of frequency manipulated in the synonym judgement task, but it was not totally absent in all patients (Theme 1). However, the standard positive effect of frequency may have been masked by the fact that frequently encountered items typically occur in a wider range of contexts than low frequency items. This may increase the executive requirements of semantic tasks, as it is necessary to direct activation towards the relevant aspects of meaning for frequently occurring concepts (Hoffman et al., 2011)(Chapter 2). Moreover, DYS patients were more inconsistent than SA patients, who all showed considerable levels of consistency when the same items were represented in an identical task context. However, both groups showed inconsistency across different semantic tasks which required different levels of control (Chapter 3). Additionally, DYS patients as a group did not show an effect of cueing, which could be related to their intact naming ability compared to SA patients in this study who have speech production impairment (which varied between cases). However, DYS did show miscuing effects which were equivalent in size to the SA group. These findings suggest that the SA and DYS patients had difficulty directing activation towards appropriate targets and away from semantic competitors (Theme 1).

Taking into account that these two groups were not matched for severity of executive/semantic deficits due to the nature of the brain injury of patients with dysexecutive syndrome, those patients were difficult to evaluate cognitively due to the associated behavioural dysfunction. Accordingly, the sample consisted of mild and moderate patients only who were relatively highly functioning comparing to SA sample in this comparison which may reflect the differences in speed and phonological deficits in related to benefit from phonemic cueing in naming (Chapter 3 and 4). Although further work may be able to overcome this limitation, there are practical difficulties in performing cognitive testing with dysexecutive patients who show severe impairment on tests such as the BADS (motivation; compliance with task instructions; aggression and disinhibition), and this is why these cases were not included in this project.

The results from the SA and DYS groups in **Chapters 2, 3** and **4** add evidence to the view that LIFG, RIFG, pMTG and dorsal AG/IPS play a role in semantic regulation. This view was supported by recent TMS application to LIFG followed by fMRI, which found compensatory activation in pMTG in tasks with strong semantic control demands, suggesting that LIFG and pMTG are both critical to executive-semantic processing (Whitney *et al.*, 2012). A large number of neuroimaging studies of healthy participants performing semantic tasks with high executive control demands suggest that LIFG is a critical region for semantic control but that this region acts in concert with other sites in posterior temporal and inferior parietal cortex (Noonan et al., submitted). Patients with SA and DYS who have large/diffuse lesions may have damage to several of these components and this may be critical in explaining the severity of their deficits in semantic control. These findings give credit to the use of tDCS in **Chapter 5** with patients with SA and brain injury, as stimulation of perilesional areas in left prefrontal cortex could augment the function of the distributed semantic control network though compensatory functioning in intact brain regions and thereby improve performance (Theme 4).

Chapter 5 directly compares the effect of anodal tDCS over LIFG on different semantic tasks requiring semantic and non-semantic control. First, the high association task involved identifying a match between words with a strong linguistic and semantic relationship, such as salt-pepper: this is thought to be achieved primarily by the automatic spread of activation between related concepts and therefore requires relatively little semantic control. Two additional semantic tasks were designed to tap different aspects of semantic control: the low association task involved detecting relationships between more distantly associated words, such as salt-grain: this is thought to load the controlled retrieval of semantic information (Badre et al., 2005). In contrast, the semantic feature selection task required participants to match words according to a specific semantic feature, such as colour or size: this is thought to load semantic selection. The final task provided a non-verbal and non-semantic analogue of the semantic feature selection task: rather than identifying a match based on the semantic features of words, participants were asked to match specific features of visual figures, while ignoring non-relevant features that might also match with the distracters.

The results showed additional activation in left inferior frontal gyrus (LIFG) was augmented by anodal tDCS enhance semantic control. Several studies showed similar findings of anodal tDCS over left prefrontal cortex improving tasks associated with high level cognitive control (Lyer et al., 2005; Gordon et al., 2010). This finding accords with the growing evidence that established the crucial role of LIFG in semantic control (Thompson-Schill et al., 1997; Badre et al., 2005; Wagner et al., 2001; Jefferies & Lambon Ralph, 2006; Whitney et al., 2011) (Theme 3).

The neural enhancement by tDCS over LIFG in this study was not restricted to performance on semantic selection and controlled retrieval. Improvement was detected on the high association task where semantic control demands were assumed to be minimal because the correct response could be competently recognized through automatic spreading activation between associated representations in the semantic network (Wagner et al. 2001; Badre et al. 2005; Whitney et al., 2011). This provides further support for partially overlapping substrates for semantic/executive control (Theme 3).

Although a single location was stimulated in this study, we cannot be assertive regarding the specificity of the results' supportive evidence for the focal effect of tDCS (e.g., Antal et al., 2003; Kincses et al., 2004). But, it might be that other areas involved in cognitive control or anodal stimulation could increase language network connectivity (Meinzer et al., 2011; Polanía et al., 2011). This observation can be very encouraging for the neurorehabilitation of patients with multi-focal lesions, because targeting one site could spread facilitation to a larger network, which could facilitate recovery in those patients (Theme 4).

Interestingly, anodal tDCS over LIFG improved semantic control in healthy volunteers with poor performance on tasks requiring strong semantic control. Anodal tDCS can improve network connectivity in stimulated brain sites, which could add advantages to this technique to be used in neurorehablitation (Theme 4).

By characterising the semantic deficits in SA and DYS (Theme 1), exploring how these impairments relate to problems with executive control (across domains) and semantic control more specifically (Theme 2), and how these deficits might relate to specific areas of brain injury and recent neuroscientific evidence (Theme 3), we hope to constrain the design of tDCS studies of the rehabilitation semantic control (Theme 4).

Future directions

- Even though tDCS has substantial potential for making a great impact on cognitive neuroscience research and has implications for neurorehabilitation, studies that explore the neural correlates associated with beneficial behavioural effects of atDCS remain very few. As far as we are aware, only a few studies assess the effects of tDCS on brain activity in the language domain (Holland et al., 2011) or the motor domain (Antal et al., 2011; Polaníaet al., 2011, 2012; Zheng et al., 2011; Meinzer et al., 2011). Further research is needed to explain the neural underpinnings of the behavioural effects that were observed in this thesis.

- Exploring refractory effects in DYS patients revealed that many of the symptoms of semantic access/refractory impairment were exhibited in this group, which is strong evidence that refractory variables are associated with difficulties in controlling activation within the semantic system. Furthermore, patients with executive control deficits can show a mixture of "storage" and "access" disorders. Refractory effects across different modalities in the DYS group and comparison of DYS patients with different lesion locations in the refractory effects have not yet been explored.

Appendices

Appendix A:

1: Standard synonym task (Experiment 1, Chapter 2)

Image	Freq	Target	Response1	Response2	Responsw3
High	High	WINTER	**SUMMER**	SEA	CLOTHES
High	High	COFFEE	NECK	KEY	**TEA**
High	High	PLANT	HEART	**TREE**	WINDOW
High	High	TELEPHONE	**RADIO**	KNIFE	DOG
High	High	STUDENT	RADIO	**PUPIL**	SUMMER
High	High	CHILD	UNIVERSITY	ROAD	**KID**
High	High	VALLEY	**HILLS**	BABY	SHIP
High	High	ROAD	STUDENT	**STREET**	FIRE
High	High	BEDROOM	GRASS	ARTIST	**KITCHEN**
High	High	MOTHER	MONEY	BED	**PARENT**
High	High	FOREST	**WOODS**	WINE	BOAT
High	High	WINDOW	EYE	**DOOR**	PLANT
High	High	RIVER	**STREAM**	DOCTOR	SQUARE
High	High	SUN	HORSE	**MOON**	BRIDGE
High	High	MONEY	CAR	CHURCH	**CASH**
High	High	ROCK	WINTER	BOTTLE	**STONE**
Low	High	CAUSE	CONSIDER	RETURN	**MAKE**
Low	High	VALUE	PURPOSE	**PRICE**	EFFECT
Low	High	PROPER	**APPROPRIATE**	APPARENT	LIMITED
Low	High	REASON	VALUE	**EXPLANATION**	INFLUENCE
Low	High	KEEP	BECOME	PUT	**SAVE**
Low	High	ORDINARY	**NORMAL**	PREVIOUS	SIGNIFICANT
Low	High	ADVANTAGE	TENDENCY	CONDITION	**BENEFIT**
Low	High	SIGNIFICANT	NORMAL	**IMPORTANT**	ORDINARY
Low	High	BASIC	RECENT	**SIMPLE**	CONSIDERABLE
Low	High	CONSTANT	**REGULAR**	ESSENTIAL	AWARE
Low	High	EFFECT	REASON	DIFFERENCE	**CONSEQUENCE**
Low	High	FACTOR	**PART**	ADVANTAGE	INSTANCE
Low	High	AVERAGE	LATTER	ACTUAL	**TYPICAL**
Low	High	CONSIDER	DEVELOP	**THINK**	DETERMINE
Low	High	FUNCTION	**PURPOSE**	RESPONSIBILITY	EXTENT
Low	High	TENDENCY	**TREND**	FACTOR	CONCEPT
Med	High	DISTANCE	**LENGTH**	SCENE	HEALTH
Med	High	CLEAN	**WASH**	PASS	SEND
Med	High	STRENGTH	LITERATURE	**POWER**	TEMPERATURE
Med	High	ANCIENT	SHARP	SWEET	**OLD**
Med	High	FASHION	SHELTER	COLUMN	**STYLE**
Med	High	RELIGION	DESIGN	**FAITH**	GROWTH

