The role of the default mode network in contextual control

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Preface

I declare that this dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration. Where reference is made to the work of others, the extent to which that work has been used is indicated. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

Data from the studies outlined in Chapter 4 and Chapter 5 have been published in a peer-reviewed journals. The references for these publications are as follows:

Smith V, Mitchell DJ, Duncan J. 2018. Role of the default mode network in cognitive transitions. Cerebral Cortex. 28, 3685-96.
Smith V, Mitchell DJ, Duncan J. 2019. The effect of rule retrieval on activity in the default mode network. NeuroImage. 116088.

The study outlined in Chapter 3 was done in collaboration with M Roca and C Pinasco, who designed the Hotel and Situations tasks, and C Pinasco and J Achterberg who collected the data with myself.

This dissertation does not exceed 60 000 words in length.

Verity Smith

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My supervisor, John Duncan, thank you for all your guidance throughout the last four years and for encouraging me to follow my research interests. My co-supervisor, Danny Mitchell, thank you for your endless patience in teaching me all I know about fMRI analysis. It's been a pleasure to discuss this project with both of you and learn from your insights and critiques.

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The role of the default mode network in contextual control

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While extensive theories outline the importance of meaningful context in guiding goal directed behaviour, little evidence has emerged about the underlying cognitive mechanisms involved. This thesis aims to addresses this gap in the literature by integrating two commonly disparate topics in neuroscience: cognitive control and the default mode network.

Chapter 2 considers why current studies of contextual control do not implicate DMN regions by comparing context-dependent decision making using rich, meaningful scenes, in comparison to arbitrary letter stimuli. DMN regions of the posterior cingulate cortex, parahippocampus and posterior inferior parietal cortex are found to show increased activity during decision making in the lifelike context only.

Chapter 3 asks whether regions beyond the 'task-positive' multiple demand network are necessary for adequate performance in more lifelike naturalistic tasks. This neuropsychology experiment used behavioural data accumulated from brain lesioned patients across a series of naturalistic tasks and a standard IQ task. Naturalistic tasks were found to capture control processes beyond IQ and multiple demand network function, most likely depending on many processes and brain regions.

Chapter 4 aims to understand to what extent the DMN contributes to non-spatial executive tasks. Replicating (Crittenden et al. 2015), DMN regions were found to represent the broader task domain and respond with greater activation to larger task switches and task restarts. A role for the DMN in transitions between distinct cognitive tasks is suggested.

Chapter 5 assesses an alternative explanation for the switch effects of the previous chapter. The fMRI experiment presented in this chapter asks whether the activation of the DMN at cognitive transitions reflects changes in task rule retrieval difficulty instead of degree of task switch. To this end, this study directly manipulated the rule retrieval demands. Contrary to the retrieval account, increased retrieval demand led to reduced DMN activity, accompanied by increased activation in MD regions.

Contents

Chapter 1

Introduction

OUTLINE

Spatial, semantic and social context is considerably helpful to everyday cognition. Context can help us to understand ambiguous sentences, to work out the meaning of a new word in the presence of learned words, and to understand a person's actions or feelings. The behavioural benefit of contextual information has been studied for many decades, particularly in memory recall and language comprehension (Zwaan and Radvansky 1998). Bransford and Johnson (1972) found that participants showed better understanding and more detailed recall of written passages when first read with a title encompassing the broad context of the passage compared to when read with no title available. Godden and Baddeley (1975) found that memory recall for word lists was more accurate for divers when the recollection phase was in the same context (underwater or on land) as the memory encoding phase where the word lists were first presented. Spivey et al. (2002) found that participants were able to use the visual context to parse syntactically ambiguous sentences such as 'Put the apple on the towel in the box' (see also Spivey and Tanenhaus 1998; Mirman 2008). The researchers found that if the participants could see an apple already on a towel, this visual context could override participants preferred sentence parsing (that the towel was in the box) in favour of moving the apple on top of a towel to an empty box. These studies therefore suggest that representations of our surroundings can influence our understanding of ongoing events.

Many theories also suggest contextual knowledge is important in guiding goal-directed behaviour. These theories suggest that contextual information, built up through repeated experiences in similar contexts, can be used to guide future behaviours by representing situational constraints and simulating common courses of events (Bar 2007, 2009; Zacks et al. 2007; Ranganath and Ritchey 2012). Levels of contextual representation can include very generalised (semantic) information (e.g. you must be quiet in libraries), to more specific knowledge of a particular place (e.g. in the study room of this library you can talk quietly) or episodic knowledge of a specific event (e.g. at this library open day you can talk).

Despite extensive theories outlining the importance of meaningful context in guiding goal directed behaviour, little evidence has emerged about the underlying cognitive mechanisms involved. This thesis aims to addresses this gap in the literature by integrating two commonly disparate topics in neuroscience: cognitive control and the default mode network. Cognitive control refers to the executive process influencing cognition in accordance with ongoing goals and is commonly associated with a network of lateral frontal and parietal regions (Duncan and Owen 2000; Duncan 2010, 2013). The default mode network (DMN) is a network of functionally connected brain regions most commonly associated with scene, episode and situational context representation in internally generated thoughts (Buckner and Carroll 2007; Hassabis and Maguire 2007; Buckner et al. 2008). Despite being often found to be negatively related to task control (Fox et al. 2005a; Kelly et al. 2008) its role in contextual representation marks its potential importance in contextual control.

THE DEFAULT MODE NETWORK

The DMN is one of the most well established brain networks, with its emergence consistently replicated through functional connectivity (Greicius et al. 2003, 2009; Fransson and Marrelec 2008; Spreng et al. 2013; Liang et al. 2016), structural connectivity (Greicius et al. 2009; Khalsa et al. 2014; Yin et al. 2016) and univariate activity (Raichle et al. 2001; Andrews-Hanna et al. 2010; see Spreng et al. 2009 for a meta-analysis). It is most commonly found to include posterior medial cortex (posterior cingulate cortex, precuneus and retrosplenial cortex), anterior medial prefrontal cortex, posterior inferior parietal lobe, parahippocampus, hippocampus, temporal parietal junction and middle lateral temporal lobes. More recent findings have also suggested the DMN may be split into core regions and two sub-networks (Andrews-Hanna et al. 2010; Yeo et al. 2011). Andrews-Hanna et al. (2010) used hierarchical clustering analysis on task-based and resting-state functional connectivity fMRI data, revealing a highly connected core network of posterior cingulate cortex (PCC) and anterior medial prefrontal cortex (amPFC) as well as a Medial Temporal subsystem and a Dorsal Medial subsystem (see Figure 1.1a). The Medial Temporal subsystem including parahippocampus (PHP), hippocampal formation (HF), retrosplenial cortex (Rsp), posterior inferior parietal lobe (pIPL) and ventromedial prefrontal cortex (vmPFC). The Dorsal Medial subsystem included regions of the dorsomedial prefrontal cortex (dmPFC), temporo-parietal junction (TPJ), lateral temporal cortex (LTC), and temporal pole (TempP). Strong functional connectivity between subnetwork regions and core DMN has been proposed to allow efficient transmission of information across subnetworks via core DMN hubs. Similar DMN subdivisions were further uncovered in a large-scale brain parcellation by (Yeo et al. 2011). Using resting state functional connectivity MRI data in a sample of 1000 participants, the researchers used clustering techniques to identify a 7 network solution which

included the DMN. In a further finer-grained analysis, a 17 network solution was uncovered which further divided the DMN into 3 sub-networks. As shown in Figure 1.1b, this approach revealed similar subnetworks to Andrews-Hanna et al. (2010) with a few differences within each subnetwork. Firstly, the vmPFC was not classified within the DMN network but a limbic network instead. Secondly, Yeo et al. (2011) found that the DM subsystem also included some lateral prefrontal regions and was left lateralized, while the core network also included the angular gyrus and right anterior temporal lobe.

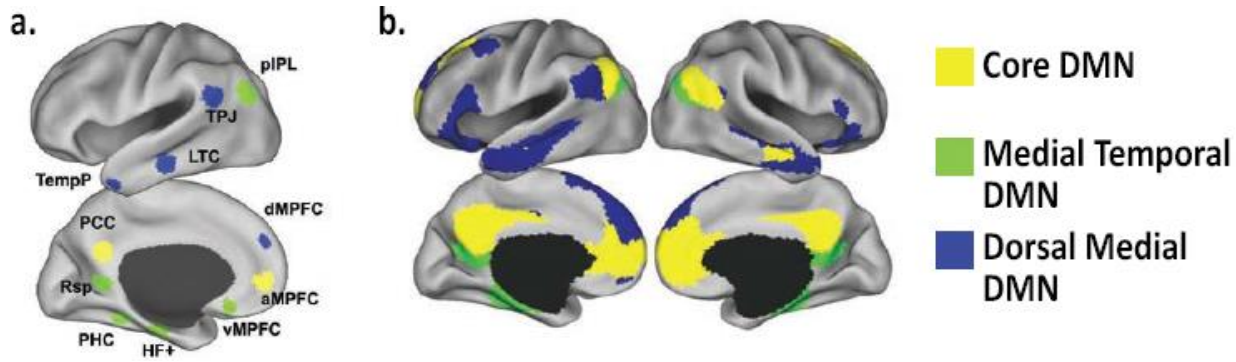

Figure 1.1. Proposed DMN Subnetworks from a. Andrews-Hanna et al. (2010) and b. Yeo et al. (2011). Figure adapted from Andrews-Hanna et al. (2014). PCC = posterior cingulate cortex, aMPFC = anterior medial prefrontal cortex, Rsp = retrosplenial cortex, PHC = parahippocampal cortex, HF+ = hippocampal formation, vMPFC = ventromedial prefrontal cortex, pIPL = posterior inferior parietal lobe, TempP = temporal pole, LTC = lateral temporal cortex, TPJ = temporo-parietal junction, dMPFC = dorsomedial prefrontal cortex.

