Investigating the neural correlates of ongoing experience

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Dedication

To my son, Konstantinos, the brightest star in my universe.

Abstract

Spontaneous thoughts are heterogeneous and inherently dynamic. Despite their time-variant properties, studies exploring spontaneous thoughts have identified thematic patterns that exhibit trait-like characteristics and are stable across time. Concurrently, structural and functional neuroimaging studies have shown unique and stable whole-brain network configurations linked to behaviour either through the static and dynamic intrinsic communication and activity of their core regions or through informational exchange with each other. This thesis aimed to explore how these within and between network interactions at different temporal scales might relate to variations in ongoing experience. We utilised different neuroimaging modalities (diffusion weighted and functional magnetic resonance imaging) and applied both static and dynamic analyses techniques. We found evidence of inter-individual variation in all cases associated with different patterns of spontaneous thoughts. Experiment 1 found that variation in white matter architecture projecting to the hippocampus, as well as the stable functional interaction of the hippocampus with the medial prefrontal cortex were linked to the tendency of experiencing thoughts related to the future or the past. Experiment 2 found that static functional connectivity of the precuneus and a lateral fronto-temporal network was related to visual imagery. Furthermore, we found that coupling of a lateral visual network with regions of the brainstem and cerebellum was associated with ruminative thinking, self-consciousness and attentional problems. Importantly, our results highlighted an interaction among these associations, where the brainstem visual network coupling moderated the relationship between parietal-frontal regions and reports of visual imagery. Finally, Experiment 3 used hidden Markov modelling to identify dynamic neural states linked to thoughts related to problem-solving and less intrusive thinking, as well as better physical and mental health. Collectively, these studies highlight the utility of using both static and dynamic measures of neural function to understand patterns of ongoing experience.

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Acknowledgements

If someone told me a few years back, while still a physics teacher in Greece, that in a few years' time, I'll be in the UK, finishing a PhD and starting a career in cognitive neuroscience and neuroimaging, I would have said that they are probably out of their mind (pun intended). And yet, here we are, constantly challenging our priors and setting onto new adventures. No one, however, can succeed in such endeavours alone. Throughout these years, I have been extremely lucky to have the support of amazing people, to all of whom I would like to give a huge thanks for all their help.

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Declaration

I declare that the research described in this thesis is original work, which I undertook at the University of York during 2015 - 2019. Except where stated, all of the work contained within this thesis represents the original contribution of the author.

Some parts of this thesis have been published in journals; where items were published jointly with collaborators, the author of this thesis is responsible for the material presented here. For each published item, the primary author is the first listed author. Publications are listed at the beginning of the chapter to which they relate.

Chapter 1

Introduction and review of literature

1.1 Introduction

Conscious thoughts are often directed to external stimuli in the here and now, however, people spend 25 to 50% of their waking hours engaged in thoughts unrelated to the external environment (Kane et al., 2007; Killingsworth and Gilbert, 2010). Disengaging attention from an ongoing task or any immediate sensory inputs and focusing on self-generated thoughts is what is often studied under the umbrella term of mind-wandering (Seli et al., 2018). Patterns of self-generated thoughts are often complex and heterogeneous in nature. They can be intentional or unintentional (Seli et al., 2016), constrained deliberately or not (Christoff et al., 2016), directly related to personal goals or just plain distracting (Schooler et al., 2011; Smallwood, 2013a). At the same time, they might help with our creativity and improve our mood (Baird et al., 2012), while more ruminative thoughts can maintain states of unhappiness (Smallwood, 2013a). Gaining insight into the psychological and neural correlates of different patterns of ongoing experience will illustrate important correlates of both beneficial and detrimental functional outcomes in daily life.

Despite the ubiquity of self-generated experiences, this area of research has grown rapidly in the last fifteen years (Callard et al., 2013). This increase is in part due to parallel findings in neuroscience, along with advances in neuroimaging methods which allowed the neural processes engaged during mind-wandering to be measured. Most particularly, the discovery of a set of brain regions which became known as the default mode network (DMN) (Raichle et al., 2001) and the increasing interest in spontaneous brain activity during rest by using functional magnetic resonance imaging (fMRI), the so-called resting state fMRI (Greicius et al., 2003). The former has been consistently found to become more active when there is no task at hand (Raichle et al., 2001), whereas the latter is investigating the functional configuration of the brain while the participants are "resting" inside the scanner, having nothing else to do but let their minds wander; properties that make them both suitable for the investigation of self-generated thought.

Despite the possibility that patterns of spontaneous brain activity may in part reflect aspects of ongoing cognition, the exact mechanism that links them is not yet fully understood. On the one hand, there are many ongoing functions of the brain at all times, so, most likely, our thoughts are being represented by only a small fraction of the constantly fluctuating neural activity (Kucyi, 2018). On the other hand, self-generated thoughts themselves exhibit great variability in content and form both within and between individuals. This connection becomes even more complex if one considers the dynamic nature of the functional configuration of the brain and of the immediate occurring thoughts, both of which quite often evolve in second or sub-second timescales.

By utilising different metrics, the goal of the thesis is to identify shared variance between brain function and conscious experience and explore the mechanisms that map one to the other, quite possibly in a not one-to-one, but in a convoluted manner. For this reason, we will consider studies that highlight the relevance of self-generated experience to different functional outcomes and then discuss contemporary psychological and neuroscientific theories of these experiences.

1.2 Costs and benefits of spontaneous thoughts

Spontaneous thought has been associated with both costs and benefits which have been shown to be dependent on the content of thoughts and the context they occur in (Smallwood and Andrews-Hanna, 2013). Higher levels of unhappiness have been linked with mind-wandering about the past (Poerio et al., 2013; Ruby et al., 2013a; Smallwood and O'Connor, 2011) and, in clinical cases, self-related, negative, repetitive thoughts are often seen in depression and anxiety (Nolen-Hoeksema, 2000; Watkins, 2008). At the same time, having interesting thoughts has been associated with a more positive mood (Franklin et al., 2013) and thinking about the future has been shown to improve mood (Ruby et al., 2013a) and reduce cortisol levels following social stress (Engert et al., 2014). This divergence in results demonstrates the importance of mapping different content in spontaneous thought.

Understanding the functional relevance of patterns of ongoing thought also depends on taking account of the context in which it occurs (Smallwood and Andrews-Hanna, 2013). For example, mind-wandering may hamper comprehension during reading (Schooler, 2004; Smallwood et al., 2013a, 2008b; Unsworth and McMillan, 2013) and lectures (Jing et al., 2016; Szpunar et al., 2013) as well as impair driving (Yanko and Spalek, 2014) and flying (Casner and Schooler, 2014) performance. Also, it can hinder sustained attention (Seli et al., 2016), working memory (McVay and Kane, 2009) and general intelligence tests (Mrazek et al., 2012a). However, self-generated thought can, quite importantly, facilitate problem solving (Smallwood and Schooler, 2006) by thinking and planning about the future (Stawarczyk et al., 2013a), refine future goals (Medea et al., 2018), enhance creativity (Baird et al., 2012), ease the feeling of loneliness (Poerio et al., 2015) and provide mental breaks as a relief from boredom (Mooneyham and Schooler, 2013). According to these findings, the ability to regulate mind-wandering episodes depending on the demands of an on-going task will largely affect their costs and benefits (Smallwood and Andrews-Hanna, 2013), what is known as the context regulation hypothesis.

1.3 Content and form of thoughts

Despite the apparent complexity and seemingly heterogeneity of spontaneous thoughts, previous studies have identified dominant patterns of mind-wandering and recurring themes in the contents of our thoughts, which have greatly helped with the investigation of their psychological and neural correlates.

For example, thinking about the future or the past, often referred to as mental time travel (Tulving, 2002), has been shown to be a prominent component of mind-wandering. A bias towards future thoughts has repeatedly been found in countries all over the world, including Japan (Iijima and Tanno, 2012), the United States (Smallwood et al., 2011a), the United Kingdom (Smallwood et al., 2009b) and Germany (Ruby et al., 2013b). In line with these findings, Baird et al. (2011) confirmed this future-oriented bias in spontaneous thoughts and showed that prospective mind-wandering frequently involved autobiographical planning, linking thoughts about one's self and the future. These two thought patterns have been found to be statistically related in many studies and independent datasets (Smallwood et al., 2016). As mind-wandering can also be considered a goal-driven process (Smallwood and Schooler, 2006), it can be argued that this future-self thought content provides a way for individuals to mentalise their future in order to better achieve their goals.

Another temporal dimension of thought that often comes out as a unique statistical category is mind-wandering about the past (Ruby et al., 2013a,b). Ruby et al. 2013a applied principal component analysis (PCA) to multi-dimensional mind-wandering scores and found that in addition to past and future thoughts coming out as separate principal thought components, future thoughts predicted better subsequent mood, while past thoughts were linked with lower mood. This association between the content of spontaneous thoughts and the valence of one's affective state has been shown in many studies (Andrews-Hanna et al., 2013; Smallwood et al., 2009b; Smallwood and O'Connor, 2011; Stawarczyk et al., 2013b) and is known as the content regulation hypothesis (Smallwood and Andrews-Hanna, 2013). According to this hypothesis, the content of self-generated thoughts can influence their positive or negative psychological outcome for an individual (see 1.2). Finally, the modality of thoughts - whether they are experienced as images or words - has been shown to be the foremost dimension, along with the level of intrusiveness and the level of detail they have (Gorgolewski et al., 2014; Smallwood et al., 2016).

1.4 Measuring mind-wandering

Due to the covert nature of ongoing thoughts, finding an effective, reliable way to measure their properties is important. Contemporary ways of measurement rely on self-reports - known as experience sampling. Among the different methods that have been used in previous studies to acquire self-reports, we find the self-caught method (Smallwood and Schooler, 2006) which asks the participants to report on their thoughts when they catch themselves mind-wandering, and the probe-caught method (Smallwood and Schooler, 2006) that interrupts them at random intervals and interrogates the content of their experience. In addition, there is the retrospective method (Barron et al., 2011), where participants are asked at the end of a resting period about the nature of their thoughts and the open-ended method (Baird et al., 2011) where, at the end of a task, they are asked to describe their experience in their own words.

However, for any method that relies on self-reports, the following points pose considerations about the quality and reliability of the measurements: i) Asking participants to report on their thoughts requires that they be aware they are mind-wandering (what is termed meta-awareness) and can be influenced by biases in memory. Previous studies have found that individuals are often unaware of their mental activity (Fox and Christoff, 2014) and fail to notice that their minds have wandered (Schooler, 2002). ii) In an analogous way to quantum mechanical measurements in physics, every time the experimenter is trying to measure this cognitive process, they inevitably disrupt it (Smallwood and Schooler, 2015). This makes it all the more difficult to know when a mind-wandering episode starts and how long it lasts. iii) This disruption also runs the risk of contaminating the content of the experience. Just knowing that one is going to be asked about their thoughts can influence their outcome, and introspection when trying to describe them can alter their psychological meaning (Smallwood and Schooler, 2015).

In an effort to address these issues and improve the quality of measurement, previous studies have explored the link between self-reports on ongoing experience and other indirect measures. In addition to neural correlates (discussed in detail in 1.6), behavioural measures, such as task performance (McVay and Kane, 2009), reading comprehension (Schooler, 2004) and eye movements (Foulsham et al., 2013), as well as physiological measures, like pupil dilation (Smallwood et al., 2011a) and eye blink rate (Smilek et al., 2010) have been identified as potential markers of mind-wandering. At the moment, a combination of these measures, which is also known as triangulation (Schooler and Schreiber, 2004), can be thought of an effective method of investigating spontaneous thought (Konishi and Smallwood, 2016). However, a way of assessing the occurrence of ongoing thoughts without interrupting the process would offer substantially more insights and is left for future research.

1.5 The psychology of mind-wandering

Three prevailing cognitive hypotheses assessing the psychological basis of mind-wandering are the current concerns hypothesis, the executive failure hypothesis and the decoupling hypothesis (Smallwood, 2013a). According to the current concerns hypothesis (Klinger et al., 1973), one of the earliest attempts on explaining self-generated thought, mind-wandering will occur most likely when self- generated material offers larger incentive value than input coming from the external environment.

A second account is known as the executive failure hypothesis (McVay and Kane, 2009, 2012). This assumes that mind-wandering occurs when executive control processes, primarily acting to suppress irrelevant self-generated experiences, fail to keep attention on the task at hand. Although plausible, there have been empirical findings with opposing results. For example, as getting older has been associated with a decline in executive functions (Salthouse et al., 1998), according to this hypothesis one would expect mind-wandering to increase with age. However, previous research has shown the opposite; that self-generated thought decreases the older we get (Maillet and Schacter, 2016).

Finally, the decoupling hypothesis (Smallwood and Schooler, 2006) proposes that mind-wandering can be considered a state of decoupled attention. During this state, attention focuses on internally oriented thoughts and ignores distractions coming from the immediate environment. The extent to which attention is decoupled would determine the level of detail and the duration of an internal train of thought (Smallwood, 2013a). This hypothesis offers an explanation on why mind-wandering has been associated with poor performance in tasks (see 1.2) and is part of what is known as the component process account of mental states (Smallwood, 2013a,b).

1.6 The neuroscience of mind-wandering

One prominent account of how the brain self-generates experience assumes that this is related to neural processes taking place within the so-called default mode network (DMN). Originally identified as being more active when participants were not performing a task (Raichle et al., 2001; Shulman et al., 1997), it has been repeatedly shown to be associated with mind-wandering (Christoff et al., 2009; Mason et al., 2007).

Based on the functional behaviour of the DMN, it has been proposed that it can be parcellated into three distinct interconnected subsystems (Andrews-Hanna et al., 2010b; Yeo et al., 2011) (Fig. 1.1): i) The core subsystem with hub-like features, which includes the anterior medial prefrontal cortex (mPFC), the posterior cingulate cortex, the dorsal angular gyrus, the superior frontal sulcus and right anterior temporal cortex, ii) the medial temporal subsystem that consists of the hippocampal formation and parahippocampal cortex, as well as the ventral angular gyrus and retrosplenial cortex, and iii) the dorsal medial subsystem that includes the dorsal mPFC, the temporoparietal junction, the lateral superior and inferior prefrontal gyrus, and the middle temporal gyrus extending into the temporal pole (Andrews-Hanna et al., 2018).

Although the precise functional role of each DMN region and subsystem in self-generated thought is not completely understood, it has been proposed that they might facilitate the different content and form our thoughts take (Andrews-Hanna et al., 2014b; Gorgolewski et al., 2014). Using functional magnetic resonance imaging (fMRI) data from participants "resting" inside the scanner and correlating the activity of various DMN re-

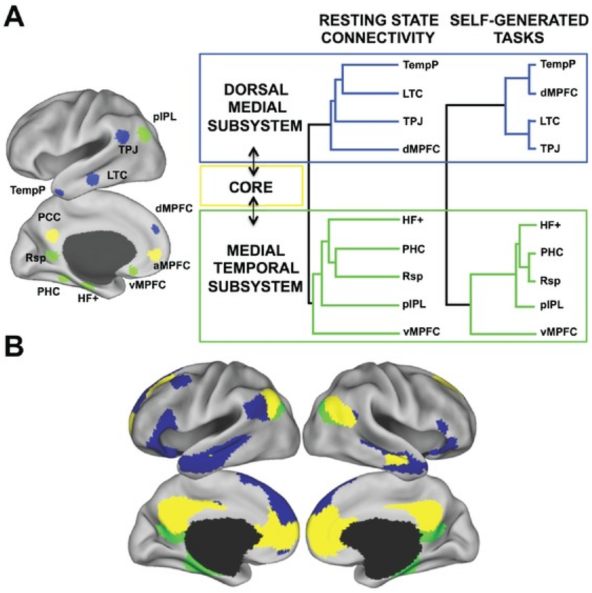

Figure 1.1: *Three distinct interconnected subsystems of the default mode network.* **A**) Graph and clustering analysis of 11 default mode network regions during passive rest and active self-generated tasks. **B**) Default mode network components as revealed by an unbiased, whole-brain parcellation of resting-state fMRI data from 1000 participants broadly consistent with panel A. Figure taken from Andrews-Hanna et al. (2014b).

gions with mind-wandering self-reports, Smallwood et al. (2016) found that differences in functional connectivity of medial and lateral temporal lobe regions were associated with different patterns of spontaneous thought. Moreover, these effects converged on the posterior cingulate cortex, highlighting its role as a functional hub. In concordance to these findings, Poerio et al. (2017) found poor external engagement to be dependent on different levels of coupling between the dorsal medial and medial temporal subsystems of the DMN and reported unique neural patterns for the contributions of off-task future thoughts and memory retrieval to mind-wandering. It is hypothesised that the medial temporal subsystem of the DMN might support contextual and temporal aspects of memory and imagination (Addis et al., 2009; Hassabis and Maguire, 2009), whereas the dorsal medial subsystem may support mentalising and emotional processing (Andrews-Hanna et al., 2014a; Hyatt et al., 2015) (Fig. 1.2).

Finally, in addition to the association of DMN regions with the content and form of spontaneous thought, it has been proposed that they might also play a role in its initiation (Szpunar et al., 2015). The hippocampus has been shown to be activated early during the generation of spontaneous thoughts (Ellamil et al., 2016), and damage to the medial temporal lobe in Alzheimer's disease has been associated with deficits in imagination (Hassabis et al., 2007). However, a recent study by McCormick et al. (2018) showed

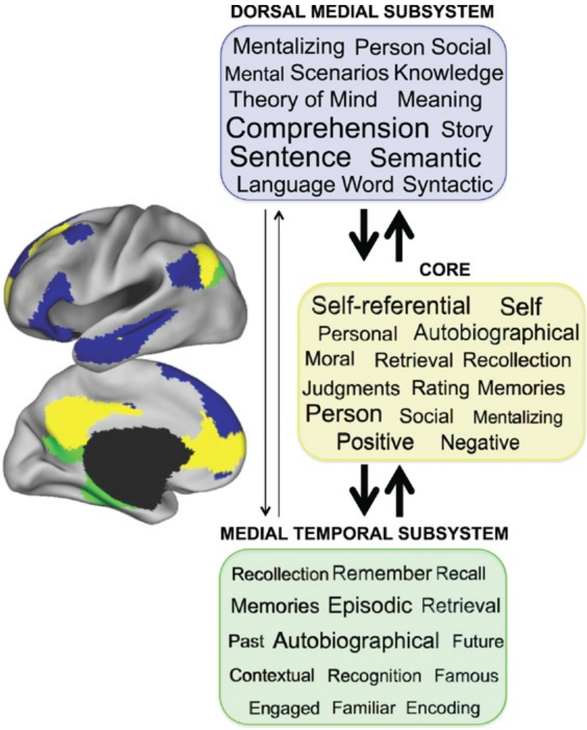

Figure 1.2: *Decoding the functions of default network components using automated fMRI meta-analyses.* Figure taken from Andrews-Hanna et al. (2014b).

that patients with hipoccampal amnesia engaged in as much mind-wandering as control participants, but their thoughts were primarily about the present. This confirms the imperative role of the hippocampus in the thought content and suggests that the inception of a mind-wandering episode is a multi-region or quite possibly a multi-network process.

Even though self-generated thought is closely related with DMN activity, there are other whole-brain networks and regions which are often reported in mind-wandering studies (Fox et al., 2015). Among them, the fronto-parietal control network (FPCN) consisting of the lateral prefrontal cortex, dorsal anterior cingulate, pre-supplementary motor area and anterior inferior parietal lobe (Yeo et al., 2011). With a known functional role of controlling attention (Banich, 2009; Dosenbach et al., 2006), it has been shown to play an important role in regulating self-generated thought by allocating attentional resources towards external and/or internal stimuli (Andrews-Hanna et al., 2018). It has also been recently proposed that its activation could be a way to distinguish between controlled and uncontrolled mind-wandering. It becomes active only when participants deliberately draw their attention away from the current task (Golchert et al., 2017) and direct the evolvement of their thoughts in a controlled manner (Irving, 2016).

1.7 Analyses approaches of the neural correlates of ongoing thoughts

A conventional way to investigate the functional organisation of the brain at rest is to examine the correlations between the activity of different brain regions for the whole duration of a resting state fMRI scan. These correlations of the often several-minute long time series are termed "static" functional connectivity and are thought to represent a stable, intrinsic functional architecture of the brain (Kucyi, 2018). Although this stable neural configuration has been shown to serve roles unrelated to spontaneous thought (i.e. unconscious processing, Fox and Raichle, 2007), previous studies have shown inter-individual variation in static functional connectivity linked to different patterns of ongoing experience (Andrews-Hanna et al., 2010a; Poerio et al., 2017).

Static functional connectivity, however, does not provide an insight on how the functional organisation of the brain changes in second or millisecond timescales and how these dynamic changes might relate to immediate occurring thoughts. To investigate these evolving neural states, an analysis that does not assume temporal stationarity can be more appropriate (Kucyi, 2018). Estimating the functional connectivity in shorter time windows (also known as the "sliding windows" approach) or applying a hidden Markov model to the time series of interest could identify transient and recurrent states corresponding to distinct neural activity patterns (Preti et al., 2017). Relating these neural patterns to patterns of ongoing experience could inform us about the occurrence of ongoing thoughts (see Ch. 2) and how they evolve to give rise to our "stream of consciousness".

Contemporary theories of consciousness describe it as a process of active inference (Rudrauf et al., 2017). A system that can predict and/or postdict the outcome of its actions can minimise surprise and make better inferences about its future, thus gaining a significant advantage from an evolutionary perspective. Contrary to a non-conscious agent, which acts based only on its sensory inputs, a conscious self can intrinsically simulate its future to minimise uncertainty, which highlights the importance of internally focused ongoing experience. This thesis is aiming to explore the relationship between the brain and ongoing experience by utilising multiple neuroimaging modalities and investigating how the structural and functional neural architecture can support different patterns of ongoing cognition.

Chapter 2

Towards a framework for dissociating process from occurrence in patterns of ongoing thought using the tools of cognitive neuroscience

Ongoing cognition is flexible; sometimes it reflects the events taking place in the environment or a task being performed, at others it reflects processes that are determined intrinsically, however, in both cases our cognition changes over time (Smallwood, 2013a; Kucyi, 2018). Although specific patterns of ongoing thought at a given moment in time are necessarily time limited (and thus a state), previous research has shown that they also have stable properties across individuals, suggesting that they also have trait-like characteristics. For example, studies suggest that even dynamic aspects of conscious experience, such as mind-wandering, can be trait related (Seli et al., 2015a; Burdett et al., 2016). Trait-like aspects of ongoing thought may be one reason why aspects of ongoing experience have links to features of well-being, including happiness (Smallwood and Andrews-Hanna, 2013; Poerio et al., 2013), creativity (Baird et al., 2012; Wang et al., 2018b; Smeekens and Kane, 2016) and intelligence (Godwin et al., 2017; Mrazek et al., 2012a; Turnbull et al., 2019).

Building on such evidence, contemporary accounts of ongoing thought suggest that it is necessary to understand two related factors that contribute to momentary patterns of cognition (Smallwood, 2013a). First, it is necessary to account for the processes that different types of thoughts depend upon. These may include perceptual systems when experience is focused externally (Smallwood, 2013a, although see Kosslyn et al., 2001). Other more domain general processes are also likely to be involved; long-term memory representations, which can contribute to both external behaviour, such as when our knowledge of objects and events in the world - semantic memory - helps guide our actions (for a review see Jefferies, 2013), and to the expression of modes of cognition that are more intrinsically determined, for example because aspects of memory representations form the basis of mental content during experiences such as mind-wandering (Poerio et al., 2017). Processes such as executive control are also important in organising patterns of thinking, with the aim to maximise the degree of fit between specific moments of cognition and an individual's goals (Smallwood, 2013a). Accordingly, measures of executive control (such as intelligence) facilitate on-task thoughts when external demands on attention are high (McVay and Kane, 2009, 2012) but can promote off-task thoughts when the tasks are easier (Levinson et al., 2012; Turnbull et al., 2019). Second, although it is undoubtedly important to understand the processes that underpin different patterns of experience, it is also necessary to understand their temporal properties. In the case of external task focused cognition, it is important to identify the appropriate neurocognitive processes activated in a timely fashion in response to changes in external demands. Understanding more intrinsically influenced patterns of thought is complicated because their self-generated nature makes them hard to resolve by an experimenter (Smallwood, 2013a). Since both perceptually and self-generated experience are dynamic, understanding when specific patterns of experience take place - i.e. their occurrence - is also important in understanding cognition.

Moving towards a mature account of patterns of ongoing cognition, therefore, requires that we improve our ability to dissociate those processes that underpin multiple aspects of experience from those that influence their occurrence. The methods of neuroscience, particularly those that can be applied to humans in-vivo, are an important resource in this regard because they provide a window into the architecture underlying cognition, allowing the 'atoms' that underpin different aspects of cognition to be resolved. In this review, we consider how the strengths and weaknesses of different neuroimaging techniques can enable researchers to understand the complex ways that different aspects of ongoing thought can be constrained by the underlying neural architecture, and how neural function can evolve within this context to give rise to different patterns of experience at different moments in time. In particular, we summarise how techniques that focus on the grey matter and white matter architecture of the brain are especially suited to understanding trait-like influences on ongoing thought, while functional measures derived from both magnetic resonance imaging (MRI) and electro-magnetoencephalography (E/MEG), and particularly those that highlight their dynamics, can provide insight into the sequence of emerging states that led William James to coin the term the "stream of consciousness" (James, 1890). We will also focus on two key goals that will determine our ability to understand the mechanism that underpins patterns of ongoing thought. First, in order to address the fact that common processes can contribute to patterns of thought with seemingly opposing features, it is important to utilise paradigms and analytic techniques that can address those processes that underlie specific phenomena to be identified. Second, since a key aspect of ongoing thought is the ability to address the occurrence of specific states, we will consider how experimental approaches and analytical techniques, such as hidden Markov modelling, are able to determine the occurrence of different cognitive states. Together, we hope this review provides a framework that allows research to efficiently utilise the tools of cognitive neuroscience to understand patterns of ongoing experience.

2.1 Non-invasive methods of measuring neural architecture and their role in understanding patterns of ongoing thought

Over the last decades there has been a tremendous increase in the use of non-invasive methods to study the neural architecture of the human brain in-vivo. The landscape of contemporary neuroimaging is dominated by two dominant families of techniques; magnetic resonance imaging (MRI) allows both cortical structure and function to be mapped with a high degree of spatial accuracy, while techniques that measure electrophysiological activity - electro-magnetoencephalography (E/MEG) - provide precise temporal descriptions of neural processing. Based on the assumption that specific neural populations are tuned to perform particular aspects of cognition, then the convergent use of techniques from these two families of approach may be important in building a more mature account of patterns of ongoing thought. In particular, the relatively stable patterns of brain structure provided by structural and diffusion weighted imaging (DWI), and traditional functional connectivity analysis from functional MRI (fMRI) are well suited for understanding the trait-like aspects of patterns of ongoing thought. More time-resolved measures available from resting state and task-based imaging in both MEG and fMRI, particularly using advanced analytical techniques, such as hidden Markov modelling, are important in understanding the more state-like properties of ongoing thought.

2.1.1 Using the methods of neuroimaging to understand trait-like influences on patterns of ongoing thought

One broad family of techniques that can enable attempts to understand the mechanisms underlying ongoing cognition is derived from MRI. These include techniques that are optimised for understanding structure - (i) diffusion weighted imaging (DWI), which measures how water diffuses across the cortex and is used to estimate the white matter tracts that support long-distance communication between different regions and (ii) structural T1-weighted imaging, that provides high quality descriptions of grey matter structure. In addition, MRI also includes techniques that can provide descriptions of the functional architecture, based on the observation that when neurons consume oxygen, this changes the relative deoxyhemoglobin concentrations within different brain regions and is used as a proxy measure of neural activity (Ogawa et al., 1990).