Med	High	PRIVATE	SINGLE	**PERSONAL**	STRONG
Med	High	SOCIETY	**PUBLIC**	PERIOD	AIR
Med	High	PROBLEM	LAW	**DIFFICULTY**	SERVICE
Med	High	FREEDOM	AID	**INDEPENDENCE**	MONTH
Med	High	BROAD	**WIDE**	FRESH	EVIL
Med	High	EDUCATION	FRONT	DEPARTMENT	**TEACHING**
Med	High	PAIR	CHILDHOOD	**COUPLE**	MASTER
Med	High	PROPERTY	**BUILDING**	COMMITTEE	RESEARCH
Med	High	MASTER	EDGE	ENEMY	**PROFESSOR**
Med	High	PATTERN	CONFERENCE	PERFORMANCE	**DESIGN**
High	Low	NECKLACE	**CHOKER**	LEMONADE	GEESE
High	Low	TULIP	BANANA	**DAFFODIL**	ALLIGATOR
High	Low	BUTTERFLY	GYM	VOLCANO	**MOTH**
High	Low	KITTEN	SUNBURN	SKI	**GOSLING**
High	Low	LOBSTER	**CRAYFISH**	BRACELET	HELMET
High	Low	KITE	ZIPPER	SQUIRREL	**TOY**
High	Low	CHESTNUT	SWAMP	**CONKER**	EAGLE
High	Low	SHRIMP	**PRAWN**	NUN	PYRAMID
High	Low	FROG	PICKLE	**TOAD**	JEWEL
High	Low	AMBULANCE	WALLET	ANT	**LIFEBOAT**
High	Low	REVOLVER	**PISTOL**	MIST	SUNSET
High	Low	HELMET	CATERPILLAR	**HEADDRESS**	SCISSORS
High	Low	JEWEL	HARP	**GEM**	LOBSTER
High	Low	ZIPPER	**FASTENER**	RASPBERRY	MOSQUITO
High	Low	PUPPY	CIDER	**KITTEN**	PEACH
High	Low	VIOLIN	RABBIT	SHED	**VIOLA**
Low	Low	AUDIT	ENIGMA	**INSPECTION**	DERIVATION
Low	Low	PROTOCOL	ALLEGORY	**ETIQUETTE**	DEBACLE
Low	Low	ALIAS	REPRISAL	CONDESCENSION	**PSEUDONYM**
Low	Low	ARBITER	**MEDIATOR**	UNDERTAKING	REFORMATION
Low	Low	IMPETUS	EQUITY	MISCONCEPTION	**MOTIVATION**
Low	Low	DESPOT	UNREALITY	**TYRANT**	DISCLOSURE
Low	Low	BEQUEST	CHRONOLOGY	COMPLICATION	**LEGACY**
Low	Low	CRITERION	**NORM**	SUFFIX	RESUMPTION
Low	Low	SUFFIX	PERPETRATOR	TEMERITY	**INFLECTION**
Low	Low	DIRGE	**LAMENT**	EMANATION	RARITY
Low	Low	DEITY	INCREDULITY	VITRIOL	**DIVINITY**
Low	Low	FALLACY	IMPROPRIETY	**MYTH**	CONJUGATION
Low	Low	INTERIM	**TEMPORARY**	INDIFFERENT	RECIPROCAL
Low	Low	VERITY	**CERTAINTY**	ARTIFICE	MEDIOCRITY
Low	Low	MORASS	SUBSTRATUM	**MIRE**	GIST
Low	Low	ATTRIBUTE	COMPLICATION	PREFERENCE	**TRAIT**
Med	Low	OMEN	**PORTENT**	RECESS	BENZENE
Med	Low	QUAKE	BUYER	**TREMOR**	INFINITY
Med	Low	ADULTERY	RELIC	MOLECULE	**INFIDELITY**
Med	Low	WICKET	RUBBLE	FLORA	**PITCH**

Med	Low	ENAMEL	MOLASSES	LABYRINTH	**COATING**
Med	Low	GALLANT	**HEROIC**	FERTILE	TAME
Med	Low	EMULSION	**PAINT**	TITBIT	RIDDLE
Med	Low	EXPANSE	CANON	**VASTNESS**	DUEL
Med	Low	ROGUE	POLKA	**SCOUNDREL**	GASKET
Med	Low	CRUSH	**SQUASH**	GASP	BLINK
Med	Low	GENTRY	**SQUIRE**	SEDATIVE	PERCH
Med	Low	CARTILAGE	DOWRY	MADNESS	**GRISTLE**
Med	Low	HUMOUR	WHIFF	CARBOHYDRATE	**WIT**
Med	Low	BOREDOM	RECRUIT	**DULLNESS**	TOKEN
Med	Low	HOSTILITY	SIEGE	**AGGRESSION**	OATH
Med	Low	OPPONENT	**FOE**	EVOLUTION	OPTIMISM

2: Frequency-reversed distractors synonym task (Experiment 3, Chapter 2)

Image	**Freq**	**Target**	**Response1**	**Response2**	**Response3**
High	High	COFFEE	LOBSTER	HARP	**TEA**
High	High	PLANT	SQUIRREL	**TREE**	ZIPPER
High	High	TELEPHON	**RADIO**	PEACH	CIDER
High	High	STUDENT	RASPBERRY	**PUPIL**	MOSQUITO
High	High	CHILD	NUN	PYRAMID	**KID**
High	High	VALLEY	**HILLS**	ANT	WALLET
High	High	ROAD	VOLCANO	**STREET**	GYM
High	High	BEDROOM	EAGLE	SWAMP	**KITCHEN**
High	High	MOTHER	PICKLE	JEWEL	**PARENT**
High	High	FOREST	**WOODS**	SUNSET	MIST
High	High	WINDOW	SKI	**DOOR**	SUNBURN
High	High	RIVER	**STREAM**	BRACELET	HELMET
High	High	SUN	SHED	**MOON**	RABBIT
High	High	MONEY	ALLIGATOR	BANANA	**CASH**
High	High	ROCK	SCISSORS	CATERPILLAR	**STONE**
Low	High	CAUSE	DISCLOSURE	UNREALITY	**MAKE**
Low	High	VALUE	RECIPROCAL	**PRICE**	INDIFFERENT
Low	High	PROPER	**APPROPRIAT**	ARTIFICE	MEDIOCRITY
Low	High	REASON	COMPLICATI	**EXPLANATION**	CHRONOLOGY
Low	High	KEEP	DERIVATION	ENIGMA	**SAVE**
Low	High	ORDINARY	**NORMAL**	VITRIOL	INCREDULITY
Low	High	ADVANTAG	REFORMATIO	UNDERTAKING	**BENEFIT**
Low	High	SIGNIFICAN	PREFERENCE	**IMPORTANT**	COMPLICATIO
Low	High	BASIC	EMANATION	**SIMPLE**	RARITY
Low	High	CONSTANT	**REGULAR**	ALLEGORY	DEBACLE

Low	High	EFFECT	REPRISAL	CONDESCENSI	**CONSEQUENC**
Low	High	FACTOR	**PART**	SUBSTRATUM	GIST
Low	High	AVERAGE	TEMERITY	PERPETRATOR	**TYPICAL**
Low	High	CONSIDER	EQUITY	**THINK**	MISCONCEPTI
Low	High	FUNCTION	**PURPOSE**	SUFFIX	RESUMPTION
Low	High	TENDENCY	**TREND**	IMPROPRIETY	CONJUGATION
Med	High	DISTANCE	**LENGTH**	POLKA	GASKET
Med	High	CLEAN	**WASH**	RECESS	BENZENE
Med	High	STRENGTH	GASP	**POWER**	BLINK
Med	High	ANCIENT	RELIC	MOLECULE	**OLD**
Med	High	FASHION	LABYRINTH	MOLASSES	**STYLE**
Med	High	RELIGION	TOKEN	**FAITH**	RECRUIT
Med	High	PRIVATE	SIEGE	**PERSONAL**	OATH
Med	High	SOCIETY	**PUBLIC**	FLORA	RUBBLE
Med	High	PROBLEM	TITBIT	**DIFFICULTY**	RIDDLE
Med	High	FREEDOM	CANON	**INDEPENDENC**	DUEL
Med	High	BROAD	**WIDE**	OPTIMISM	EVOLUTION
Med	High	EDUCATIO	MADNESS	DOWRY	**TEACHING**
Med	High	PAIR	CARBOHYDR	**COUPLE**	WHIFF
Med	High	PROPERTY	**BUILDING**	INFINITY	BUYER
Med	High	MASTER	PERCH	SEDATIVE	**PROFESSOR**
Med	High	PATTERN	TAME	FERTILE	**DESIGN**
High	Low	NECKLACE	**CHOKER**	DOG	SEA
High	Low	TULIP	CAR	**DAFFODIL**	CHURCH
High	Low	BUTTERFL	STUDENT	FIRE	**MOTH**
High	Low	KITTEN	PLANT	EYE	**GOSLING**
High	Low	LOBSTER	**CRAYFISH**	SQUARE	DOCTOR
High	Low	KITE	WINDOW	HEART	**TOY**
High	Low	CHESTNUT	GRASS	**CONKER**	ARTIST
High	Low	SHRIMP	**PRAWN**	UNIVERSITY	ROAD
High	Low	FROG	BED	**TOAD**	MONEY
High	Low	AMBULAN	SHIP	BABY	**LIFEBOAT**
High	Low	REVOLVER	**PISTOL**	WINE	BOAT
High	Low	HELMET	BOTTLE	**HEADDRESS**	WINTER
High	Low	JEWEL	NECK	**GEM**	KEY
High	Low	ZIPPER	**FASTENER**	SUMMER	RADIO
High	Low	PUPPY	CLOTHES	**KITTEN**	KNIFE
High	Low	VIOLIN	BRIDGE	HORSE	**VIOLA**
Low	Low	AUDIT	BECOME	**INSPECTION**	PUT
Low	Low	PROTOCOL	ESSENTIAL	**ETIQUETTE**	AWARE
Low	Low	ALIAS	DIFFERENCE	REASON	**PSEUDONYM**
Low	Low	ARBITER	**MEDIATOR**	TENDENCY	CONDITION