Early research looking at DMN activations characterised the DMN as 'task-negative', finding reductions in activity during many externally-focused tasks in comparison to rest or easier versions of the same task (Shulman et al. 1997; McKiernan et al. 2003, 2006). DMN activity has instead been associated with off-task thinking or mind wandering during external task performance (McKiernan et al. 2006; Mason et al. 2007; Christoff et al. 2009). For example, using an event sampling technique, Christoff et al. (2009) found stronger DMN activation immediately before thought probes where participants indicated off-task thoughts compared to before thought probes indicating on-task cognition. These inter-trial increases in DMN activity during external task performance have also been linked to attention lapses and negative effects on performance (Weissman et al. 2006). In line with these findings of task-related deactivations and associations between DMN activity and poor performance, the DMN has often been found to be negatively correlated with regions associated with on-task executive function (Fox et al. 2005a; Kelly et al. 2008; Uddin et al. 2009; Newton et al. 2011). As such, early research suggested the DMN was a 'task-negative' network, preferentially active during a default state of rest.

Since these initial findings, the DMN has been implicated in a number of different tasks, indicating its role in representing scenes, episodes and contexts. In an influential meta-analysis using the activation likelihood estimation approach, Spreng et al. (2009) found extensive overlap in voxels active in episodic (autobiographical) memory retrieval, social cognition (measured by Theory of Mind tasks), navigation and the DMN, as presented in Figure 1.2. These findings were replicated by Spreng and Grady (2010) who also found common neural activation during cognitive processes involved in social cognition, episodic memory retrieval and future episodic simulation within the same 16 participants.

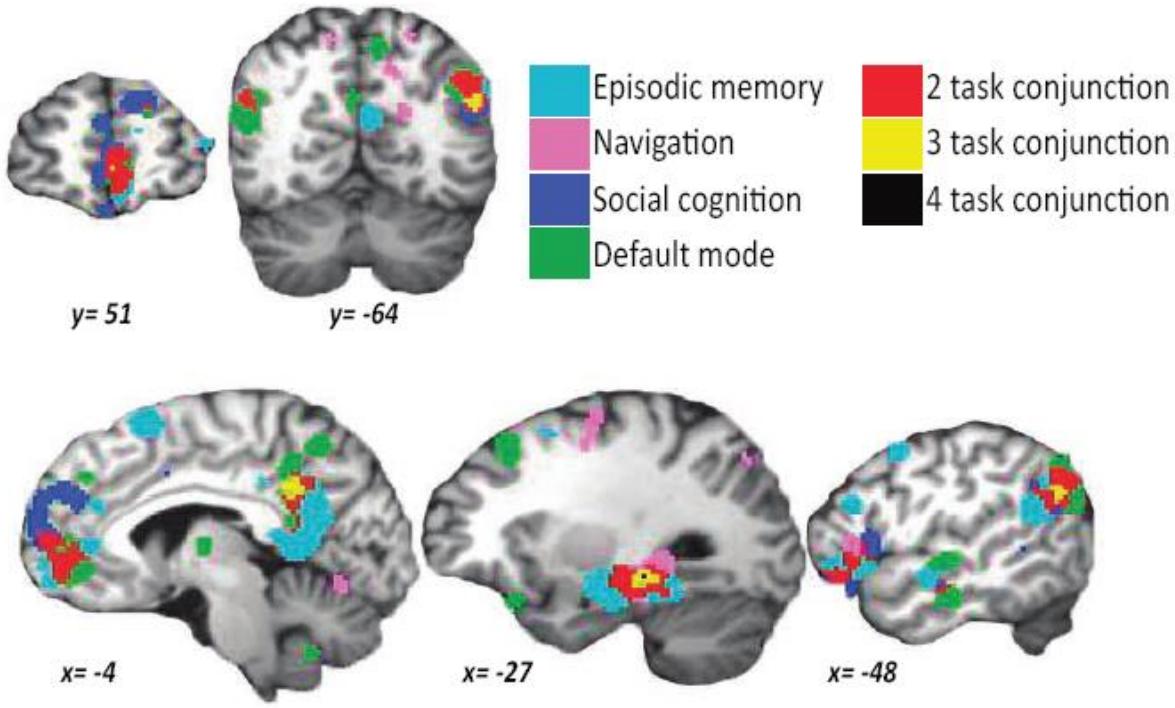

Figure 1.2. Results of Spreng et al. (2009) activation likelihood estimation (ALE) meta-analysis for each term (episodic memory, navigation, social cognition and default mode) and their conjunction. Figure adapted from Spreng et al. (2009). MNI coordinates presented for slices.

Social Cognition

Social cognition, or mentalizing, refers to the ability to infer someone else's thoughts, feelings and emotions. This ability is often tested using false belief (Theory of Mind) tasks. In these tasks (see Figure 1.3) participants are presented with scenarios where the subject of a story has a belief which is at odds with the current reality. Participants are asked to infer the subject's false belief in order to predict their actions. Neuroimaging studies have revealed DMN involvement in a number of social cognition tasks including false beliefs, moral judgements, person perception and self-knowledge tasks (Fletcher et al. 1995; Greene et al. 2001; Frith and Frith 2003; Amodio and Frith 2006; Gilbert et

al. 2007). In one of the first imaging studies to research the neural basis of social cognition, Fletcher et al. (1995) presented participants with stories in which one of the characters acts in line with their false beliefs. In comparison to reading unlinked sentences, medial prefrontal, posterior medial and the superior temporal sulcus showed increased activations when reading the stories. Further studies with more stringent baselines have also implicated these regions as being particularly active when participants were asked to make judgements about other people's beliefs (see Frith and Frith 2003 for a review).

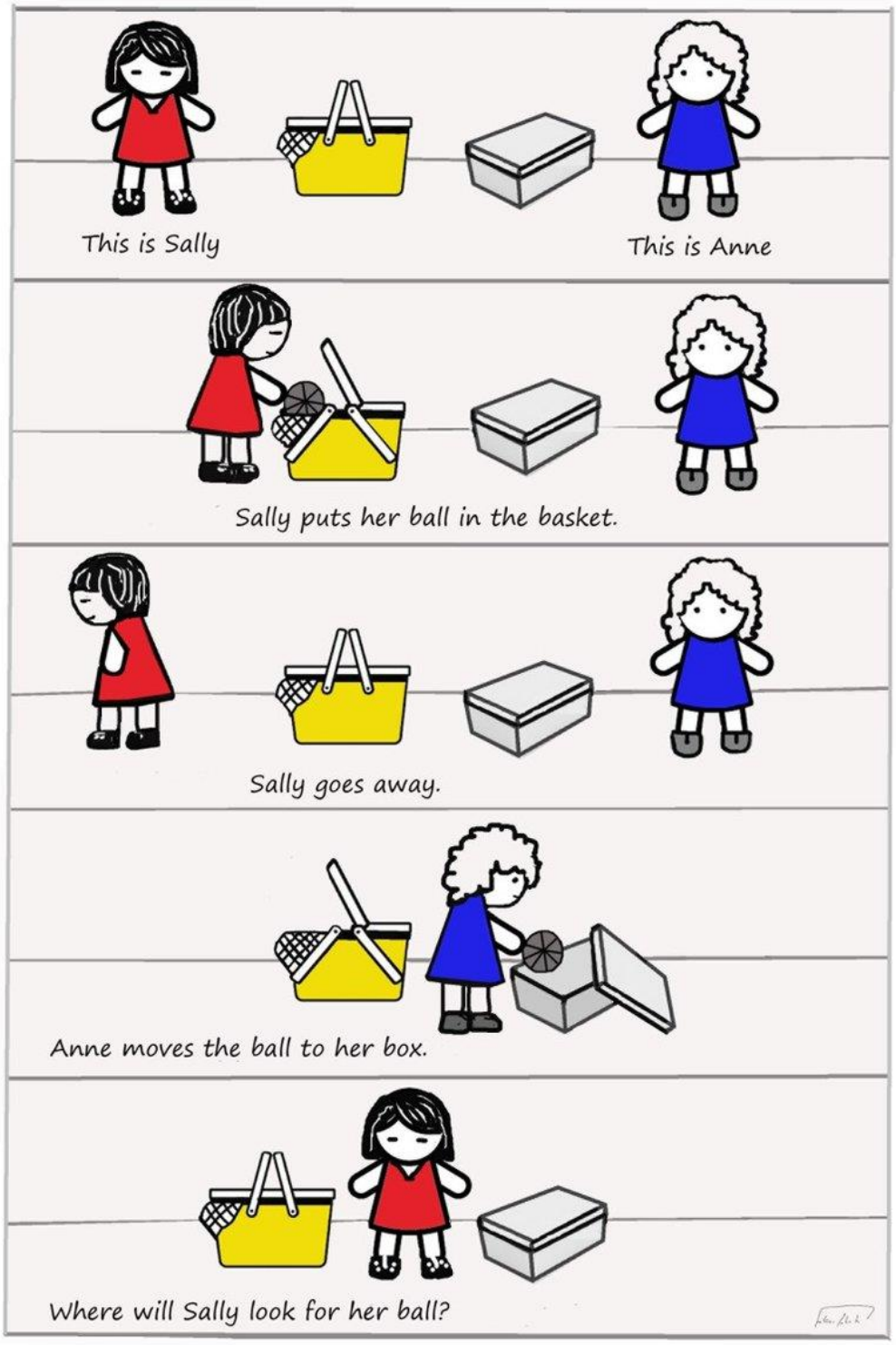

Figure 1.3. The Sally-Anne false belief Task. Image from Felisberti and King (2017).