2.1.1.1 Investigating structure with Diffusion Weighted Imaging

One key property of the cortex is the complex set of long-distance connections that support the interaction of distributed networks of neural regions. Studies focusing on the reconstruction of macroscale connections have exposed a complex structural organisation of the mammalian brain (Hagmann et al., 2008; Markov et al., 2013; Oh et al., 2014). State-of-the-art fibre reconstruction methods, like invasive tract-tracing, have been able to provide remarkably detailed wiring diagrams of the non-human mammalian brain (i.e. macaques, Stephan et al., 2001; Markov et al., 2012, mice, Oh et al., 2014), establishing them as the gold standard for assessing white matter connectivity. As tract-tracing is not applicable for in-vivo human research, an increasingly popular technique to investigate the structural organisation of the human brain, in vivo and non-invasively, is the diffusion weighted imaging (DWI) (Basser et al., 1994).

By measuring the diffusion of water in brain tissues, which diffuses differently depending on the tissue type and architecture, DWI and diffusion tensor imaging (DTI) (a specific type of modelling of DWI data) (Pierpaoli et al., 1996), provide a large number of metrics describing the structural properties of the brain (Soares et al., 2013). This insight to white matter architecture has allowed researchers to reconstruct white matter fibre bundles (Jones, 2008), and investigate any structural alterations in clinical cases (Sundgren et al., 2004). DWI has ongoing technical issues and limitations, often arising from the quality of the DWI data collected and the pre-processing and analyses methods applied (Soares et al., 2013) or more generally having to do with the complexity of the underlying fibre structure (i.e. crossing fibres) (Wiegell et al., 2000). Nevertheless, DWI reconstructions compared to tract-tracing methods have been shown to represent a reasonably realistic estimate of the white matter projections (van den Heuvel et al., 2015).

Importantly, for the purpose of understanding the underlying mechanisms that support different patterns of ongoing thought, studies suggest that the white matter tracts identified using DWI are relatively stable. Lebel and colleagues have shown that many of the key white matter tracts - including the corpus callosum and the fornix - stabilised in early adulthood (around the age of 20) and began to change around the mid 40s (Lebel et al., 2012). The stability of these white matter tracts suggests that it may provide a useful metric to describe the underlying trait-like properties of patterns of ongoing thought.

2.1.1.2 Investigating structure with T1 imaging

As well as describing the white matter structure of the cortex, MRI can also be used to produce high resolution measures of the cortical landscape. These are achieved through the use of T1-weighted imaging, which describes the layout of the cortex in relatively high levels of detail, although as typically employed (i.e. using 3 Tesla imaging) these measures are not able to describe features of the cortical microstructure (such as the different cortical layers, Ferguson et al., 2018). Measures defined by T1 structural imaging can provide descriptions of the degree of cortical thickness at each point on the cortical surface. As with diffusion imaging, these measures are relatively stable across the life span (Sowell et al., 2003), suggesting they reflect relatively stable neuroanatomical features of the brain. Furthermore, this metric is significantly influenced by genetic factors (Panizzon et al., 2009; Winkler et al., 2010) and closely associated with traits and neuropsychiatric disorders (e.g. Hardan et al., 2006; Lazar et al., 2005; Schilling et al., 2013. Together, DWI and T1 imaging provide stable descriptions of cortical organisation and suggest that they may be well suited to provide descriptions of the neural traits that underlie patterns of ongoing thought.

2.1.1.3 Investigating functional organisation using the BOLD signal

A final method for exploring the contribution of neural traits to patterns of ongoing thought is through methods that describe the organisation of cortical function as defined using functional MRI during rest. Functional MRI estimates neural activity by measuring the blood oxygen-level dependent (BOLD) signal, an indirect measure of the underlying neuronal activity (Ogawa and Lee, 1990; Belliveau et al., 1991; Bandettini et al., 1992). In brief, the fMRI technique is based on a process known as neurovascular coupling, which has the premise that a change in local neuronal activity would be linked to a change in regional blood flow and blood oxygenation (termed as the haemodynamic response), which ultimately would alter the magnetic field properties of any region being measured by the MRI scanner (Kwong et al., 1992, also for a review see Logothetis, 2008). Unlike task-based (see 2.1.2), resting state fMRI (rs-fMRI) acquires data while participants are at rest in the scanner (Biswal et al., 1997; Lowe et al., 2000).

The data produced using rs-fMRI are often analysed by examining the temporal profile of neural signals using a family of techniques based on the correlations of their time series. This approach is based on the assumption that neural regions showing similar temporal profiles are involved in similar processes and might be sharing mutual information. Intrinsic brain activity at rest has been shown to exhibit increased temporal correlations among regions that are spatially distant (Biswal et al., 1995; Cordes et al., 2000; Greicius et al., 2003), revealing stable large-scale functional networks (Biswal et al., 1997; Damoiseaux et al., 2006; Fox and Raichle, 2007; Lowe et al., 1998), which may however vary with age, with more consistent patterns observed in younger than older adults (Song et al., 2012), and with the metrics that are used to identify them (Braun et al., 2012). Resting state fMRI has been highly influential in our understanding of brain organisation, in part because of the increased power and generalizability of the metrics that can be described by this method. For example, Yeo and colleagues (2011) have demonstrated that this method can be used to provide consistent evidence that underlying cortical dynamics can be well described by a relatively small number of large-scale functional networks. Examples of the neural networks produced via resting state fMRI are presented in Figure 2.1. Importantly, there is a reasonable level of agreement between the neural networks, as described by resting state fMRI, and the pattern of communication highlighted by DWI (Skudlarski et al., 2008) suggesting that both provide valid methods to investigate the organisation of neural processing.

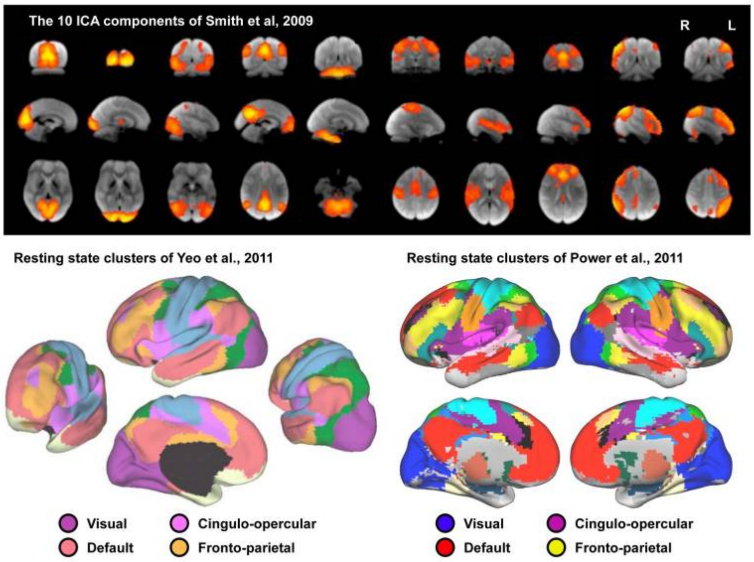

Figure 2.1: *Large-scale resting state functional networks.* Three parcellations of spatial patterns of correlated BOLD signal: a 10-component ICA analysis (Smith et al., 2009), a surface-based analysis of surface vertex clustering (Power et al., 2011), and a volume-based analysis of voxelwise clustering (Yeo et al., 2011). Images adapted from the indicated publications. Figure taken from Power et al., 2014b.

2.1.1.4 Evidence for trait-like properties of ongoing thought based on measures of brain architecture

Although resting state fMRI may be the most ambiguous measure of trait-like neural features (see Box 1), it is also the most common method to investigate patterns of ongoing thought. These studies have examined the relationship between the functional architecture at rest and aspects of ongoing thought measured as a trait (e.g. the Mind-wandering Frequency Scale, Mrazek et al., 2013, the Mindful Attention Awareness Scale, Brown and Ryan, 2003, or the Deliberate Mind-wandering Scale, Carriere et al., 2013). Others have characterised the relationship with ongoing thought as measured in laboratory sessions outside the scanner (Smallwood et al., 2016; Karapanagiotidis et al., 2017; Wang et al., 2018b). Finally, a smaller number of studies have explored the possibility that the functional architecture at rest is related to the patterns of thought that emerge over the course of the resting state session (Wang et al., 2018a; Vatansever et al., 2017a; Karapanagiotidis et al., 2018).

One common theme that has emerged from these studies is that the different patterns of ongoing thought have been linked to associations in connectivity between regions with more task positive features (such as the fronto-parietal network) and the default mode network (DMN). For example, Godwin et al. (2017) found that increased connectivity between the fronto-parietal network (FPCN) and default mode network was linked to increased mind-wandering (see also Mooneyham et al., 2016). In a similar vein, Golchert et al. (2017) found that neural signals of regions linked to patterns of controlled cognition (e.g. the intraparietal sulcus) was linked to regions within the default mode network (the dorsal medial prefrontal cortex) for individuals who reported more deliberate mind-wandering. Finally, Vatansever et al. (2017a) demonstrated that patterns of thematic cognition at rest were associated with stronger patterns of connectivity between the inferior frontal gyrus and the anterior temporal lobe. Other studies have found that mindfulness, a state that has been argued to be the opposite of mind-wandering (Mrazek et al., 2012b), is linked to reductions in connectivity between hubs in the DMN and regions linked to control (Bilevicius et al., 2018). As well as evidence for such patterns of connectivity linked to the mind-wandering state, similar neural motifs are present in states that are correlated with such experiences at the level of a trait. For example, mind-wandering is often associated with thinking about the future (Baird et al., 2011; Smallwood et al., 2009b) and can play a role in helping individuals define more concrete personal goals (Medea et al., 2018). Importantly, neural activity during periods of autobiographical planning shows similar patterns of coupling between the DMN and FPCN (Spreng et al., 2010). Similarly, studies have demonstrated an association between creative solution and patterns of off-task thinking (Baird et al., 2012; Wang et al., 2018b; Smeekens and Kane, 2016; Godwin et al., 2017) and periods of creative thought also involve co-operation between the DMN and FPCN (Beaty et al., 2018). Theoretically, increases in the coupling between default mode network and systems of control are consistent with accounts of internal thought which emphasise the co-operation between these systems in the organisation of trains of self-generated thought (Smallwood et al., 2012; Smallwood, 2013a; Smallwood and Schooler, 2015).

A more limited set of studies have used metrics that describe grey or white matter to investigate patterns of ongoing thought. Bernhardt et al. (2014) explored the correlation between whole brain cortical thickness and identified that greater thickness of the anterior cingulate and medial prefrontal cortex was associated with greater levels of off-task thinking when individuals were in the context of a task with low demands. Elevated levels of off-task thinking when task demands are low are linked to making more cautious economic decisions (Smallwood et al., 2013b). Bernhardt and colleagues (2014) found that regions in which increased cortical thickness was linked to increased off-task thought also showed greater cortical thickness for individuals who tended to make patient economic decisions. This pattern suggests that there may be important shared processes between the tendency to avoid discounting the future and the ability to limit mind-wandering to situations with low levels of external demands. More recently, Ho and colleagues (under review) showed that lab-based measures of patterns of experience, including its focus on a task and its level of detail, were uniquely associated with cortical thickness within adjacent non overlapping regions of the hippocampus. In terms of studies assessing white matter tracts using diffusion parameters, Karapanagiotidis et al. (2017) found that episodic aspects of ongoing thought (i.e. thoughts about the past and the future) were associated with white matter tract differences in the fornix, a region that is important in interactions between the hippocampus and the cortex, and particularly within the default mode network (Kernbach et al., 2018b). Importantly, Karapanagiotidis and colleagues (2017) were able to show that connectivity between the hippocampus and regions of medial prefrontal cortex, within the DMN, was enhanced for individuals showing higher levels of episodic experience.

Box 1: The paradoxical nature of resting state MRI as a measure of neural traits

Unlike task-based approaches, in resting state fMRI the lack of external manipulation allows the experimenters to capture the neural signal without any constraints or assumptions of a particular experimental design. In addition, unlike DWI and T1 imaging, resting state generates time series data of neural functioning in an efficient manner, allowing spatial patterns to be described with minimum levels of scanning time. Over that last ten years, resting state methods have been shown to generate individual connectome fingerprints (Finn et al., 2015; Gratton et al., 2018) and to predict a large range of traits, including higher order features of cognition such as intelligence (Finn et al., 2015), meta cognition (Baird et al., 2013), creativity (Beaty et al., 2018), self-consciousness (de Caso et al., 2017a,b) and semantic and episodic memory (Mollo et al., 2016; Sormaz et al., 2017). The conditions under which resting state data are recorded involve minimal external demands, and studies of spontaneous thought indicate that these tend to increase the level of thoughts that are self-generated rather than produced based on information from the environment (Teasdale et al., 1995; Smallwood et al., 2002b). Thus, although the resting state paradigm offers the opportunity to collect data that illuminates the organisation of neural function in an efficient manner, it also does so in a situation which is biased to specific types of thought. It remains unclear though, how much of the neural patterns observed at rest are related to the way cognition unfolds under these situations (Kucyi, 2018). Although only a small number of studies have directly explored links between the thoughts at rest and patterns of ongoing neural function, those that have done so have found evidence of associations (Gorgolewski et al., 2014; Wang et al., 2018a; Vatansever et al., 2017a). However, in studies such as these, both brain and experience are often only measured once, thus it is unclear whether the patterns of cognition should be best conceived of as a state or a trait. It is important to emphasise that the uncertainty in how to interpret relationships between resting state networks and patterns of cognition is not limited to studies of ongoing thought. Studies have shown that patterns of ongoing thought are linked to a number of traits for which there are resting state correlates, including intelligence (Mrazek et al., 2012a; McVay and Kane, 2009), self-consciousness (Smallwood et al., 2011b) and creativity (Baird et al., 2012). Importantly in this regard, Wang et al. (2018a) demonstrated that a parcellation of neural function derived from thoughts at rest was predictive of an individual's intellectual abilities as measured by tests such as the Wechsler Adult Intelligence Scale. Accordingly, it remains an open question the extent to which studies linking patterns of neural activity at rest to measures such as intelligence indicate the types of thoughts that these individuals experience at rest.

2.1.2 Using neuroimaging to understand the occurrence of patterns of ongoing thought

While brain imaging techniques that address stable features of neural function have promise in understanding the more trait-like properties of ongoing thought, other measures of neural activity have promise in identifying more momentary features of experience. One simple method for addressing this question is by combining online experience sampling with measures of neural function while individuals perform a cognitive task, and to examine how changes in neural function track with changes in ongoing state.

Many of these studies have used simple, nondemanding tasks, with no engaging semantic information and in which the tendency to think about matters unrelated to the task at hand is common. One often used paradigm is the sustained attention to response task (SART) (Robertson et al., 1997; Smallwood et al., 2004). This task is a simple go/no-go paradigm in which individuals are asked to respond to frequent go targets, and withhold responses to infrequent no-go events. The simple monotonous nature of this task paradigm leads to reasonably high levels of off-task thought, and failure to effectively inhibit response to the no/go targets provides a behavioural example of a situation where task relevant attention has lapsed (although the relationship between off-task thinking and errors in this context remains a matter of contention, see Seli, 2016; Dang et al., 2018). Another approach is to measure ongoing thoughts in a signal detection paradigm, which is broadly similar to the SART but lacks the role for response inhibition (see Makovac et al., 2019). An alternative paradigm exploits the fact that manipulating working memory loads provides a method for varying the amount of attention that individuals devote to task related or self-generated information (Teasdale et al., 1993; Smallwood et al., 2009b). Understanding the patterns of experience across multiple conditions has the advantage of providing more nuanced accounts of patterns of ongoing thought since it varies whether this aspect of experience is appropriate to the context or not (Smallwood and Andrews-Hanna, 2013). One such paradigm is the 0-back / 1-back paradigm (Konishi et al., 2015; Sormaz et al., 2018).

A growing number of studies have utilised online experience sampling to understand patterns of experience. One common observation from neuroimaging studies indicates that periods of off-task thought involve a reduction in the amount of attention that individuals deploy to task relevant material. These experiments often use evoked responses derived from the EEG signal, and find that the average amplitude of these signals varies under conditions where individuals report that ongoing thought is directed to information that is unrelated to the task, relative to periods of task focused attention (Smallwood et al., 2008a; Kam et al., 2011; Barron et al., 2011; Baird et al., 2014). The most consistent evidence is a reduction in the amplitude of an evoked component between 300-500 ms, known as the P3, and that is thought to indicate effective external attention (Polich and Kok, 1995).

A smaller number of studies have used online thought sampling in combination with fMRI to understand the neural networks that underpin different aspects of ongoing thought. Of them, several have examined the relationship between patterns of ongoing thought in the context of the SART (Christoff et al., 2009; Stawarczyk et al., 2011b; Allen et al., 2013). These studies found evidence that aspects of the default mode network are active during periods of off-task thought. More recent studies have used machine learning techniques to identify the similarity between online neural activity and reports of ongoing experience. Tusche and colleagues (2014) used experience sampling at rest to demonstrate that regions of orbito-frontal cortex showed heightened activity during periods of emotional experience. More recently, Sormaz et al. (2018) used representational similarity analysis (Kriegeskorte et al., 2008) to demonstrate that patterns of activity in regions of the default mode network can contribute to patterns of detailed experience during periods of active working memory maintenance, highlighting the broad role that this system plays in experience.

Box 2: Using electrophysiological imaging to understand patterns of ongoing thought

MRI provides increased spatial resolution (the ability to discriminate between nearby locations) relative to other scanning modalities (e.g. E/MEG). However, due to the sluggish nature of the haemodynamic response (it lags the neuronal events triggering it by a couple of seconds, Kwong et al., 1992) and the fact that fMRI measurements are usually made at the scale of seconds, the temporal resolution (the smallest time period of neural activity that can be reliably detected) of fMRI is limited.

Other techniques, such as Magnetoencephalography (MEG), can be used to measure neural activity more directly. MEG measures direct neuronal activity through external magnetic field changes generated by a large population of neurons being synchronously active (Cohen, 1972; Hämäläinen et al., 1993). MEG has the advantage of enhanced spatial localisation relative to its counterpart electrophysiological technique, electroencephalography (EEG) (Singh, 2014), and it offers a significantly improved temporal resolution relative to fMRI, as it can measure neural signal with a sampling rate of up to several thousands Hz. This allows the recording of fast oscillatory neural activity at different frequency bands and can inform us about the spectral profiles of various brain regions (Mandal et al., 2018). Given that neural function can dynamically adapt to process externally or internally generated input, these time-varying interactions can be captured during MEG resting state or task-based scans, and provide an insight into how information might be communicated among regions and functional networks down to millisecond timescales and varying frequencies (Hillebrand et al., 2016). Nevertheless, the technique does not come without its limitations, mainly those of being extremely sensitive to noise and the difficulty in determining the exact neural source of the signal measured by the sensors (Wendel et al., 2009). Large-scale resting state functional networks identified with MEG have been shown to correspond to ones seen in fMRI (Brookes et al., 2011; De Pasquale et al., 2010), confirming the neural basis of the haemodynamic networks and the effectiveness of the fMRI BOLD signal as a proxy of an average neural oscillatory activity. To our knowledge, no MEG studies to date have investigated patterns of unconstrained ongoing cognition, and such studies will be important to reveal the temporal profile of different patterns of experience in more detail.

2.2 Using neuroimaging analysis methods to address process and occurrence in ongoing thought

Contemporary accounts of ongoing thought assume that certain aspects of experience that are organised by more intrinsic features can be understood as the self-generation of processes such as long term memory, cognitive control or emotion that can also be captured by task paradigms (Smallwood, 2013a; Smallwood and Schooler, 2015). Modern neuroimaging techniques are important in advancing such theoretical perspectives for two reasons. First, they offer the ability to determine common mechanisms that contribute to aspects of cognition that can occur either as part of an explicit task or can be self-generated in the absence of an explicit external cue, and thus help refine our understanding of the **processes** that are important for different patterns of ongoing thought. Second, modern neuroimaging approaches offer the chance to reveal the covert neural changes that reflect the onset of specific patterns of ongoing thought and hence identify the **occurrence** of these experiences. In this final section of our review, we consider experimental paradigms and analytical techniques that are important for disentangling these aspects of ongoing experience.

2.2.1 Experimental paradigms for revealing the processes underlying different patterns of experience

Advances in neuroimaging, and in particular machine learning approaches, can help investigators characterise the underlying processes that contribute to specific patterns of ongoing thought. Techniques such multi-voxel pattern analysis (MVPA) allow investigators to identify the association between neural patterns and particular aspects of perception and cognition. For example, Haxby et al. (2001) used this technique to identify neural representations that support the perception of faces in objects in ventral aspects of temporal cortex. Importantly, neural patterns determined in this way can be tested on data from another cognitive context, allowing inferences to be drawn about the functions that are common across both contexts (Kaplan et al., 2015). This approach has been used to identify a common system important for both the expression and perception of motor actions (Dinstein et al., 2008), and to determine that visual imagery during dreams shares important features with perception (Horikawa et al., 2013).

This process of cross-classification can be used to understand the processes that are involved in patterns of ongoing experience. In such a study, a participant would have neural activity recorded under two conditions. In one condition, participants would be engaged in tasks that share hypothesised features with patterns of experiences that individuals are likely to engage in spontaneously. In a second condition, the same participants would be asked to perform a task, or rest, with minimal external demands, and measures of ongoing experience could be recorded via self-report. Using these data, it is possible to use MVPA to identify the neural processes that support the task-based example of cognition from the first session, and these patterns can be tested on measures of neural functions linked to patterns of experience in the second session. The ability to predict self-generated neural activity based on that generated by a task provides quantitative evidence that both patterns of cognition share the same neural features.

Tusche and colleagues (2014) employed such a paradigm to identify the possibility that neural features linked to emotional processing are common to both task-based and self-generated experiences. In their study, neural activity was measured under two conditions; when participants were explicitly asked to generate memories with varying positive and negative features, and in a second session they were intermittently probed regarding the contents of their experience during a period of wakeful rest. MVPA identified that neural activity within the orbitofrontal cortex contained information that discriminated between the emotional tone of experiences during the task. Critically, they were able to discriminate between positive and negative experiences that occurred spontaneously at rest, using the pattern determined from the analysis of the first session. This study provides clear evidence that processes within the orbitofrontal cortex play an important role in emotional experience, regardless of whether this occurs as part of a task or as it emerges naturally during periods when experience is not constrained by a task.

2.2.2 Temporally specific methods as a tool for understanding the occurrence of different states

Modern neuroimaging approaches also hold the possibility that they can inform our understanding of the occurrence of different patterns of ongoing cognition through the application of advanced analytical approaches to the time series of neural activity, as observed using scanning modalities such as MEG or fMRI. Although many common analytic approaches assume that any functional dependence structure between regions remains constant for the duration of a scan, there has recently been a growing interest in the dynamic (time-varying) functional organisation of the brain using models that estimate the functional connectivity among regions, at each individual time point during the duration of a scan. Such methods attempt to identify recurring patterns in the neural signal, label them as distinct dynamic states and provide the temporal evolution of each state, along with its transition probabilities and various other dynamic metrics, revealing what has been termed as chronnectome (Calhoun et al., 2014). Even though there has been increased evidence that suggests dynamic neural states can be modulated by an ongoing task (Gonzalez-Castillo and Bandettini, 2018) or a particular cognitive state (Kucyi and Davis, 2014), there is still no clear consensus about the magnitude of this dynamic functional reconfiguration, to what extent it is constrained by the neural trait characteristics of the brain, and the mechanism that links these to behaviour and ongoing experience (Lurie et al., 2018). Common approaches to examine dynamic neural activity include sliding windows (Sakoğlu et al., 2010; Handwerker et al., 2012) and hidden Markov modelling (HMM, Vidaurre et al., 2016, see Box 3). Given their ability to resolve time-limited states, dynamic techniques hold promise to be useful in the description of the occurrence of patterns of ongoing thought.

Recently, Karapanagiotidis and colleagues (2018) applied HMM to understand whether aspects of dynamics at rest are related to the patterns of experiences at rest. They found modest evidence that specific states identified by HMM were linked to reports of specific patterns of experience (e.g. reports of engaging in autobiographical planning at rest showed a marginal association with the frequency of a state in which a functional network associated with language played an important role). More importantly, they found that the degree with which individuals switched between different states was predictive of experiences reported at the end of the session. In particular, individuals whose experiences were highly intrusive tended to show fewer switches across the resting state session, while the reverse pattern (i.e. more frequent switching) was predictive of patterns of autobiographical planning. This study highlights the important role that analytic techniques targeting neural dynamics play in describing features of ongoing experience, and also provide support for theoretical approaches emphasising that the occurrence of different experiences is an important aspect of spontaneous thoughts (Smallwood, 2013a).

Box 3. Hidden Markov models as a tool for describing the occurrence of different patterns of ongoing thought

HMM is a probabilistic generative model that can be used to describe the neural time series acquired during a neuroimaging scan as a sequence of hidden states. Each state has its own observational model, characterised by a probability distribution from which the observed neural data are generated when the system occupies that state. Detailed information about the HMM implementation in neuroimaging data can be found in Baker et al., 2014; Vidaurre et al., 2016, 2017a. Two defining properties of the HMM is that an observation at a time t is generated by an unobservable process occupying a hidden state S_t, and that this process satisfies the Markov property. That is, the current state S_t is only dependent on the previous one S_{t-1}; a property of, what is often known as, a "memoryless" system. The states are mutually exclusive, which means that only one state can be active at each point in time. In the case of neuroimaging data, this should not be confused with the idea that only one brain region or network is active at a time, as a state usually represents whole-brain configurations rather than any brain regions in particular. Also, this rule can be relaxed when, instead of appointing the state with the highest probability as the only active one ("winner-takes-all"), one opts to represent all states at each time point with their respective occurrence probabilities.

Choosing the HMM observational model to be described by a multivariate normal distribution will lead to identifying states characterised by different mean activity and functional connectivity (Fig. 2.2). If y_t represents the data and S_t the hidden state k at a time point t then

$$y_t \mid S_t = k \sim \mathcal{N}(\mu_k,\, \Sigma_k)$$

where μ_k is a vector describing the mean activity of the whole-brain and Σ_k is the covariance matrix, showing the variance within each network and the functional connectivity between them for state k.

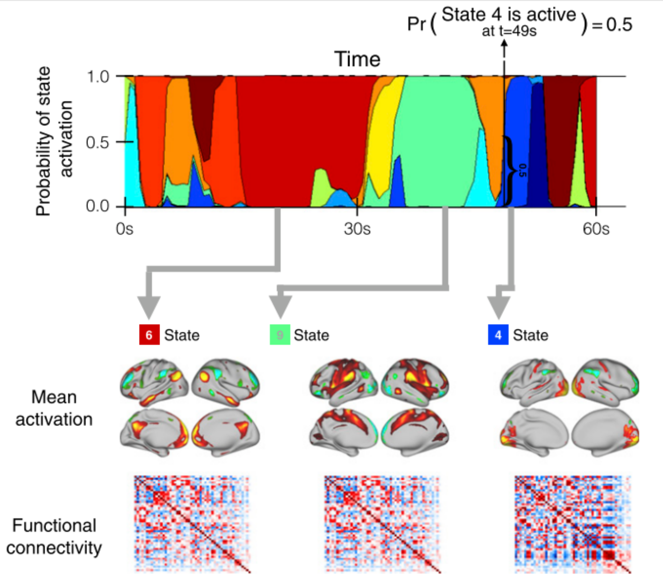

Figure 2.2: *HMM states.* HMM estimates a number of states that are common to all subjects, together with a specific state time course for each subject indicating the probability of each state being active. The states can be characterised by their mean activation and functional connectivity matrix. Figure adapted from Vidaurre et al. (2017b).

Inferring the model parameters will identify the unique recurring states (μ_k, Σ_k), the probabilities of each state being active at each time point (state time series) and the transition probabilities between them. The inference can be achieved by using variational Bayes and the minimisation of free energy, an approximation of Bayesian model evidence that provides an estimate for the goodness of fit of the model (Nasrabadi, 2007). Applying the HMM on concatenated data will identify states at the group level, however, when a state becomes active will be specific to each subject.

2.3 Summary

This review has highlighted how different neuroimaging methods can be an important tool in attempts to understand patterns of ongoing thought. These methods are suitable for uncovering both trait-like features, as well as ones that are more directly related to the ongoing states. More generally, advances in analytic techniques such as MVPA and HMM provide the researcher with tools that allow them to separately probe the underlying processes that support aspects of cognition, as well as identifying parameters which reflect the occurrence of different patterns of experience. Moving forward, the systematic use of different neural techniques will help provide the foundations for a more mature scientific account of ongoing experience, and so help shed light on an important yet poorly understood aspect of the human condition.