Low	Low	IMPETUS	DETERMINE	DEVELOP	**MOTIVATION**
Low	Low	DESPOT	CONSIDER	**TYRANT**	RETURN
Low	Low	BEQUEST	INFLUENCE	VALUE	**LEGACY**
Low	Low	CRITERION	**NORM**	RESPONSIBILIT	EXTENT
Low	Low	SUFFIX	LATTER	ACTUAL	**INFLECTION**
Low	Low	DIRGE	**LAMENT**	CONSIDERABL	RECENT
Low	Low	DEITY	SIGNIFICANT	PREVIOUS	**DIVINITY**
Low	Low	FALLACY	FACTOR	**MYTH**	CONCEPT
Low	Low	INTERIM	**TEMPORARY**	EFFECT	PURPOSE
Low	Low	VERITY	**CERTAINTY**	LIMITED	APPARENT
Low	Low	MORASS	ADVANTAGE	**MIRE**	INSTANCE
Low	Low	ATTRIBUTE	ORDINARY	NORMAL	**TRAIT**
Med	Low	OMEN	**PORTENT**	SEND	PASS
Med	Low	QUAKE	COMMITTEE	**TREMOR**	RESEARCH
Med	Low	ADULTERY	SWEET	SHARP	**INFIDELITY**
Med	Low	WICKET	PERIOD	AIR	**PITCH**
Med	Low	ENAMEL	SHELTER	COLUMN	**COATING**
Med	Low	GALLANT	**HEROIC**	PERFORMANCE	CONFERENCE
Med	Low	EMULSION	**PAINT**	LAW	SERVICE
Med	Low	EXPANSE	AID	**VASTNESS**	MONTH
Med	Low	ROGUE	HEALTH	**SCOUNDREL**	SCENE
Med	Low	CRUSH	**SQUASH**	LITERATURE	TEMPERATURE
Med	Low	GENTRY	**SQUIRE**	EDGE	ENEMY
Med	Low	CARTILAGE	DEPARTMENT	FRONT	**GRISTLE**
Med	Low	HUMOUR	MASTER	CHILDHOOD	**WIT**
Med	Low	BOREDOM	GROWTH	**DULLNESS**	DESIGN
Med	Low	HOSTILITY	SINGLE	**AGGRESSION**	STRONG

Target word is in bold text.

Appendix B:

Dysexecutive cases description (Chapters 3 and 4)

The patients were tested in 2010 and 2011.

GR: was a 59 year old right-handed male who left school at 16 and was employed as a factory worker until his first head injury in 1986. Following a road traffic accident, GR received damage to the lateral portions of the left frontal lobe, secondary to a pulmonary embolism. In 2004, GR fell from a ladder and suffered a subarachnoid haemorrhage accompanied by damage to the right frontal and parietal lobes (patient data from Noonan, 2011- unpublished PhD work).

JG: was a 22 year old right-handed female who left school at 16. In 2001, at the age of 17, JG suffered a pituitary haemorrhage and apoplexy due to a pituitary macroadenoma. JG underwent neurosurgery for resection of the tumour, involving a partial frontal lobectomy – centred on the inferior aspects of the left medial frontal lobe (patient data from Noonan, 2011- unpublished PhD work).

CR: was a 22 year old right-handed male who left school at 16 and was employed as a mechanic until his head injury. In April 2004, at the age of 19, CR was involved in a road traffic accident, which resulted in contusions to the right frontal and left parietal lobes (patient data from Noonan, 2011- unpublished PhD work).

AP: was a 25 year old, right-handed male. In 2001 he was knocked over by a car in a road traffic accident and was in a coma for 2 weeks; no scan report was available. At that time, he was described as having acute brain injury, cerebral oedema, post traumatic seizures and spastic quadriplegia, with spinal cord compression.

TG: was 25 year old right-handed male, who used his left hand because of tremors in the right hand. In 2003 he had traumatic brain injury due to a road traffic accident in wich he was a pedestrian. His Glasgow coma scale (GCS) was 3/15 indicating deep coma; after 11 days his GCS increased to 6. He was ventilated for 7 days. The exact length of post traumatic amnesia was unclear; he was non-verbal for a period of just over 2 months. A CT scan at the time of the injury showed multiple scattered small contusions in the cerebellum and cerebrum, blood in the right lateral ventricle, a small contusion in the left thalamic area, a small right subdural haematoma, no mass effect, and no mid-line shift.

Cognitive assessment in 2007 revealed a cognitive profile consistent with an acceleration – deceleration –type traumatic brain injury with particular damage to the temporal lobes and anterior brain structures. There were severe impairments in memory, attention and many aspects of frontal-executive functioning.

JYS: was 23 year old right-handed male. In 2011 he sustained brain injury due to a road traffic accident: he was in a coma for a week, his GCS was 3/15, and a CT brain scan showed diffuse axonal injury with a small intraventracular bleed. It reported that he had prolonged post traumatic amnesia, indicating severe traumatic brain injury.

PAG: was a 52 year old female, right-handed, who sustained brain injury in 2010 following a series of CVAs. She suffered a right hemisphere occlusive CVA which developed into a malignant middle cerebral artery syndrome. Raised intracranial pressure necessitated a decompressive craniotomy. She had left side weakness and aphasia. CT scans showed no acute abnormality. After 24 hours, her stroke symptoms worsened with dropping in her GCS of 12/15 and inappropriate movements and behaviour noted. A second CT showed anterior cerebral artery (ACA) infarcts. 6 months after her injury, a follow-up CT scan showed infarction in her right MCA territory and frontal lobes bilaterally. She had perseveration in her speech, poor problem solving and executive dysfunction.

HM: was a 59 year old right -handed male. He had a history of multiple neurolololgical insults. His first cerebral vascular accident (CVA) occurred in November of 1998. He has a left sided subdural haematoma. Subsequent to his accident he had at least two other traumatic head injuries. Approximately one year after his participation in this study, he was diagnosed with vascular dementia.

MrL: was a 45 year old right-handed male, who was diagnosed with a left adenocarcinoma and underwent maxillectomy and left orbital enucleation in April 2007. Further to this he had radiotherapy and reconstructive surgery. He later developed difficulties in walking, slurred speech and right sided weakness. He further required a series of surgeries including the repair of the middle cranial fossa, drainage of an extradural empyema and excision of lesions of tissue in the temporal lobe.

MK: was a 38 year old right-handed female. She sustained a severe brain injury in 2004. Type I diabetes led to a hypoglycaemia attack with severe ketoacidosis and resulted in encephalopathy. On regaining consciousness, she was reported to have memory and language difficulties. MRI scan showed bilateral ischemic encephopathy of the basal ganglia.

JS: was a 64 year old right-handed male, with a diploma in mechanics. He sustained brain injury in October 2003 during a hypoxic episode whilst in cardiac arrest. He was ventilated and early confusion was reported.

MC: was a 28 year old right handed male, he sustained a severe traumatic brain injury in 2003 as a result of an alleged assault. His initial GCS was 3/15. CT scan at that time revealed a large right –sided extradural haematoma. Further scans showed a right thalamic infarct and left internal capsular infarct that were linked to left–sided weakness and co-ordination difficulties. An MRI scan at the time of testing for this thesis work showed white matter damage in left prefrontal cortex and right parietal contusion.

DL: was a 40 year old right handed male, who left school at 14. There were brief details in his records about his brain injury: a CT scan revealed left prefrontal and temporal lesions.