Within the DMN, social cognition has been particularly related to lateral temporal, temporo-parietal junction and dorsal medial prefrontal regions. Using automated meta-analytic software (NeuroSynth), Andrews-Hanna et al. (2014) found meta-analyses maps for social cognition terms such as 'mentalizing', 'theory of mind' and 'social' were particularly strongly related to the Dorsal Medial subsystem of the DMN. Similarly Kumaran and Maguire (2005) found dmPFC and core DMN

regions were strongly related to social cognitive processes. In a novel task the researchers asked participants to work out how to get a case of wine from Friend A to Friend B by exchanging the wine through as many other friends as possible. In the social condition, participants could only exchange wine between their friends who knew each other. In the spatial condition the case of wine had to be passed closer and closer to the goal location (Friend B's house) via other friend's houses. Despite no significant behavioural differences between the two conditions, the researchers found increased activity in core DMN, dmPFC, vmPFC, superior temporal sulcus and the temporal poles when directly comparing the social condition to the spatial condition.

Episodic Memory

As was made famous by amnesic patient HM, the medial temporal lobe is known to play a fundamental role in episodic memory encoding and retrieval (Scoville and Milner 1957; Penfield and Milner 1958; Corkin 2002). HM had a bilateral medial temporal lobectomy, in order to cure his epilepsy, incurring lesions to the hippocampus, parahippocampus, amygdala and entorhinal cortex bilaterally. His surgery left him with a striking impairment in forming new memories (anterograde amnesia) and, to a lesser extent, recalling pre-surgery events (retrograde amnesia). HM showed severe anterograde memory deficits regardless of the domain of to-be remembered stimuli (words, sounds, pictures, personal events, and public events) and the type of memory test used (free recall, cued recall, multiple choice recognition). HM's retrograde amnesia, on the other hand, appeared to be temporally graded in that HM's memory impairment affected events from the three years prior to surgery but most of his memories before this period in time were intact. Despite such prolific memory impairments, HM's general intelligence and language were unaffected, if not improved by reduced epileptic symptoms (Scoville and Milner 1957). Intriguingly performance on short term memory tasks were also intact (Sidman et al. 1968; Corkin 1982) and HM also showed good visuomotor skill learning. Over repeated sessions HM was asked to trace a star while seeing only the mirror image of his drawing hand. Despite no memory or feelings of familiarity for any of the testing events, HM was able to show marked improvement on a mirror drawing task as well as other procedural learning tasks where an explicit knowledge of learnt events is unnecessary. Given these findings, researchers have suggested that these medial temporal regions are particularly important in forming new declarative memories and consolidating them into long term memory (Squire and Zola 1996).

Due to the severity of memory impairments in patient HM, most lesion and animal electrophysiology research in memory initially focused on medial temporal lobe regions. With the development of new neuroimaging methods, researchers have been able to further establish regions beyond the medial temporal lobe that are related to episodic memory. These studies tend to implicate DMN regions

within and beyond the medial temporal lobe in episodic memory retrieval (Lepage et al. 2000; Diana et al. 2007; Schacter et al. 2007; Vilberg and Rugg 2012).

Lepage et al. (2000) developed the idea of an episodic retrieval mode (REMO), a state where one is focused on holding a personal past event in mind and using external information to cue memory for specific details of the event. The researchers suggest that neural correlates of REMO should show increased activity for attempted retrieval regardless of retrieval success and as such, tested for a conjunction between brain regions active during successful item retrieval ('old' judgements) and unsuccessful item retrieval ('new' judgements) compared to a control task block in which there was no requirement for memory retrieval. The researchers identified activity in anterior medial frontal regions as well as the anterior cingulate cortex and frontal operculum related to attempted retrieval.

Other researchers have investigated the neural correlates of episodic memory by testing for regions associated with accurate memory for contextual details surrounding a cued event. In Hayama et al.'s (2012) source memory study participants were given two sets of 30 words to study. Each word started with a unique three-letter word stem. In the study phase words were presented to the left or right of the screen and participants were asked to make judgements about the degree of abstractness of the words. At the test phase 90 three-letter word stems (60 studied, 30 new) were presented to the centre of the screen. Participants were asked to complete the word stem with the previously studies word (if possible) and, if the word had been previously studied, retrieve the position of the studied word. Hayama et al. (2012) found DMN regions of the anterior medial prefrontal cortex, parahippocampus, posterior medial cortex and posterior inferior parietal lobe were active for both successful (vs. unsuccessful) word recall and successful (vs. unsuccessful) word position retrieval, implicating the DMN regions in successful memory for episodic details of an event.

Tulving (1985) outlined three key properties of episodic memory: a subjective sense of time (a feeling of mental time travel), connection to the self (self-relevance), and autonoetic consciousness (the cognitive ability to mentally project oneself to an imagined time and place). Particularly supporting these ideas, DMN regions have been found to show increased activity with increased self-relevance and vividness of the remembered episode, and subjective reliving of an event (Andrews-Hanna et al. 2010; St. Jacques et al. 2011; Richter et al. 2016). D'Argembeau et al. (2005) further found dorsomedial prefrontal, ventromedial prefrontal, middle temporal gyrus and temporal pole regions were particularly active whilst engaging in self-referential reflections. In accordance with these ideas, Buckner and Carroll (2007) have argued that self-projection, or imagining events from a first person perspective, may be the main function of the DMN.

Episodic Simulation

In line with the understanding of episodic memory retrieval as mental time travel to past events, much research has been carried out to test for neural overlap between episodic memory recall and episodic simulation of future events, which can be thought of as mental time travel to the future. As predicted, DMN regions have been found to be implicated in simulating both past episodes and future events as well as imaging events in the present (Addis et al. 2007, 2009; Szpunar et al. 2009; Andrews-Hanna et al. 2010). Addis et al. (2009) tested for neural overlap as well as differences in neural activation between recalling autobiographical past events and imagining autobiographical past and future events using spatiotemporal partial least squares analysis. On each trial Addis et al. (2009) presented participants with three cues corresponding to location, person and object details for three different past events, personal to each participant. With these cues participants were asked to either recall the cued details from each event or reimagine each of the cued details in a new event situated in the past or future. Confirming the hypothesis that autobiographical retrieval and construction involve overlapping cognitive processes, conjunction analyses showed neural overlap between these three conditions, relative to a sentence construction control, in DMN regions of posterior medial cortex, anterior medial prefrontal cortex, hippocampus, parahippocampus, middle temporal gyrus and posterior inferior parietal lobe. However, recollection was more associated with the hippocampus, parahippocampus and visual cortex, perhaps due to more rich visual imagery. In comparison, imagined events were more related to medial prefrontal cortex, anterior hippocampus, posterior medial cortex and inferior frontal gyrus, perhaps reflecting construction and integration processes.

Andrews-Hanna et al. (2010) further tested whether DMN regions were activated for imagining either self-relevant or non-self-relevant events in the present as well as the future by asking participants to make decisions concerning different scenarios varying in temporal situation and self-relevance. All DMN regions showed increased sensitivity for autobiographical decisions compared to non-self-relevant conditions. Unlike Addis et al. (2009), who found no differences in activity between events imagined at different points in time, Andrews-Hanna et al. (2010) found MTL subnetwork regions were preferentially active during future self judgements whereas dmPFC subnetwork regions were preferentially active during present self judgements. Extending these findings, the researchers found that several self-reported ratings explained the variance in activity in core and MTL subnetworks, suggesting some underlying contents of cognition that these regions are most involved in. Core DMN activity was particularly related to ratings of personal significance, self-introspection and evoked emotion, whereas the MTL DMN subnetwork was associated with episodic memory, event imagination and scene content ratings.

Hassabis et al. (2007a, 2007b), however, suggest that DMN regions are still necessary for detailed imagination of events that are not personally relevant or positioned in time. Hassabis et al. (2007a) asked 5 bilateral hippocampal lesioned patients with amnesia and 10 matched controls to imagine a new event based on a short verbal cue. Participants were then asked to describe the contents of their imagination and judge the degree of vividness. Their descriptions were also scored by researchers on the basis of information content, spatial coherence and overall quality. Although there was no significant difference between patient and controls on subjective judgements of vividness, patients scored lower in informational content, spatial coherence and quality. The researchers suggest that the hippocampus might be particularly important for setting up the spatial context in which further details of a scene can be bound. To check whether other regions beyond the hippocampus were also related to construction of imagined experiences, the researchers scanned healthy participants whilst undertaking a similar version of this task. In this fMRI version, participants were asked to imagine or remember scenes and objects. Hassabis et al. (2007b) found that, in comparison to object construction, during construction of imagined and recalled scenes there was increased activity in the hippocampus, parahippocampus, retrosplenial cortex, posterior cingulate cortex, posterior parietal cortex and anterior medial prefrontal cortex. However, in comparison to the recalled events, imagined events showed less activity in the core DMN regions.

In accordance with Hassabis et al. (2007a), Szpunar et al. (2009) suggest the key component driving DMN activation during event simulation is not self-relevance but context familiarity. The researchers asked 27 participants to imagine autobiographical events in a cued spatial context that had happened in the past or could happen in the future. In 24 of the trials participants were asked to imagine future events in an unfamiliar context (e.g. a hot air balloon) and in 48 trials participants were asked to either imagine future events or recall past events in familiar contexts. Whole brain analyses found increased activity in posterior medial cortex, parahippocampus, anterior medial prefrontal cortex and temporo-parietal junction for familiar remembering and imagining in familiar contexts compared to unfamiliar contexts.

Navigation

While amnesiac patient HM was most famous for having difficulties with episodic memory formation and retrieval, he was also found to show impairments in spatial navigation of new environments first experienced post-surgery (Scoville and Milner 1957; see also Spiers et al. 2001). Findings from animal lesion studies have continued to implicate posterior DMN regions in navigation. Lesions to the hippocampus, parahippocampus and retrosplenial cortex have been found to impair performance during radial arm maze and water maze tasks where the subject is required to navigate from memory

towards a rewarded spatial location or hidden platform (Logue et al. 1997; Vann and Aggleton 2002; Bohbot et al. 2006; Pothuizen et al. 2008).