Chapter 3

Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering

The following chapter has been adapted from: **Karapanagiotidis, T.**, Bernhardt, B. C., Jefferies, E., & Smallwood, J. (2017). Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering. Neuroimage, 147, 272-281. [1]

3.1 Abstract

The capacity to imagine situations that have already happened or fictitious events that may take place in the future is known as mental time travel (MTT). Studies have shown that MTT is an important aspect of spontaneous thought, yet we lack a clear understanding of how the neurocognitive architecture of the brain constrains this element of human cognition. Previous functional magnetic resonance imaging (MRI) studies have shown that MTT involves the coordination between multiple regions that include mesiotemporal structures such as the hippocampus, as well as prefrontal and parietal regions commonly associated with the default mode network (DMN). The current study used a multimodal neuroimaging approach to identify the structural and functional brain organisation that underlies individual differences in the capacity to spontaneously engage in MTT. Us-

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[1] The author, Theodoros Karapanagiotidis, designed the experiment, collected and analysed the data and wrote the article under the supervision of Prof. Elizabeth Jefferies and Prof. Jonathan Smallwood. Dr. Boris Bernhardt provided assistance with the statistical analyses.

ing regionally unconstrained diffusion tractography analysis, we found increased diffusion anisotropy in right lateralised temporo-limbic, corticospinal, inferior fronto-occipital tracts in participants who reported greater MTT. Probabilistic connectivity mapping revealed a significantly higher connection probability of the right hippocampus with these tracts. Resting-state functional MRI connectivity analysis using the right hippocampus as a seed region revealed greater functional coupling to the anterior regions of the DMN with increasing levels of MTT. These findings demonstrate that the interactions between the hippocampus and regions of the cortex underlie the capacity to engage in MTT, and support contemporary theoretical accounts that suggest that the integration of the hippocampus with the DMN provides the neurocognitive landscape that allows us to imagine distant times and places.

3.2 Introduction

Conscious experience is not restricted to events in the here and now. The prominence of states such as daydreaming and mind-wandering in our mental lives illustrates that we often mentally escape from the constraints of the moment and generate thoughts regarding people, places and situations other than those in the immediate environment (Killingsworth and Gilbert, 2010). It is now known that these states are accompanied by a measurable reduction in the processing of external events, indicating a disengagement, or decoupling, of attention from the external environment (Smallwood et al., 2008a). Instead of relying on perceptual input for their mental content, it is hypothesised that these experiences are built almost exclusively from representations in semantic and episodic memory (see Smallwood and Schooler 2015 for a review).

Evidence from functional neuroimaging is consistent with the view that memory retrieval is a core process with which we generate spontaneous thought. Prior work has demonstrated that a large-scale brain system known as the default mode network (DMN) is important for the thoughts that are generated during the mind-wandering state (Mason et al., 2007; Christoff et al., 2009). The DMN is generally identified as a distributed regional assembly anchored by hubs in the medial prefrontal cortex, the posterior cingulate cortex and the angular gyrus (Raichle et al., 2001; Raichle, 2015). During tasks that involve retrieving information from memory, the DMN often integrates information from medial and lateral temporal regions known to play a pivotal role in episodic and semantic memory, such as the hippocampus (Sestieri et al., 2011) and the anterior temporal lobe

(Patterson et al., 2007). Several studies have linked the DMN, as well as related structures such as the hippocampus, to processes such as imagining events from the future or past (Schacter et al., 2007), which are collectively known as mental time travel (MTT). Studies have shown that MTT is an important element of the mind-wandering state (Smallwood et al., 2009b; Baird et al., 2011) and a meta analytic study has shown similarities between the neural activation during mind-wandering and episodic future thinking (Stawarczyk and D'Argembeau, 2015). A recent study (Ellamil et al., 2016) has also indicated that the hippocampus is activated early during the spontaneous generation of thoughts while mind-wandering.

Although previous functional magnetic resonance imaging (MRI) studies have established a functional role of the DMN in the mind-wandering state (Mason et al., 2007; Allen et al., 2013; Ellamil et al., 2016), the extent to which the neural architecture of this network and associated regions of cortex constrain naturally occurring spontaneous thought remains uncertain. In the current study, we tested the hypothesis that variations in spontaneous thoughts across participants emerge as a consequence of the large-scale structural network organisation of the brain. We applied regionally unconstrained tractography analysis to diffusion magnetic resonance imaging data in a cohort of healthy adults and assessed whether individual variability in the contents of their thoughts related to markers of structural connectivity. Our analysis approach was complemented with probabilistic connectivity mapping, to identify the cortical grey matter with the highest connection probability to these tracts. Finally, we used seed-based resting-state functional MRI connectivity mapping to identify associated functional networks. Based on functional studies of the role of the DMN and regions in the medial and lateral temporal lobe in thoughts generated during the mind-wandering state (Christoff et al., 2009; Stawarczyk et al., 2011b), we anticipated our structural analysis to highlight a constellation of regions, including the medial prefrontal, posterior cingulate, as well as lateral and medial temporal cortices, including the hippocampus.

3.3 Methods

3.3.1 Participants

A total of 86 healthy participants were recruited by advert from the Department of Psychology at the University of York (51 women, age range 18 - 31). They were offered either a payment of £20 or a commensurate amount of course credits. Written consent was obtained for all participants and the study was approved by the York Neuroimaging Centre Ethics Committee. Participants were recruited in two cohorts (Sample A, n = 47; Sample B, n = 39) in different time periods, although there were no differences relevant to the study. While both samples participated in the behavioural session and underwent a resting state (rs) functional MRI scan, we acquired diffusion MRI data only for sample A. We excluded 8 out of 39 participants from Sample B due to incomplete brain coverage (whole-brain coverage $< 94\%$). Having two samples gave us the opportunity to treat them separately in our analyses and investigate the robustness of our behavioural and functional MRI results. The behavioural and functional MRI data in this study are the same as those reported in Smallwood et al. (2016).

3.3.1.1 Independent sample

We also used an independent dataset to provide independent confirmation of functional connectivity results. These data were obtained from a publicly available dataset: the Nathan Kline Institute (NKI)/Rockland Enhanced Sample and contained 141 subjects. Full details of this sample can be found in Gorgolewski et al. (2014).

3.3.2 Behavioural Methods

3.3.2.1 Choice Reaction Time Task

To acquire information about the content of spontaneous thought in a situation conducive to the mind-wandering state, participants performed a simple non-demanding choice reaction time task. This task is routinely used in studies of spontaneous thought because it creates periods when spontaneous thoughts are generated with as similar a frequency as when participants are not engaging in a task (Smallwood et al., 2009b). Participants sat in a testing booth and were asked to make a parity judgement to numerals that were coloured red. These stimuli were presented in a stream of non-coloured numerals, to which no response was required. Stimuli were presented with a slow inter-stimulus interval (2200-4400 ms) and remained on screen for 1000 ms. The task lasted 15 min and participants performed a single run. The occurrence of the target and non-target stimuli was randomly determined with a mean target number of M = 25.2, SE = 0.6 and a mean non-target number of M = 109.6, SE = 1.1. Participants responded by using the mouse button. Accuracy was high (mean±SD = 0.93±0.08), with a mean response time of 900 ms (SD =

161). Participants performed this task in a laboratory testing session, scheduled one day after the scanning.

3.3.2.2 Multi-Dimensional Experience Sampling (MDES)

At unpredictable moments while performing the laboratory task, participants were interrupted and asked to rate different aspects of their experience. They were asked to focus their answers on the contents of their experience the moment immediately prior to the interruption, thereby reducing demands on memory. They responded using a continuous Likert scale. The specific questions used are described in Table 3.1 and they were all asked during each probing. They were selected from prior studies (Smallwood et al., 2016) and examined the content of thoughts (e.g. temporal content relating to the past or future, referent of thought - themselves or another person - and emotional valence), as well as the form these thoughts took (whether the thoughts were in words or images, the level of detail and intrusiveness, etc.).

Whenever experience sampling occurred, the questions were administered in a quasi-random order. The first question was always about task focus, followed by blocks of questions about the content and form of thoughts. On each occasion, the order of each block, as well as the order of questions within each block, was randomised. Participants were probed an average of 8 times during the fifteen-minute task. We used a fully randomised sequence of experience sampling probes to ensure that regularities in our probing schedule did not bias the results of our experiment (Seli et al., 2013).

Table 3.1: Experience sampling questions used in this experiment.

Dimension	Question (My thoughts ...)	Left	Right
Task	... were focused on the task I was performing	Not at all	Completely
Future	... involved future events	Not at all	Completely
Past	... involved past events	Not at all	Completely
Self	... involved myself	Not at all	Completely
Other	... involved other people	Not at all	Completely
Emotion	The content of ... was	Negative	Positive
Images	... were in the form of images	Not at all	Completely
Words	... were in the form of words	Not at all	Completely
Intrusive	... were intrusive	Not at all	Completely
Detail	... were vague and non-specific	Not at all	Completely

As in previous studies, data from each individual was concatenated into a single matrix. We z-scored the data from each sample separately to minimise differences between them, and fed them into a principal component analysis (PCA) with varimax rotation, allowing patterns of covariance that broadly correspond to different types of thought to be identified. The decomposition of these data, as well as a replication sample, has previously been reported by Smallwood et al. (2016). The decomposition was performed in separate analyses, one for the content of the experience and one for the form. We chose to decompose the components of content and form separately because our method of experience sampling presented them in these conceptual groups, reflecting our a priori interest in decomposing them as separate factors. In addition, we have successfully employed this technique of experience sampling in several prior studies (Ruby et al., 2013a,b; Engert et al., 2014; Medea et al., 2018) and applying the same procedure in the current study provided the chance to relate our data to these prior investigations. Table 3.2 presents the eigenvalues for the first four components generated from the decomposition of the content and the form questions, where it can be seen that the scores change rapidly after the third component. For this reason, and to remain consistent with these previous studies, we opted for a three-component solution.

Table 3.2: Eigenvalues from the decomposition of the experience sampling data for the content and form questions.

Questions	Component			
	1	2	3	4
Content	1.77	1.11	1.08	.87
Form	1.3	1.05	.94	.67

3.3.3 Neuroimaging Methods

3.3.3.1 MRI data acquisition

MRI data were acquired on a GE 3 Tesla Signa Excite HDxMRI scanner, equipped with an eight-channel phased array head coil at York Neuroimaging Centre, University of York. For each participant, we acquired a sagittal isotropic 3D fast spoiled gradient-recalled echo T1-weighted scan (TR = 7.8 ms, TE = minimum full, flip angle = 20°, matrix = 256x256, voxel size = 1.13x1.13x1 mm^3, FOV = 289x289 mm^2). Resting-state functional MRI data based on blood oxygen level-dependent contrast images with fat saturation were acquired using a gradient single-shot echo-planar imaging sequence (TE = minimum full ($\approx$19 ms), flip angle = 90°, matrix = 64x64, FOV = 192x192 mm^2, voxel size = 3x3x3 mm^3). Sample A had a scan duration of 9 min and the following additional parameters TR = 3000 ms, 180 volumes, slice thickness 3 mm, no gap, 60 slices. Sample B had a scan duration of 7 min, TR = 2000 ms, 210 volumes, slice thickness 3 mm, 0.5 mm gap and 32 slices. The duration of the diffusion MRI scan was 13 minutes. A single-shot pulsed gradient spin-echo echo-planar imaging sequence was used with the following parameters: b = 1000 s/mm^2, 45 directions, 7 T2-weighted EPI baseline scans (b0), 59 slices, FOV = 192x192 mm^2, TR = 15 s, TE = 86 ms (minimum full), voxel size = 2x2x2 mm^3, matrix = 96x96.

3.3.3.2 Structural connectivity analysis

Diffusion MRI data pre-processing involved eddy-current distortion correction and motion correction using FDT v3.0, part of FSL (Smith et al., 2004). The fractional anisotropy (FA) was calculated by fitting a tensor model at each voxel of the pre-processed diffusion data and the resulting images were brain-extracted using BET (Smith, 2002). Voxel-wise FA maps were analysed using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). No advanced options were used. After subjects' FA data were non-linearly aligned to the FMRIB58 template in MNI152 space, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. Using a generalised model, we assessed correlations between measured FA values across the skeleton and the mind-wandering PCA scores of each participant. T-statistics maps for contrasts of interest were calculated using FSL's Randomize (a nonparametric permutation inference tool) with 5000 permutations (Nichols and Holmes, 2002). Resulting maps were thresholded at a Family-Wise Error (FWE) corrected $p < 0.05$ using Threshold-Free Cluster Enhancement (TFCE) (Smith and Nichols, 2009).

We fitted voxel-wise probabilistic diffusion models using BEDPOSTX (Behrens et al., 2003) with 2 fibres modelled per voxel and 1000 iterations. Subsequent to BEDPOSTX, probabilistic tractography was performed using PROBTRACKX (Behrens et al., 2007) to reconstruct fibres passing through a single-mask or connecting two masks at a time. Tractography was performed in native diffusion space. To this end, we transformed our seed masks from standard space back to diffusion space using the inverse of the nonlinear registration calculated in the TBSS pipeline. PROBTRACKX was used with standard parameters (5000 samples/voxel, curvature threshold 0.2, step length 0.5 mm, samples terminated after 2000 steps or when they reached the surface as defined by a 40% probabilistic whole-brain WM mask). In the single-mask case, the connectivity maps of each individual were thresholded at 1% of total samples sent from the seed mask, mapped back to standard space using nonlinear registration, and concatenated into a single 4D file. Nonparametric voxelwise statistical testing with 25000 permutations was then performed to obtain a group-level probabilistic tractography map, thresholded using TFCE at $p < 0.05$, FWE-corrected as above. In the dual-mask case, we performed seed-to-target analyses, with atlas volumes as the seeds and clusters of significant findings from our analyses as the targets. We also ran seed-to-target analyses using diffusion imaging data ($b = 1500$ s/mm^2, 127 directions plus 9 interspersed b0 images, voxel size = 2x2x2 mm^3) from a subset ($n = 9$, 4 women, age range 21 - 48) of the Test-Retest Pilot Dataset/enhanced NKI sample. Full details of this sample, as well as all the parameters of the diffusion-weighted imaging sequence used, can be found online here: http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/FrontPage.html.

3.3.3.3 Functional connectivity analysis

Functional MRI pre-processing and analyses were performed using FSL. Following the co-registration of functional and structural data, we extracted the brain using BET and linearly registered them to MNI152 space. Prior to functional connectivity analysis, resting state data underwent motion correction using MCFLIRT, slice-timing correction using Fourier-space time-series phase shifting, brain extraction using BET, spatial smoothing using a Gaussian kernel with a full width at half maximum of 6 mm, grand-mean intensity normalisation followed by high-pass (sigma = 100 s) and low-pass temporal filtering (sigma = 2.8 s).

In each subject, we extracted the time series from seed regions of interest (i.e. atlas volumes or significant clusters identified in previous steps) and used them as explanatory variables in separate functional connectivity analyses that also included 11 nuisance regressors: the top five principal components extracted from WM and cerebrospinal fluid masks in accordance with the CompCor method (Behzadi et al., 2007) and six motion parameters. No global signal regression was performed (Murphy et al., 2009).

Group-level statistical modelling was carried out using FEAT/FLAME stage 1 (Woolrich et al., 2004) with automatic outlier detection (Woolrich, 2008). A 50% probabilistic

GM mask was applied and results were thresholded at the whole-brain level using cluster-based Gaussian random field theory, with a cluster-forming threshold of $z > 3.1$ (and $z > 2.3$ when the two samples were analysed independently) and a FWE corrected cluster significance level of $p < 0.05$. To further confirm our group-level findings we also ran the analysis using permutation testing with the obtained maps thresholded using TFCE at $p < 0.05$, FWE-corrected. Unthresholded maps were uploaded onto Neurovault and can be found here: http://neurovault.org/collections/1448.

3.4 Results

3.4.1 Analysis aims

The goal of this experiment was to identify connections between the structural and functional organisation of the brain and variations in different types of spontaneous thought. We first calculated the principal components of the type of spontaneous thoughts as reported in a laboratory session. Next we determined whether there was any relationship between the fractional anisotropy of tractography-derived white matter tracts and inter-individual variation in the content and form of spontaneous thought. Finally, we explored the functional connectivity of grey matter regions that received projections from the tracts identified in the previous step, with the aim of identifying whether the functional connectivity of these regions is modulated by the same aspects of spontaneous thought. The analysis pipeline is outlined in Figure 3.1.

3.4.2 Components of spontaneous thought

For the decomposition of content, we focused on questions relating to temporal focus, referent of thought, task focus, and emotional content. Consistent with prior investigations (Ruby et al., 2013a,b; Engert et al., 2014; Medea et al., 2018), we found three orthogonal factors: i) Future and self-focused thoughts: individuals with high weighting on this component were often thinking about themselves in the future, accounting for 29% of the observed variance; ii) Past-focused social thoughts: individuals with high weighting were often thinking about self and others in the past, accounting for 19% variance; iii) Task-related thoughts: individuals with high weighting were often thinking about the task itself and experienced fewer negatively valenced off-task thoughts, accounting for 18% variance. The average of the future and past components, which we refer to as MTT, accounted for

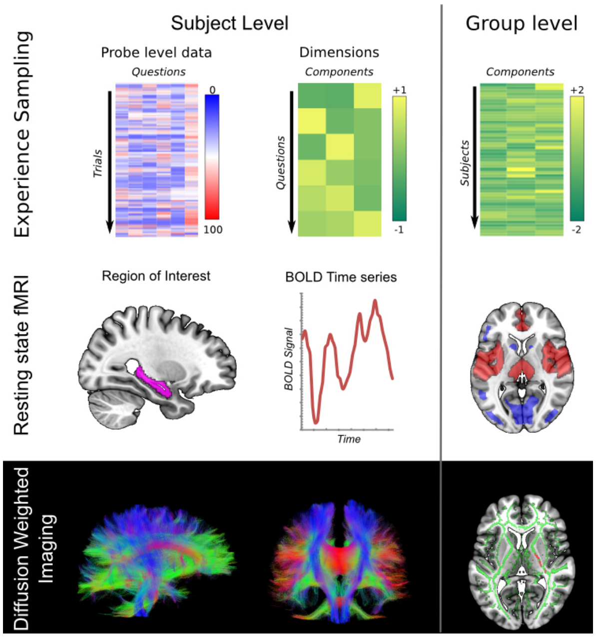

Figure 3.1: *Overview of analysis pipeline.* The upper panel describes the analysis steps which allow the dimensions that underlie the trial level experience sampling data to be calculated. The middle panel describes how the functional connectivity maps for our regions of interest are calculated from the resting state functional Magnetic Resonance Imaging data (MRI). The lower panel describes how the fractional anisotropy maps are calculated from the whole-brain diffusion MRI data.

48% of the overall variance.

Our next step was to decompose the questions regarding the form of thoughts - such as whether these were experienced as images or words, if they were detailed and whether they were intrusive - following a similar procedure. This yielded three components: i) The modality of the thoughts (images or words): individuals with high weighting often described their thoughts as containing words rather than images and this reflected 33% of the variance; ii) The level of intrusiveness of the thoughts: individuals with high weighting often described their thoughts as intrusive, accounting for 26%; iii) The level of detail in the thoughts: individuals with low weighting on this reported more detail in their thoughts accounting for 23%. These patterns of the form of cognition are consistent with prior investigations (Medea et al., 2018; see also the replication sample in Smallwood et al., 2016).

3.4.3 Identifying the relationship between white matter fractional anisotropy and the contents of spontaneous thought

Relating component weighting of the mind-wandering PCA scores to skeleton-wide FA values derived from the TBSS analysis revealed a specific increase in the fractional anisotropy of a temporo-limbic white matter region for people engaging more in MTT (Fig. 3.2i-top, Table 3.3). No other components showed any significant association. In order to describe the whole-brain structural connectivity profile of this region, we performed a probabilistic tractography analysis using it as a seed (Fig. 3.2i-bottom). This analysis showed (Fig. 3.2ii) that the clusters' structural connectogram closely overlapped with the right fornix, the right corticospinal tract, and the right inferior fronto-occipital fasciculus, as defined by the Johns Hopkins University DTI-based white-matter atlases (Mori et al., 2005).

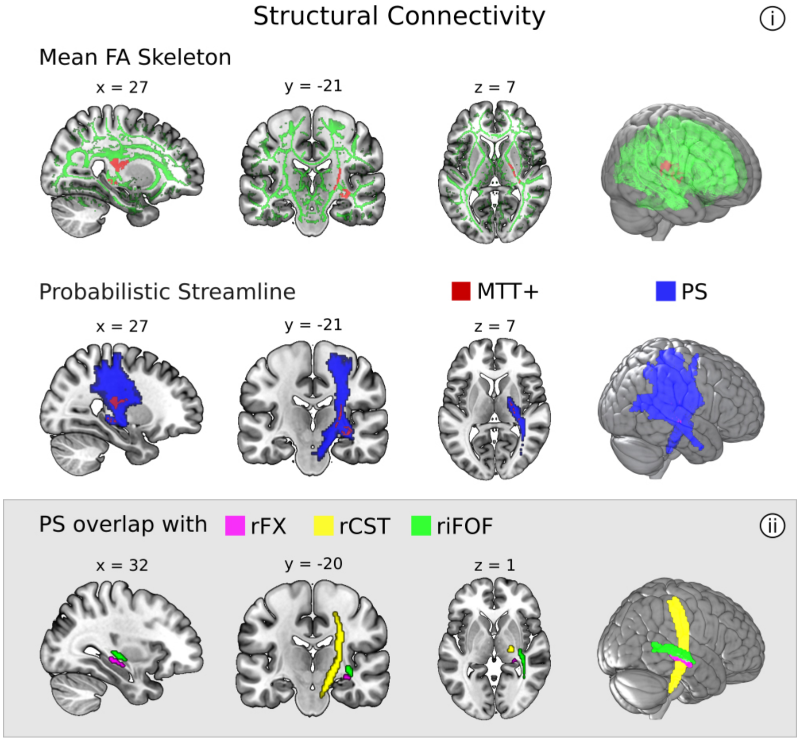

Figure 3.2: *Identifying the relationship between structural connectivity and the contents of spontaneous thought.***i**: The upper panel shows the results of the whole-brain diffusion MRI analysis. The clusters where a significant increase in fractional anisotropy was found for participants engaging more in mental time travel are indicated in red and are overlaid on the mean fractional anisotropy skeleton. Results were thresholded at a Family-Wise Error (FWE) corrected $p < 0.05$ using Threshold-Free Cluster Enhancement. The lower panel presents these significant clusters along with the probabilistic streamline that was found to pass through them. The streamline was thresholded using Threshold-Free Cluster Enhancement at $p < 0.05$, FWE-corrected.**ii**: This panel demonstrates the overlap of the probabilistic streamline with the right fornix, the right corticospinal tract, and the right inferior fronto-occipital fasciculus. Acronyms: FA - fractional anisotropy , MTT+ - increased mental time travel, PS - probabilistic streamline, rFX - right Fornix, rCST - right corticospinal tract, riFOF - right inferior fronto-occipital fasciculus.

Table 3.3: Clusters showing a significant association between the MTT weights and the FA of the whole-brain, corrected for multiple comparisons with a family-wise error rate of $p < 0.05$.

Cluster size (voxels)	Cluster centre of gravity X,Y,Z (mm)
481	25, -18, 9
172	32, -22, -5
8	27, -31, -3

As this region falls in an area with a high degree of crossing fibres, we also performed an additional analysis using a model that incorporates fibre-specific measurements (tbss_x) (Jbabdi et al., 2010). We estimated the primary and secondary fibre orientations, together with their partial volume fractions, and found a significant increase in the partial volume fraction of the primary orientation for people engaging more in MTT. No other component was significant for any of the two orientations. The identified regions (Fig. 3.3) include the areas discovered in our original analysis, but being more widespread did not improve their structural classification. For this reason and due to the potential limitations of our diffusion imaging sequence in regard to probabilistic analyses and crossing fibres (see Discussion), we did not consider them any further.

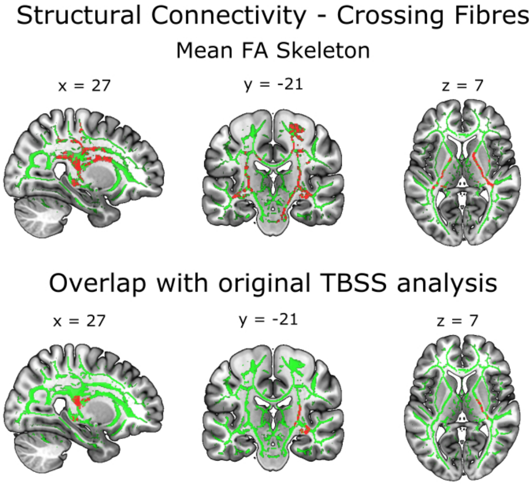

Figure 3.3: *Identifying the relationship between structural connectivity and the contents of spontaneous thought using a crossing fibre model.* The upper panel shows the results of the whole-brain diffusion MRI analysis while accounting for crossing fibres. The voxels where a significant increase in the partial volume fraction of the primary fibre orientation was found for participants engaging more in mental time travel are indicated in red and are overlaid on the mean fractional anisotropy skeleton. Results were thresholded at a Family-Wise Error (FWE) corrected $p < 0.05$ using Threshold-Free Cluster Enhancement. The lower panel shows the overlap between these results and the ones from our original TBSS analysis presented in the main manuscript.

To identify those grey matter regions most likely to be connected to the temporo-limbic white matter substrate of MTT, we used the seeds-to-target mode of PROBTRACKX with no advanced options and calculated probabilistic streamline counts that reach our target mask when seeding from 116 regions-of-interest, as defined by the automated anatomical labelling (AAL) (Tzourio-Mazoyer et al., 2002) for a given participant. This generated a 116 x 47 connectivity matrix, in which streamline counts were normalised by the total number of generated tracts (waytotal), thus translated to connection probabilities. The results demonstrate that the most likely grey matter region connected with the MTT substrate is the right hippocampus (Fig. 3.4). To quantitatively assess this, we calculated the difference between the hippocampus connection probability to our target mask and the second highest connection probability, per participant. The generated distribution was significantly greater than 0 (one-sample Wilcoxon Signed Ranked test, $p < 0.0001$).

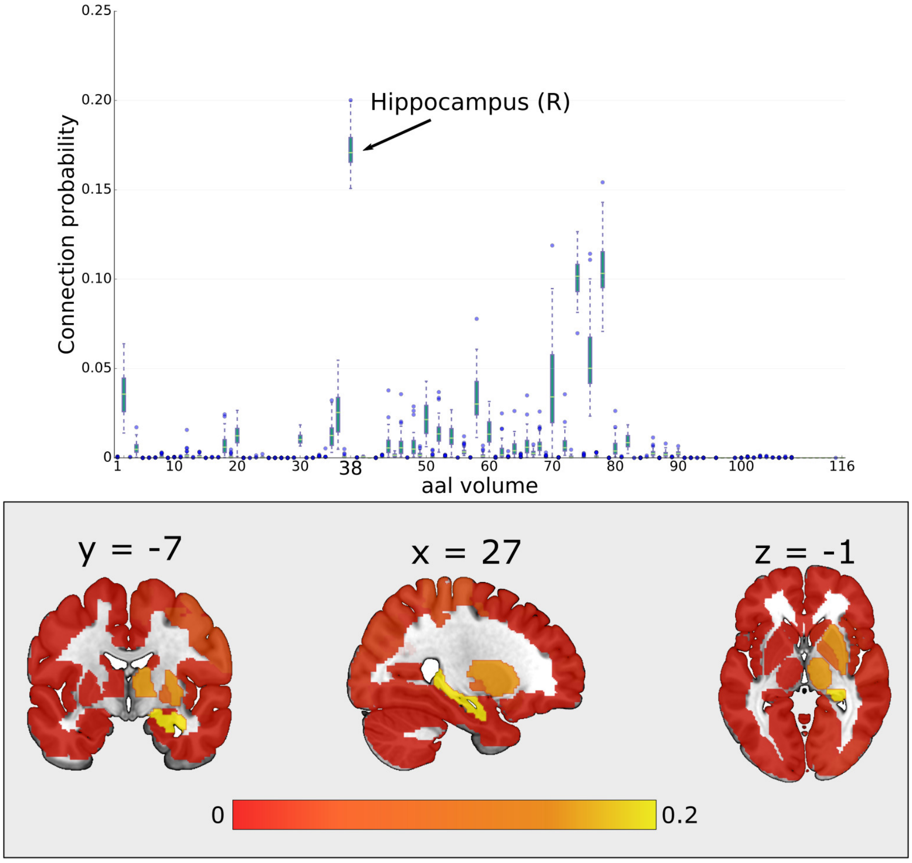

Figure 3.4: *Identifying the grey matter regions connected to the temporo-limbic white matter substrate of mental time travel.* The box plots in the upper panel show the connection probability of each one of the 116 grey matter volumes of the Automated Anatomical Labelling atlas with the white matter substrate of mental time travel found in our whole-brain tractography analysis. In the lower panel, the volumes are presented with each region coloured according to its average connection probability among participants. It is clear in both panels that the right hippocampus has the highest number of streamlines connecting it to the cluster obtained in the prior step of our analysis.