Appendix C: tDCS suitability screening form (Chapter 5)

THE UNIVERSITY of York

York Neuroimaging Centre
The Biocentre, York Science Park, Heslington, York, YO10 5DG
Tel. 01904 435329, Fax 01904 435356

Confidential
Safety Screening Form

If you agree to take part in this study, please answer the following questions. It is essential that you answer truthfully. The information you provide is for screening purposes only and will be kept completely confidential.

1. Have you ever suffered from any neurological or psychiatric conditions?

YES/NO If YES please give details (nature of condition, duration, current medication, etc).

2. Have you ever suffered from epilepsy, febrile convulsions in infancy, had a fit or seizure

YES/NO or recurrent fainting spells?

3. Does anyone in your immediate or distant family suffer from epilepsy?

YES/NO If YES please state your relationship to the affected family member.

4. Have you ever had an operation on your head or spine (including eye surgery)?

YES/NO If YES please give details.

5. Do you currently have any of the following fitted to your body?

YES/NO
Heart pacemaker
Cochlar (ear) implant
Medication pump
Surgical clips
Any other biomechanical implant

6. Have you ever had an injury to your eye involving metal fragments?

YES/NO

7. Do you have any skin damage or disease affecting your scalp of face?

YES/NO

8. Are you currently taking any unprescribed or prescribed medication?

YES/NO If YES please give details.

9. Are you currently undergoing anti-malarial treatment?

YES/NO

10. Have you drunk more than 3 units of alcohol in the last 24 hours?

YES/NO

11. Have you already drunk alcohol today?

YES/NO

12. Have you had more than one cup of coffee, or other sources of caffeine, in the last hour? YES/NO

13. Have you used recreational drugs in the last 24 hours?

YES/NO

14. Did you have very little sleep last night?

YES/NO

15. Have you already participated in a TMS/tDCS experiment today?

YES/NO

16. Are you or could you be pregnant?

YES/NO

Participant details:

17. Are you left or right handed?

Left/Right

18. Date of birth

__/__/__

I understand that the above questions check for serious risk factors. I CONFIRM THAT I HAVE READ, UNDERSTOOD AND CORRECTLY ANSWERED THE ABOVE QUESTIONS

IN CASE OF ANY DOUBT, please inform the investigator before signing this form.

Participant's Name ………..…………….…..… Signature ……………………… Date ……………..

Researcher's Name ………..……………….…... Signature ……………………… Date

Appendix D:

Sensation rating questionnaire (Chapter 5)

Participant code: **Date:**
Experiment:
Session:

Did you experience any sensations during the DC stimulation? Please describe your experiences by ticking the relevant boxes, using the scale below:

None: I did not feel the described sensation

Mild: I felt the sensation a little bit

Moderate: I clearly felt the sensation

Considerable: I felt the sensation to a considerable degree

Strong: The sensation was strong/intense

	None	Mild	Moderate	Considerable	Strong
Itchiness					
Pain					
Burning					
Warmth/Heat					
Pinching					
Iron taste					
Fatigue					
Other --------					

If you felt any sensations, please give more details by circling the appropriate descriptions below:

When did the sensations begin:

At the beginning of the stimulation In the middle Towards the end

How long did they last:

They stopped soon They lasted some minutes Until stimulation ended

How much did the sensations affect your performance?

Not at all A little Quite a lot A lot A huge amount

Please give any more information below:

Appendix D: Frequency of sensation ratings after first session of tDCS (Chapter 5)

i) Sensation ratings after sham tDCS (n=18)

Rating	Itchiness	Pain	Burning	Heat	Pinching	Iron taste	Fatigue	Stinging	Begin	Length	Affected
0	6	14	14	6	6	16	13	16	N/A	N/A	9
1	9	4	4	11	10	1	4	2	18	10	8
2	2	-	-	1	2	1	-	-	-	8	-
3	1	-	-	-	-	-	1	-	-	-	-
4	-	-	-	-	-	-	-	-	N/A	N/A	1

ii) Sensation ratings after anodal tDCS (n=17)

Rating	Itchiness	Pain	Burning	Heat	Pinching	Iron taste	Fatigue	Stinging	Begin	Length	Affected
0	5	11	10	4	10	16	16	16	N/A	N/A	12
1	4	6	6	11	5	1	1	-	16	4	5
2	6	-	1	1	2	-	-	1	1	9	-
3	2	-	-	1	-	-	-	-	-	4	-
4	-	-	-	-	-	-	-	-	N/A	N/A	-

NB: From pain rating questionnaire given to a random sample of 25 participants. Scales for sensation types: 0 = none, 1 = mild, 2 = moderate, 3 = considerable, 4= strong; for sensation onset: 1= at the beginning of the stimulation, 2 = in the middle, 3 = towards the end; for sensation duration: 1 = they stopped soon, 2 = they lasted some minutes, 3 = they lasted until the stimulation ended; for affect on performance: 0 = not at all, 1 = a little, 2 = quite a lot, 3 = a lot, 4 = a huge amount.

Appendix E: Stimuli used in tDCS expermints (Chapter 5)

Block A

Block	Probe	choice1	choice2	choice3	Cond	Task
1	PrCGPLi.bmp	ChTGMDo.bmp	ChCBLLi.bmp	ChSGPLi.bmp	shape	figure feature
2	PrCRLSq.bmp	ChSRLSq.bmp	ChTRPLi.bmp	ChCGPLi.bmp	shape	figure feature
3	PrSRLSq.bmp	ChTRPDo.bmp	ChCRLSq.bmp	ChSGPLi.bmp	shape	figure feature
4	PrTBLDo.bmp	ChTGPSq.bmp	ChSGMDo.bmp	ChCBLDo.bmp	shape	figure feature
5	PrCBPSq.bmp	ChSGPLi.bmp	ChCRLDo.bmp	ChTBPSq.bmp	shape	figure feature
6	PrSBMDo.bmp	ChSRLSq.bmp	ChCBMDo.bmp	ChTGMSq.bmp	shape	figure feature
7	PrTRMLi.bmp	ChTBLSq.bmp	ChSBMDo.bmp	ChCRMLi.bmp	shape	figure feature
8	PrSGPSq.bmp	ChCGPSq.bmp	ChSRMLi.bmp	ChTGLLi.bmp	shape	figure feature
9	PrTGLLi.bmp	ChCBMLi.bmp	ChTGPLi.bmp	ChSRLDo.bmp	size	figure feature
10	PrSGLLi.bmp	ChSGPLi.bmp	ChCRLSq.bmp	ChCBMLi.bmp	size	figure feature
11	PrCGPLi.bmp	ChCGMLi.bmp	ChTGLDo.bmp	ChTRPDo.bmp	size	figure feature
12	PrSBLLi.bmp	ChCBPDo.bmp	ChSBMLi.bmp	ChCGLDo.bmp	size	figure feature
13	PrSBPLi.bmp	ChTGMLi.bmp	ChTRPDo.bmp	ChSBMLi.bmp	size	figure feature
14	PrCRLSq.bmp	ChTGLLi.bmp	ChCRMSq.bmp	ChSRPLi.bmp	size	figure feature
15	PrCGLDo.bmp	ChSBLLi.bmp	ChSBMDo.bmp	ChCGMDo.bmp	size	figure feature
16	PrSBMDo.bmp	ChSBLDo.bmp	ChSRMSq.bmp	ChSGPSq.bmp	size	figure feature
17	PrTRMLi.bmp	ChTGPSq.bmp	ChCRLDo.bmp	ChTBMLi.bmp	colour	figure feature
18	PrTGLLi.bmp	ChCGMSq.bmp	ChTRLLi.bmp	ChCBMLi.bmp	colour	figure feature
19	PrCRMSq.bmp	ChCBMSq.bmp	ChCRPDo.bmp	ChTGLSq.bmp	colour	figure feature
20	PrSGLLi.bmp	ChCBMLi.bmp	ChSRLLi.bmp	ChCGPDo.bmp	colour	figure feature
21	PrSBPLi.bmp	ChCBMDo.bmp	ChTRMLi.bmp	ChSGPLi.bmp	colour	figure feature
22	PrCBLDo.bmp	ChCGLDo.bmp	ChSRMDo.bmp	ChSBMLi.bmp	colour	figure feature
23	PrCBPSq.bmp	ChTGPLi.bmp	ChCRPSq.bmp	ChTBLDo.bmp	colour	figure feature
24	PrSRLSq.bmp	ChTRMLi.bmp	ChSGLSq.bmp	ChSBPLi.bmp	colour	figure feature
25	PrSBPLi.bmp	ChTGPDo.bmp	ChSBPDo.bmp	ChTGMLi.bmp	texture	figure feature
26	PrSGLLi.bmp	ChCBLLi.bmp	ChSGLDo.bmp	ChTGPDo.bmp	texture	figure feature
27	PrSGPSq.bmp	ChSGPLi.bmp	ChCRMSq.bmp	ChCBPDo.bmp	texture	figure feature
28	PrCGLDo.bmp	ChTBPDo.bmp	ChSBLLi.bmp	ChCGLSq.bmp	texture	figure feature
29	PrTRMLi.bmp	ChCRLSq.bmp	ChCGPLi.bmp	ChTRMDo.bmp	texture	figure feature
30	PrTRPSq.bmp	ChTGLDo.bmp	ChTRPDo.bmp	ChCGPSq.bmp	texture	figure feature
31	PrCGPLi.bmp	ChTRMLi.bmp	ChCGPDo.bmp	ChSGMDo.bmp	texture	figure feature
32	PrCBPSq.bmp	ChCGLLi.bmp	ChTRMSq.bmp	ChCBPLi.bmp	texture	figure feature
33	camel	slug	coin	hump	high	semantic high
34	leaf	brace	tree	pupil	high	semantic high
35	melon	angel	cantelope	thief	high	semantic high
36	emerald	jewel	prophet	screw	high	semantic high
37	Hat	head	recipe	grade	high	semantic high
38	Rug	queen	cliche	carpet	high	semantic high
39	blackboard	body	rubber	blonde	high	semantic high
40	house	home	lesson	census	high	semantic high
41	author	writer	tea	cloth	high	semantic high
42	aspirin	mine	tablet	deputy	high	semantic high
43	Tusk	ivory	town	savage	high	semantic high
44	tortoise	mold	mantle	turtle	high	semantic high
45	pound	hearts	shilling	saviour	high	semantic high
46	highway	road	teen	toilet	high	semantic high
47	square	alumni	triangle	wrath	high	semantic high
48	mouse	cat	gospel	heaven	high	semantic high