The finding that these regions play a major role in spatial navigation has been extended by electrophysiology recordings in animals. O'Keefe and Dostrovsky (1971) first discovered the presence of place cells in the hippocampus of rats and since their initial finding, place cells have been identified in monkeys and humans (Ono et al. 1991; Ekstrom et al. 2003). Place cell populations characteristically fire at unique locations within an environment regardless of the orientation or trajectory of the animal, allowing for representation of one's allocentric spatial location in an environment. Furthermore, place fields have been found to be differently configured for distinct environments and remain stable in familiar environments for several weeks, suggesting the hippocampus can generate long-term memories unique to specific spatial contexts (Lever et al. 2002).

Location-sensitive cells have also been identified in another DMN region in the medial temporal lobe: the parahippocampus. In comparison to hippocampal place cells, place cells in the parahippocampus have much broader place fields and are more sensitive to changes in external environment (Burwell and Hafeman 2003). Results from imaging studies also suggest that the parahippocampus is particularly sensitive to the external visual properties of an environment. The parahippocampus has been found to show increased activity in response to pictures of scenes, places and landmarks compared to other visual stimuli (Epstein and Kanwisher 1998; Epstein et al. 1999; Janzen and Van Turennout 2004; Mullally and Maguire 2011). As such, a region within the parahippocampus has been termed the "Parahippocampal Place Area" (Epstein and Kanwisher 1998). In line with the findings from neuroimaging, patients with lesions to the parahippocampus have been found to show poor recognition of familiar rooms or buildings, termed landmark agnosia, despite maintaining the ability to draw accurate allocentric spatial maps (Landis et al. 1986; Takahashi and Kawamura 2002).

The retrosplenial cortex has also been found to contain neurons which encode information important for navigation. Chen et al. (1994) reported cells in the retrosplenial cortex of rats which showed selective preference for certain head orientations even in the absence of visual cues or when rats were in the dark. In line with an emerging role for the retrosplenial cortex in representing information about one's orientation, damage to the retrosplenial cortex in humans is associated with topographical amnesia. Topographical amnesia is a condition which is associated with a poor ability to orient oneself by visual landmarks despite preserved scene perception (Aguirre and D'Esposito 1999; Epstein 2008).

According to the cognitive map theory (O'Keefe and Nadel 1978), and the model presented in Byrne et al. (2007), the hippocampus is important in representing an allocentric, spatially coherent world, given visual inputs from the parahippocampus and orientation information from the retrosplenial cortex. These allocentric maps are thought to be translated into a first person perspective with the aid of heading information from head direction cells in the retrosplenial cortex. The resulting egocentric scene is proposed to be represented in the posterior cingulate cortex. This translation of stored allocentric spatial information into an egocentric image has been suggested to be important for simulating an upcoming journey during navigation but also constructing a spatial environment during episodic simulation (Bird and Burgess 2008; Ranganath and Ritchey 2012).

In line with findings from electrophysiology, imaging studies also find activity in posterior DMN regions related to spatial navigation (Spiers and Maguire 2007; Howard et al. 2014; Javadi et al. 2017, 2018). Howard et al. (2014) asked participants to navigate around London's Soho district. Increased activation in many DMN regions was found during the active navigation condition compared to the passive control condition which kept the same visual background but did not require participants to navigate from memory. Regions of the posterior medial cortex and medial temporal lobe also showed strong activity at decision points (when participants had to choose which road to turn down). Interestingly, the posterior hippocampus appeared to code path distance to goal, showing greater activity during travel periods further from goal than closer to the goal. Furthermore, in a similar paradigm, Javadi et al. (2017) found that after entering a new street the posterior hippocampus showed increased activity to increases in the number of upcoming routes available. The researchers suggest that the posterior hippocampus might be simulating all upcoming routes and therefore showing increased activation when the number of route available increased.

Further imaging studies suggest other regions of the DMN are also related to spatial navigation. Balaguer et al. (2016) found the ventromedial prefrontal cortex and hippocampus coded distance to goal with these regions showing increased activity the closer to goal (although this ramping of DMN activity at the end of a trial may not be specific to spatial navigation, or to the DMN, see Farooqui and Manly 2018). Patai et al. (2019) scanned participants during virtual navigation through newly experienced university campuses and frequently visited university campuses with which participants had a minimum of 2 years' experience. The researchers found that navigation through the newly learnt campus was associated with a map-like representation of space and related to hippocampal encoding of distance to goal. In contrast, navigation though the well-known campus was found to be more associated with egocentric experiences and in this case, the retrosplenial cortex was found to code distance to goal. These findings may link well to the model presented by Byrne et al. (2007) suggesting medial posterior regions are important for translating spatial information into an

egocentric perspective whereas the hippocampus is more important for establishing an allocentric map of space.

While the Spreng et al. (2009) meta-analysis showed great overlap between regions related to episodic memory, social cognition and navigation, it should be noted that most studies of spatial navigation do not implicate the Dorsal Medial subnetwork of the DMN. Indeed, when contrasting activity during spatial and social tasks, Kumaran and Maguire (2005) found the Rsp, PHP, and pIPL were more active during the spatial version compared to the social version of the wine task (described above) marking the Medial Temporal DMN subnetwork as especially important in spatial navigation. These regions were also more active during a spatial control task, asking participants to assess the building type of different friends' houses, compared to a social task, where participants answered whether various friends wore glasses. These findings suggest that the MTL subnetwork of the DMN plays a role in spatial processing that is more general than just spatial navigation.

Broad Function of the DMN

How the DMN contributes to all these disparate cognitive processes is a subject of ongoing discussion. Consistent among all these tasks is the requirement for the construction of egocentric scenes or episodes from internal sources of information. As a result, the role of the DMN has been reconceptualised from a 'task-negative' network to having a main role in projection of oneself into an imagined scene (Buckner and Carroll 2007) or construction of a spatial context with which to bind social or episodic details (Hassabis and Maguire 2007). Some studies have attempted to differentiate between these theories, finding conflicting results. Hassabis et al. (2007a) found DMN activity related to imagination for scenes that are not self-relevant whereas Alzheimer's patient DB showed specific impairment in thinking about personal futures compared to imagining futures that were not self-relevant. Despite these differences, one commonality is the focus on internally constructed simulations, distinct from that of the current surroundings (Buckner and Carroll 2007; Buckner et al. 2008; Andrews-Hanna 2012).

This focus on internal scene representations has led researchers to overlook the simple possibility that the DMN also represents the current external context for context-guided cognition. With new multivariate methods, more recent studies have found a role for the DMN in representing the content of both externally perceived, recalled and imagined scenes and events (Baldassano et al. 2016, 2017; Chen et al. 2017; Robin et al. 2018). In Chen et al. (2017) participants watched a 50 minute episode of Sherlock and then immediately recalled the episode from memory in an MRI scanner. Average voxel activity for 50 independently labelled scenes was computed for each individual during the movie watching and movie recall phases. Using a spatial searchlight, the

researchers found that patterns of activity in posterior medial cortex, medial prefrontal cortex and parahippocampal cortex were more similar during watching and recall of the same scene compared to different scenes. Along with sensory regions, these regions also showed highly similar scene-specific patterns of activity between subjects during movie watching, indicating a role for DMN regions in perception of the current scene which is stable across participants. Furthermore, Baldassano et al. (2017) found activity patterns in the same data set were more stable across a longer time scale in several brain regions, including posterior DMN, compared to sensory regions, during both the movie watching and recall phases (see Figure 1.4). Medial prefrontal DMN regions were not included in the searchlight analysis. By defining reductions in cross-temporal correlations as neurally defined event boundaries, the researchers went on to compare neurally defined event boundaries from movie watching data with data when hearing an audio-description of the same movie and perceived event boundaries as judged by human observers. Compared to sensory regions, neural event boundaries from movie watching data in DMN regions of interest, the angular gyrus and posterior medial cortex, were found to better match with boundaries defined by human annotations and were consistent across movie perception modalities (watching and audio-narration). These findings led Baldassano et al. (2017) to suggest that the angular gyrus and posterior medial cortex represent a stable, gist-like representation of a scene (see also Simony et al. 2016).