Arguably, the TBSS-derived cluster was situated in a white-matter region that may harbour extensive fibre crossing, which may challenge tractography-based fibre reconstruction, particularly when a low number of diffusion directions is used. We therefore repeated the diffusion tractography analyses based on data from the NKI Enhanced repository (see Structural connectivity analysis), which were acquired using a sequence with a substantially increased number of diffusion directions. Theoretically, such sequences should better resolve crossing-fibres and thus minimise the risk of erroneous tractography results (see Discussion). Our analyses at this higher angular resolution confirmed that the right hippocampus was the grey matter region most likely to be connected to the temporo-limbic white matter substrate of MTT (Fig. 3.5), supporting our initial findings.

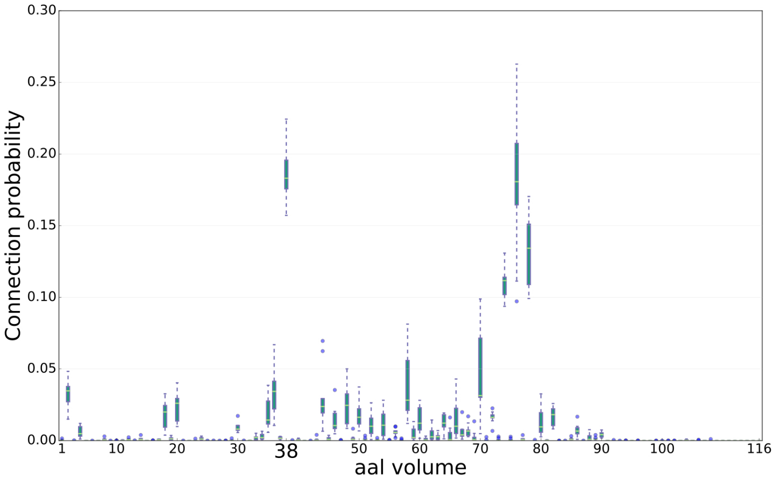

Figure 3.5: *Identifying the grey matter regions connected to the temporo-limbic white matter substrate of mental time travel using the NKI dataset.* The box plots show the connection probability of each one of the 116 grey matter volumes of the Automated Anatomical Labelling atlas with the white matter substrate of mental time travel found in our whole-brain tractography analysis, using diffusion-weighted imaging data from a subset of the NKI enhanced sample. The right hippocampus is identified again as the region with the highest number of streamlines connecting it to our cluster.

3.4.4 Determining the link between the functional connectivity of the hippocampus and the content of spontaneous thought

Having identified the hippocampus as the region with the highest connection probability to our white matter MTT substrate, we assessed its functional connectivity profile and the modulation of these patterns by inter-individual differences in the propensity to engage in MTT. Our motivation for performing this analysis was two-fold. First, we wanted to test the robustness of the diffusion imaging results by investigating whether the selected region had a specific relationship to MTT using data from another scanning modality. Second, we wished to understand whether the mechanism that underlies the role of the hippocampus in MTT was related to its integration into the DMN. To assess these two questions we took advantage of the fact that we had two cohorts of participants for whom resting state functional MRI data were available and who also had MDES descriptions of their thoughts. We calculated the functional connectivity of the AAL mask of the right hippocampus for each participant in each cohort. These maps were used as the dependent variables in a multiple regression analysis with the 6 dimensions from the PCA decomposition of MDES scores used as independent variables, all in the same model.

Group-level functional connectivity of the right hippocampus indicated extensive connections to the ventromedial prefrontal cortex, the retrosplenial cortex, the brain stem and the cerebellum (Fig. 3.6i). Next, we assessed regions whose connectivity with the right hippocampus correlated with individual differences in the content and form of participants' thoughts. This analysis revealed a region of dorsal anterior cingulate cortex/medial prefrontal cortex as can be seen in Figure 3.6i (cluster: size 646 voxels, volume 5168 mm^3, centre of gravity -4, 48, 11 mm), whose connectivity to the hippocampus increased for individuals with higher MTT scores (MTT+) compared to those with lower scores. These results were thresholded at the whole-brain level with a cluster-forming threshold of $z > 3.1$ and a FWE corrected cluster significance level of $p < 0.05$. The same regions (Fig. 3.7) were also highlighted for the MTT+ comparison from our group-level permutation testing analysis.

We also repeated these analyses separately in both datasets to investigate whether idiosyncratic features of one sample may have contributed to our findings. Comparing each group separately, only Sample B passed a cluster forming threshold of $z > 3.1$, however both groups produced significant cluster corrected regions at a more lenient value of $z > 2.3$. In both cases these regions fell in the mPFC and are shown in Figure 3.6ii, alongside their overlap (cluster: size 82 voxels, volume 656 mm^3, centre of gravity -4, 47, 11 mm) and separate scatter plots from each sample. These analyses show a robust pattern of strengthened correlation between the right hippocampus and the medial prefrontal cortex for individuals who engage in greater MTT when the sample is treated as a group; however, we also find a converging pattern when both groups are treated as separate populations. These two features of our data suggest that our findings are statistically robust and are reasonably consistent across both groups of participants.

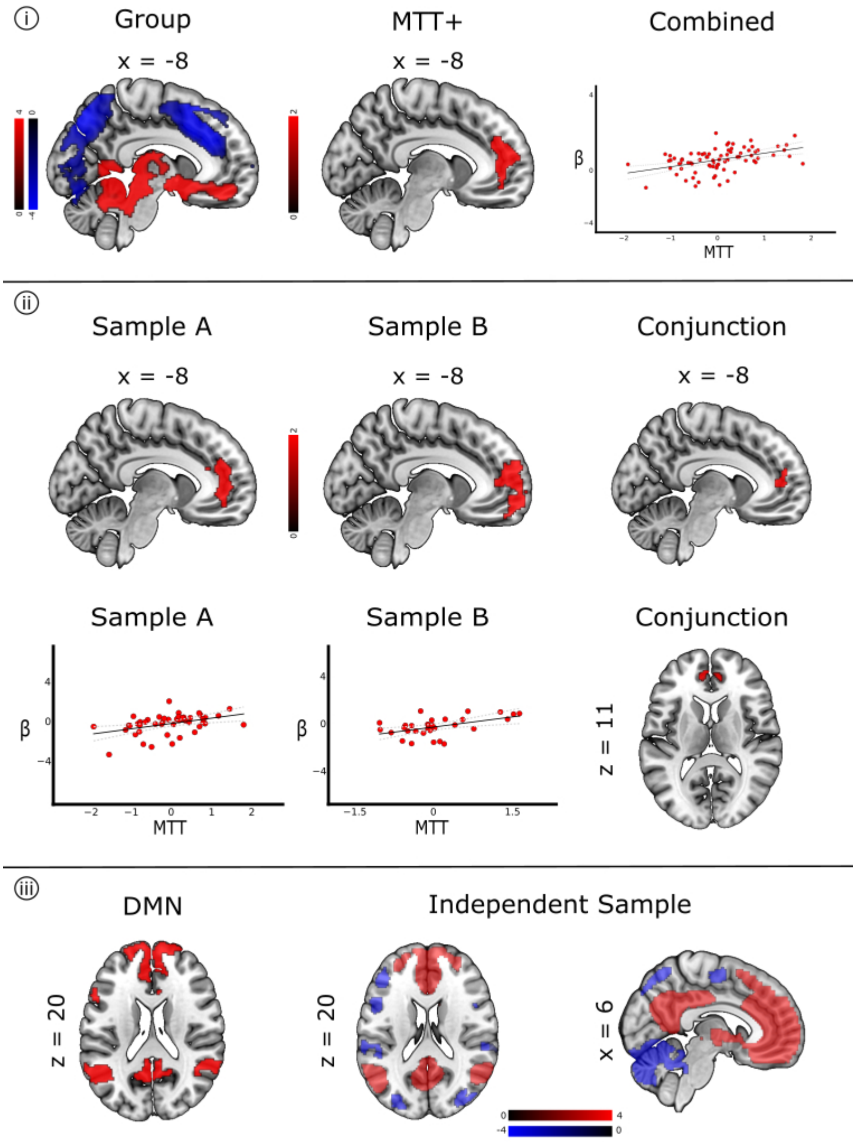

Figure 3.6: *Determining the link between the functional connectivity of the hippocampus and the content of spontaneous thought.* **i**: The group-level functional connectivity of the right hippocampus (left), the region showing a stronger temporal connectivity with it for individuals with higher MTT (middle) and the scatter plot (right) showing the average beta values extracted from this region plotted against the mental time travel scores for each participant. Maps were thresholded at the whole-brain level with a cluster-forming threshold of $z > 3.1$ and a FWE corrected cluster significance level of $p < 0.05$. **ii**. The upper panel shows the regions with increased functional connectivity with the right hippocampus for individuals with higher MTT, when each sample is analysed separately (top left and top middle), as well as their overlap (top right). The lower panel presents an axial slice of the overlap cluster and the two scatter plots from each sample that illustrate the average beta values extracted from this region plotted against the mental time travel scores for each participant. It is apparent that this relationship is consistent across both datasets. Maps were thresholded at the whole-brain level with a cluster-forming threshold of $z > 2.3$ and a FWE corrected cluster significance level of $p < 0.05$. **iii**: The relationship between the default mode network as defined in the Yeo et al. (2011) study and the group-level functional connectivity of the mental time travel conjunction cluster produced through the analysis of an independent dataset. Maps were thresholded at the whole-brain level with a cluster-forming threshold of $z > 3.1$ and a FWE corrected cluster significance level of $p < 0.05$. Acronyms: MTT - mental time travel, DMN - default mode network.

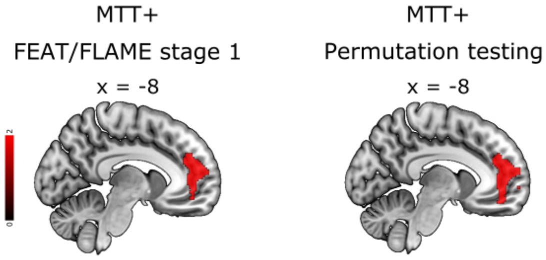

Figure 3.7: *Determining the link between the functional connectivity of the hippocampus and the content of spontaneous thought using permutation testing.* The figure highlights the region showing a stronger temporal connectivity with the right hippocampus for individuals with higher MTT, as was derived from our group-level permutation testing analysis (right). Results were thresholded using TFCE at $p < 0.05$, FWE-corrected. It is clear that it is the same region as the one identified from using FEAT/FLAME stage 1 (left) thresholded at the whole-brain level with a cluster-forming threshold of $z > 3.1$ and an FWE corrected cluster significance level of $p < 0.05$. Acronyms: MTT - Mental time travel.

The observation that coupling between the right hippocampus and the medial prefrontal cortex was greater for participants who engaged in increasing levels of MTT suggests that this experience may depend upon integration between the medial temporal lobe and the DMN. To quantitatively assess this possibility, we used the overlap region identified in the previous step as a seed in a functional connectivity analysis of an independent dataset (see 3.3.1.1, "Independent sample"). This analysis confirmed a pattern of connectivity focused on the posterior cingulate and medial prefrontal cortex, which reflects the canonical DMN (Fig. 3.6iii).

Finally, in addition to the modulation of hippocampal connectivity by mental time travel (MTT), people who reported thinking more in words (W+) and less in images were found to have an increased functional connectivity pattern between the right hippocampus and a region extending from the dorsal posterior cingulate cortex, anteriorly to the precentral gyrus. Moreover, a similar increase in correlation was found between the right hippocampus and a region in the occipital lobe, involving the primary visual cortex and the lingual gyrus for people having more detailed, less vague thoughts (D+). These regions can be seen in Figure 3.8, and the unthresholded maps can be found in Neurovault. The clusters spatial characteristics are presented in Table 3.4. As with the MTT+ cluster, we used the clusters produced through the regression of hippocampal connectivity as seeds in a functional connectivity analysis in a publicly available independent data set. As shown in Figure 3.8-bottom, the cluster in the motor cortex showed a pattern of coupling that extends along the cingulate cortex into the ventromedial prefrontal cortex and into insular cortex, and reduced coupling with regions of the occipital cortex. By contrast, the regions of occipital cortex showed the reverse pattern, with heightened connectivity within the occipital cortex and reduced connectivity with the mid cingulate cortex and insular cortex. However, these results did not survive more stringent analyses, so we do not consider them further.

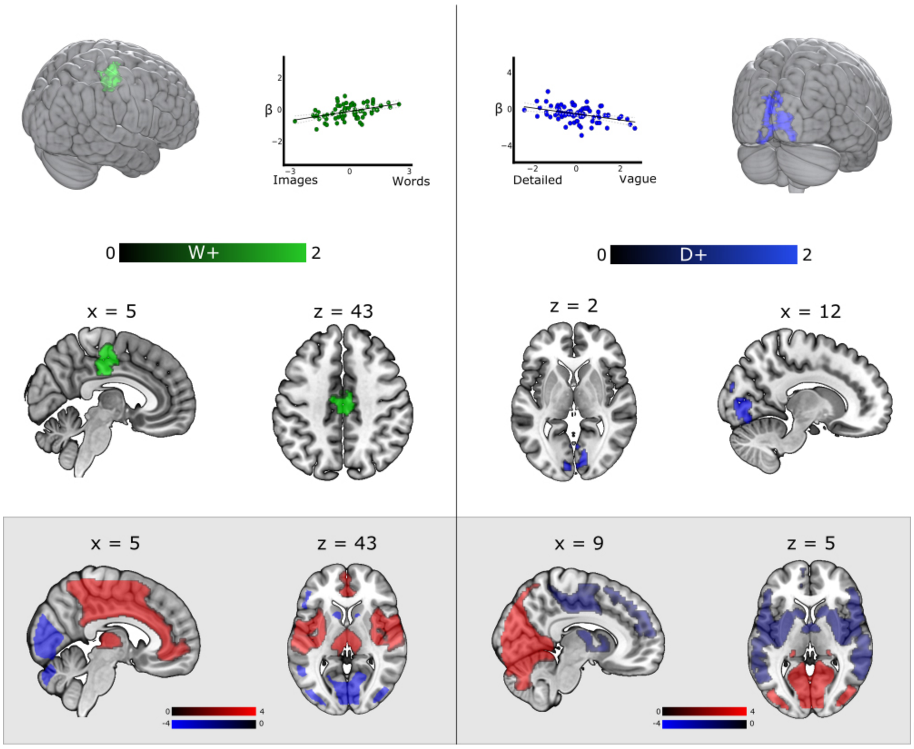

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Figure 3.8: *Determining the link between the functional connectivity of the hippocampus and the form of spontaneous thought.* This figure displays two clusters exhibiting higher functional connectivity with the right hippocampus, one for people thinking more in words and less in images and the other one for people having more detailed, less vague thoughts. The scatter plots illustrate the average beta values extracted from these regions and plotted against the scores for each dimension for each participant. Maps were thresholded at the whole-brain level with a cluster-forming threshold of $z > 2.3$ and an FWE corrected cluster significance level of $p < 0.05$. The lower grey panel illustrates the group-level functional connectivity of these clusters from analysing an independent dataset. Maps were thresholded at the whole-brain level with a cluster-forming threshold of $z > 3.1$ and an FWE corrected cluster significance level of $p < 0.05$. Acronyms: W+ - thinking more in words and less in images, D+ - having more detailed, less vague thoughts.

Table 3.4: Clusters showing a significant association between a dimension of experience and the functional connectivity of the right hippocampus at rest. The p-values representing the level of significance are FWE cluster-corrected.

MDES dimension	Cluster size (voxels)	P-value	Cluster centre of gravity X,Y,Z (mm)
W+	743	0.01	2, -17, 45
D+	960	0.003	1, -83, 1

3.5 Discussion

We demonstrated that the content and form of spontaneous thought is partly constrained by structural and functional brain network organisation. Structural connectivity analyses identified a temporo-limbic white matter region, highly connected to the right hippocampus, for people who spontaneously engaged in more mental time travel (MTT). Using resting state functional connectivity, we found that the temporal correlation of the right hippocampus with the dorsal anterior cingulate cortex, a core region of the default mode network (DMN), was also modulated by inter-individual variation in MTT. These converging lines of evidence provide unambiguous support that the spontaneous thoughts experienced during the mind-wandering state are in fact reliant upon the hippocampus and its integration into the DMN.

Component process accounts of the mind-wandering state suggest that this class of experience depends upon distinct neurocognitive components. These include the ability to disengage attention from external input, known as perceptual decoupling, and processes more directly related to the generation and coordination of the experiential content (Smallwood and Schooler, 2015). Among them, episodic memory processes have been considered to play a key role in the generation of the mental content during mind-wandering, particularly those episodes that entail imagining distant times and places (MTT). People frequently use MTT to consider autobiographical goals (Baird et al., 2011), solve personal problems (Ruby et al., 2013b), reduce social stress (Engert et al., 2014) and to generate creative solutions to problems (Baird et al., 2012): all tasks that draw on multiple types of memory and involve the hippocampus. The hippocampus has been linked to a broad range of cognitive processes, including episodic or autobiographical memory (Eichenbaum, 1993; Aggleton and Brown, 1999), spatial navigation (O'keefe and Nadel, 1978; O'Keefe et al., 1996) and the binding of temporally extended events into a sequence (for a review see Eichenbaum 2013). These distinct accounts have led to the proposal that the hippocampus may serve an integrative function in cognition by combining information from different domains to form coherent scenes (Hassabis and Maguire, 2007; Maguire et al., 2015), allowing autobiographical information to be placed in a temporal and spatial context (Eichenbaum and Cohen, 2014). Building on this view, it is possible that the hippocampus integrates different aspects of knowledge from memory into an ongoing train of thought. It could do so by its dense structural and functional connectivity profile to multiple areas of cortex (Squire et al., 2004; Moscovitch et al., 2016; Bernhardt et al., 2016; Strange et al., 2014). Our demonstration that the structural and functional connectivity of the hippocampus is important in MTT may reflect a hippocampal contribution to the process through which we use our memory to consciously organise our life goals and evaluate our past experiences. It is worth noting that, although our main diffusion tractography analysis targeted the right hippocampus, our supplementary analysis after accounting for crossing fibres highlighted tracts more symmetrical across hemispheres (see Fig. 3.3), suggesting an involvement of both left and right hippocampi. Thus, while prior studies have found that the right hippocampus is important in mental time travel especially when imagining events (see Arzy et al. 2009, Experiment 2, see also Addis and Schacter 2012 for further consideration of this issue), further work is needed to identify the role of the hippocampus in different hemispheres in spontaneous mental time travel.

Our functional data showed that the region with heightened hippocampal coupling for increased mental time travel fell outside of the group connectivity map of the hippocampus (see Fig. 3.6). This suggests that the contribution of the hippocampus to MTT involves integration with the medial prefrontal cortex, a core node of the DMN (Gusnard and Raichle, 2001; Greicius et al., 2003; Buckner et al., 2008). Contemporary accounts of this network (Andrews-Hanna et al., 2014a) propose that the DMN consists of discrete subsystems, whose coupling to the medial core - the medial prefrontal cortex and posterior cingulate cortex - influences ongoing cognitive processing (Andrews-Hanna et al., 2014b). In concordance with this view, it has been shown that, during memory retrieval, the hippocampus couples with other DMN regions more strongly than it does at rest (Huijbers et al., 2011), while hippocampal - DMN interactions have also been highlighted in conceptual processing (Constantinescu et al., 2016). Our demonstration that increased functional connectivity between the hippocampus and the medial prefrontal cortex is associated with increased MTT supports this component process view of the DMN function, suggesting that engaging in spontaneous episodic thought is a situation when the hippocampus and the DMN act together in an integrated fashion. Our data from the domain of spontaneous thought provides further evidence that the DMN is important in attending to distant times and places (Peer et al., 2015), perhaps because it functions to integrate information from across the cortex (Margulies et al., 2016). This hypothesis could be further explored by looking at the content of thought while ongoing measures of neural function are recorded (Tusche et al., 2014). In addition, as recent studies have demonstrated ways of measuring activity in white matter from a functional MRI acquisition (Gawryluk et al., 2014; Ding et al., 2016), it could be of interest to explore the temporal correlations along white matter tracts and how these might relate to spontaneous thoughts and DMN connectivity.

There are some limitations that should be borne in mind when considering our data. First, we only measured the functional and structural organisation of neural functioning in the participants on one occasion. Although the converging evidence produced by two independent imaging methodologies, and especially the diffusion data, show that these data are most parsimoniously described as reflecting a trait, there remains a possibility that the experience sampling observations are partly influenced by state related changes. Future studies may gain greater power by measuring experience across several days, which would provide measures of the content of mind-wandering that are more closely tied to an individual's trait. Also, our study explored the neural correlates of latent patterns within a multi dimensional experience sampling space by performing a data reduction using principal components analysis. This allows us to characterise the largest patterns within the experience sampling data in a statistically robust manner; however, its weakness is that it does not provide the specificity to determine whether it is the self-relevant or temporal aspects of cognition, or a combination of both, that our data capture. Future work with a larger sample size could profitably explore this issue by modelling the interactions at the level of each question. In addition, our whole-brain tractographic findings did not survive a superordinate Bonferonni correction additionally adjusting family-wise error levels for the number of different contrasts included in our model. We believe that this is quite possibly due to the sample size of our diffusion MRI data and unlikely to be a Type 1 error, as the MTT score was found to be a significant predictor of a fractional anisotropy increase in a white matter region highly connected to the hippocampus, a region for which there are strong a priori reasons to expect it to play an important role in the mind-wandering state (Schacter et al., 2007). Moreover, the functional connectivity of the hippocampus to core regions of the DMN showed a similar pattern of modulation by MTT across two datasets. Finally, it is also important to note that the current study was carried out using a conventional diffusion imaging sequence with 45 diffusion directions and only one b-value shell. While it has been argued previously (Jones, 2004; Jones et al., 2013) that 30 or more unique orientations allow to obtain robust estimates of tensor-derived properties (fractional anisotropy and principal eigenvector orientation), tractographic analysis and estimation of tensor parameters may generally be challenged when different fibre populations cross in a given voxel. These limitations motivate more targeted follow-up diffusion

MRI studies on the observed relation, that can take advantage of increased angular resolution by moving to higher fields, using longer scans, and/or by utilizing accelerated image acquisition techniques (Feinberg et al., 2010).

In conclusion, our study highlights that although spontaneous thoughts seem to emerge independently of external input, they are nonetheless constrained by the structure of the cortex. Our results provide evidence that the connections between the hippocampus and other areas of the cortex support the contribution of episodic content during spontaneous thought. These findings complement prior studies linking individual differences in spontaneous thought to (i) neural measures such as cortical thickness (Bernhardt et al., 2014), functional connectivity (Smallwood et al., 2013a; Tusche et al., 2014; Smallwood et al., 2016), and (ii) psychological measures such as executive control (Smallwood et al., 2013b; Kane et al., 2007; Levinson et al., 2012; McVay and Kane, 2009) and personality (McVay et al., 2009; Diaz et al., 2014; Golchert et al., 2017). Together, these complimentary lines of research demonstrate that although the specific content our thoughts take is doubtlessly influenced by our current concerns (Klinger and Cox, 1987) or our mood (Smallwood et al., 2009a; Killingsworth and Gilbert, 2010; Poerio et al., 2013), aspects of how they emerge may be determined by more stable aspects of a person. Thus, even though our clear sense is that spontaneous thoughts emerge from nowhere (Schooler, 2002), the manner in which this process occurs is likely influenced by the organisation of our neurocognitive system.

Chapter 4

Population level interactions between the neural correlates of dispositional internal thought and visual imagery

4.1 Abstract

Experience is not always tied to events taking place in the environment. We often generate thoughts, images and feelings unrelated to the events in the here and now. Important aspects of these self-generated experiences are stable over time within an individual but are also associated with various dispositional traits (such as ADHD or depression). In our current study, we explored whether task-free functional imaging can shed light on whether these associated dispositional features depend on common or distinct underlying mechanisms. We acquired resting state functional magnetic resonance imaging data from a large cohort of participants and sampled their experience during the scan by asking them to retrospectively report their thoughts. In a separate experimental session, participants completed a battery of measures reflecting a range of different dispositional traits.

The author, Theodoros Karapanagiotidis, designed the experiment, collected and analysed the data and wrote the article under the supervision of Prof. Elizabeth Jefferies and Prof. Jonathan Smallwood.

Independent component analysis identified a set of whole-brain functional networks, and we modelled how the associations between each of these nodes correlated with metrics of ongoing thought at rest as well as with dispositional indices of physical and mental health. Behaviourally, we found evidence of association between patterns of ongoing experience emphasising visual imagery and aspects of disposition that reflected high levels of self-consciousness, depression and attentional problems. We found that increased connectivity between a posterior parietal network and a lateral fronto-temporal network was associated with more reports of visual imagery at rest. Furthermore, a pattern of decoupling between the brainstem and a lateral visual network was associated with dispositional internal focus (elevated self-consciousness, rumination and attentional problems). Critically, we found that these two brain-cognition relationships were related: the correlation between parietal-frontal regions and reports of visual imagery was stronger for individuals who also had stronger connectivity between aspects of the brain stem and cerebellum with visual cortex. Together, these results suggest that unique patterns of neural organisation reflect trait variance both in ongoing patterns of thought at rest and associated dispositional traits. Furthermore, our results suggest that accounting for trait-like dispositional patterns associated with different patterns of ongoing experience is important when exploring the neural mechanisms supporting different elements of self-generated experience.

4.2 Introduction

Whether we are thinking about a task at hand or mind-wandering about our future plans, our restless brain (Raichle, 2011) drives our restless mind (Smallwood and Schooler, 2006) at any given point in time. Investigating this dynamic relationship, recent studies have identified thematic patterns, or "dimensions" of thought, (Wang et al., 2018b) that have a reproducible structure across studies and time (Medea et al., 2018; Smallwood et al., 2016; Poerio et al., 2017; Konishi et al., 2017; Sormaz et al., 2018). Recurring themes in experience capture variation in the content and form of our thoughts (Gorgolewski et al., 2014) and highlight stable patterns, such as thoughts about the future or the past (Ruby et al., 2013a; Smallwood et al., 2016; Karapanagiotidis et al., 2017), the modality within which experience unfolds, i.e. whether it is dominated by imagery or inner speech (Wang et al., 2018a; Konishi et al., 2017; Smallwood et al., 2016), or the level of subjective detail (Sormaz et al., 2018; Smallwood et al., 2016; Gorgolewski et al., 2014).