49	sickness	top	desk	disease	high	semantic high
50	cookie	biscuit	bait	army	high	semantic high
51	Novel	wart	market	book	high	semantic high
52	strand	drawer	hair	break	high	semantic high
53	Ocean	purpose	waves	worker	high	semantic high
54	Heat	joy	tower	sweat	high	semantic high
55	blouse	shirt	lid	fool	high	semantic high
56	Cat	dog	tenant	method	high	semantic high
57	Coin	salami	pound	potato	high	semantic high
58	Nose	face	errand	guide	high	semantic high
59	Date	canoe	coast	fig	high	semantic high
60	Moon	star	crisis	boat	high	semantic high
61	Dish	molehill	plate	easel	high	semantic high
62	backbone	pit	horror	spine	high	semantic high
63	music	coal	lunch	sound	high	semantic high
64	dinner	grudge	supper	cavity	high	semantic high
65	Iron	ring	midwife	hitch	low	semantic low
66	house	name	curve	tent	low	semantic low
67	Vat	ramp	tub	creek	low	semantic low
68	antelope	school	wave	stag	low	semantic low
69	Omen	paper	hotel	charm	low	semantic low
70	sickness	sore	cabin	bag	low	semantic low
71	mustard	sailor	oak	paste	low	semantic low
72	Sheep	tappet	dip	sack	low	semantic low
73	dolphin	shore	porpoise	firm	low	semantic low
74	Wax	grease	relative	car	low	semantic low
75	briefcase	canvas	satchel	lip	low	semantic low
76	spring	aisle	hatch	loop	low	semantic low
77	circus	banker	nerve	acrobat	low	semantic low
78	blouse	necklace	inning	knife	low	semantic low
79	pillow	rail	sheet	elder	low	semantic low
80	whisker	scratch	media	widow	low	semantic low
81	blossom	wit	sponge	magnolia	low	semantic low
82	barracuda	wheel	lobe	snake	low	semantic low
83	River	bridge	breast	cup	low	semantic low
84	whistle	dish	tone	atmosphere	low	semantic low
85	Dart	ranch	dagger	vow	low	semantic low
86	Cider	juice	race	comedy	low	semantic low
87	Pupil	jet	liquor	eyelid	low	semantic low
88	tortoise	zone	entry	snail	low	semantic low
89	Celery	tail	lettuce	joint	low	semantic low
90	Pilot	navigator	motherland	rival	low	semantic low
91	tablecloth	square	farm	train	low	semantic low
92	Street	piano	gutter	note	low	semantic low
93	Beach	lock	whip	boat	low	semantic low
94	Priest	hood	bomb	gear	low	semantic low
95	mountain	director	mound	regime	low	semantic low
96	Thing	creature	disc	aim	low	semantic low
97	grass	record	emerald	hay	colour	semantic feature
98	salmon	business	stream	rose	colour	semantic feature
99	tooth	dentist	cloud	pet	colour	semantic feature
100	Ivy	jade	wall	bulb	colour	semantic feature

101	Pig	sty	skull	bubblegum	colour	semantic feature
102	dandelion	canary	gun	weed	colour	semantic feature
103	parsley	arch	leprechaun	garnish	colour	semantic feature
104	snow	cottonbud	rain	basket	colour	semantic feature
105	coin	hoop	purse	shield	shape	semantic feature
106	helmet	bowl	tombstone	bicycle	shape	semantic feature
107	bow	lump	banana	arrow	shape	semantic feature
108	diary	ring	date	butter	shape	semantic feature
109	barrel	gun	basket	finger	shape	semantic feature
110	clock	button	elbow	bell	shape	semantic feature
111	shed	tool	pan	hut	shape	semantic feature
112	wand	fairy	meat	branch	shape	semantic feature
113	Bee	factory	berry	honey	size	semantic feature
114	lantern	bulb	corpse	bottle	size	semantic feature
115	battery	pecan	radio	elbow	size	semantic feature
116	grenade	gun	apple	villa	size	semantic feature
117	chisel	statue	whisk	car	size	semantic feature
118	ladder	fingernail	step	plank	size	semantic feature
119	nurse	baboon	coin	hospital	size	semantic feature
120	knife	seed	butter	pen	size	semantic feature
121	butter	pet	clay	bread	texture	semantic feature
122	vaseline	lips	paper	mayonnaise	texture	semantic feature
123	bandanna	cloth	cowboy	hook	texture	semantic feature
124	squirrel	mobile	nuts	blanket	texture	semantic feature
125	poppy	pad	napkin	opium	texture	semantic feature
126	glass	pipe	timber	drink	texture	semantic feature
127	Flag	country	curtain	slide	texture	semantic feature
128	bandage	wound	lips	tablecloth	texture	semantic feature

Block D

Block	Probe	choice1	choice2	choice3	Cond	Condition
1	flower	wage	yankee	daisy	low	semantic low
2	town	meeting	baby	injury	low	semantic low
3	screw	picnic	bolt	crew	low	semantic low
4	pony	bust	mane	crane	low	semantic low
5	detective	offer	pond	search	low	semantic low
6	apricot	member	nectarine	party	low	semantic low
7	tusk	tooth	reflex	hawk	low	semantic low
8	zebra	tune	chapel	zoo	low	semantic low
9	entrance	column	front	magnet	low	semantic low
10	Gin	breed	ale	finale	low	semantic low
11	thunder	cloud	musket	family	low	semantic low
12	Hat	scarf	steak	chart	low	semantic low
13	swamp	atlas	mush	novel	low	semantic low
14	rope	booth	tie	myriad	low	semantic low
15	rake	hole	labour	fork	low	semantic low
16	fork	spoon	ham	misery	low	semantic low
17	monsoon	parish	climate	enzyme	low	semantic low
18	ant	accord	beetle	watch	low	semantic low
19	whiskey	outfit	travel	ice	low	semantic low
20	jacket	industry	suit	crest	low	semantic low

21	fence	reef	picket	tank	low	semantic low
22	fruit	bowl	vector	salt	low	semantic low
23	pea	dad	mattress	mail	low	semantic low
24	death	pollen	odour	coffin	low	semantic low
25	man	tree	child	tweed	low	semantic low
26	pound	brow	gate	pence	low	semantic low
27	problem	matter	column	gaze	low	semantic low
28	message	kitten	call	diet	low	semantic low
29	kitchen	support	donor	set	low	semantic low
30	gown	robe	rage	trap	low	semantic low
31	queen	card	elephant	list	low	semantic low
32	Bee	history	salami	hum	low	semantic low
33	wagon	sun	hydrant	wheel	colour	semantic feature
34	tobacco	coffee	smoke	dishwasher	colour	semantic feature
35	clarinet	ebony	flute	postbox	colour	semantic feature
36	balloon	air	lollipop	sludge	colour	semantic feature
37	burger	fries	lace	log	colour	semantic feature
38	pepper	tar	pear	salt	colour	semantic feature
39	lawn	revolver	sprite	mower	colour	semantic feature
40	onion	tears	boot	kleenex	colour	semantic feature
41	club	member	father	baguette	size	semantic feature
42	owl	hoot	pool	football	size	semantic feature
43	razor	bit	shave	tree	size	semantic feature
44	brick	belly	squash	wall	size	semantic feature
45	camel	callbox	hump	handbag	size	semantic feature
46	lobster	mountain	crab	mailbox	size	semantic feature
47	boot	car	pigeon	nail	size	semantic feature
48	peanut	cake	paperclip	telly	size	semantic feature
49	web	candyfloss	site	newspaper	texture	semantic feature
50	scarf	neck	cab	tissue	texture	semantic feature
51	List	groceries	receipt	ladder	texture	semantic feature
52	scissors	cloth	bracelet	toe	texture	semantic feature
53	broom	hay	cupboard	spider	texture	semantic feature
54	brush	milk	paint	porcupine	texture	semantic feature
55	plaster	styrofoam	wound	lagoon	texture	semantic feature
56	pineapple	drink	plastic	womb	texture	semantic feature
57	painter	cart	drawing	chef	shape	semantic feature
58	cross	washbasin	intersection	jesus	shape	semantic feature
59	volleyball	heart	net	boulder	shape	semantic feature
60	comet	sperm	sky	book	shape	semantic feature
61	record	tape	frisbee	frame	shape	semantic feature
62	saucer	tea	pizza	model	shape	semantic feature
63	eagle	nest	scoop	jet	shape	semantic feature
64	hook	cane	room	line	shape	semantic feature
65	PrTBLDo.bmp	ChSRPDo.bmp	ChCBPLi.bmp	ChTGLDo.bmp	colour	figure feature
66	PrTBPSq.bmp	ChSBLDo.bmp	ChSGPLi.bmp	ChTRPSq.bmp	colour	figure feature
67	PrSGPSq.bmp	ChTGMSq.bmp	ChSRPSq.bmp	ChSBLLi.bmp	colour	figure feature
68	PrSBLLi.bmp	ChCRPLi.bmp	ChTBPDo.bmp	ChSGLLi.bmp	colour	figure feature
69	PrCRLSq.bmp	ChCGLSq.bmp	ChSBLLi.bmp	ChCRMDo.bmp	colour	figure feature
70	PrCGLDo.bmp	ChSBMDo.bmp	ChCRLDo.bmp	ChCGPLi.bmp	colour	figure feature
71	PrCGLSq.bmp	ChCRLSq.bmp	ChSGMDo.bmp	ChSBLLi.bmp	colour	figure feature
72	PrTBLLi.bmp	ChCBMDo.bmp	ChSRLLi.bmp	ChTGLLi.bmp	colour	figure feature