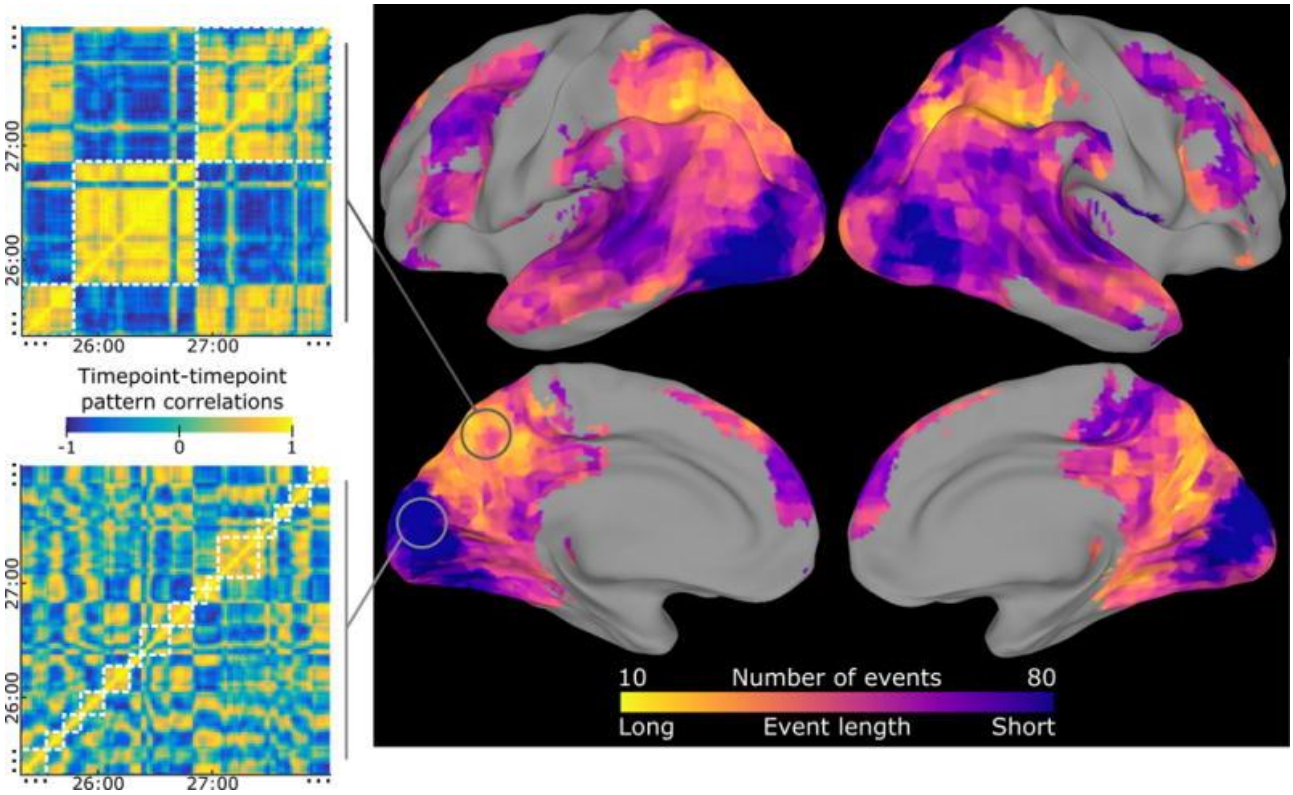

Figure 1.4. Figure from Baldassano et al. (2017). Results from a neural event segmentation searchlight from movie watching data in cortical regions with high between-subject correlation (Chen et al. 2017). The optimal number of events found, as tested using a Hidden Markov Model, were

found to vary throughout the cortex. Early sensory regions optimally divide the movie into greater numbers of short events (purple regions) and higher multimodal cortex divide the movie into fewer numbers of long events (yellow regions). Events here are defined as periods of similarity in cross-temporal correlation. Example cross-temporal pattern correlations during movie watching for long timescale events and short timescale events are presented from posterior medial cortex (top) and early visual cortex (bottom), respectively.

In keeping with these findings, Ranganath and Ritchey (2012) suggest that the DMN, particularly the parahippocampus, hippocampus and retrosplenial cortex, are important for the construction and representation of situation models. Situation models have been described as a mental representation of the current situational context (or schema) along with its social, semantic and temporal associative relationships. For example, the situation model for the event of studying with a friend at a library would hold information about the place of study (along with further locational information about libraries), the person you are with (along with further information about them and their connection to you), what you are doing and perhaps the temporal order of events leading up to the requirement to study. An example situational model, as described in Ranganath and Ritchey (2012) is presented in Figure 1.5. The researchers suggest that the parahippocampus is particularly important for identifying the current spatial context while the retrosplenial cortex integrates external information with stored associative information. The hippocampus has been proposed to integrate situational context with more specific details encoded in the perirhinal cortex and connected anterior temporal regions while the situation model itself is suggested to be represented in other regions of the DMN. The representation of this associative structure of the current context has been thought to be important for context-guided cognition and action by representing situational constraints and simulating common courses of events (see also Bar 2007, 2009; Zacks et al. 2007). According to these theories, the DMN should therefore be fundamental for context-dependent decision making.

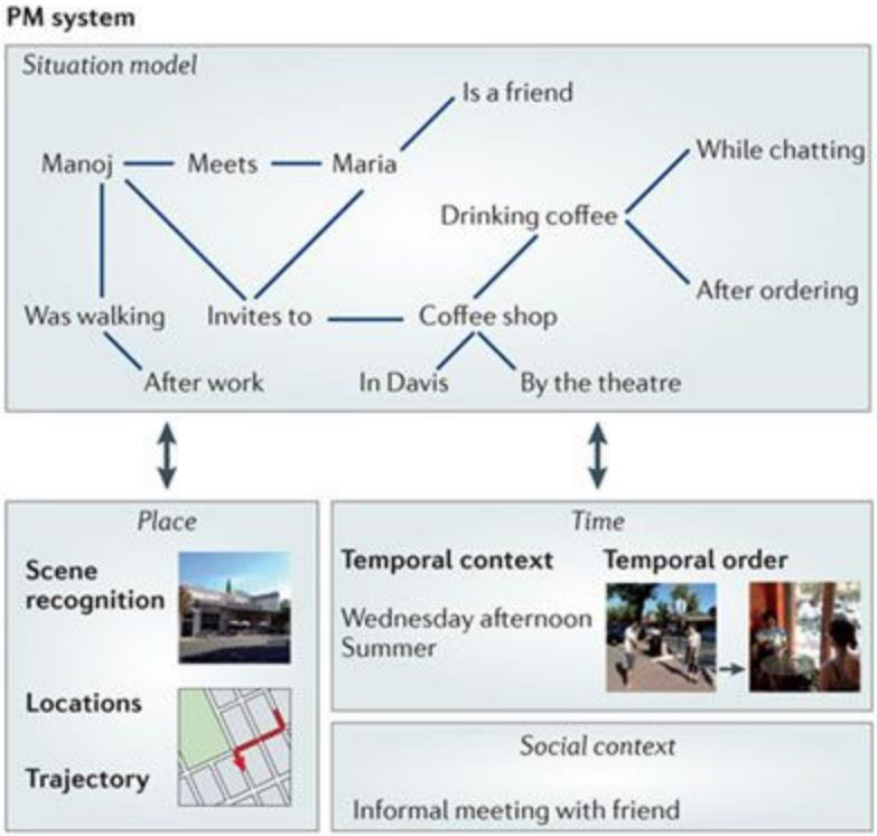

Figure 1.5. Figure from Ranganath and Ritchey (2012) displaying the associative spatial, temporal and social information proposed to be represented in the posterior medial (PM) system, closely overlapping with posterior DMN regions, in the event of having coffee with a friend after meeting them in the street. The situation model represents associative links including the sequence of events and spatial trajectory, semantic information about Maria (a friend), spatial information about the coffee shop (by the theatre in UC Davis) and the overall social context (an informal meeting).

CONTEXT-DEPENDENT DECISION MAKING

Despite the relation between DMN and context representation, the role of the DMN in context-dependent decision making is far from well established. Studies aiming to understand the neural basis of context-dependent decision making have mainly used arbitrary cues as substitutes for life-like contextual control. In one such task, Koechlin et al. (2003) compared brain activity between 3 different levels of cognitive control with increasing levels of rule abstraction. The experimental design is presented in Figure 1.6. In the Sensory Control condition, button presses were cued by stimulus colour (i.e. colour-response trials). In the Contextual Control condition, participants were asked to make either vowel/consonant or uppercase/lowercase judgements based on the colour of

the presented letter (i.e. colour-feature-response trials). In the Episodic Control condition, colour-response mappings were not fixed but were cued at the start of each block so participants were required to keep in mind temporally abstract information (i.e. the start of block cue-colour-response). The experimenters also designed control blocks for each experimental condition also presented in Figure 1.6. Comparing experimental block to control block activity, Koechlin et al. (2003) implicated the dorsolateral prefrontal cortex, not DMN regions, in contextual control, with the more anterior inferior frontal sulcus implicated in episodic cognitive control and more posterior regions of the premotor cortex associated with sensory control. Furthermore, using effective functional connectivity methods the researchers suggested a direction of information transfer from the anterior frontal regions to posterior regions.

Since this original study, similar cognitive control gradients have also been found in a number of different studies manipulating different types of task complexity (Badre and D'Esposito 2007, 2009; Race et al. 2009; Badre and Nee 2018). Although the specific regions identified in contextual control vary across these experiments (Badre and Nee 2018), a lack of DMN contextual control related activity is common across them all. In fact, the lateral prefrontal regions identified in these cognitive control tasks fall within another well-established brain network; the multiple demand (MD) network (Duncan 2010, 2013).

Importantly for this thesis, Badre and Nee (2018) now suggest a difference between 'contextual control', associated with the dorsolateral prefrontal cortex in the MD network, and 'schematic control'. Schematic control refers to generalised knowledge gained after repeated experiences and is suggested to be related to the anterior prefrontal cortex and ventromedial prefrontal cortex in the DMN. The extent to which the DMN and MD network contribute to cognitive control processes in naturalistic contexts which include both schematic and more context-specific information is, as yet, an unanswered question in the field.