These patterns of thought have associations with dispositional variables related to affect, psychological well-being, and problems in attention. For example, the temporal focus of spontaneous thoughts is linked to levels of happiness. Future thinking has been shown to improve mood (Ruby et al., 2013a; Engert et al., 2014) and facilitate problem solving by refining future goals (Baird et al., 2011; Medea et al., 2018; McMillan et al., 2013). By contrast, thinking about the past is associated with negative mood (Ruby et al., 2013a; Killingsworth and Gilbert, 2010) and in the case of intrusive, ruminative thoughts, to depression and anxiety (Watkins, 2008). In addition, identified patterns of spontaneous thought have been linked to creativity and intelligence (Baird et al., 2012; Wang et al., 2018b; Turnbull et al., 2019) as well as ADHD (Seli et al., 2015b), neuroticism (Perkins et al., 2015) and measures of self-consciousness (Smallwood et al., 2002a). These studies demonstrate that different themes of ongoing thought are likely to be partly influenced by population variation in a range of dispositional variables.

These associations between specific dispositional variables and patterns of ongoing experience highlight a methodological challenge for the increasing number of studies that explore their neural correlates. For example, a popular line of investigation examines the hypothesis that the default mode network (DMN, Raichle et al., 2001) plays a particularly important role in self-generated thought (i.e. Andrews-Hanna et al., 2014b). Consistent with this view studies, which combine experience sampling with online neural measures, have shown that core regions of the DMN, such as the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC), can have greater activity when patterns of ongoing thought shift from task relevant information (Mason et al., 2007; Christoff et al., 2009; Allen et al., 2013; Stawarczyk et al., 2011b, although see Sormaz et al., 2018). Studies suggest the PCC may be an integrative hub associated with the content and form of thoughts (Smallwood et al., 2016), while connectivity between the hippocampus and the mPFC has been linked to episodic contributions to ongoing experience (Karapanagiotidis et al., 2017). Likewise, increased low frequency fluctuations in the PCC have been associated with greater imagery (Gorgolewski et al., 2014). However, studies have also shown that the patterns of default mode network connectivity are also predictive of mindfulness (Mooneyham et al., 2016), attention deficit disorder (Castellanos et al., 2008), depression (Sheline et al., 2009), and life satisfaction and unhappiness (Smith et al., 2015; Luo et al., 2015), each of which have associations with patterns of ongoing thought (Mindfulness, Mrazek et al., 2012b; ADHD, Seli et al., 2015b; Vatansever et al., 2018; Depression and unhappiness, Smallwood and O'Connor, 2011). Together, such evidence indicates that while regions within the DMN play a role in patterns of ongoing experience, they are also implicated in dispositional traits that are associated with aspects of the experience within the general population.

More recent studies have highlighted neural processes outside the DMN that make an important contribution to ongoing cognition, either directly or by supporting dispositional traits that are linked to patterns of experience. Executive (Christoff et al., 2009; Mooneyham et al., 2017; Golchert et al., 2017; Godwin et al., 2017) and attention systems (Wang et al., 2018a; Chou et al., 2017; Turnbull et al., 2019) have been related to variations in spontaneous thoughts. At the same time, neural patterns within the fronto-parietal system have been linked to intelligence (Finn et al., 2015), a dispositional trait that has links with ongoing experience (Turnbull et al., 2019; Mrazek et al., 2012a). Likewise, resting state functional connectivity of networks associated with social, affective, mnemonic and executive systems has been linked to different personality traits (Nostro et al., 2018), which have been shown to relate to different patterns of ongoing thought (Kane et al., 2017; Robison et al., 2017; Smeekens and Kane, 2016). Alterations in the stable functional interactions of large-scale networks at rest have also been observed in studies of psychological disorders, like ADHD (Fair et al., 2013; Hoekzema et al., 2014), generalised anxiety (Rabany et al., 2017), obsessive compulsive disorder (Jung et al., 2013; de Vries et al., 2017) and major depression (Greicius et al., 2007, Wang et al., 2012 for a review), all linked with variations in spontaneous thought (ADHD, Seli et al., 2015b; Vatansever et al., 2018; OCD, Seli et al., 2017; Anxiety and depression, Nolen-Hoeksema, 2000; Watkins, 2008).

Current study

It is clear, therefore, that (i) patterns of ongoing thought show a complex relationship to other dispositional traits at a population level and (ii) both of these psychological dimensions share similarities at the neural level. In this study, we set out to understand the relationship between trait variance in patterns of ongoing thoughts, dispositional features and neural organisation. We acquired retrospective descriptions of ongoing thoughts while participants underwent a resting state functional magnetic resonance scan (rs-fMRI). In a separate session, we acquired measures of dispositional traits spanning both physical and mental health. We then calculated the functional connectivity of whole-brain functional networks and investigated how these functional interactions relate to ongoing cognition and psychological traits, as well as whether there are any neural patterns that can shed light on their shared features. We hoped that these analyses would highlight the interactions between multiple large-scale networks as important for both patterns of ongoing thought, and for psychological traits.

4.3 Methods

4.3.1 Participants

We recruited 206 healthy participants from the University of York by advert. We obtained written consent for all participants and the study was approved by the York Neuroimaging Centre Ethics Committee. 37 participants were excluded from analyses due to technical issues during the neuroimaging data acquisition, excessive movement during the fMRI scan (mean framewise displacement > 0.3 mm and/or more than 15% of their data affected by motion) (Power et al., 2014a) or not completing the whole battery of behavioural tasks, resulting in a final cohort of N = 169 (111 females, $\mu_{age} = 20.1$ years, $\sigma_{age} = 2.3$). The behavioural and functional MRI data in this study are the same as those reported in Ch. 5 (Karapanagiotidis et al., 2018).

4.3.2 Behavioural methods

We sampled the participants' experiences, by using a series of self-report questions at the end of a resting state fMRI scan asking them about the thoughts they experienced during the scan. The question order was randomised (all 25 questions are shown in Table A.1) and the answers were given on a 4-scale Likert scale. We also assessed the participants' physical and mental health by administering well-established surveys at a later separate session outside of the scanner. Details about each questionnaire are presented in the Appendix. Analyses controlled for age, gender and motion during the resting state fMRI scan.

4.3.3 Neuroimaging methods

4.3.3.1 MRI data acquisition

MRI data were acquired on a GE 3 Tesla Signa Excite HDxMRI scanner, equipped with an eight-channel phased array head coil at York Neuroimaging Centre, University of York. For each participant, we acquired a sagittal isotropic 3D fast spoiled gradient-recalled echo T1-weighted structural scan (TR = 7.8 ms, TE = minimum full, flip angle = 20°, matrix = 256x256, voxel size = 1.13x1.13x1 mm^3, FOV = 289x289 mm^2). Resting-state functional MRI data based on blood oxygen level-dependent contrast images with fat saturation were acquired using a gradient single-shot echo-planar imaging sequence with the following parameters: TE = minimum full ($\approx$19 ms), flip angle = 90°, matrix = 64x64, FOV = 192x192 mm^2, voxel size = 3x3x3 mm^3 TR = 3000 ms, 60 axial slices with no gap and slice thickness of 3 mm. Scan duration was 9 minutes which allowed us to collect 180 whole-brain volumes per participant.

4.3.3.2 fMRI data pre-processing

Functional MRI data pre-processing was performed using the Configurable Pipeline for the Analysis of Connectomes (C-PAC) (Craddock et al., 2013). Pre-processing steps included motion correction by volume realignment (Friston 24-Parameter Model) (Friston et al., 1996), nuisance signal regression of the 24 motion parameters calculated in the previous step plus five nuisance signals obtained by running a principal components analysis on white matter and cerebrospinal fluid signals using the CompCor approach (Behzadi et al., 2007), slice time correction, temporal filtering 0.009-0.1 Hz, spatial smoothing using a 6mm Full Width at Half Maximum of the Gaussian kernel and normalisation to MNI152 stereotactic space (2 mm isotropic) using linear and non-linear registration (boundary-based registration) (Greve and Fischl, 2009). No global signal regression was performed.

4.3.3.3 Group-ICA spatial maps

In order to reduce the dimensionality of the resting state fMRI data, following pre-processing, the data were masked by a 20% probabilistic whole-brain grey matter mask, temporally demeaned, had variance normalisation applied (Beckmann and Smith, 2004) and were fed into the MIGP algorithm (Smith et al., 2014). The output of MIGP, which is a very close approximation to running PCA on the temporally concatenated data, was then fed into group-ICA using FSL's MELODIC tool (Beckmann and Smith, 2004), where spatial-ICA was applied, resulting in 16 distinct group-ICA spatial maps. We chose this number of components in order to identify large-scale functional networks resembling those presented in previous studies that deployed similar dimensionality reduction algorithms (i.e. Yeo et al. 2011). On visual inspection of the derived components, we marked one as artefactual and removed it. The remaining 15 group spatial maps were subsequently mapped onto each subject's pre-processed data by running the first stage in

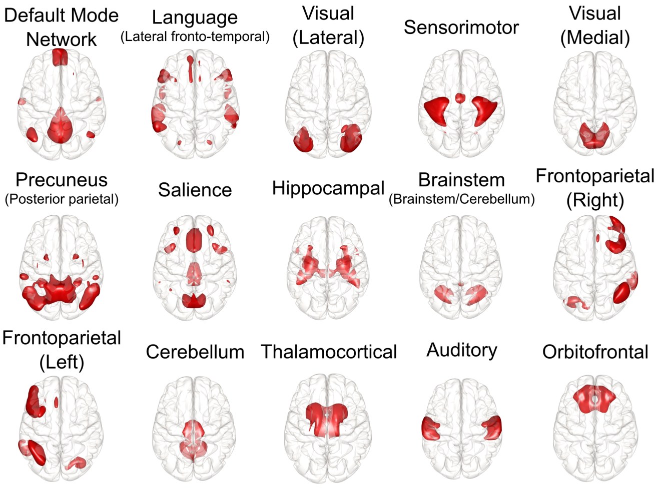

Figure 4.1: *ICA decomposition of fMRI data.*The panel shows the 15 spatial maps obtained from an independent component analysis on the temporally concatenated fMRI data. The maps correspond to well-known whole-brain functional networks and were named based on the top-loading term acquired from decoding each map on Neurosynth.

a dual-regression analysis, which produced one time series per map per participant. We named the group-ICA maps based on the top-loading term acquired from decoding each map on Neurosynth (Yarkoni et al., 2011) and present them in Figure 4.1. This naming convention was extremely accurate for most maps. However, there were a few cases where the spatial ICA maps were slightly more extensive compared to the ones they were named after based on the Neurosynth decoding (i.e. the "language" and the "precuneus" maps). In Figure 4.1, we present the more generic names for these cases in brackets along with the Neurosynth generated ones.

4.3.3.4 Static functional connectivity

Network modelling was carried out by using the FSLNets toolbox. We calculated the partial temporal correlation between the 15 ICA components' timeseries, creating a 15 x 15 matrix of connectivity estimates for each participant. To improve the stability of the estimates of partial correlation coefficients, a small amount of L2 regularisation was applied (Smith et al., 2013a). The connectivity values were converted from Pearson correlation scores into z-statistics with Fisher's transformation (including an empirical correction for temporal autocorrelation). For group-level between-subject comparisons, we combined all participants' network matrices into one and ran a univariate general linear model combined with permutation testing (FSL's randomise (Nichols and Holmes, 2002), 5000 permutations) for each edge. Edge weight was the dependent variable and behavioural measures (thought questions or component loadings from the general and mental health PCA decomposition) the independent ones. We used FWE-correction to account for multiple comparisons and all analyses controlled for age, gender and motion (mean frame-wise displacement) during the rs-fMRI scan.

4.4 Results

Analytic aims

The aim of our study was to understand the complex relationship between patterns of ongoing thoughts, dispositional traits and their associated neural correlates. Accordingly, our analytic approach had three steps. First, we examined the pattern of association between disposition traits and stable features of ongoing experience. Second, we examined the neural correlates of both these psychological features. Third, we examined whether associations between patterns of ongoing experience and dispositional features observed within our population are also reflected in the combination of neural correlates we identified in the second step of our analysis.

4.4.1 Describing experience and well-being

In order to identify the measures of experience with the best reliability and thus the most trait-like features, we repeated the resting state scanning session for a subset of our sample (N = 40) approximately 6 months later. This revealed 6 questions the responses to which were consistent within individuals across sessions (Fig. 4.2a): normal thoughts (i.e. experiences that I often have, intraclass correlation coefficient = 0.28, p = 0.035), deliberate vs spontaneous thoughts (ICC = 0.27, p = 0.044), intrusive thoughts (ICC = 0.29, p = 0.034), thoughts that took the form of attempts at problem-solving (ICC = 0.454, p = 0.001), thoughts about the here and now (ICC = 0.281, p = 0.036) and thoughts in the form of images (ICC = 0.3, p = 0.026). We used these items in subsequent analyses.

To reduce the dimensionality of the measures of physical and mental health, we performed a principal components analysis (PCA) decomposition with varimax rotation. This identified three principal components with eigenvalues greater than 1 (Fig. 4.2b). Component 1 loaded positively on measures of quality of life and psychological well-being and negatively on indices of depression and anxiety, a component which we will refer to as well-being. Component 2 loaded on self-consciousness, attention deficit hyperactivity disorder

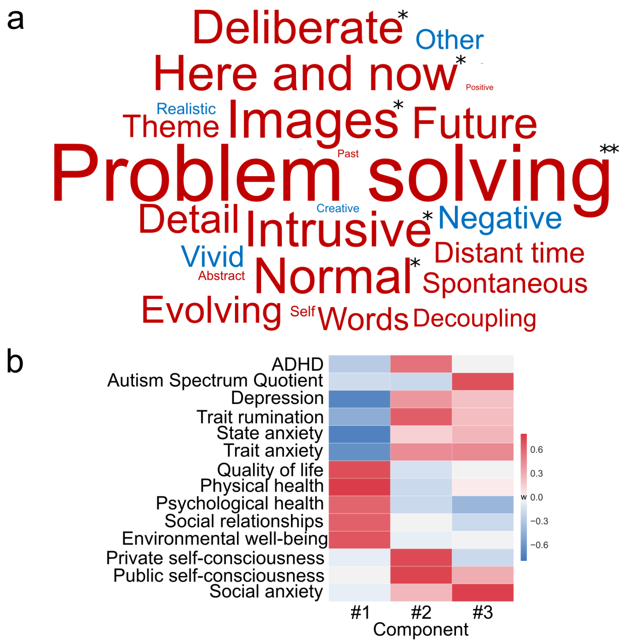

Figure 4.2: *Behavioural variables.* **a**) Test-retest reliability of responses to items at the end of two resting state fMRI scans for 40 participants. Intraclass correlation coefficient (ICC) visualised using a word cloud. Font size represents the absolute ICC value and font colour its sign (red for positive and blue for negative values). * $p < 0.05$, ** $p = 0.001$. **b**) Component weights from a principal component analysis on the participants' responses to dispositional measures of physical and mental health. Analyses controlled for age, gender and motion during the resting state fMRI scan.

(ADHD) and rumination, a pattern we refer to as internally directed attention. Component 3 loaded on social anxiety and autism and we refer to this pattern as reflecting social difficulties.

4.4.2 Comparing common variance in disposition and descriptions of ongoing experience at rest

Our first analytic goal was to explore the links between measures of well-being and self-reports of experience at rest within our sample. Using bivariate correlations, we found a positive correlation between well-being with 'normal' patterns of thoughts ($r = 0.17$, $p < 0.05$). Internally directed attention was associated with both patterns of intrusive thoughts ($r = 0.19$, $p < 0.05$) and of thinking in images ($r = 0.16$, $p < 0.05$). Finally, social difficulties were negatively associated with thinking in images ($r = -0.16$, $p < 0.05$). These analyses are presented in the form of a heat map in Figure 4.3a. To evaluate the multivariate associations between this set of variables, we ran a canonical correlation analysis (CCA) using the PCA components of the physical and mental health scores and the six reliable self-report items. This analysis yielded three canonical components, or modes, out of

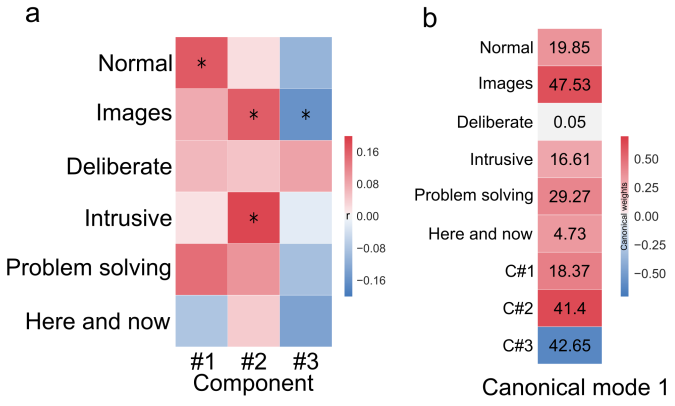

Figure 4.3: *Relationship between measures of well-being and self-reports of experience at rest.* **a**) Bivariate correlation between the 6 thought probes that were significantly reliable and the component scores from the PCA decomposition of physical and mental health scores. **b**) Heat map showing the standardised canonical weights of each item for the significant canonical mode 1. The annotations indicate the item variance explained by the CCA mode. Analyses controlled for age, gender and motion during the resting state fMRI scan.

which the first was statistically significant using the Wilks's $\lambda = 0.823$ criterion, F(18, 453.03) = 1.795, p = 0.023, explaining 11.5% of the variance shared between the variable sets (modes 2 and 3 explained 4.1% and 3% of the remaining variance in the variable sets respectively). The variables' associations for the first CCA mode are shown in Figure 4.3b. Descriptions of experience as in the forms of images was the strongest experiential predictor of this mode (standardised canonical weight = 0.62, $r_s^2 = 47.53$). It was also linked to patterns of internally directed attention (component 2, standardised canonical weight = 0.64, $r_s^2 = 41.4$) and to a relative absence of social difficulties (component 3, standardised canonical weight = -0.62, $r_s^2 = 42.65$).

4.4.3 Comparing common variance in patterns of neural organisation and descriptions of ongoing experience

Having identified the common variance shared by measures of disposition and reports of ongoing experience, our next analysis examined the relationship between static (time-averaged) functional connectivity of whole-brain networks and the experiential reports that individuals gave at the end of the scan. For each participant, we calculated the correlation between each whole-brain spatial ICA map (see 4.3.3.3), using partial instead of full correlation, as it is considered to be a good estimate of direct functional connections (Smith et al., 2013b). Figure 4.4 shows the average partial correlation matrix across subjects (thresholded for visualisation) in the form of a chord plot. Strong interactions

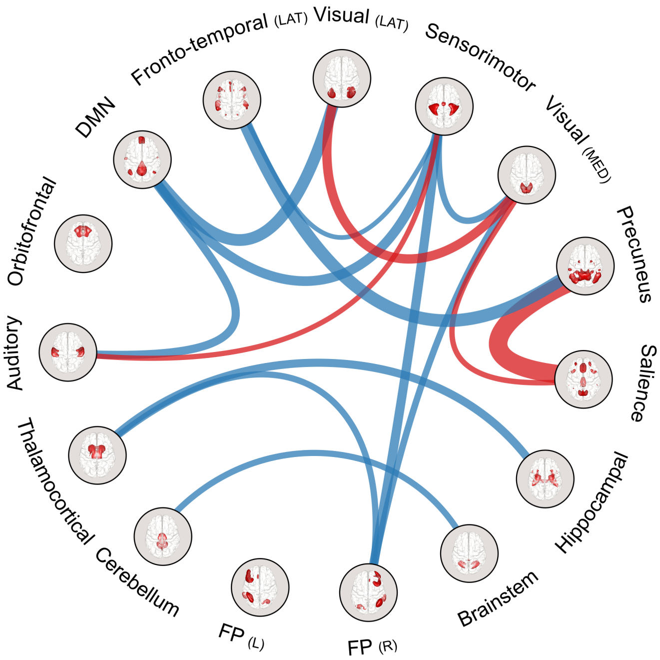

Figure 4.4: *Partial correlation of ICA maps.* Network circle graph of the average partial correlation matrix across subjects. The circle graph was thresholded at the 85^{th} percentile of absolute z-values as estimated from an r to z Fisher's transformation. Red is for positive and blue for negative values and edge width is weighted by their absolute value. L:Left, R:Right, LAT:Lateral, MED:Medial.

highlight the relatively decreased correlation between the DMN and sensory networks, the auditory with the sensorimotor and the two visual networks forming synchronised pairs of sensory processing, and the precuneus with the salience networks as positively coupled.

We then explored the links between static functional connectivity and the six experiential reports with the most trait-like features. As we were interested in both focal and widespread effects, we chose to run our analyses using multiple edge weight thresholds that resulted in varying numbers of edges included in each analysis. Taking into account only the strongest edges on average across subjects (top 15% of partial correlation weights), we regressed the edges' partial correlations against participants' thoughts, while controlling for age, gender and motion during the rs-fMRI scan. Using permutation testing, we found that more positive correlations between the precuneus and the lateral fronto-temporal network for subjects reporting thinking more in images (Fig. 4.5a) ($p = 0.016$, FWE-corrected). The pattern remained significant for a lower correlation weight threshold that included weaker edges in the analysis (top 30% of partial correlation weights) ($p = 0.037$, FWE-corrected). No significant relationship was found for a threshold that kept the top 50% of connections and when no threshold was applied at all. This analysis highlights that an increase in a functional connection between the precuneus and the lateral fronto-temporal networks at rest was observed for people who rated their experience as taking the form of images.

4.4.4 Comparing common variance in patterns of neural organisation and dispositional traits

Using the same connection thresholds (top 15%, 30%, 50% and no threshold), we found that a lower correlation between the lateral visual and the brainstem networks was associated with increased internally directed attention (Fig. 4.5b). The link was significant for the top 50% of connections (p = 0.021, FWE-corrected) and when no threshold was applied (p = 0.05, FWE-corrected). That is, there was a decrease in the functional interaction between the brainstem and lateral visual networks for people who scored higher in dispositional internal focus.

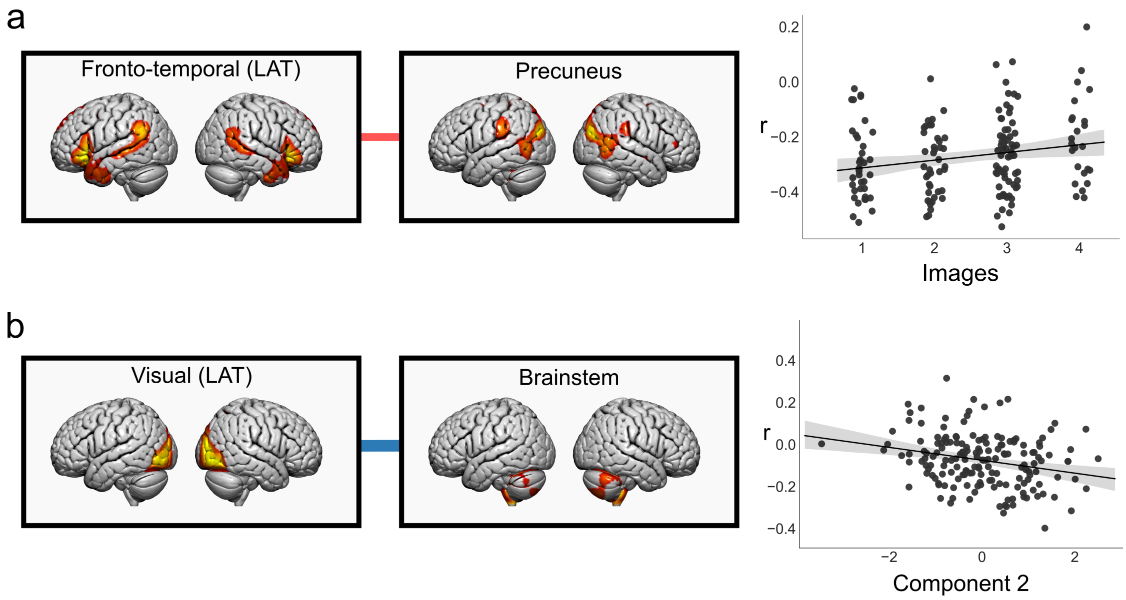

Figure 4.5: *Static functional connectivity associated with behaviour.* **a**) Left. The lateral fronto-temporal and precuneus networks. The edge highlights an increase in their partial correlation for people thinking more in images. Right. Scatter plot of thinking in images scores with correlation values between these two networks for each participant. **b**) Left. The lateral visual and brainstem networks. The edge highlights a decrease in their partial correlation for higher ADHD and rumination scores (PCA Component 2). Right. Scatter plot of Component 2 scores from the PCA of the physical and mental health questionnaires with correlation values between these two networks for each participant.

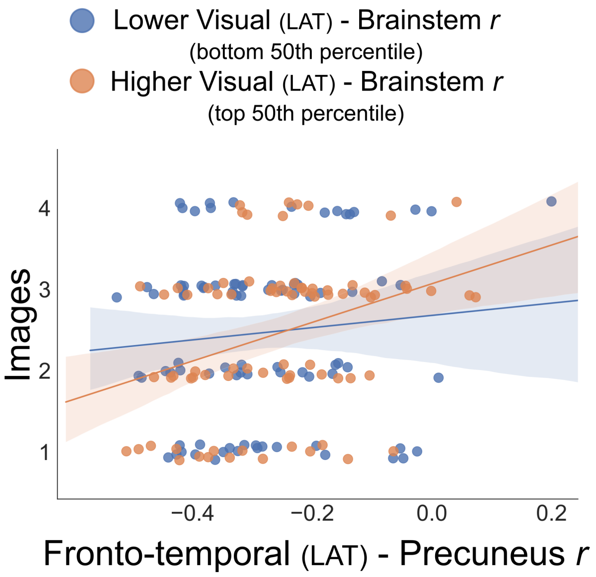

Figure 4.6: *Moderation effect of the lateral visual - brainstem coupling to the relationship between thinking in images and lateral fronto-temporal - precuneus functional connectivity.* The scatter plot shows the correlation values between the lateral fronto-temporal and precuneus networks and thinking in images scores grouped, by a median split, into higher and lower connectivity groups between the lateral visual and brainstem networks.

4.4.5 Examining the relationship between neural "fingerprints" of disposition and patterns of ongoing experience

Together, our analyses suggest that reports of imagery at rest were associated with traits of internally directed attention (Fig. 4.3) and that both had reliable, yet distinct neural correlates. To understand if the identified neural patterns moderated the relationship between the psychological measures, we ran two multiple regression analyses; in one, the dependent variable was reports of visual imagery and in the other, dispositional internal focus (component 2, see 4.4.1). In each model, the remaining three scores were entered as predictors and we modelled their main effects and their three pairwise interactions (while controlling for age, gender, and motion during the resting state fMRI scan). The analysis with visual imagery as the dependant variable identified two main effects: thinking in images was positively correlated with the connectivity between the lateral fronto-temporal and precuneus networks ($\beta = 0.19$, p = 0.016) and with component 2 scores ($\beta = 0.18$, p = 0.026). Critically, it also indicated an interaction ($\beta = 0.16$, p = 0.043) suggesting that the correlations between the precuneus and lateral fronto-temporal regions and reports of imagery were stronger for participants who also had higher lateral visual and brainstem connectivity (associated with low loadings on internally focused attention). This is displayed in Figure 4.6 in the form of a scatter plot. The second analysis, with dispositional internal focus as the dependent variable identified two main effects, but not an interaction: internally focused attention was negatively correlated with the connectivity between the lateral visual and brainstem networks (β = -0.25, p = 0.001) and positively correlated with thinking in images (β = 0.17, p = 0.024).

4.5 Discussion

This study set out to explore how associations between patterns of unconstrained ongoing experience and dispositional traits are reflected in the underlying neural architecture. Within our population we found a positive correlation between a style of thinking which emphasises visual imagery and a pattern of dispositional internal focus. Both of these psychological features had distinct neural correlates. Thinking more in images was related to an increase in correlation between the precuneus and a lateral fronto-temporal network, while a decreased correlation between the lateral visual and a brainstem/cerebellar network was linked to internal attention. Critically, we found a significant interaction between these two neural traits: the correlation between precuneus - lateral fronto-temporal connectivity and visual imagery was more pronounced for individuals who also had stronger coupling between the brainstem/cerebellar network and visual cortex. Our results, therefore, indicate that there are distinct stable neural interactions that support ongoing experience as well as dispositional traits, and highlight there are indirect neural relationships that link these discrete phenomena together. In this discussion, we first consider the links between our findings and prior studies examining relationships between neural organisation and both ongoing thought and dispositional processes, before considering the implications of our findings for brain-experience correlations more generally.