73	PrTRLSq.bmp	ChTBMLi.bmp	ChCRLSq.bmp	ChSGPSq.bmp	shape	figure feature
74	PrCRMSq.bmp	ChCBLLi.bmp	ChSGLSq.bmp	ChTRMSq.bmp	shape	figure feature
75	PrCGLSq.bmp	ChTRLLi.bmp	ChCRMDo.bmp	ChSGLSq.bmp	shape	figure feature
76	PrSBPLi.bmp	ChTGMLi.bmp	ChCBPLi.bmp	ChSRLDo.bmp	shape	figure feature
77	PrTRPSq.bmp	ChCRPSq.bmp	ChTBLDo.bmp	ChSGPLi.bmp	shape	figure feature
78	PrCGLDo.bmp	ChTGLDo.bmp	ChSBMDo.bmp	ChCBMLi.bmp	shape	figure feature
79	PrTBLLi.bmp	ChCBLLi.bmp	ChTGPSq.bmp	ChSBPDo.bmp	shape	figure feature
80	PrSBLLi.bmp	ChSGPSq.bmp	ChCBLLi.bmp	ChTBPDo.bmp	shape	figure feature
81	PrCBLDo.bmp	ChSGPDo.bmp	ChSBPSq.bmp	ChCBLSq.bmp	texture	figure feature
82	PrTRLSq.bmp	ChTRLLi.bmp	ChCRMLi.bmp	ChSGPSq.bmp	texture	figure feature
83	PrTBPSq.bmp	ChCRMSq.bmp	ChTRLDo.bmp	ChTBPLi.bmp	texture	figure feature
84	PrTBLLi.bmp	ChSGMLi.bmp	ChTBLDo.bmp	ChSBPSq.bmp	texture	figure feature
85	PrCGLSq.bmp	ChCGLLi.bmp	ChSRMSq.bmp	ChCBPDo.bmp	texture	figure feature
86	PrTBLDo.bmp	ChTBLSq.bmp	ChSRLSq.bmp	ChCBMDo.bmp	texture	figure feature
87	PrTGLLi.bmp	ChCBLDo.bmp	ChTGLDo.bmp	ChSBMLi.bmp	texture	figure feature
88	PrCRMSq.bmp	ChTRLLi.bmp	ChTGPSq.bmp	ChCRMLi.bmp	texture	figure feature
89	PrCBPSq.bmp	ChSRPLi.bmp	ChCBMSq.bmp	ChTGLSq.bmp	size	figure feature
90	PrCBLDo.bmp	ChCBMDo.bmp	ChSGPDo.bmp	ChSGLLi.bmp	size	figure feature
91	PrSGPSq.bmp	ChTRPDo.bmp	ChSGMSq.bmp	ChTGLLi.bmp	size	figure feature
92	PrSBLDo.bmp	ChSBMDo.bmp	ChTGLLi.bmp	ChTGMDo.bmp	size	figure feature
93	PrCRMSq.bmp	ChTGPSq.bmp	ChTBMDo.bmp	ChCRLSq.bmp	size	figure feature
94	PrTRLSq.bmp	ChSBLDo.bmp	ChSGPSq.bmp	ChTRMSq.bmp	size	figure feature
95	PrTRMLi.bmp	ChSBLLi.bmp	ChCGMDo.bmp	ChTRPLi.bmp	size	figure feature
96	PrSRLSq.bmp	ChSRMSq.bmp	ChTBPSq.bmp	ChCGLDo.bmp	size	figure feature
97	stair	kid	way	amen	high	semantic high
98	thunder	lightning	manuscript	science	high	semantic high
99	dart	arrow	cereal	python	high	semantic high
100	harbour	machine	head	boat	high	semantic high
101	balloon	buck	lotion	ball	high	semantic high
102	mustard	peak	hotdog	post	high	semantic high
103	mass	weight	lady	club	high	semantic high
104	pilot	drum	nose	plane	high	semantic high
105	bronze	slope	statue	deal	high	semantic high
106	butterfly	trip	moth	barrel	high	semantic high
107	fuse	box	driver	glory	high	semantic high
108	pebble	stone	person	decade	high	semantic high
109	problem	oxygen	bee	maths	high	semantic high
110	dress	pause	skirt	limb	high	semantic high
111	scarf	legion	manure	neck	high	semantic high
112	Bill	algae	money	team	high	semantic high
113	Calf	cow	wood	class	high	semantic high
114	table	male	hip	chair	high	semantic high
115	lamp	cast	shade	towel	high	semantic high
116	patio	glow	porch	grant	high	semantic high
117	screw	shade	fur	nail	high	semantic high
118	briefcase	suitcase	fin	deck	high	semantic high
119	sweater	machine	client	wool	high	semantic high
120	zebra	stripe	coach	ruin	high	semantic high
121	ankle	arrow	carbon	leg	high	semantic high
122	stick	morning	horse	stone	high	semantic high
123	town	city	monk	lane	high	semantic high
124	roach	scotch	attic	ant	high	semantic high

125	sock	gland	maid	shoe	high	semantic high
126	justice	tarmac	peace	madame	high	semantic high
127	Cup	mug	wick	glare	high	semantic high
128	leaflet	dessert	pamphlet	scale	high	semantic high

Block B

Block	probe	choice1	choice2	choice3	cond	task
1	stair	kid	way	amen	high	semantic high
2	thunder	lightning	manuscript	science	high	semantic high
3	dart	arrow	cereal	python	high	semantic high
4	harbour	machine	head	boat	high	semantic high
5	balloon	buck	lotion	ball	high	semantic high
6	mustard	peak	hotdog	post	high	semantic high
7	mass	weight	lady	club	high	semantic high
8	pilot	drum	nose	plane	high	semantic high
9	bronze	slope	statue	deal	high	semantic high
10	butterfly	trip	moth	barrel	high	semantic high
11	fuse	box	driver	glory	high	semantic high
12	pebble	stone	person	decade	high	semantic high
13	problem	oxygen	bee	maths	high	semantic high
14	dress	pause	skirt	limb	high	semantic high
15	scarf	legion	manure	neck	high	semantic high
16	bill	algae	money	team	high	semantic high
17	calf	cow	wood	class	high	semantic high
18	table	male	hip	chair	high	semantic high
19	lamp	cast	shade	towel	high	semantic high
20	patio	glow	porch	grant	high	semantic high
21	screw	shade	fur	nail	high	semantic high
22	briefcase	suitcase	fin	deck	high	semantic high
23	sweater	machine	client	wool	high	semantic high
24	zebra	stripe	coach	ruin	high	semantic high
25	ankle	arrow	carbon	leg	high	semantic high
26	stick	morning	horse	stone	high	semantic high
27	town	city	monk	lane	high	semantic high
28	roach	scotch	attic	ant	high	semantic high
29	sock	gland	maid	shoe	high	semantic high
30	justice	tarmac	peace	madame	high	semantic high
31	cup	mug	wick	glare	high	semantic high
32	leaflet	dessert	pamphlet	scale	high	semantic high
33	flower	wage	yankee	daisy	low	semantic low
34	town	meeting	baby	injury	low	semantic low
35	screw	picnic	bolt	crew	low	semantic low
36	pony	bust	mane	crane	low	semantic low
37	detective	offer	pond	search	low	semantic low
38	apricot	member	nectarine	party	low	semantic low
39	tusk	tooth	reflex	hawk	low	semantic low
40	zebra	tune	chapel	zoo	low	semantic low
41	entrance	column	front	magnet	low	semantic low
42	gin	breed	ale	finale	low	semantic low
43	thunder	cloud	musket	family	low	semantic low
44	hat	scarf	steak	chart	low	semantic low