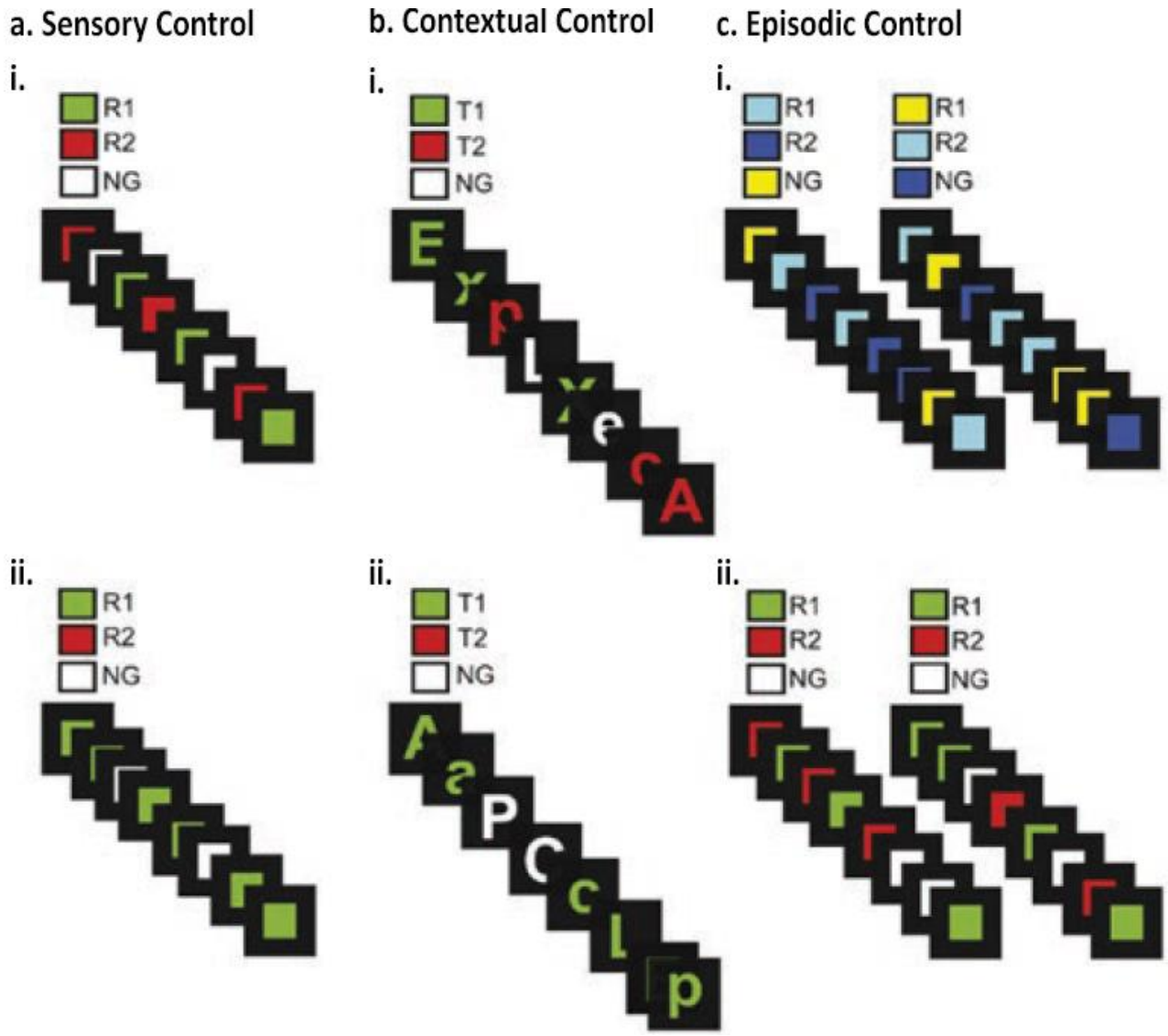

Figure 1.6. Hierarchical cognitive control experimental design, adapted from Koechlin and Summerfield (2007). *In Sensory Control trials (ai.) respond using different button presses (R1 and R2) depending on the colour of stimuli with participants asked to make no response (NG=no go) to white squares. In Contextual Control trials (bi.) the colour of the letters represents the task (T1 and T2, vowel/consonant judgement and upper/lowercase judgement) with white letters reflecting a no-go (NG) trial. Episodic Control trials (ci.) were similar to the Sensory Control task where button presses and no-go trials (R1, R2 and NG) were cued by colour of stimulus but the colour-response mappings were not fixed but dependent on a cue prior to the block of episodic control trials. ii. Control tasks used for each executive control condition.*

THE MULITPLE DEMAND NETWORK

The MD network is a set of highly connected frontoparietal regions including parts of the inferior frontal sulcus, dorsal prefrontal cortex, inferior frontal junction, anterior insula, presupplementary motor area and intraparietal sulcus (often accompanied by activity in lateral occipital cortex). Some researchers suggest that the MD system can be further subdivided into a frontoparietal network (FPN) containing lateral frontal and parietal MD regions, and the cinglular-opercular, or salience network (SN) containing the anterior insula and presupplementary motor area and sometimes anterior frontal cortex (Dosenbach et al. 2006, 2007, 2008; Seeley et al. 2007; Crittenden et al. 2016). A map of canonical MD regions is presented in Figure 1.7. While resting-state functional connectivity analyses have typically found these regions to be highly temporally correlated (Seeley et al. 2007; Vincent et al. 2008), this network is most typically defined from univariate task activations. These frontoparietal regions have been consistently linked to task demand in a diverse range of executive tasks including working memory, response inhibition, executive planning, memory span and fluid intelligence (Duncan and Owen 2000; Duncan et al. 2000; Duncan 2006; Bishop et al. 2008; Fedorenko et al. 2013; Assem et al. under review). In Fedorenko et al. (2013) 40 participants were scanned whilst performing a selection of seven different tasks testing language, arithmetics, response inhibition and spatial and verbal working memory. The tasks were presented in a blocked design with participants tested on hard and easier versions of each task in order to assess activity related to cognitive demand. One of the tasks performed by all participants was used to localise MD voxels in each subject. Activation for the hard vs. easy contrasts in all other tasks was found to overlap with voxels sensitive to the localiser. Uniquely, only voxels within MD regions, and not neighbouring language selective regions, showed consistent sensitivity to the difficulty contrast.

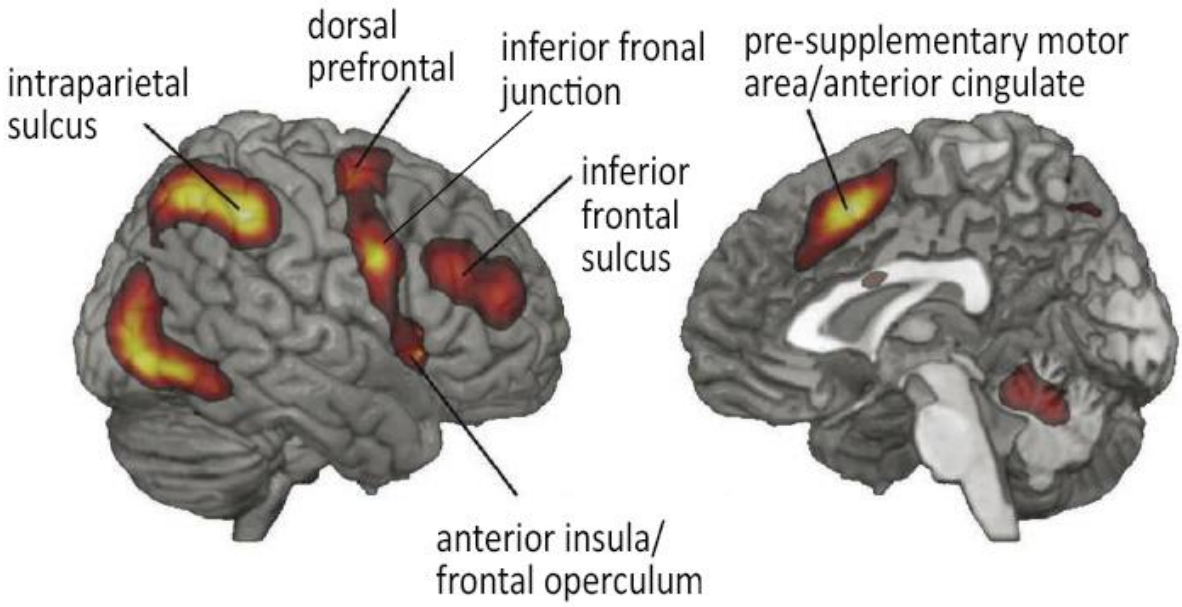

Figure 1.7. MD network regions from group-level hard vs. easy contrasts across all seven tasks in Fedorenko et al. (2013). The map presented was made symmetrical across hemispheres by averaging across hemispheres and thresholding the map at t = 1.5.

Further evidence from the neuropsychology literature demonstrates the necessity of MD regions for good cognitive function. Woolgar et al. (2010, 2018) tested 80 patients with focal brain lesions on a fluid intelligence task, the Cattell Culture Fair (Cattell 1971). This fluid intelligence measure contained four timed tasks including series completion, finding the odd-one-out, matrix judgements and topological relations. Cattell performance has been found to be predictive of task performance on a number of executive tasks (Roca et al. 2010, 2011; Duncan et al. 2012) and is thought to be a robust measure of executive function. Woolgar et al. (2010, 2018) found that patient MD lesion volume, but not total lesion volume or lesion volume in language specific regions, was negatively related to fluid intelligence scores.

The properties of MD regions are perhaps most clearly understood in studies of single unit activity in monkeys. These studies find a large percentage of neurons in lateral prefrontal cortex and intraparietal sulcus that selectively and flexibly code for a wide range of task-relevant information including target stimulus identity and location, response, reward and task rules (Rao et al. 1997; Duncan et al. 2000; Freedman et al. 2001; Freedman and Assad 2006; Roy et al. 2010). For example, in Roy et al. (2010) monkeys were trained to make orthogonal categorisation decisions on a single stimulus set depending on the colour of cue preceding the trial (see Figure 1.8). Separate populations of prefrontal neurons were found to show category selectivity with stronger categorical responses measured when that dimension was relevant in the current trial. Further research has also shown that task selective coding in prefrontal cortex dynamically changes throughout a trial (Rao et al. 1997; Kusunoki et al. 2009; Stokes et al. 2013).