4.5.1 Precuneus interactions with lateral frontal and temporal systems are important for visual imagery.

Prior studies have shown that thinking in the form of images is an important feature of ongoing experience (Andrews-Hanna et al., 2013; Delamillieure et al., 2010) and our study suggests that this process is linked to the functional organisation of the precuneus. Although posterior medial cortex is functionally heterogeneous (Margulies et al., 2009; Cavanna and Trimble, 2006), the precuneus has been related to visuospatial mental imagery (for a review see Fletcher et al., 1995), episodic memory retrieval of imagined pictures

(Lundstrom et al., 2003) and imagining past episodes related to self (Lou et al., 2004). Our analysis suggests that visual imagery is linked to functional connectivity between the precuneus and regions of the temporal lobe that are thought to contribute to multi-modal forms of semantic cognition (Jefferies, 2013). Contemporary accounts, for example, suggest that the anterior temporal lobe supports cognition with different representational features (pictures versus words, Murphy et al., 2018b; Vatansever et al., 2017a; Ralph et al., 2017 for a review). Generally therefore, our results are consistent with the hypothesis that the production of visual imagery may depend upon the integration of a system important for visual processing (the precuneus), with regions that support multi-modal elements of cognition (lateral temporal and frontal cortex).

4.5.2 Lateral visual cortex and brainstem interactions relate to rumination, self-consciousness and ADHD

We also found that internally focused cognition was linked to reduced correlation between the brainstem/cerebellum and the lateral visual cortex. Previous studies have shown that brainstem abnormalities can support increased accuracy of diagnostic classification in ADHD (Johnston et al., 2014). Decreased axial diffusivity (a marker of axonal degeneration in clinical cases, Song et al. 2002) in the occipital lobe and brainstem has also been associated with an ADHD diagnosis (Gehricke et al., 2017). In addition, processes within the brainstem have been related to rumination, worry and anxiety by influencing heart rate variability (Porges, 2007; Aldao et al., 2013) and by its functional interactions with the limbic network in anxiety disorders (Engel et al., 2009). Our findings for increased rumination, self-consciousness and ADHD scores may highlight a functional neural configuration where visual input becomes increasingly incoherent with the activity of a network regulating autonomic functions and modulating global connectivity (Van den Heuvel and Sporns, 2013). This could indicate the reduced processing of sensory input that is thought to be important for periods of internal focused experience (Smallwood and Schooler, 2015).

4.5.3 Interactions between neural correlates of disposition and patterns of ongoing thought

Importantly, our study not only identified patterns of neural organisation correlated with both visual imagery and internally focused attention, it also highlighted that the neural correlates of these associated traits interact in an important manner. Our results suggest that the association between precuneus-lateral fronto-temporal connectivity and reports of visual imagery was more pronounced for individuals who had stronger connectivity between regions of the brainstem and lateral occipital cortex. Based on our data, it is plausible that not only are patterns of visual experience linked to dispositional variance in internally focused attention, but their neural correlates interact in a complex way to produce the observed patterns of functional connectivity at rest. These observations suggest that studies exploring the cognitive significance of patterns of neural organisation, either in terms of understanding their relationships with disposition, or the nature of ongoing experience, would benefit by accounting for both types of traits in their analyses. Based on our study, understanding the dispositional influences on patterns of ongoing thought can help improve our understanding of the neural basis of ongoing experience. Likewise, our understanding of the neural mechanisms underlying patterns of dispositional traits which are associated with certain aspects of ongoing experience may be improved by accounting for features of the experience when neural activity is recorded. As well as the questionnaire administered in our study, there is now an emerging number of measures of ongoing experience such as the New York Cognition Questionnaire (Gorgolewski et al., 2014), the Amsterdam Resting State Questionnaire (Diaz et al., 2013) and Resting state questionnaire (Delamillieure et al., 2010). The low economic cost of these measurements and the ease of their administration suggest that collecting data on patterns of ongoing thought can improve our understanding of neural correlates of specific dispositional states. We recommend that in the future these sorts of measures become part of the standard resting state protocol.

4.5.4 Conclusion

In conclusion, our study highlights that neural functioning during rest relates to both ongoing experience and patterns of dispositional traits. Our test-retest analyses revealed recurring themes of spontaneous thoughts that remain relatively stable within individuals. These themes were associated with physical and mental health and ultimately linked to the static functional coupling between large-scale brain networks. Along with the unique neural functional patterns facilitating each behaviour, our results revealed an interaction between these relationships, demonstrating how neural and dispositional traits can influence ongoing cognition. Together, our findings complement previous studies investigating the neural structural (Karapanagiotidis et al., 2017; Bernhardt et al., 2014) and functional

(Sormaz et al., 2018; Martinon et al., 2019) substrates of ongoing experience and suggest that its inherently dynamic nature is shaped by the stable functional interactions of the brain and can be better understood by accounting for trait behaviour.

Chapter 5

Neural dynamics at rest associated with patterns of ongoing thought

The following chapter has been adapted from: **Karapanagiotidis, T.**, Vidaurre, D., Quinn, A.J., Vatansever, D., Poerio, G.L., Jefferies, E., Margulies, D.S., Nichols, T.E., Woolrich, M.W. & Smallwood, J. (2018). Neural dynamics at rest associated with patterns of ongoing thought. bioRxiv, 454371. [1]

5.1 Abstract

Conscious experience is dynamic, and its fluidity is particularly marked when attention is not occupied by events in the external world and our minds are free to wander. Our study used measures of neural function, and advanced analyses techniques to examine how unconstrained neural state transitions relate to patterns of ongoing experience. Neural activity was recorded during wakeful rest using functional magnetic resonance imaging and Hidden Markov modelling identified recurrent patterns of brain activity constituting functional dynamic brain states. Individuals making more frequent transitions between states subsequently described experiences highlighting problem solving and lacking unpleasant intrusive features. Frequent switching between states also predicted better health and well-being as assessed by questionnaire. These data provide evidence that the fluidity

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[1] The author, Theodoros Karapanagiotidis, designed the experiment, collected and analysed the data and wrote the article under the supervision of Prof. Elizabeth Jefferies and Prof. Jonathan Smallwood. Dr. Diego Vidaurre, Dr. Andrew J. Quinn, Dr. Deniz Vatansever, Prof. Thomas E. Nichols and Prof. Mark W. Woolrich provided assistance with the statistical analyses. Dr. Deniz Vatansever and Dr. Giulia L. Poerio provided assistance with the collection of the data and Dr. Daniel S. Margulies provided assistance with the experimental design.

with which individuals shift through dynamic neural states has an impact on the nature of ongoing thought, and suggest that greater flexibility at rest is an important indicator of a healthy mind.

5.2 Introduction

William James (James, 1890) emphasised experience unfolds dynamically over time, using the analogy of a "stream of consciousness". The fluidity of experience is clearly illustrated by the fact that our attention tends to flit from topic to topic, particularly when we are not focused on events in the external world (Smallwood and Schooler, 2006, 2015). Such "mind-wandering" is a broad class of experience (Seli et al., 2018) that is common in daily life (Killingsworth and Gilbert, 2010), consistent across cultures (Singer and McCraven, 1961) and declines with age (Giambra, 1989). Mind-wandering is linked with improved creativity (Baird et al., 2012) and problem solving (Medea et al., 2018) suggesting that it may facilitate our ability to navigate the complex social environment in which we exist (Stawarczyk et al., 2011a; Smallwood and Schooler, 2015). In contrast, less flexible patterns of conscious thought can get "stuck" in a cycle of intrusive rumination, with detrimental consequences. Unpleasant moods, for example, can encourage patterns of negative thoughts about the past (Smallwood and O'Connor, 2011; Poerio et al., 2013) which in turn reduce subsequent mood (Ruby et al., 2013a). These studies highlight links with mental health since patterns of recurrent rumination can maintain states of anxiety and depression (Watkins, 2008). It is apparent that mind-wandering has both beneficial and detrimental associations and what dissociates these two extremes may be the flexibility with which cognition dynamically unfolds over time.

Recent advances in neuroimaging analysis make it possible to test the impact that covert cycling through neural states has on patterns of ongoing experience. Traditional functional connectivity analyses exploit temporal correlations in brain activity to identify the spatial extent of large-scale distributed neural networks (Smith et al., 2013b). These networks are relevant to cognition given their associations with population variation in intelligence and well-being (Smith et al., 2015; Finn et al., 2015), as well as more specific cognitive factors such as cognitive flexibility (Vatansever et al., 2017b) and creativity (Beaty et al., 2014). These traditional methods, however, describe neural networks in a static (time-averaged) manner, and so do not explicitly address the temporal profile of neural function. Contemporary research has begun to address the dynamic properties of neural activity in a more direct manner using Hidden Markov Modelling (HMM). This method identifies 'states', defined as recurrent patterns of neural activity, and studies have shown that states revealed in this manner track cognitive processes during tasks (Gonzalez-Castillo et al., 2015), and at rest, relate neural processing to cognitive flexibility, life satisfaction, anger and perceived stress (Vidaurre et al., 2017b). By providing a quantified description of covert states and how individuals transition between them, HMM allows us to test how the underlying neural dynamics impact upon aspects of ongoing experience.

The current study mapped patterns of intrinsic neural activity using functional Magnetic Resonance Imaging (fMRI) in a large cohort of individuals (N = 169) while they rested in the scanner. We interrogated undisturbed wakeful rest, rather than probing during a task (e.g. Sormaz et al., 2018) for two reasons. First, wakeful rest is conducive to experiences such as mind-wandering (Smallwood et al., 2009b). Second, the absence of external interruptions during rest ensures that neural dynamics unfold in a relatively natural way. At the end of the scan, participants retrospectively described their experience, answering a set of questions based on those used in prior studies exploring variability in static functional connectivity across subjects (Smallwood et al., 2016; Karapanagiotidis et al., 2017). In a separate session, participants completed a set of validated measures of physical and mental health. Following the HMM inference of the dynamic states, we calculated indices of the temporal flexibility of neural function and the time spent in a particular state. We used these metrics as explanatory variables in separate regression analyses examining their relationship to descriptions of subjective experience reported at the end of the scan, as well as their links to the validated measures of health and well-being. To foreshadow our results, individuals who made more transitions between states described experiences emphasising problem solving and fewer intrusive thoughts. They also scored higher on measures of health and well-being. These data provide evidence that the fluidity with which an individual shifts through unconstrained states is linked to the emergence of more apparently useful patterns of ongoing thought.

5.3 Methods and Materials

5.3.1 Participants

206 healthy participants were recruited by advert from the University of York. Written consent was obtained for all participants and the study was approved by the York Neu-

roimaging Centre Ethics Committee. 37 participants were excluded from analyses due to technical issues during the neuroimaging data acquisition, excessive movement during the fMRI scan (mean framewise displacement $>$ 0.3 mm and/or more than 15% of their data affected by motion) (Power et al., 2014a) or not completing the whole battery of behavioural tasks, resulting in a final cohort of N = 169 (111 females, $\mu_{age} = 20.1$ years, $\sigma_{age} = 2.3$). The behavioural and functional MRI data in this study are the same as those reported in Ch. 4.

5.3.2 Behavioural methods

We sampled the participants' experiences during the resting state fMRI scan by asking them at the end of the scan to retrospectively report their thoughts, using a series of self-report questions. These items were measured using a 4-scale Likert scale with the question order being randomised (all 25 questions are shown in supplementary Table A.1). In order to assess the participants' physical and mental health, we administered well-established surveys at a later separate session outside of the scanner. Details about each questionnaire are presented in the Appendix. Analyses controlled for age, gender and motion during the resting state fMRI scan.

5.3.3 Neuroimaging methods

5.3.3.1 MRI data acquisition

MRI data were acquired on a GE 3 Tesla Signa Excite HDxMRI scanner, equipped with an eight-channel phased array head coil at York Neuroimaging Centre, University of York. For each participant, we acquired a sagittal isotropic 3D fast spoiled gradient-recalled echo T1-weighted structural scan (TR = 7.8 ms, TE = minimum full, flip angle = 20°, matrix = 256x256, voxel size = 1.13x1.13x1 mm^3, FOV = 289x289 mm^2). Resting-state functional MRI data based on blood oxygen level-dependent contrast images with fat saturation were acquired using a gradient single-shot echo-planar imaging sequence with the following parameters TE = minimum full ($\approx$19 ms), flip angle = 90°, matrix = 64x64, FOV = 192x192 mm^2, voxel size = 3x3x3 mm^3 TR = 3000 ms, 60 axial slices with no gap and slice thickness of 3 mm. Scan duration was 9 minutes which allowed us to collect 180 whole-brain volumes.

5.3.3.2 fMRI data pre-processing

Functional MRI data pre-processing was performed using the Configurable Pipeline for the Analysis of Connectomes (C-PAC) (Craddock et al., 2013). Pre-processing steps included motion correction by volume realignment (Friston 24-Parameter Model) (Friston et al., 1996), nuisance signal regression of the 24 motion parameters calculated in the previous step plus five nuisance signals obtained by running a principal components analysis on white matter and cerebrospinal fluid signals using the CompCor approach (Behzadi et al., 2007), slice time correction, temporal filtering 0.009-0.1 Hz, spatial smoothing using a 6mm Full Width at Half Maximum of the Gaussian kernel and normalisation to MNI152 stereotactic space (2 mm isotropic) using linear and non-linear registration (boundary-based registration) (Greve and Fischl, 2009). No global signal regression was performed.

5.3.3.3 Group-ICA spatial maps and time series

Following pre-processing, the neuroimaging data were masked by a 20% probabilistic whole-brain grey matter mask, temporally demeaned, had variance normalisation applied (Beckmann and Smith, 2004) and were fed into the MIGP algorithm (Smith et al., 2014). The output of MIGP, which is a very close approximation to running PCA on the temporally concatenated data, was then fed into group-ICA using FSL's MELODIC tool (Beckmann and Smith, 2004), where spatial-ICA was applied, opting for a 16-component solution. On visual inspection of the derived group-ICA spatial maps, one was marked as artefactual, while the rest resembled well-known whole-brain functional networks. These group spatial maps were subsequently mapped onto each subject's pre-processed data by running the first stage in a dual-regression analysis, which produced one time series per map per participant. After removal of the artefactual component, the remaining 15-dimensional time series for each participant with $\mu = 0$ and $\sigma = 1$ were concatenated to form a (180 x 169) x 15 matrix and used as input for subsequent analyses. The 15 spatial maps were named based on the top-loading term acquired from decoding each map on Neurosynth (Yarkoni et al., 2011) and are shown in Figure 5.1.

5.3.3.4 Hidden Markov model

To characterise the dynamics of neural activity, we applied a hidden Markov model to the concatenated time series of the ICA networks. The inference of the model parameters was based on variational Bayes and the minimisation of free energy, as implemented in the

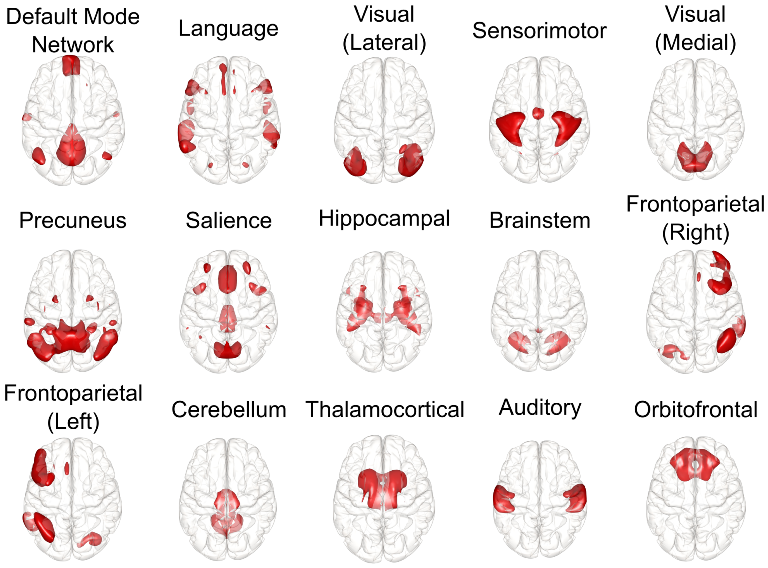

Figure 5.1: *ICA decomposition of fMRI data.* The panel shows the 15 spatial maps obtained from an independent component analysis on the temporally concatenated fMRI data. The maps correspond to well-known whole-brain functional networks and were named based on the top-loading term acquired from decoding each map on Neurosynth.

HMM-MAR toolbox (Vidaurre et al., 2016). The HMM's inference assigns state probabilities to each time point of the time series (i.e. reflecting how likely is each time point to be explained by each state) and estimates the parameters of the states, where each state has its own model of the observed data. Each state can be represented as a multivariate Gaussian distribution (Vidaurre et al., 2017a), described by its mean and covariance. As we were primarily interested in identifying changes in functional connectivity, we chose to discount changes in absolute signal level and defined the states by their covariance matrix. Inference was run at the group level, such that the state descriptions are defined across subjects. This allowed us to discover dynamic temporal patterns of whole-brain functional interactions along with their occurrence (state time series) and transition probabilities for the duration of the whole resting state fMRI scan. Detailed information about the HMM implementation and the variational Bayes inference can be found in (Vidaurre et al., 2017b,a; Baker et al., 2014). Fractional occupancy was defined as the proportion of time spent on each state and switching rate as the total number of switches from one state to any other. All analyses controlled for age, gender and motion during the resting state fMRI scan.

5.3.3.5 Accounting for HMM run-to-run variability

As with other probabilistic unsupervised learning methods (e.g. independent component analysis), hidden Markov modelling (HMM) is sensitive to initial values. We accounted for this run-to-run variability by using 100 restarts with different initial conditions, producing slightly different results each time. For the results relating HMM metrics to behaviour that integrated over all 100 HMM runs, we used the NPC algorithm (Vidaurre et al., 2018; Pesarin, 2001). In particular, the 100 results were each used when testing each behavioural variable, producing a set of 100 nonparametric p-values that were subsequently combined with Fisher's p-value combining function (equivalent to taking the geometric mean of the p-values (Winkler et al., 2016)). Permutation testing was used to obtain the final p-values.

5.3.3.6 Static functional connectivity

Network modelling was carried out by using the FSLNets toolbox. We calculated the partial temporal correlation between the 15 components' timeseries creating a 15 x 15 matrix of connectivity estimates for each participant. To improve the stability of the estimates of partial correlation coefficients, a small amount of L2 regularisation was applied (Smith et al., 2013a). The connectivity values were converted from Pearson correlation scores into z-statistics with Fisher's transformation (including an empirical correction for temporal autocorrelation). In order to test the similarity between the correlation matrices (NxN) of each dynamic state and the mean static partial correlation matrix (NxN), we kept the lower diagonal of each matrix, "unwrapped" it to a vector of length 105 ((N*N - N)/2), Fisher's z transformed its values and calculated the pairwise correlations.

5.3.3.7 Code availability

Code used for data analyses can be accessed on https://github.com/OHBA-analysis/HMM-MAR and https://github.com/vidaurre/HBM2018.

5.3.3.8 Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

5.4 Results

5.4.1 Describing experience and well-being

In order to identify the measures of experience with the best reliability, we repeated the resting state scanning session for a subset of our sample (N = 40) approximately 6 months later. This revealed 6 questions that were consistent across sessions (Fig. 5.2a): normal thoughts (i.e. experiences that I often have, intraclass correlation coefficient = 0.28, p = 0.035), deliberate vs spontaneous thoughts (ICC = 0.27, p = 0.044), intrusive thoughts (ICC = 0.29, p = 0.034), problem-solving thoughts (ICC = 0.454, p = 0.001), thoughts about the here and now (ICC = 0.281, p = 0.036) and thinking in images (ICC = 0.3, p = 0.026). We used these items in subsequent analyses.

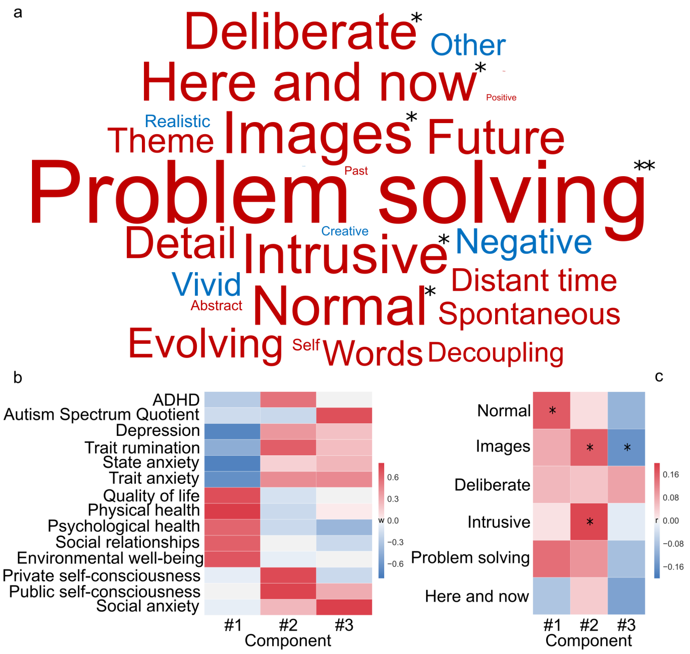

Figure 5.2: *Behavioural variables.* **a**) Test-retest reliability of responses to items at the end of two resting state fMRI scans for 40 participants. Intraclass correlation coefficient (ICC) visualised using a word cloud. Font size represents the absolute ICC value and font colour its sign (red for positive and blue for negative values). * $p < 0.05$, ** $p = 0.001$. **b**) Component weights from a principal component analysis on the participants' responses to physical and mental health questionnaires. **c**) Correlation between the 6 thought probes that were significantly reliable in (a) and the component scores from (b). Analyses controlled for age, gender and motion during the resting state fMRI scan.

To reduce the dimensional structure of the measures of physical and mental health, we performed a principal components analysis decomposition with varimax rotation. This identified three principal components with eigenvalues greater than 1 (Fig. 5.2b). Component 1 loaded positively on measures of physical health and psychological well-being and negatively on indices of depression and anxiety. Component 2 loaded on self-consciousness, ADHD and rumination. Component 3 loaded on social anxiety and autism.

Exploring links between measures of well-being and items describing experience at rest, we found a positive correlation between normal patterns of thoughts with component 1 ($r = 0.17$, $p < 0.05$), intrusive thoughts ($r = 0.19$, $p < 0.05$) and thinking in images ($r = 0.16$, $p < 0.05$) with component 2 and a negative correlation of thinking in images ($r = -0.16$, $p < 0.05$) with component 3 (Fig. 5.2c). The above associations are the same as the ones reported in Ch. 4. The focus of this study was to investigate their links with the dynamic functional properties of the brain rather than with the more traditionally explored time-averaged functional interactions.

5.4.2 Describing neural dynamics

Recent work has highlighted that patterns of ongoing thought can be meaningfully related to interactions between multiple large-scale networks (Golchert et al., 2017; Hasenkamp et al., 2012; Mooneyham et al., 2017). To capture network-to-network relationships, we conducted spatial independent component analysis (ICA) on the resting state fMRI data, identifying 15 functional networks and then ran the HMM (variational Bayes) inference on their time courses (Vidaurre et al., 2017b). HMM allows the whole multi-dimensional fMRI time course to be decomposed into a set of recurring functional states, each characterised by unique patterns of network activity. In determining the number of states for the HMM, we tested models with 7, 9 and 12 states and evaluated the stability of the decompositions by running the algorithm 100 times in each case and investigating the similarity of the models. Similarity was measured as the overlap between the state occurrence probabilities, after optimally reordering the states of each model using the Munkres assignment algorithm (Munkres, 1957). We found that the average similarity among the HMMs with 7 states was $\mu_7 = 0.58$ with a standard deviation of $\sigma_7 = 0.07$ (Fig. 5.3a). We repeated the procedure for number of states $K = 9$ and 12 and found that the stability of the solutions was progressively reduced as the average similarity got lower ($\mu_9 = 0.48$, $\mu_{12} = 0.38$) (Fig. 5.3). As the models with fewer states were found to be generally more stable, we discuss the 7 state solution in the main body of our paper.

Out of the 100 runs of the algorithm, we selected the best solution (optimal HMM) according to the free energy (Quinn et al., 2018), a measure related to the Bayesian inference process that ranks the solutions based on their complexity and accuracy in

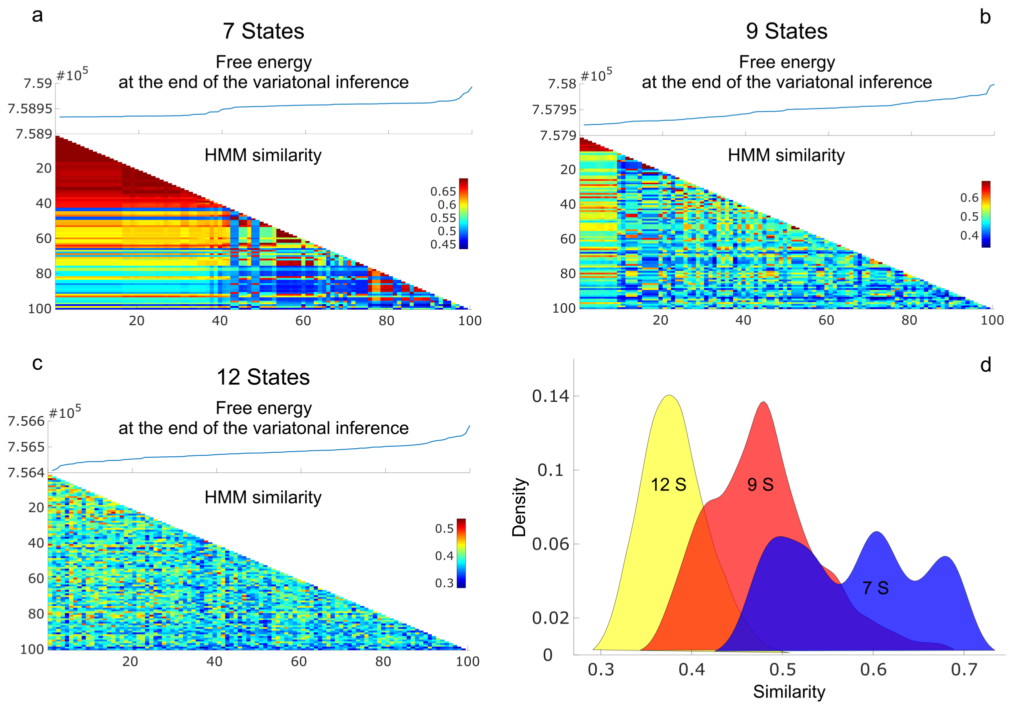

Figure 5.3: *Hidden Markov models similarities.* Similarities between the hidden Markov models after multiple runs, along with a line plot of the free energy that was used for selecting each model at the end of the variational inference cycle, sorted in ascending free energy values for **a**) 7 states, **b**) 9 states, **c**) 12 states. **d**) Density plots of the similarities between the hidden Markov models for 7, 9 and 12 states.

representing the data (see Methods). All 7 states as inferred by the optimal HMM are presented in supplementary Figure B.1. Our results utilise dynamic metrics inferred from this optimal HMM solution, however they were also robust when taking into account the run-to-run variability across all 100 models produced by the algorithm (Vidaurre et al., 2018).

From the HMM decomposition, a number of summary metrics describing the dynamics in the data can be extracted. The overall switching rate across states (histogram shown in Fig. 5.4a), represents the lability of the dynamics. The transition probabilities across states (see Fig. 5.4b) describe how likely transitions between different states are. Several brain states have a high probability of transitioning into State 4 ($\mu_{tS4} = 0.22$) and, to a lesser degree, to State 3 ($\mu_{tS3} = 0.17$, the full asymmetric transition probability matrix is presented in supplementary Figure B.2). Finally, the fractional occupancy (FO) describes the proportion of time spent in each state. Most states had comparable FO with the exception of State 5, which was lower than all other states (Fig. 5.4c).