45	swamp	atlas	mush	novel	low	semantic low
46	rope	booth	tie	myriad	low	semantic low
47	rake	hole	labour	fork	low	semantic low
48	fork	spoon	ham	misery	low	semantic low
49	monsoon	parish	climate	enzyme	low	semantic low
50	ant	accord	beetle	watch	low	semantic low
51	whiskey	outfit	travel	ice	low	semantic low
52	jacket	industry	suit	crest	low	semantic low
53	fence	reef	picket	tank	low	semantic low
54	fruit	bowl	vector	salt	low	semantic low
55	pea	dad	mattress	mail	low	semantic low
56	death	pollen	odour	coffin	low	semantic low
57	man	tree	child	tweed	low	semantic low
58	pound	brow	gate	pence	low	semantic low
59	problem	matter	column	gaze	low	semantic low
60	message	kitten	call	diet	low	semantic low
61	kitchen	support	donor	set	low	semantic low
62	gown	robe	rage	trap	low	semantic low
63	queen	card	elephant	list	low	semantic low
64	bee	history	salami	hum	low	semantic low
65	wagon	sun	hydrant	wheel	colour	semantic feature
66	tobacco	coffee	smoke	dishwasher	colour	semantic feature
67	clarinet	ebony	flute	postbox	colour	semantic feature
68	balloon	air	lollipop	sludge	colour	semantic feature
69	burger	fries	lace	log	colour	semantic feature
70	pepper	tar	pear	salt	colour	semantic feature
71	lawn	revolver	sprite	mower	colour	semantic feature
72	onion	tears	boot	kleenex	colour	semantic feature
73	club	member	father	baguette	size	semantic feature
74	owl	hoot	pool	football	size	semantic feature
75	razor	bit	shave	tree	size	semantic feature
76	brick	belly	squash	wall	size	semantic feature
77	camel	callbox	hump	handbag	size	semantic feature
78	lobster	mountain	crab	mailbox	size	semantic feature
79	boot	car	pigeon	nail	size	semantic feature
80	peanut	cake	paperclip	telly	size	semantic feature
81	web	candyfloss	site	newspaper	texture	semantic feature
82	scarf	neck	cab	tissue	texture	semantic feature
83	list	groceries	receipt	ladder	texture	semantic feature
84	scissors	cloth	bracelet	toe	texture	semantic feature
85	broom	hay	cupboard	spider	texture	semantic feature
86	brush	milk	paint	porcupine	texture	semantic feature
87	plaster	styrofoam	wound	lagoon	texture	semantic feature
88	pineapple	drink	plastic	womb	texture	semantic feature
89	painter	cart	drawing	chef	shape	semantic feature
90	cross	washbasin	intersection	jesus	shape	semantic feature
91	volleyball	heart	net	boulder	shape	semantic feature
92	comet	sperm	sky	book	shape	semantic feature
93	record	tape	frisbee	frame	shape	semantic feature
94	saucer	tea	pizza	model	shape	semantic feature
95	eagle	nest	scoop	jet	shape	semantic feature
96	hook	cane	room	line	shape	semantic feature

97	PrTBLDo.bmp	ChSRPDo.bmp	ChCBPLi.bmp	ChTGLDo.bmp	colour	figure feature
98	PrTBPSq.bmp	ChSBLDo.bmp	ChSGPLi.bmp	ChTRPSq.bmp	colour	figure feature
99	PrSGPSq.bmp	ChTGMSq.bmp	ChSRPSq.bmp	ChSBLLi.bmp	colour	figure feature
100	PrSBLLi.bmp	ChCRPLi.bmp	ChTBPDo.bmp	ChSGLLi.bmp	colour	figure feature
101	PrCRLSq.bmp	ChCGLSq.bmp	ChSBLLi.bmp	ChCRMDo.bmp	colour	figure feature
102	PrCGLDo.bmp	ChSBMDo.bmp	ChCRLDo.bmp	ChCGPLi.bmp	colour	figure feature
103	PrCGLSq.bmp	ChCRLSq.bmp	ChSGMDo.bmp	ChSBLLi.bmp	colour	figure feature
104	PrTBLLi.bmp	ChCBMDo.bmp	ChSRLLi.bmp	ChTGLLi.bmp	colour	figure feature
105	PrTRLSq.bmp	ChTBMLi.bmp	ChCRLSq.bmp	ChSGPSq.bmp	shape	figure feature
106	PrCRMSq.bmp	ChCBLLi.bmp	ChSGLSq.bmp	ChTRMSq.bmp	shape	figure feature
107	PrCGLSq.bmp	ChTRLLi.bmp	ChCRMDo.bmp	ChSGLSq.bmp	shape	figure feature
108	PrSBPLi.bmp	ChTGMLi.bmp	ChCBPLi.bmp	ChSRLDo.bmp	shape	figure feature
109	PrTRPSq.bmp	ChCRPSq.bmp	ChTBLDo.bmp	ChSGPLi.bmp	shape	figure feature
110	PrCGLDo.bmp	ChTGLDo.bmp	ChSBMDo.bmp	ChCBMLi.bmp	shape	figure feature
111	PrTBLLi.bmp	ChCBLLi.bmp	ChTGPSq.bmp	ChSBPDo.bmp	shape	figure feature
112	PrSBLLi.bmp	ChSGPSq.bmp	ChCBLLi.bmp	ChTBPDo.bmp	shape	figure feature
113	PrCBLDo.bmp	ChSGPDo.bmp	ChSBPSq.bmp	ChCBLSq.bmp	texture	figure feature
114	PrTRLSq.bmp	ChTRLLi.bmp	ChCRMLi.bmp	ChSGPSq.bmp	texture	figure feature
115	PrTBPSq.bmp	ChCRMSq.bmp	ChTRLDo.bmp	ChTBPLi.bmp	texture	figure feature
116	PrTBLLi.bmp	ChSGMLi.bmp	ChTBLDo.bmp	ChSBPSq.bmp	texture	figure feature
117	PrCGLSq.bmp	ChCGLLi.bmp	ChSRMSq.bmp	ChCBPDo.bmp	texture	figure feature
118	PrTBLDo.bmp	ChTBLSq.bmp	ChSRLSq.bmp	ChCBMDo.bmp	texture	figure feature
119	PrTGLLi.bmp	ChCBLDo.bmp	ChTGLDo.bmp	ChSBMLi.bmp	texture	figure feature
120	PrCRMSq.bmp	ChTRLLi.bmp	ChTGPSq.bmp	ChCRMLi.bmp	texture	figure feature
121	PrCBPSq.bmp	ChSRPLi.bmp	ChCBMSq.bmp	ChTGLSq.bmp	size	figure feature
122	PrCBLDo.bmp	ChCBMDo.bmp	ChSGPDo.bmp	ChSGLLi.bmp	size	figure feature
123	PrSGPSq.bmp	ChTRPDo.bmp	ChSGMSq.bmp	ChTGLLi.bmp	size	figure feature
124	PrSBLDo.bmp	ChSBMDo.bmp	ChTGLLi.bmp	ChTGMDo.bmp	size	figure feature
125	PrCRMSq.bmp	ChTGPSq.bmp	ChTBMDo.bmp	ChCRLSq.bmp	size	figure feature
126	PrTRLSq.bmp	ChSBLDo.bmp	ChSGPSq.bmp	ChTRMSq.bmp	size	figure feature
127	PrTRMLi.bmp	ChSBLLi.bmp	ChCGMDo.bmp	ChTRPLi.bmp	size	figure feature
128	PrSRLSq.bmp	ChSRMSq.bmp	ChTBPSq.bmp	ChCGLDo.bmp	size	figure feature

Block C

Block	**probe**	**choice1**	**choice2**	**choice3**	**cond**	**task**
1	iron	midwife	hitch	ring	low	semantic low
2	house	curve	tent	name	low	semantic low
3	vat	tub	creek	ramp	low	semantic low
4	antelope	wave	stag	school	low	semantic low
5	omen	hotel	charm	paper	low	semantic low
6	sickness	cabin	bag	sore	low	semantic low
7	mustard	oak	paste	sailor	low	semantic low
8	sheep	dip	sack	tappet	low	semantic low
9	dolphin	porpoise	firm	shore	low	semantic low
10	wax	relative	car	grease	low	semantic low
11	briefcase	satchel	lip	canvas	low	semantic low
12	spring	hatch	loop	aisle	low	semantic low
13	circus	nerve	acrobat	banker	low	semantic low
14	blouse	inning	knife	necklace	low	semantic low
15	pillow	sheet	elder	rail	low	semantic low
16	whisker	media	widow	scratch	low	semantic low
17	blossom	sponge	magnolia	wit	low	semantic low
18	barracuda	lobe	snake	wheel	low	semantic low