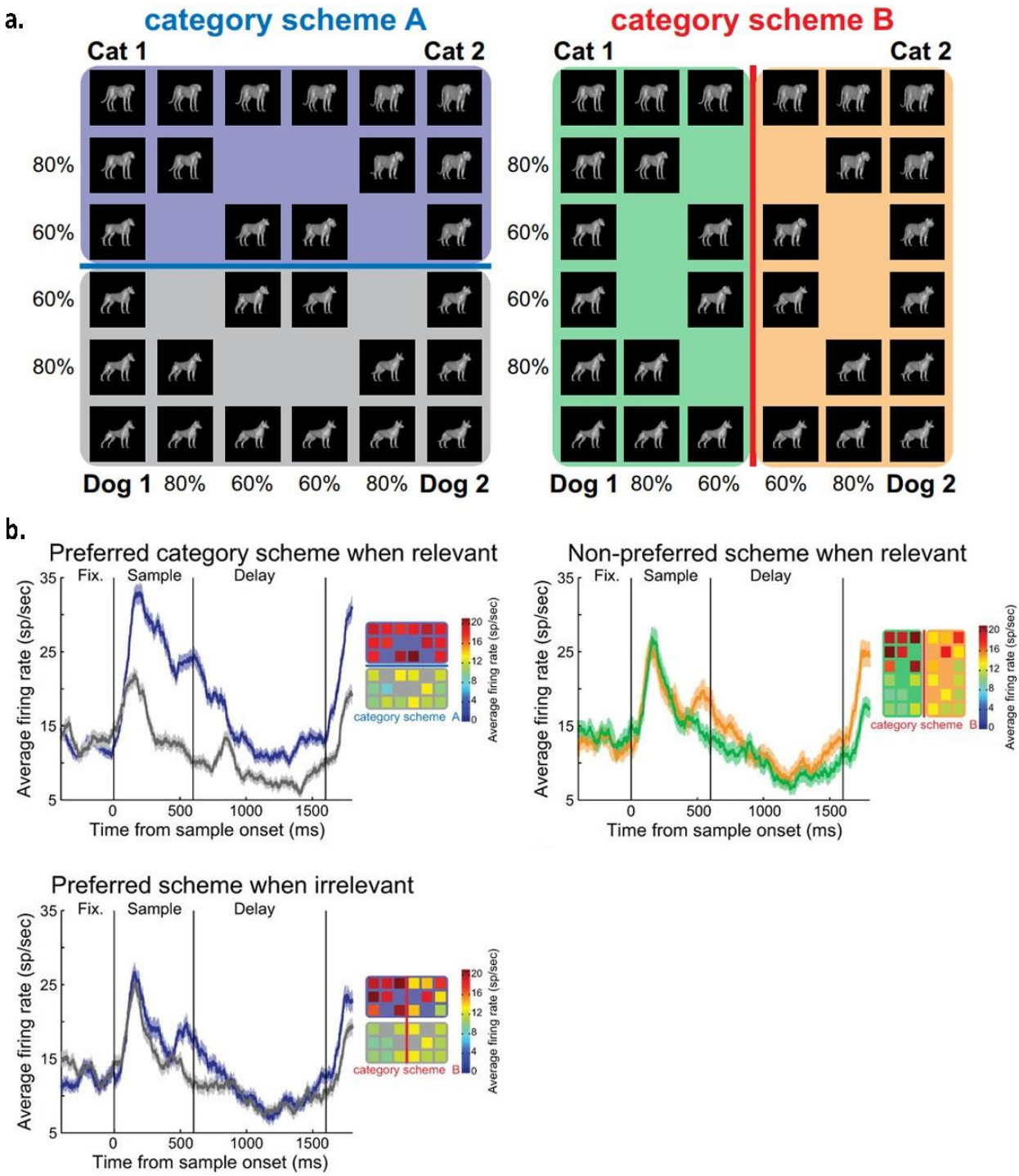

Figure 1.8. a. The stimulus set presented in Roy et al. (2010), grouped according to each category decision. The stimulus set was comprised of morphed images of cats and dogs of two different types. Each of the corner stimuli represent prototype cats and dogs while stimuli in between represent mixtures. Category scheme A was cat/dog, category scheme B was type 1/2. b. Responses of an example prefrontal neuron showing category sensitivity. The neuron specifically distinguishes between cats and dogs (showing greater activation for cats) but only when that is the relevant category decision.

Adaptive coding of task-relevant information has also been found in human MD regions in fMRI studies. Woolgar et al. (2011a) found that patterns of activity in MD regions could be used to discriminate between all task-relevant features in a simple stimulus location-response task including stimulus position, stimulus-response rule and response. Furthermore, Woolgar et al. (2011b) went on to establish that the degree of task-relevant feature coding was related to the level of task demand. At low levels of perceptual difficulty in identifying object location, patterns of activity in MD regions did not discriminate object location. However, at odds with visual discriminability, in trials of high perceptual difficulty, MD regions did discriminate object location. These findings suggest that the greater univariate activity in the MD system during more demanding tasks may reflect adaptive coding of task features most challenging for task completion.

Given the importance of MD regions across such a diverse range of task demands, Duncan (2010, 2013) suggests that the core function of the MD system is to control complex behaviour in line with current task goals. This function is thought to be achieved through decomposition of abstract goals into achievable sub-goals (Christoff et al. 2001; Bhandari and Duncan 2014), selective coding of information relevant to the current sub-goal (Duncan 2001), and influencing selection bias in other brain systems to process task-relevant information (Desimone and Duncan 1995; Stokes et al. 2009).

DMN AND MD IN 'EXTERNAL' TASK-RELATED COGNITION

As discussed above, the MD system has been found to be important for task control and the DMN has been implicated in representing context. Given these findings it seems plausible that both networks would work together during real-world contextual control. Historically, however, the DMN and MD network have been found to be negatively related.

As described previously, in univariate analyses of demanding external tasks, MD regions show increases in activity with increased task demand (Fedorenko et al. 2013) whereas DMN regions show the opposite pattern of task related deactivations (McKiernan et al. 2003, 2006). Functional connectivity studies have also been used to assess the relationship between these two networks. Using resting state functional connectivity Fox et al. (2005a) found that 'task-negative' regions (anterior medial prefrontal, posterior cingulate and posterior inferior parietal lobe) and 'task-positive' regions (dorsolateral prefrontal, inferior parietal sulcus and middle temporal region) as defined using peak coordinates from previously published data, were negatively correlated. Kelly et al. (2008) further established that the strong negative correlation between these 'task-negative' and

‘task-positive’ regions in each subject during the Eriksen flanker task was associated with low intra-subject variability in task reaction times. Given that intra-subject variability has also been found to be negatively related to general intelligence (Jensen 1992), the researchers suggest that a competitive relationship between MD and DMN regions is important for good task performance. In accordance with this proposal, Newton et al. (2011) found that the degree of negative correlation between ‘task-positive’ and ‘task-negative’ regions, which closely reflect MD and DMN regions respectively, strengthened with increased task load. Cole et al. (2012) further highlighted the importance of these negative correlations between DMN and task-positive regions in task performance. The researchers tested the connectivity strength, during an N-back task, between networks defined through meta-analyses of network names (e.g. “Default Mode Network”) with the lateral prefrontal cortex whose activity was found to predict N-back performance. The researchers found that the degree of negative correlation between DMN and the lateral prefrontal cortex was predictive of participant IQ as tested by the Cattell Culture Fair (“Institute for Personality and Ability Testing” 1973) and Raven’s progressive matrices (Raven 1981). In comparison, the strength of positive connectivity between cognitive control regions and lateral prefrontal cortex and the absolute strength of sensory-motor network connectivity with lateral prefrontal cortex was predictive of IQ (see Figure 1.9).

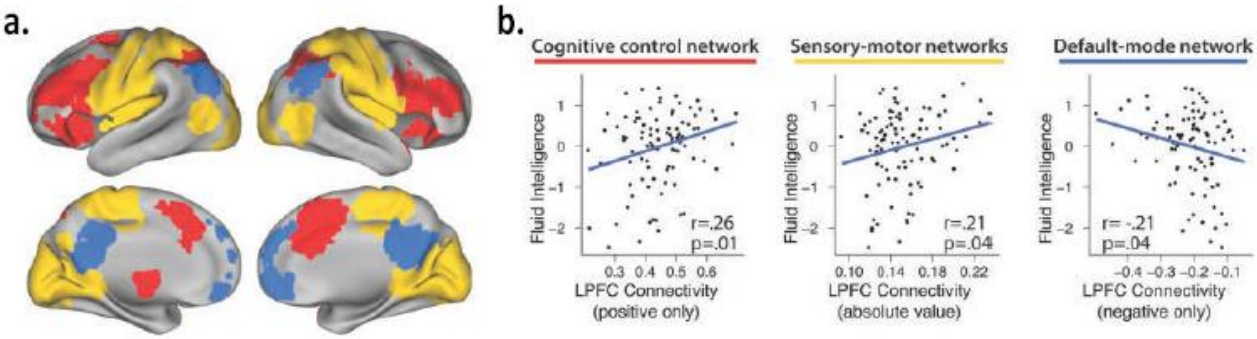

Figure 1.9. Regions of interest and correlation results from Cole et al. (2012). a. The network regions of interest as found through meta-analyses by using network names as search terms. Red = cognitive control network, yellow = sensory-motor network, blue = default mode network. b. Significant correlations between connectivity strength of networks with lateral prefrontal cortex vs. fluid intelligence score. Figure from Cole et al. (2012).