As expected, relating the correlation matrix of each state with the group static functional connectivity (i.e. the time averaged partial correlation matrix), we found that the

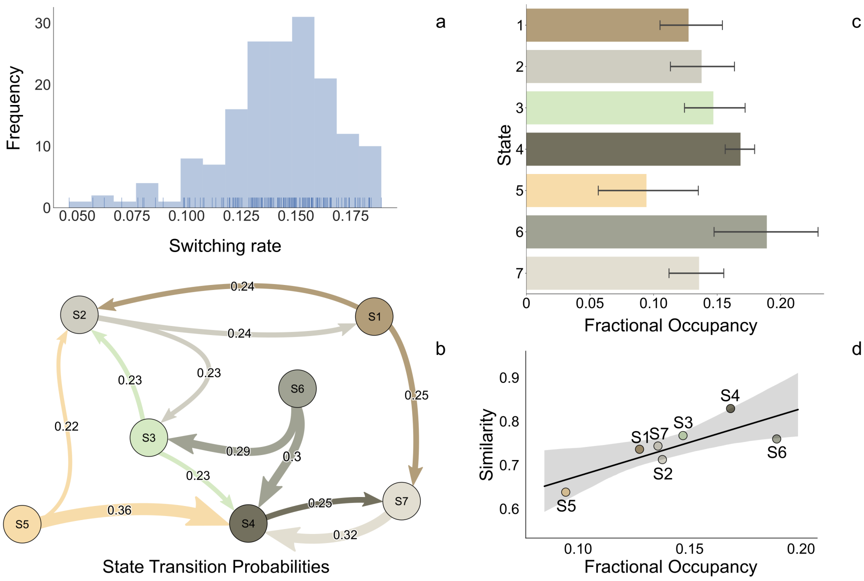

Figure 5.4: *Dynamic metrics.* **a**) Histogram of subjects' switching rate between all states. **b**) The states' transition probabilities as a thresholded graph, with edge width weighted by the respective probability (the probabilities of staying in the same state are not shown). **c**) Bar plots of the average fractional occupancy of each state over subjects (± 99.9% bootstrap confidence intervals). **d**) Scatter plot of the average fractional occupancy of each dynamic state and its similarity with the mean static functional connectivity across subjects.

more time spent in a particular dynamic state, the more similar states were (in terms of whole-brain connectivity) to the average static functional connectivity pattern ($p = 0.031$) (Fig. 5.4d). This is consistent with the idea that the patterns of static connectivity observed across the entire period of rest can be understood as the superposition of the dynamic states identified through the HMM.

5.4.3 Relationship between brain dynamics and ongoing experience

Having identified metrics that describe dynamic brain activity at rest, we tested whether these relate to descriptions of subjective experience at the end of the scan.

5.4.3.1 Overall dynamics and ongoing experience

We used overall state switching rate during the resting state scan as an explanatory variable in a multivariate GLM, combined with permutation testing, to determine statistical significance. We identified a significant association with concurrent thoughts at the end of the scan ($p = 0.003$) (Fig. 5.5, top). Follow-up univariate analyses and permutation testing showed that increased switching between states was predictive of less intrusive thoughts ($r = -0.21$, $p = 0.014$ uncorrected, $p = 0.04$ FDR-corrected for 6 tests (number

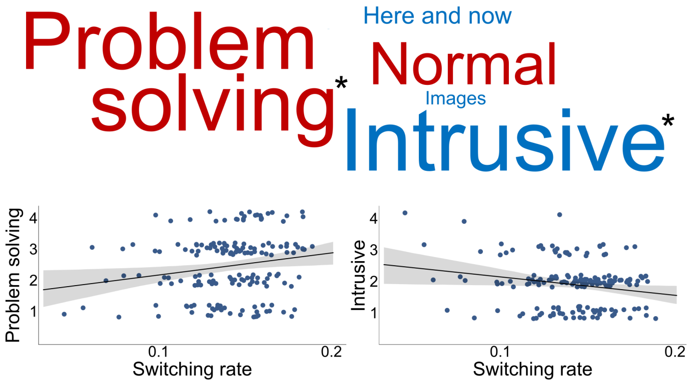

Figure 5.5: *Overall dynamics associated with ongoing experience.* Correlation coefficients between thoughts and state switching rate visualised using a word cloud (top) and the associated scatter plots for the significant relationships (bottom). Font size in world cloud represents the absolute correlation value and font colour its sign (red for positive and blue for negative correlations). * $p < 0.05$ (FDR-corrected).

of questions)), and more related to problem solving (r = 0.20, p = 0.005 uncorrected, p = 0.03 FDR-corrected) (Fig. 5.5, bottom).

By integrating model fits across the 100 runs of the algorithm (see Methods), the state switching rate was again negatively correlated with intrusive thoughts ($\bar{r}$ = -0.1841, p = 0.036, FDR-corrected) and positively correlated with problem solving ($\bar{r}$ = 0.1837, p = 0.036, FDR-corrected) (Fig. 5.7, left). None of the other items showed a significant relationship with switching rate.

Finally, parallel analyses indicated similar associations with the switching rate for an HMM decomposition of 9 states and 12 states, demonstrating this relationship was robust to the number of *a priori* states selected. Utilising the metrics from the optimal HMM, we identified, via permutation testing, that the overall state switching rate during the resting state scan was predictive of concurrent thoughts, as reported at the end of the scan both for the HMM with K = 9 states (p = 0.019) and K = 12 states (p = 0.0005). For K = 9, follow up univariate analyses and permutation testing showed that increased switching between neural states was predictive of more thoughts related to problem solving (r = 0.179, p = 0.013, no-correction). For K = 12 states, the switching rate was again positively correlated with problem solving thoughts (r = 0.263, p = 0.0006, FDR-corrected) and negatively with thinking in images (r = -0.146, p = 0.01, FDR-corrected). No other questionnaire items showed a significant relationship with switching rate.

We found similar associations when integrating model fits across the 100 runs of the algorithm. For K = 9, the state switching rate was positively correlated with problem

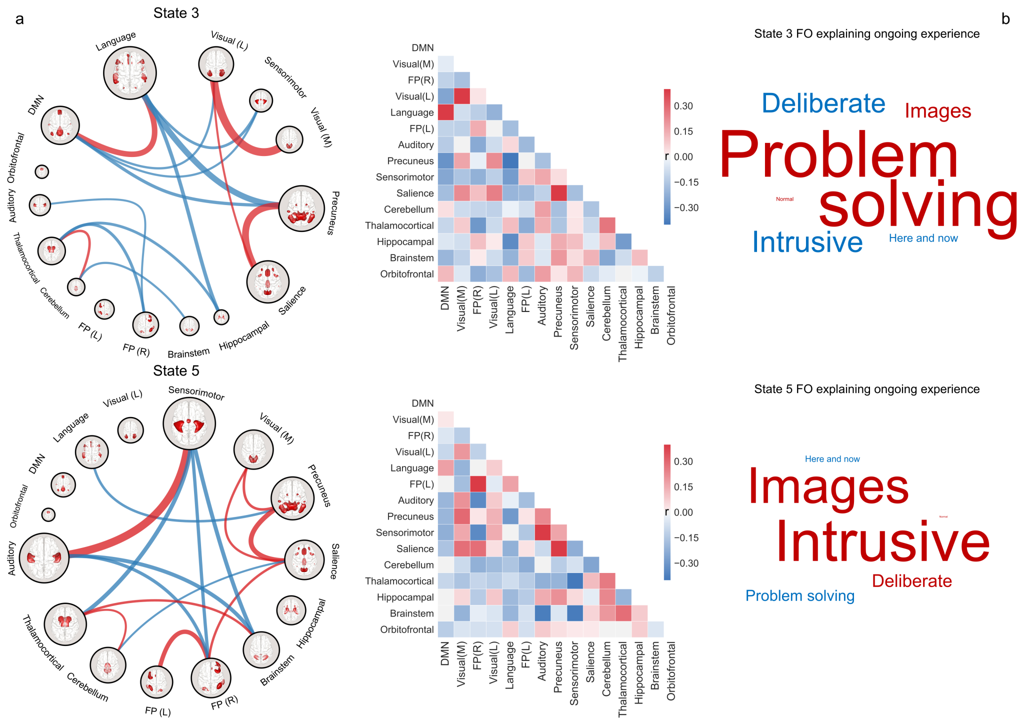

Figure 5.6: *State-specific dynamics associated with ongoing experience.* **a**) This panel presents chord graphs of states 3 and 5 (left) along with their corresponding correlation matrices (middle). The chord graphs were thresholded, for visualisation, at the 85^{th} percentile of absolute correlation values for each state. Red lines refer to positive and blue lines refer to negative correlations, with edge width representing the magnitude of the correlation. Node size shows the node's "strength", computed as the sum of the absolute correlation of each network with the rest of the brain. **b**) Correlation coefficients between thoughts and fractional occupancy of state 3 (top) and state 5 (bottom) visualised using word clouds. Font size in world clouds represents the absolute correlation value and font colour its sign (red for positive and blue for negative correlations). Note, the relationship between the FO of the states and ongoing experience does not pass correction for multiple comparisons.

solving ($\bar{r}$ = 0.17, p = 0.047, FDR-corrected) and negatively with intrusive thinking ($\bar{r}$ = -0.15, p = 0.032, no-correction). For K = 12, only the relationship with problem solving was significant ($\bar{r}$ = 0.18, p = 0.03, FDR-corrected). All analyses controlled for age, gender and motion during the rs-fMRI scan.

5.4.3.2 State-specific dynamics and ongoing experience

We also explored the relationship between the FO of the states and the descriptions of ongoing experience. Using the FO of each state as an explanatory variable in separate multivariate GLM, we found a significant relationship between the FO of state 3 and the FO of state 5 with thoughts (p = 0.018 and p = 0.036 respectively, uncorrected) (Fig. 5.6b). State 3 was dominated by three motifs of increased connectivity between (i) the default mode (DMN) and language network, (ii) lateral and medial visual cortex and (iii)

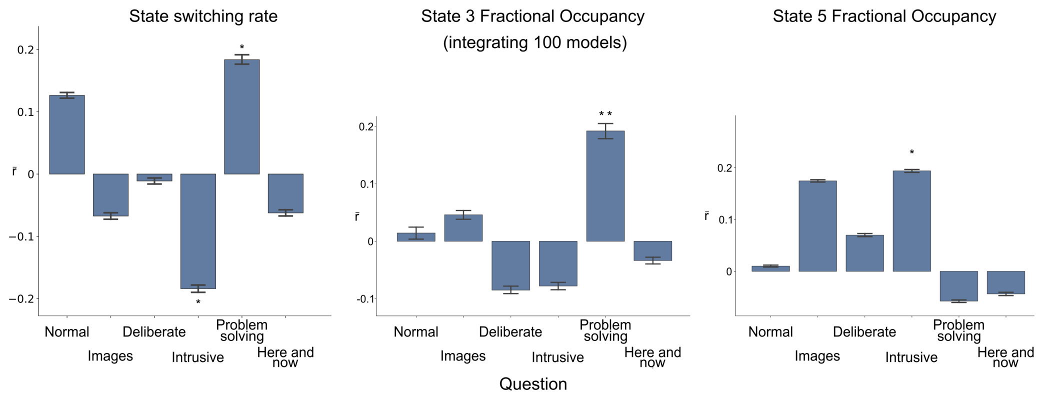

Figure 5.7: *Brain dynamics associated with thoughts.* Integrating over 100 hidden Markov models (K=7). Average correlation coefficient $\bar{r}$ between thoughts and state switching rate (left). Average correlation coefficient $\bar{r}$ between thoughts and fractional occupancy of state 3 (middle) and average correlation coefficient between thoughts and fractional occupancy of state 5 (right). * $p < 0.05$, ** $p < 0.01$ (FDR-corrected).

the precuneus and saliency network. Whereas, state 5 was marked by strong coupling between sensory systems (sensorimotor and auditory) (Fig. 5.6a). These results, however, did not pass correction for multiple testing (p = 0.13, FDR-corrected for 7 tests (number of states)), rendering them less robust than the effects of the overall dynamics and so we do not consider them in detail further.

Integrating across all HMM runs revealed that problem solving was positively correlated with the FO of state 3 ($\bar{r}$ = 0.1922, p = 0.009, FDR-corrected) (Fig. 5.7, middle), while intrusive thinking was associated with the FO of state 5 ($\bar{r}$ = 0.1941, p = 0.046, FDR-corrected) (Fig. 5.7, right).

5.4.4 Relationship between brain dynamics and measures of general health and well-being

After demonstrating links between brain dynamics and reports of experience, we next examined associations between dynamic neural metrics and measures of physical and mental health. The analysis showed that state switching rate was related to well-being (p = 0.04). In particular, increased dynamic brain activity, as identified by our temporal classification, was linked with increased general health and psychological well-being and with less depression and anxiety (Component 1 in Fig. 5.2b) (r = 0.20, p = 0.007 uncorrected, p = 0.02 FDR-corrected for 3 tests (number of PCA components), Fig. 5.8). The FO of the HMM states was not significantly correlated with any of the 3 PCA components.

Utilising the metrics derived from the multiple HMM runs, increased dynamic brain

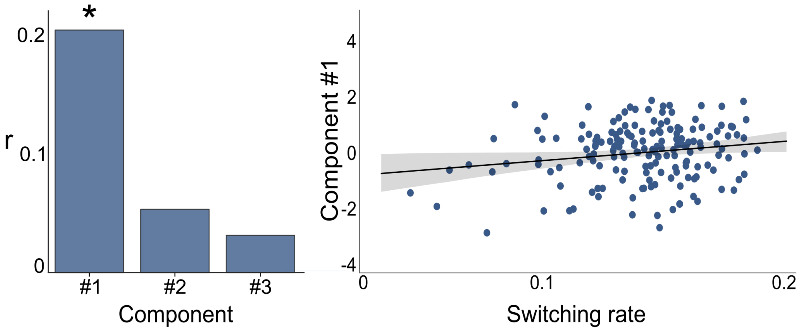

Figure 5.8: *Brain dynamics associated with physical and mental health.* Correlation coefficients between PCA components from the physical and mental health scores and state switching rate and the associated scatter plot for the significant relationship with component 1. * $p < 0.05$ (FDR-corrected).

activity was linked with increased general health and psychological well-being and with less depression and anxiety (component 1 from our PCA decomposition of the physical and mental health scores) ($\bar{r} = 0.1973$, p = 0.019, FDR-corrected, Fig. 5.9). The FO of the HMM states was not significantly correlated with any of the 3 PCA components.

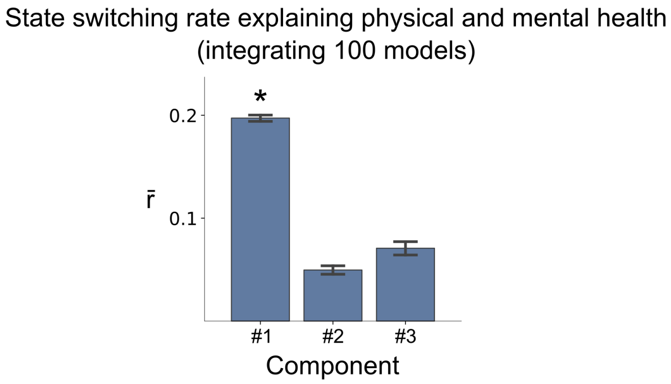
State switching rate explaining physical and mental health (integrating 100 models)

Figure 5.9: *Brain dynamics associated with physical and mental health.* Integrating over 100 hidden Markov models (K=7). Average correlation coefficient $\bar{r}$ between the PCA components from the physical and mental health scores and state switching rate. * $p < 0.05$ (FDR-corrected).

5.5 Discussion

Consistent with the view that temporal dynamics are an integral aspect of unconstrained cognition, we found the degree of switching between different intrinsic neural states was associated with self-reported experiential states emerging during this period. Greater flexibility was linked to less intrusive thoughts and more related to attempts at problem solving, as well as better physical and mental well-being. In constrast, we found only modest evidence relating patterns of experience to the occupancy of individual states.

These data support contemporary accounts of ongoing experience that emphasise temporal dynamics as important for understanding patterns of concurrent experience (Smallwood, 2013a; Christoff et al., 2016; Kucyi et al., 2016), and we consider the significance of this observation for our understanding of ongoing cognition.

Our study suggests the flexibility of intrinsic neural activity may be a mechanism determining whether patterns of ongoing thought are linked to beneficial or deleterious aspects of cognition and behaviour (Smallwood and Andrews-Hanna, 2013). More transitions between neural states at rest was linked to patterns of experience that emphasised problem solving. Autobiographical planning and problem solving are widely accepted benefits that can emerge from unconstrained thought (Smallwood and Schooler, 2015) which have been shown to help refine personal goals (Medea et al., 2018) and reduce psycho-social stress (Engert et al., 2014). In contrast, individuals for whom neural dynamics were inflexible reported experiences that were more intrusive in nature. Intrusive thinking is central to multiple psychiatric conditions, including obsessive compulsive disorder (Najmi et al., 2009), depression/rumination (Smith and Alloy, 2009) and post-traumatic stress disorder (de Silva and Marks, 1999). Critically, greater switching between states at rest was also linked to better well-being. Together, our data suggests that more flexible neural activity is linked to more beneficial associated outcomes.

More generally, our study suggests that abstract properties of neural dynamics, such as the ease of transition between states, can be psychologically relevant (Kucyi, 2018). Previous studies have focused on the consistency of the states, for example, by documenting their heritability (Vidaurre et al., 2017b). Others have examined the influence of particular states on cognition and behaviour. Cabral and colleagues (Cabral et al., 2017b), for example, found higher cognitive performance for older individuals was predicted by the prevalence of a global brain state. Our study found modest evidence that particular experiences are related to states with specific neural motifs, however, we found stronger evidence that eases of transition between states is linked to experience, and health and well-being. Based on these findings, it will be important to understand the manner through which the flexibility of cycling through different neural states contributes to cognition and also whether this can change across the life cycle and with clinical conditions. Studies have shown specific sequences of neural processing support the expression, recognition and supression of mind-wandering in experienced meditators (Hasenkamp and Barsalou, 2012), and so part of the flexibility we observe may reflect a process implicated in the monitoring of ongoing thought (Schooler, 2002). More generally, understanding how state transitions are constrained by cortical architecture (Margulies et al., 2016) and influenced by the distributed activity of neuromodulators (Harris-Warrick, 2011) are important questions for future research to address.

Finally, our demonstration that HMM can reveal covert neural states relevant to patterns of ongoing thought constitutes an important methodological advance for the study of ongoing conscious experience. Although famous for highlighting dynamics, William James argued against introspection as an approach to understanding experience, likening it to trying to "turn up the gas quickly enough to see the darkness" (James, 1890). While the last two decades have seen increased interest in investigating self-generated thoughts (Callard et al., 2013), we lack a method to study them in a manner that does not disrupt their natural dynamics (Konishi and Smallwood, 2016; Kucyi, 2018). Our study shows that the HMM captures features of neural dynamics that are relevant to ongoing thought in a manner that does not rely on introspective information for their identification. The ability of the HMM to 'parse' neural data into underlying temporal states, without disrupting their evolution, provides a window into how cognition unfolds without the concern that the disruptive nature of experience sampling may contaminate it. We anticipate future studies will be able to apply this method to gain unprecedented access to covert changes in cognition that are a pervasive, yet poorly understood aspect of our mental lives.

Chapter 6

General discussion

Ongoing experience can be complex and heterogeneous. Depending on the context, its manifestations may draw from multiple cognitive domains and exhibit varying temporal properties. Contemporary neuroimaging methods and analytic tools offer the opportunity to disentangle these two features (see Ch. 2). For example, diffusion weighted imaging provides a way to explore how the relatively stable structural architecture of the brain may support trait-like properties of patterns of ongoing thought, while functional MRI allows researchers to investigate how this architecture is utilised by interacting functional networks to give rise to ongoing cognition. In addition, analyses techniques, such as hidden Markov modelling, provide an opportunity to explore the dynamic temporal evolution of these interactions and explore how they might be linked to the dynamic properties of ongoing experience. The aim of the thesis was to utilise such neuroimaging tools and explore how the structural and functional organisation of the brain at different temporal scales can help us identify the cognitive processes that support different types of unconstrained ongoing experience at different moments in time.

6.1 Summary of data acquisition and findings

6.1.1 Data acquisition

Spontaneous thoughts arise following the disengagement of attention from the external environment as the brain is entering a self-organised functional mode (Smallwood et al., 2008a). In order to facilitate the initiation of such neural states and mind-wandering episodes, we opted to acquire resting state scans in all our empirical fMRI studies (Smallwood et al., 2009b). To interrogate structure, we acquired diffusion weighted imaging data

(Ch. 3) that allowed us to calculate structural metrics for each participant and explore their inter-individual variation and relation to different types of spontaneous thought. Finally, we sampled the participants' ongoing experience via questionnaire retrospectively at the end of the scans (Ch. 4 and 5) or outside of the scanner while they were performing a non-demanding choice reaction time task in a separate session (Ch. 3).

6.1.2 Chapter 3 findings

The first empirical chapter (Ch. 3) investigated how the relatively time-invariant structure of the human brain can inform us about trait-like features of ongoing experience. Our findings highlighted stable trait-like patterns in the content and form of thoughts that have been identified in previous studies (Smallwood et al., 2016). Investigating the white matter structure of the adult brain, we found, using whole-brain tractography analysis, that an increase in the diffusion fractional anisotropy of a temporo-limbic white matter region was related to experiences with increased mental time travel. Probabilistic tractography analyses revealed that this white matter region had a high number of fibres projecting to the right hippocampus. Leveraging functional connectivity data, we found that the propensity to mental time travel was associated with increased functional connectivity of the hippocampus with the medial prefrontal cortex, a core hub of the default mode network (Andrews-Hanna et al., 2010b).

Chapter 3 demonstrates how the structure of the human brain can influence its function and regulate the content of unconstrained ongoing cognition, highlighting the hippocampus and its functional coupling with the medial pre-frontal cortex as important for spontaneous thoughts about the future or the past. Combined, our results provide evidence of neural traits underlying trait-like features of spontaneous thoughts.

6.1.3 Chapter 4 findings

Chapter 4 explored how static functional connectivity at rest can be collectively related to ongoing experience as well as various associated dispositional traits. It found links between patterns of ongoing experience emphasising visual imagery and dispositional traits reflecting high levels of self-consciousness, depression and attentional problems. Our resting state functional connectivity analyses showed an increased correlation between the precuneus (posterior DMN) and a lateral fronto-temporal network for increased reports of visual imagery. We also found a decrease in connectivity between the lateral visual and brainstem networks for increased self-consciousness, rumination and attentional problems. Finally, our results highlighted an interaction between these associations: stronger brainstem visual network coupling was associated with a stronger correlation between parietal-frontal regions and reports of visual imagery.

Together, these results highlight that unique neural motifs relating to both ongoing patterns of thought and dispositional traits can vary together within individuals. Our findings complement previous studies showing how stable functional interplay between large scale functional networks is linked to different patterns of spontaneous thought (Medea et al., 2018; Turnbull et al., 2019; Wang et al., 2018a; Golchert et al., 2017). Importantly, our results also highlight the need for future studies to consider both sources of variation when investigating patterns of neural functioning observed at rest.

6.1.4 Chapter 5 findings

Despite the influence of the static functional architecture of the brain to neural and consequently behaviour states, there is still a vast amount of time-varying activity in the brain, responding to intrinsic or extrinsic inputs at any given point in time (Kucyi, 2018), facilitating non-conscious functions and giving rise to our stream of consciousness (Demertzi et al., 2019). In order to investigate how differences in the dynamic functional configuration of the brain might relate to ongoing experience, the third empirical chapter of the thesis (Ch. 5) applied hidden Markov modelling and explored the association of dynamic neural activity metrics to spontaneous thoughts as well as physical and mental health. It found distinct recurring whole-brain neural patterns involving large-scale functional networks, and found that increased transitions between these states described experiences emphasising problem solving and fewer intrusive thoughts, as well as better physical health and psychological well-being.

Our findings advance previous dynamic analyses results showing how time-variant functional connectivity relates to experimentally constrained ongoing cognition (Gonzalez-Castillo et al., 2015), daydreaming (Kucyi and Davis, 2014) and more generally population level traits (Vidaurre et al., 2017b). Importantly, our results demonstrate that the occurrence of particular neural states is linked to specific patterns of spontaneous thoughts, suggesting a potential use of this feature as a biomarker of different types of self-generated thoughts. Such an approach would have the potential to mitigate certain problems associated with measuring this covert cognitive process (see 1.4). Finally, the relationship between the rate of switching among distinct whole-brain neural patterns and ongoing experience and well-being suggests that, despite the important role of the DMN in regulating ongoing cognition, the dynamic fluctuations of the whole brain also relate to the content and form of our thoughts as well as to trait behaviour.

6.1.5 Summary

Collectively, our results advance our understanding of the neural mechanisms that support unconstrained ongoing experience and the cognitive processes that it relies upon. They highlight how structural properties of the brain can constrain its function and influence the patterns of our thoughts (Ch. 3), and show stable neural interactions linked to episodic memory processes (Ch. 3) and visual imagery (Ch. 4), both consistently recruited for generating ongoing thought content (Smallwood and Schooler, 2015; Andrews-Hanna et al., 2013; McCormick et al., 2018). Finally, by utilising time-variant analyses techniques (Ch. 5), our results offer novel insights into the relationship between whole-brain dynamic functional organisation at rest with ongoing experience and psychological well-being. Together, these results are important in terms of understanding how the occurrence of specific neural patterns relates to distinct patterns of experience as well as facets of mental health. Conceptually, these studies highlight a number of important features for contemporary accounts of unconstrained experiences.

6.2 Structure and function of the default mode network and whole-brain functional interplay associated with ongoing experience

One common hypothesis advanced in the literature reflects the role of the DMN in shaping ongoing experience (i.e. Andrews-Hanna et al., 2014b). In this context, our empirical studies provided the chance to consider this hypothesis from structural, static and dynamic perspectives.

6.2.1 DMN static functional connectivity

The default mode network (DMN) is a functional heterogeneous network (Laird et al., 2009; Raichle, 2015). DMN regions have been shown to reduce their activity during tasks (Raichle et al., 2001; Gusnard and Raichle, 2001) and have been repeatedly highlighted in studies investigating the neural substrates of spontaneous thoughts (Christoff et al., 2009; Mason et al., 2007; Kucyi et al., 2016; Allen et al., 2013; Smallwood et al., 2012). At the same time, DMN more recently has been shown to increase its activity while performing tasks that require access to short and long-term memory (Sormaz et al., 2018; Murphy et al., 2018a; Spreng et al., 2014; Vatansever et al., 2017b), challenging traditional views of this system as "task negative" (Fox et al., 2005). Core hubs of the network have been associated with different types of spontaneous thought (Smallwood et al., 2016). Static functional connectivity between its sub-systems (Andrews-Hanna et al., 2014b) and other large-scale networks has been linked to task unrelated thoughts, through decoupling from the environment (Poerio et al., 2017; Konishi et al., 2015). It has also been associated with psychological well-being, both indirectly by regulating the contents of spontaneous thoughts (Andrews-Hanna et al., 2014b) and directly in clinical cases (Kernbach et al., 2018a; Lefort-Besnard et al., 2018; Sheline et al., 2009). Our static functional connectivity results support these perspectives by showing how variation in the connectivity of the DMN with the hippocampal (Ch. 3) and a lateral fronto-temporal network (Ch. 4) is related to thoughts about the future or the past and visual imagery respectively.