19	river	breast	cup	bridge	low	semantic low
20	whistle	tone	atmosphere	dish	low	semantic low
21	dart	dagger	vow	ranch	low	semantic low
22	cider	race	comedy	juice	low	semantic low
23	pupil	liquor	eyelid	jet	low	semantic low
24	tortoise	entry	snail	zone	low	semantic low
25	celery	lettuce	joint	tail	low	semantic low
26	pilot	motherland	rival	navigator	low	semantic low
27	tablecloth	farm	train	square	low	semantic low
28	street	gutter	note	piano	low	semantic low
29	beach	whip	boat	lock	low	semantic low
30	priest	bomb	gear	hood	low	semantic low
31	mountain	mound	regime	director	low	semantic low
32	thing	disc	aim	creature	low	semantic low
33	grass	hay	emerald	record	colour	semantic feature
34	salmon	rose	stream	business	colour	semantic feature
35	tooth	pet	cloud	dentist	colour	semantic feature
36	ivy	bulb	wall	jade	colour	semantic feature
37	pig	bubblegum	skull	sty	colour	semantic feature
38	dandelion	weed	gun	canary	colour	semantic feature
39	parsley	garnish	leprechaun	arch	colour	semantic feature
40	snow	basket	rain	cottonbud	colour	semantic feature
41	coin	purse	shield	hoop	shape	semantic feature
42	helmet	tombstone	bicycle	bowl	shape	semantic feature
43	bow	banana	arrow	lump	shape	semantic feature
44	diary	date	butter	ring	shape	semantic feature
45	barrel	basket	finger	gun	shape	semantic feature
46	clock	elbow	bell	button	shape	semantic feature
47	shed	pan	hut	tool	shape	semantic feature
48	wand	meat	branch	fairy	shape	semantic feature
49	bee	honey	factory	berry	size	semantic feature
50	lantern	bottle	bulb	corpse	size	semantic feature
51	battery	elbow	pecan	radio	size	semantic feature
52	grenade	villa	gun	apple	size	semantic feature
53	chisel	car	statue	whisk	size	semantic feature
54	ladder	plank	fingernail	step	size	semantic feature
55	nurse	hospital	baboon	coin	size	semantic feature
56	knife	pen	seed	butter	size	semantic feature
57	butter	clay	bread	pet	texture	semantic feature
58	vaseline	paper	mayonnaise	lips	texture	semantic feature
59	bandanna	cowboy	hook	cloth	texture	semantic feature
60	squirrel	nuts	blanket	mobile	texture	semantic feature
61	poppy	napkin	opium	pad	texture	semantic feature
62	glass	timber	drink	pipe	texture	semantic feature
63	flag	curtain	slide	country	texture	semantic feature
64	bandage	lips	tablecloth	wound	texture	semantic feature
65	PrCGPLi.bmp	ChCBLLi.bmp	ChSGPLi.bmp	ChTGMDo.bmp	shape	figure feature
66	PrCRLSq.bmp	ChTRPLi.bmp	ChCGPLi.bmp	ChSRLSq.bmp	shape	figure feature
67	PrSRLSq.bmp	ChCRLSq.bmp	ChSGPLi.bmp	ChTRPDo.bmp	shape	figure feature
68	PrTBLDo.bmp	ChSGMDo.bmp	ChCBLDo.bmp	ChTGPSq.bmp	shape	figure feature
69	PrCBPSq.bmp	ChCRLDo.bmp	ChTBPSq.bmp	ChSGPLi.bmp	shape	figure feature
70	PrSBMDo.bmp	ChCBMDo.bmp	ChTGMSq.bmp	ChSRLSq.bmp	shape	figure feature

71	PrTRMLi.bmp	ChSBMDo.bmp	ChCRMLi.bmp	ChTBLSq.bmp	shape	figure feature
72	PrSGPSq.bmp	ChSRMLi.bmp	ChTGLLi.bmp	ChCGPSq.bmp	shape	figure feature
73	PrTGLLi.bmp	ChSRLDo.bmp	ChCBMLi.bmp	ChTGPLi.bmp	size	figure feature
74	PrSGLLi.bmp	ChCBMLi.bmp	ChSGPLi.bmp	ChCRLSq.bmp	size	figure feature
75	PrCGPLi.bmp	ChTRPDo.bmp	ChCGMLi.bmp	ChTGLDo.bmp	size	figure feature
76	PrSBLLi.bmp	ChCGLDo.bmp	ChCBPDo.bmp	ChSBMLi.bmp	size	figure feature
77	PrSBPLi.bmp	ChSBMLi.bmp	ChTGMLi.bmp	ChTRPDo.bmp	size	figure feature
78	PrCRLSq.bmp	ChSRPLi.bmp	ChTGLLi.bmp	ChCRMSq.bmp	size	figure feature
79	PrCGLDo.bmp	ChCGMDo.bmp	ChSBLLi.bmp	ChSBMDo.bmp	size	figure feature
80	PrSBMDo.bmp	ChSGPSq.bmp	ChSBLDo.bmp	ChSRMSq.bmp	size	figure feature
81	PrTRMLi.bmp	ChTBMLi.bmp	ChTGPSq.bmp	ChCRLDo.bmp	colour	figure feature
82	PrTGLLi.bmp	ChCBMLi.bmp	ChCGMSq.bmp	ChTRLLi.bmp	colour	figure feature
83	PrCRMSq.bmp	ChTGLSq.bmp	ChCBMSq.bmp	ChCRPDo.bmp	colour	figure feature
84	PrSGLLi.bmp	ChCGPDo.bmp	ChCBMLi.bmp	ChSRLLi.bmp	colour	figure feature
85	PrSBPLi.bmp	ChSGPLi.bmp	ChCBMDo.bmp	ChTRMLi.bmp	colour	figure feature
86	PrCBLDo.bmp	ChSBMLi.bmp	ChCGLDo.bmp	ChSRMDo.bmp	colour	figure feature
87	PrCBPSq.bmp	ChTBLDo.bmp	ChTGPLi.bmp	ChCRPSq.bmp	colour	figure feature
88	PrSRLSq.bmp	ChSBPLi.bmp	ChTRMLi.bmp	ChSGLSq.bmp	colour	figure feature
89	PrSBPLi.bmp	ChSBPDo.bmp	ChTGMLi.bmp	ChTGPDo.bmp	texture	figure feature
90	PrSGLLi.bmp	ChSGLDo.bmp	ChTGPDo.bmp	ChCBLLi.bmp	texture	figure feature
91	PrSGPSq.bmp	ChCRMSq.bmp	ChCBPDo.bmp	ChSGPLi.bmp	texture	figure feature
92	PrCGLDo.bmp	ChSBLLi.bmp	ChCGLSq.bmp	ChTBPDo.bmp	texture	figure feature
93	PrTRMLi.bmp	ChCGPLi.bmp	ChTRMDo.bmp	ChCRLSq.bmp	texture	figure feature
94	PrTRPSq.bmp	ChTRPDo.bmp	ChCGPSq.bmp	ChTGLDo.bmp	texture	figure feature
95	PrCGPLi.bmp	ChCGPDo.bmp	ChSGMDo.bmp	ChTRMLi.bmp	texture	figure feature
96	PrCBPSq.bmp	ChTRMSq.bmp	ChCBPLi.bmp	ChCGLLi.bmp	texture	figure feature
97	camel	hump	slug	coin	high	semantic high
98	leaf	pupil	brace	tree	high	semantic high
99	melon	thief	angel	cantelope	high	semantic high
100	emerald	screw	jewel	prophet	high	semantic high
101	hat	grade	head	recipe	high	semantic high
102	rug	carpet	queen	cliche	high	semantic high
103	blackboard	blonde	body	rubber	high	semantic high
104	house	census	home	lesson	high	semantic high
105	author	cloth	writer	tea	high	semantic high
106	aspirin	deputy	mine	tablet	high	semantic high
107	tusk	savage	ivory	town	high	semantic high
108	tortoise	turtle	mold	mantle	high	semantic high
109	pound	saviour	hearts	shilling	high	semantic high
110	highway	toilet	road	teen	high	semantic high
111	square	wrath	alumni	triangle	high	semantic high
112	mouse	heaven	cat	gospel	high	semantic high
113	sickness	disease	top	desk	high	semantic high
114	cookie	army	biscuit	bait	high	semantic high
115	novel	book	wart	market	high	semantic high
116	strand	break	drawer	hair	high	semantic high
117	ocean	worker	purpose	waves	high	semantic high
118	heat	sweat	joy	tower	high	semantic high
119	blouse	fool	shirt	lid	high	semantic high
120	cat	method	dog	tenant	high	semantic high
121	coin	potato	salami	pound	high	semantic high
122	nose	guide	face	errand	high	semantic high

123	date	fig	canoe	coast	high	semantic high
124	moon	boat	star	crisis	high	semantic high
125	dish	easel	molehill	plate	high	semantic high
126	backbone	spine	pit	horror	high	semantic high
127	music	sound	coal	lunch	high	semantic high
128	dinner	cavity	grudge	supper	high	semantic high

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