6.2.2 DMN structural properties

One recent view of the DMN is that it plays an important role in organising global brain dynamics (Vatansever et al., 2015), however, it is not yet clear the extent to which its role in cognitions emerges from its structural properties and its ability to interact with and integrate information from multiple brain regions. Previous research has shown that the structural connectivity of the DMN undergoes significant developmental changes when passing from childhood to adulthood (Supekar et al., 2010), and that during childhood there are reduced dynamic functional interactions between the DMN and other networks (Ryali et al., 2016). Such reduction could lead to a decrease in integration in early years, which might explain the later maturation of higher-level executive and self-related cognitive functions. In adulthood, DMN core regions are structurally connected in a way that supports their coupled function (Greicius et al., 2009), and have the interesting structural property of being significantly spatially distant from each other and equidistant to other unimodal sensory functional regions (Margulies et al., 2016), which could facilitate the information integration from these regions. Likewise, recent work has highlighted the thalamus and basal forebrain as nodes of the DMN's structural network with increased centrality (a measure of a node's "importance" within a network graph), implicating another integrating structural mechanism that supports the functional role of the network (Alves et al., 2019). Finally, fornix white matter microstructure has been associated with grey matter differences in the DMN, suggesting a structural mechanism that drives the functional interaction between the DMN and hippocampal networks (Kernbach et al., 2018b). In this context, our tractography results from our diffusion weighted imaging study (Ch. 3) are important because they show that a white matter region overlapping with the fornix was related with the ability to mental time travel. Along with the corresponding static functional connectivity results from the same study, our findings suggest that white matter variation in the structural connectivity of the extended DMN could alter its stable functional interactions and the information being integrated at core DMN regions, leading to different patterns of ongoing thoughts.

6.2.3 DMN dynamic function and whole-brain functional connectivity

Dynamic properties of the brain have also associated the DMN with behaviour and trait characteristics. Vidaurre et al. (2017b) identified recurring whole-brain functional network patterns and showed that the transitions between them were hierarchically organised in two distinct sets, or metastates. One set was related to sensory and motor networks and the other, which included the DMN, was linked to higher-order cognitive functions. Interestingly, they showed that the time spent in these metastates was linked to behaviour and, specifically, that spending more time in the DMN metastate was associated with positive traits, like increased inhibitory control, cognitive flexibility and better life satisfaction. The results from our HMM modelling build on these findings. They show a trend where spending more time in a neural state where the DMN is coupled with the language network is linked with engaging more in problem solving, a positive outcome of spontaneous thought (Ruby et al., 2013b). Knowing when these neural states occur and how they relate to cognition provides a unique opportunity to explore the temporal properties of conscious thought, both in task and rest states, without interrupting their natural evolution and without the need to rely upon subjective self-report measures and meta-cognition (see 1.4, "Measuring mind-wandering").

However, the DMN is not the only network that has been linked to ongoing experience. Fox et al. (2015) performed a meta-analysis of 24 functional neuroimaging studies of spontaneous thought and found that in addition to the DMN, there were numerous non-

DMN regions recruited, belonging to different large-scale functional networks supporting different cognitive processes (i.e. the fronto-parietal control network). Our HMM results, in Chapter 5, confirmed this involvement of non-DMN networks and further highlighted that dynamic properties of the brain as a whole, such as the rate of switching from one whole-brain functional configuration to another, were also linked to different types of spontaneous thoughts. This implies that, besides individual regions and networks, the functional organisation and hierarchy of the whole-brain is also important for higher order cognitive functions.

6.2.4 DMN as a whole-brain functional integrator

Ongoing experience often requires the simultaneous engagement of various cognitive functions, such as executive control, episodic, and semantic memory processes. Given the hypothesised involvement of the DMN in ongoing cognition, we would expect DMN to selectively couple with a variety of functional networks that underlie the required cognitive processes based on given cognitive demands. Indeed, neural signals within the DMN have been found to represent properties, or "echoes", of neural activity from other remote large-scale brain networks (Leech et al., 2012; Braga et al., 2013). This capacity of the DMN to map global neural functioning has situated the network, according to recent accounts, at the top of a whole-brain functional hierarchy, holding the important role of a global integrative system (Margulies et al., 2016; Wang et al., 2019) (Fig. 6.1a). At the top of a corresponding gradient of cognitive functions, related with DMN activity, we find spontaneous thoughts and other higher order cognitive processes that draw from multiple cognitive domains (Margulies et al., 2016). Our static functional connectivity results, from Chapters 3 and 4, support these findings by showing that the functional interactions of different core regions of the network, like the precuneus and the medial prefrontal cortex with a lateral fronto-temporal and hippocampal networks respectively, support different types of ongoing experience.

This layered system architecture has also been described by empirical Bayes and the statistical notion of "Markov blankets" (Friston, 2005; Allen and Friston, 2018) (Fig. 6.1b). Markov blankets (Pearl, 1988) set boundaries around any particular node of a system rendering internal and external states conditionally independent from each other and have been used to describe the autonomous organisation of biological systems (Friston, 2013; Kirchhoff et al., 2018). They can be redundant and nested, with Markov blankets enclosing

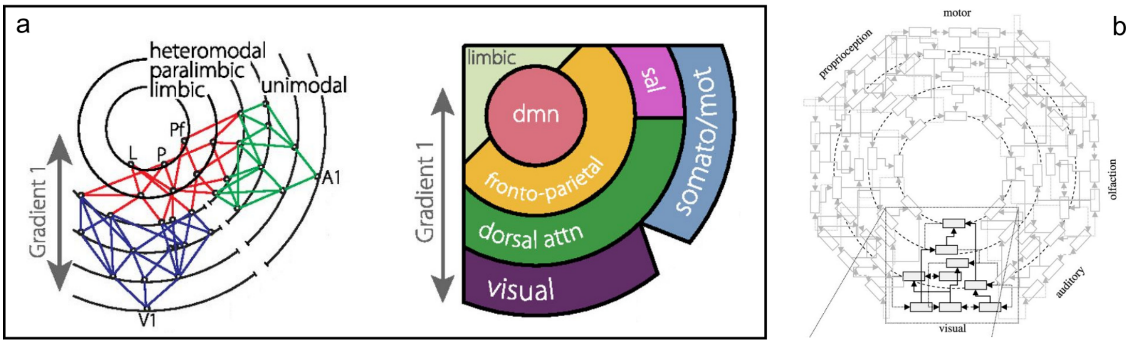

Figure 6.1: *Schematic depictions of hierarchical structures in the brain.* **a**) Left: Connectivity organisation suggested by Mesulam (1998), proposing a hierarchy of processing from distinct unimodal areas to integrative transmodal areas. Middle: A schematic of the spatial relationships of canonical resting-state networks (Yeo et al., 2011) applying the schema suggested in Mesulam (1998), presented on the left. Label Gradient 1 corresponds to the first connectivity embedding gradient shown in Margulies et al. (2016), where the figure was adapted from. **b**) Hierarchical structures in the brain and the distinction between forward, backward and lateral connections. Schematic inspired by Mesulam (1998). Figure adapted from Friston (2005).

smaller Markov blankets and so on (Friston, 2013), while integrating information as we move higher up in the hierarchy. DMN has been shown to be composed of distributed modules, each encompassing their own submodules (Leech et al., 2011; Kernbach et al., 2018b). Based on such evidence and our findings on the selectively integrative role of the DMN depending on the pattern of ongoing experience, we speculate that the DMN can be considered as a higher level Markov blanket, integrating necessary information to support different types of higher-order cognition. Even though we did not consider our HMM model as a biophysical model, it might be interesting for future work to explore in detail how similar findings of time-variant whole-brain functional interactions in relation to ongoing experience could fit the theoretical view of Markov blankets at different spatial and temporal scales.

6.3 Neural trait-state interactions through a representational framework of vectors

Collectively, the studies in this thesis suggest important links between neural functioning and ongoing cognition at the level of a trait. Using different neuroimaging modalities and analyses techniques, we found structure relating to trait mind-wandering and highlighting a mechanism that constrains stable neural function (Ch. 3), and stable patterns of spontaneous thought linked to static functional interactions at rest (Ch. 4). Finally, Chapter 5 identified dynamic neural fluctuations relating to ongoing cognition. Our results add to the growing number of studies that highlight complex associations between neural structure and function and their links to ongoing thought and behaviour, both at the level of trait and during transient states. However, underpinning these studies is the question of how dynamic "states" can emerge from an architecture that is also influenced by stable "traits".

There are many studies that show how structural neural traits can influence behaviour (e.g. Roberts et al., 2013). Structural brain networks have been shown to correspond to stable functional interactions (Greicius et al., 2009) and play an important role in global brain dynamics (Bansal et al., 2018; Cabral et al., 2017a). In addition to structural connectivity, the volume of particular brain regions is correlated with personality traits (DeYoung et al., 2010; Wang et al., 2018c) and differs across clinical populations (Hong et al., 2018; Whelan et al., 2018).

Parallel to structure, the influence of the environment can change the stable and dynamic function of the brain, particularly during learning. Dynamic changes in functional network modularity (a measure of dynamic network reconfiguration) have been shown to have an increased rate at the beginning of the learning process and gradually decrease onwards (Bassett et al., 2011), while large-scale functional networks like the DMN have been shown to dynamically change their connectivity in order to facilitate task demands (Vatansever et al., 2015; Krieger-Redwood et al., 2016). This dynamic variability has been suggested to be strongly modulated by stable neural traits within subjects (Gratton et al., 2018). Finally, there has been evidence of structural change of the brain following extensive training and acquiring expertise (Zatorre et al., 2012; Maguire et al., 2000; Engen et al., 2018).

6.3.1 Vector dynamic equilibrium

Collectively, studies from this thesis, as well as other lines of evidence, highlight the need to understand how momentary aspects of cognition emerge from a neural system that is also influenced by stable traits. We suggest this problem can be schematically represented in the following way. The neural patterns that support cognition at a given moment can be considered as a set of neural priors (represented with a vector $\mathbf{p}$), which are influenced by information in the immediate environment (environment vector $\mathbf{e}$) as well as more stable features that may arise from either genetic influences or from the consolidation of past experience (structure vector $\mathbf{s}$). For present purposes, the structure vector $\mathbf{s}$ can be considered to be largely time-invariant, at least in the adult brain (Park and Friston, 2013). The environment vector $\mathbf{e}$ can change dynamically both in magnitude and direction depending on the nature of stimulus input into the system, as well as the current task at hand. However, there are still many environmental properties that remain constant due to the physical laws of nature and the routine of our everyday lives. Thus, large changes in $\mathbf{e}$ would occur when external events deviate significantly from expectations (i.e. an event that violates prior encoded information). In this framework, the structure and the environment vectors influence the priors by acting as dynamic attractors of different strength (i.e. like springs with a different spring constant k_s, k_e).

The different influences ($\mathbf{p}$, $\mathbf{e}$ and $\mathbf{s}$) and how they interact are represented schematically in Figure 6.2. When left on its own, a system will aim to reduce its computational costs and more likely converge to its local and global minima (Friston, 2010). This suggests that the system will attempt to reach an optimal dynamic equilibrium that minimises computational surprise. Consequently, any dynamic neural states ($\mathbf{d}$) at rest will fluctuate around this optimal configuration (Deco and Jirsa, 2012) in a manner that is influenced by the strength of the priors (k_p) and by the degree to which the environment deviates from them (Fig. 6.2a). Over time, this could help the system update and refine its priors, but could also lead to an inner loop that might prove difficult to break in maladaptive cases (i.e. intrusive thinking in obsessive compulsive disorder, Najmi et al., 2009).

A brief change in the environment (i.e. in order to perform a task) would temporarily break the equilibrium and change the magnitude and/or direction of $\mathbf{e}$. This would alter the dynamic fluctuations to follow the direction of change of $\mathbf{e}$, while the priors would "resist" the change. In the spring-like example presented in Figure 6.2b, a bigger k_p would represent a stronger prior opposing change, which would decrease the functional flexibility for the system. If $\mathbf{i}$ is the vector representing where the priors should have been for an ideal performance to a particular task, then the angle σ would represent the system's "surprise" to the environmental change ($\uparrow \sigma \Rightarrow \uparrow$ "surprise"), angle φ would determine the task performance ($\uparrow \varphi \Rightarrow \downarrow$ performance) and angle θ would determine the dynamic changes in neural configuration measured while performing the task ($\uparrow \theta \Rightarrow \uparrow$ dynamic fluctuations) (Fig. 6.2b). Any change in the dynamic neural activity would update the priors accordingly. A small brief change in the environment would briefly alter $\mathbf{d}$. After $\mathbf{e}$ returns to its initial state, the system will return to equilibrium, with recovery time depending on the angle θ and the priors strength k_p.

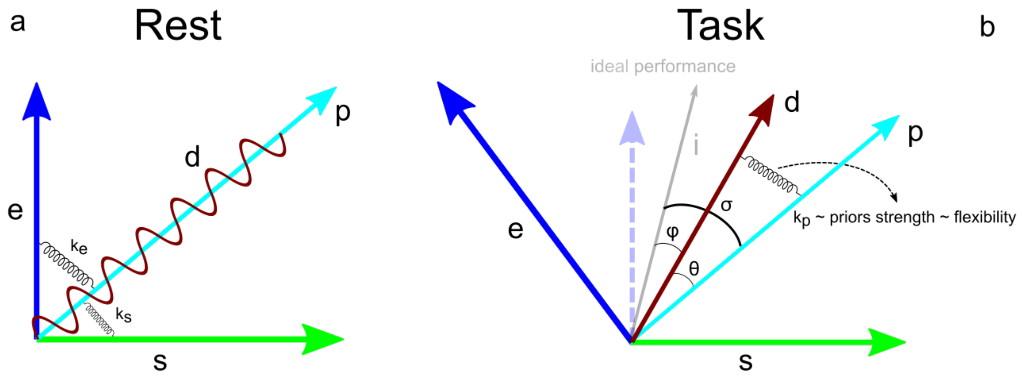

Figure 6.2: *Schematic of the vector dynamic equilibrium representational framework.* **a**) Dynamic equilibrium during rest. **b**) Dynamic changes following a change in the environment. **variables**: **e**: environment, **s**: structure, **p**: priors, **d**: dynamic fluctuations, **i**: priors for ideal performance, k_e, k_s, k_p: spring constants representing attractor strengths of the environment, structure and priors.

Over time, large stable changes in the environment will repeatedly alter the dynamic neural fluctuations and "move" the priors vector **p** to a new stable state that minimises "surprise" (angle σ). This would involve functional reconfiguration and, depending on the magnitude of the priors' change, even alterations in structure, so that the system reaches a new dynamic equilibrium. This could prove beneficial when training, as it can significantly improve performance but can also be harmful in cases of negative environmental changes, as the system might get "stuck" on a dysfunctional equilibrium.

One important aspect of this framework is that it provides a way of characterising how structural and functional properties of the brain interact to give rise to the complex dynamics of cognition. In the case of our empirical findings, it provides an intuitive account of the way that structure (e.g. Ch. 3) can constrain the stable functional organisation of the brain (Ch. 3 and 4) and its ongoing neural dynamics (Ch. 5). We suggest that neural fluctuations around the priors at rest are predictive of relatively stable patterns of ongoing experience, while large deviations from this mean reflect less common aspects of thought.

This perspective makes a number of important predictions. First, when a system is at "rest", fluctuations will be heavily influenced by its priors, acting as a strong attractor. In contrast, forcing the system to perform a specific task may perturb this equilibrium. The "distance" between the system's priors and its current task state will determine how much it will deviate from its norm. Accordingly, resting state, which is often regarded as unconstrained, would be more restricted by an individual's priors and so would exhibit less within individual variation than when the individual performs different tasks. On

Table 6.1: Task performance related to representational framework metrics

Expertise	Priors "distance" to task demands (angle σ)	Priors strength (k_p)	Dynamic changes during task (angle ϑ)	Task performance
High	Very low	High	Very low	High
Low	High	High	Medium (restricted from strong opposing priors $\Rightarrow$ reduced flexibility)	Low
Low	High	Low	High	Medium

the above account, ironically, even though spontaneous thoughts may seem to be highly dynamic, they might be in fact relatively stable in their themes.

Second, previous studies have shown that fluctuations in functional network architecture relate to distinct patterns of behaviour during cognitive tasks (Vatansever et al., 2015; Alavash et al., 2016) and that cognitive performance is linked to the ability of the brain to dynamically reconfigure its organisation (Shine et al., 2016). It is possible that the expected magnitude of these dynamic neural changes that occur while performing a task will relate to a subject's prior expertise in the specific domain (see Table 6.1). This is because high expertise on any particular task would indicate that the subject's functional priors are already configured to respond to task input in an efficient manner, since the system is already optimised and there is no "surprise" to disturb neural activity. In the other extreme of low expertise, there may be two categories that depend on how flexibly an individual can alter these priors. We would expect a more flexible system to adapt better to the requirements of the task by dynamically changing its configuration more compared to a less flexible one, which would also be reflected in the individual's performance.

6.4 Limitations and future research

There are a number of limitations that should be borne in mind when considering the studies in this thesis. First, despite being able to identify how static and dynamic functional network variability relates to unconstrained ongoing cognition, our between-subjects design did not provide information about the magnitude of the effects within individuals, across sessions and cognitive states. Dynamic fluctuations have been used to decode and track subject-specific constrained cognitive states (Shirer et al., 2012; Gonzalez-Castillo et al., 2015), however, there are reports of these fluctuations explaining a relatively small amount of the total variance compared to the group and within-subject stable functional interactions (Gratton et al., 2018). A future study with an increased number of repeated scans could aim to explore how much of this time-variant activity within subjects is associated with spontaneous thoughts and in what way it might be related to specific thought patterns or even to the evolution of particular thoughts.

Second, we did not have the opportunity to acquire physiological data (i.e. heart and respiration rate) during the fMRI scans. Along with motion, cardiac and respiratory cycles have been suggested as potential confounds in the resting-state BOLD signal (Murphy et al., 2013). More interestingly though, heart rate and other internal bodily signals have been shown to have a strong influence on cognition and shaping behaviour (Critchley and Garfinkel, 2018). Advancing our static functional connectivity results that related the connectivity of a neural regulator of interoceptive signals to different patterns of spontaneous thought (see 4.5), it would be of great interest to further investigate how the signals themselves shape the static and dynamic functional interactions of the whole-brain (i.e. in the case of heart rate signal acting as a coupled oscillator) and modulate unconstrained ongoing experience (Babo-Rebelo et al., 2016).

Finally, our results suggest that the variation in dynamics associated with cognition was also dependent on the stable trait-like structural and functional organisation of the brain. However, the nature of our studies focused on variations across individuals rather than those that may also occur within a person. Future research could aim to quantify this influence, investigating how it relates to neural and cognitive flexibility, as well as learning, and explore hypotheses described in the latter section. For example, it could be important to apply hidden Markov modelling to repeated fMRI scans while participants practise learning a novel task.

6.5 Concluding remarks

In conclusion, this thesis set out to explore the neural underlying mechanisms of unconstrained ongoing cognition. We utilised different neuroimaging modalities and analyses techniques to investigate the relationship of whole-brain structural and functional organisation with spontaneous thoughts as well as physical and mental health. We found evidence linking both structure and function, static and dynamic, to ongoing experience. Our results from our empirical studies highlighted the extended structural and functional network of the DMN as important neural substrate of spontaneous thoughts. Either through changing its within-network functional properties or through its connectivity with other large-scale networks, we found the DMN associated with different themes of ongoing experience. Furthermore, our investigation of the time-variant properties of neural activity showed that the dynamic functional interplay of the whole-brain was also related to the content and form of our thoughts. This suggests a complex overall mechanism linking structure, neural traits and dynamics to our behaviour at each point in time. Future research should aim to further explore how these factors modulate each other, and investigate the role of the DMN in relation to spontaneous thoughts, as a potential orchestrator of a whole-brain neural synchronised "dance", integrating information at the top of a whole-brain functional hierarchy.

Appendix A

Supplementary materials - Chapters 4 and 5

A.1 Experience sampling questions

We asked participants to answer 25 questions shown in Table A.1 at the end of the resting state functional Magnetic Resonance Imaging (rs-fMRI) scan, relating to their thoughts during this period. Answers were given on a 4-scale Likert scale ranging from "Not at all" to "Completely".

A.2 Physical and mental health questionnaires

Quality of life, physical and psychological health, social relationships and environmental well-being were measured by the World Health Organization Quality of Life WHOQOL-BREF instrument (Organization et al., 2012). Private and public self-consciousness and social anxiety were assessed using the Self-Consciousness scale (Scheier and Carver, 2013), state and trait anxiety by the State-Trait Anxiety inventory (Spielberger and Gorsuch, 1983) and trait rumination by the Ruminative response scale (Treynor et al., 2003). Finally, depression was measured using the CES-D scale (Radloff, 1977), autism by the Autism Spectrum Quotient (Baron-Cohen et al., 2001) and ADHD by the World Health Organization Adult ADHD Self-Report scale (Kessler et al., 2005).

Table A.1: Experience sampling questions asked at the end of the resting state fMRI scan.

Dimension	Question (My thoughts)
Vivid	... were vivid as if I was there
Normal	... were similar to thoughts I often have
Future	... involved future events
Negative	... were about something negative
Detail	... were detailed and specific
Words	... were in the form of words
Evolving	... tended to evolve in a series of steps
Spontaneous	... were spontaneous
Positive	... were about something positive
Images	... were in the form of images
Other	... involved other people
Past	... involved past events
Deliberate	... were deliberate
Self	... involved myself
Stop	... were hard for me to stop
Distant time	... were related to a more distant time
Abstract	... were about ideas rather than events or objects
Decoupling	... dragged my attention away from the external world
Important	... were on topics that I care about
Intrusive	... were intrusive
Problem solving	... were about solutions to problems (or goals)
Here and now	... were related to the here and now
Creative	... gave me a new insight into something I have thought about before
Realistic	... were about an event that has happened or could take place
Theme	... at different points in time were all on the same theme

Appendix B

Supplementary materials - Chapter 5

B.1 SI Results

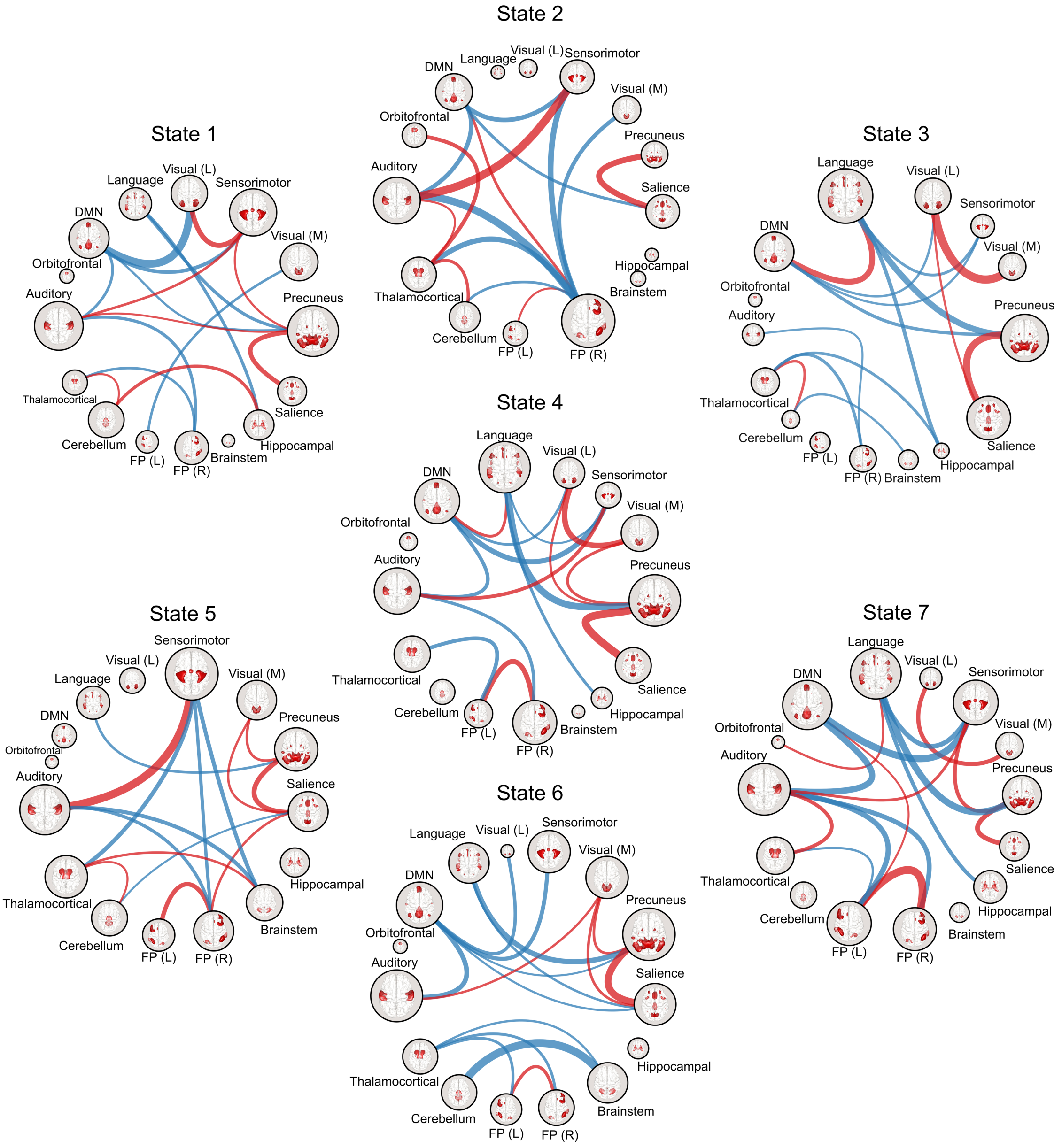

Figure B.1: *Dynamic HMM states.* Network circle graphs of all 7 states. The circle graphs were thresholded at the 85^{th} percentile of absolute correlation values for each state for visualisation. Red is for positive and blue for negative correlations and edge width is weighted by their absolute value. Node size represents the node's "strength", computed as the sum of the absolute correlation of each network with the rest of the brain.

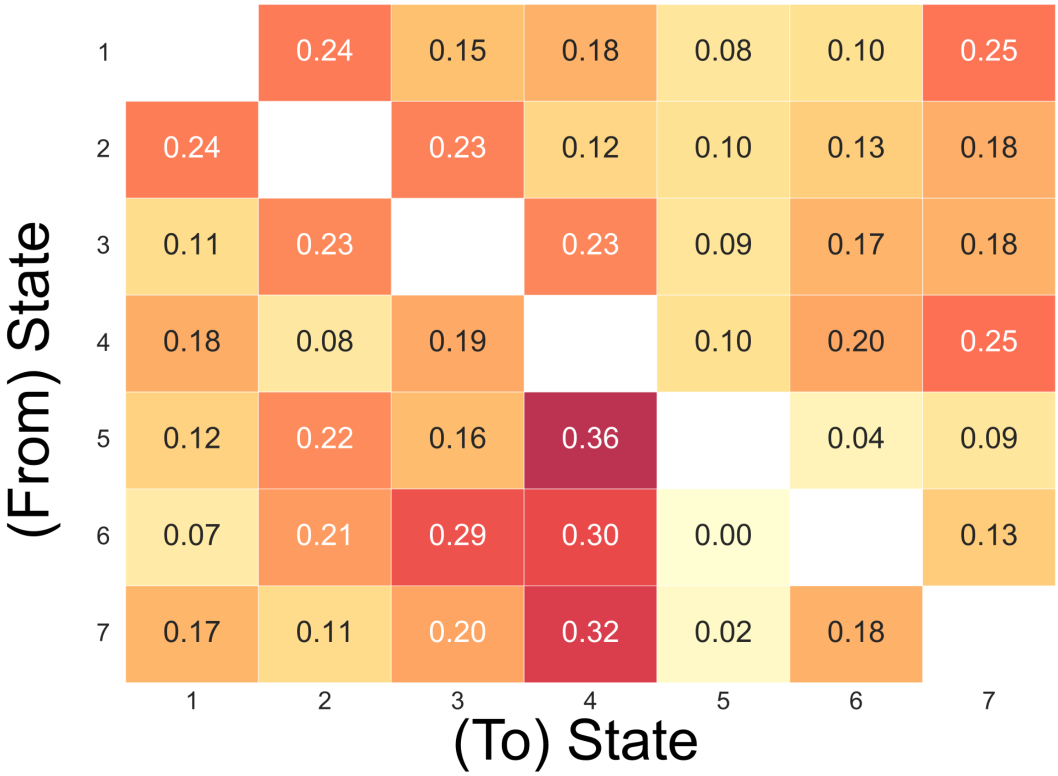

Figure B.2: *Transition probabilities.* The states' transition probabilities as a full asymmetric heatmap rounded to two-digit accuracy. The probabilities of staying in the same state (diagonal) are not shown.

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