The above functional connectivity studies defined seed regions as ‘task-negative’ and ‘task-positive’ based on univariate activity from the same task or using pre-defined ‘task-negative’ and ‘task-positive’ regions of interest. More recent studies using whole brain network connectivity analyses to define DMN and MD on the basis of connectivity alone, also confirm the negative relationship between DMN and MD regions, suggesting this result is not just a consequence of how these regions of interest have been defined. Cole et al. (2014) compared functional connectivity between brain

networks from rest and task-related activity in two data sets. The first data set, from Cole et al. (2010) consisted of a 10 minute resting state scan followed by 10 short task runs. The task, presented in Figure 1.10a, asked 15 participants to make relational judgements about item properties by particular button presses. The relation, property and button to press would change for each trial creating 64 different 'tasks'. A second dataset from the Human Connectome Project (Van Essen et al. 2013) was also used as a comparison. This fMRI data was collected in 118 participants over two days. Each scanning session started with 28 minutes of rest followed by 30 minutes of task. FMRI data for 7 different tasks were collected over the two days; the particular tasks used are presented in Figure 1.10b. Cole et al. (2014) calculated functional connectivity matrices for the task-based and resting-state data for each of the datasets from time course correlations across 264 brain regions as defined by Power et al. (2011). The researchers then used a standard community detection approach to cluster the 264 regions into brain networks from their functional connectivity profiles. The resulting parcellation showed good correspondence to the resting state networks found by Power et al. (2011) identifying the same networks including the DMN and FPN. When comparing connectivity between these networks during rest and task, Cole et al. (2014) found that in both data sets, connectivity between DMN regions and FPN regions decreased during tasks compared to rest (see Figure 1.10c), suggesting the negative relationship between DMN and MD regions is particularly strong during tasks. Whole brain network analyses therefore mirror the findings of initial 'task-negative' connectivity experiments suggesting that DMN and MD are negatively related during task performance in a way that affects performance.

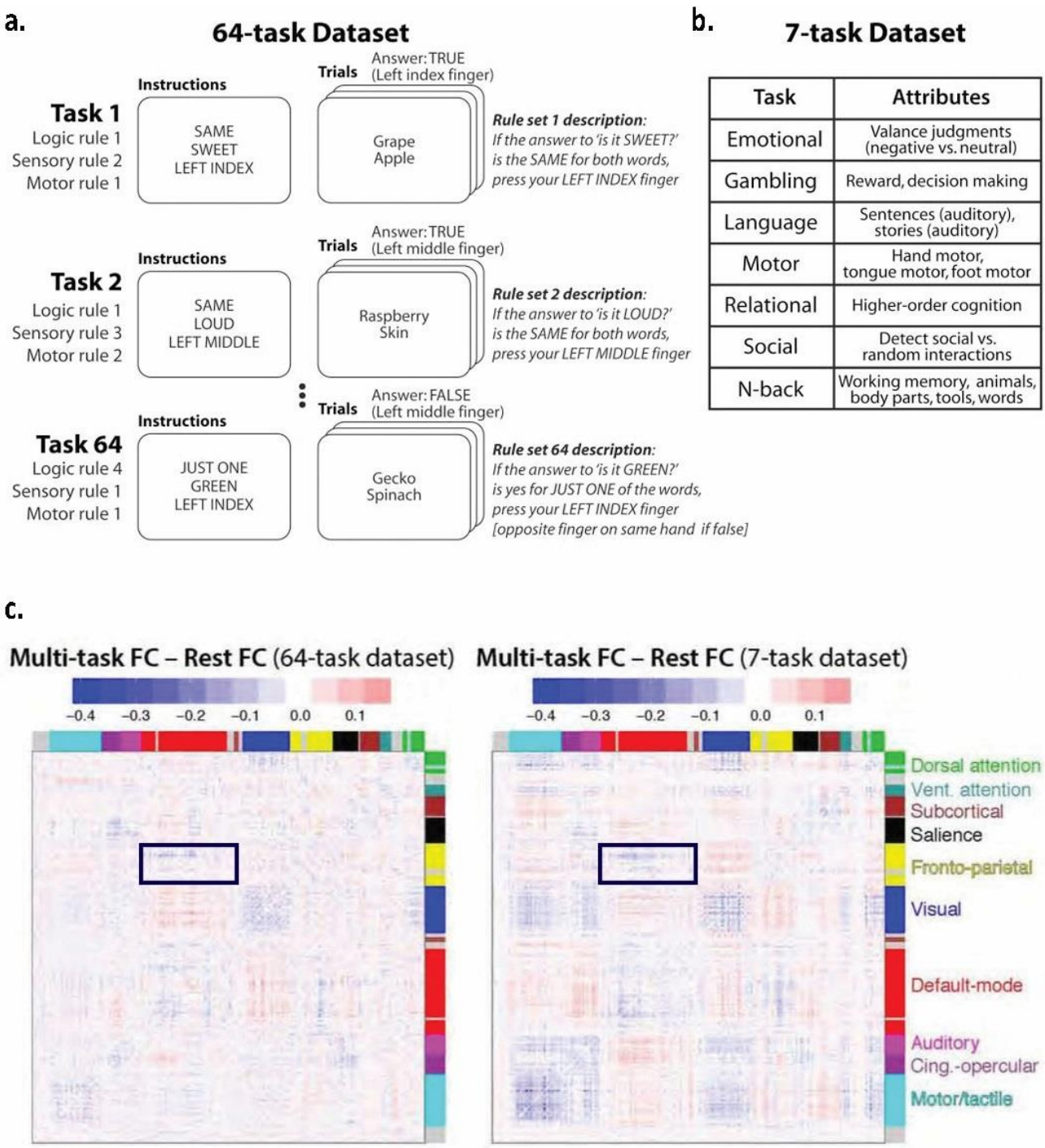

Figure 1.10 Tasks and connectivity results from Cole et al. (2014). a. Experimental design from Cole et al. (2010). The task asked participants to use 64 different combinations of logic x sensory x motor rules to make relational judgements based on properties of pairs of items. b. The 7 tasks from the Human Connectome Project scans (Van Essen et al. 2013). c. Differences in connectivity strength between task functional connectivity and resting state functional connectivity for 264 brain regions as organized by brain network. Cole et al. (2010) dataset on the left and Human Connectome Project dataset on the right. The black box signifies the increasingly negative correlation between DMN and FPN for task-state functional connectivity compared to resting-state functional connectivity. Figure adapted from Cole et al. (2014).

Given that several studies report DMN deactivation related to improved task performance (Daselaar et al. 2004; Shulman et al. 2007; Anticevic et al. 2010) and increased DMN activity predictive of attention lapses (Weissman et al. 2006), it has been suggested that the cognitive control regions are responsible for suppressing DMN activity during task performance (Fox et al. 2005a; Sridharan et al. 2008). Effective functional connectivity methods have been used to assess the direction of these negative correlations in order to test this prediction. Some papers have found a modulatory influence of MD regions on DMN regions (Sridharan et al. 2008; Spreng et al. 2013; Liang et al. 2016). For example, Sridharan et al. (2008) used Granger causality methods to test the direction of influence of proposed MD subnetworks SN and FPN with the DMN during an auditory event segmentation task, a visual oddball task and periods of rest. The researchers found a causal influence of SN regions, presupplementary motor area and particularly anterior insula, on DMN and FPN. The degree of influence to DMN and FPN changed depending upon the task with SN regions showing greater connectivity with DMN regions during rest and with FPN regions during task. However, other papers come to the opposite conclusion (Uddin et al. 2009). Uddin et al. (2009) performed seed-based resting state functional connectivity from two spherical core DMN seeds based on peak coordinates from a previous study (De Luca et al. 2006). From these two posterior cingulate and anterior medial prefrontal seeds the researchers found thresholded maps of regions positively (amPFC-, PCC-) and negatively (amPFC+, PCC+) correlated to the seed regions. While there were some differences, the PCC+ and amPFC+ connectivity maps were generally associated with DMN regions including extensive medial prefrontal cortex, precuneus, temporo-parietal junction, posterior inferior parietal lobe, middle temporal cortex and parahippocampus. PCC and amPFC were negatively associated with MD regions including pre-supplementary motor area, anterior insula, dorsal lateral prefrontal cortex, intraparietal sulcus and extrastriate visual cortex. To test for causal relationships between DMN regions and the regions negatively correlated to DMN, the researchers performed Granger causality analysis on the average time course of the positive and negative connectivity maps generated by each seed region. Uddin et al. (2009) found that changes in signal in amPFC+ and PCC+ could significantly predict activity in amPFC- and PCC- at a later point in time. In comparison to the findings from Sridharan et al. (2008), therefore, Uddin et al. (2009) suggest DMN activity modulates activity in task-positive regions during rest.

Despite prevalent findings of a competitive relationship between the DMN and MD network, more recent research has suggested that these networks are not exclusively in opposition. During a visuospatial planning task and an autobiographical planning task, Spreng et al. (2010) assessed functional connectivity and univariate activation patterns in independently defined DMN and FPN regions. The Tower of London task was used as the visuospatial planning task. In the fMRI version of

this task, participants were presented with a starting configuration and a goal configuration of three coloured discs on three sticks of different heights (see Figure 1.11a). By only moving one disk at a time participants had to judge the fewest number of moves required to transition the disks from the starting positions to the goal positions. The autobiographical planning task used a similar visual layout (see Figure 1.11b). Participants were given an autobiographical goal in the bottom of the screen and shown 3 steps and obstacles associated with achieving that goal on the top half of the screen in the three disks. Participants were asked to plan a way of achieving the desired goal using the three steps in a way specific to the participant. Upon completion of their personalised plan, participants were asked to press a button and indicate how detailed their plan was. As a control condition, participants were also asked to count the number of vowels from the 6 discs on the screen (see Figure 1.11c). Between-network connectivity results showed that DMN regions were significantly positively correlated with the FPN during the goal-directed autobiographical planning task. These results were also reflected in the univariate analyses, with both the DMN and FPN showing increased activation during autobiographical planning task relative to control. During the visuospatial planning task FPN and DMN were not significantly correlated. FPN regions showed univariate increases in activity and DMN regions showed univariate decreases relative to the control task. These results suggest that, depending on the task, DMN activity can couple with 'task-positive' MD regions to support goal-directed cognition. Similarly, Gao et al. (2013) found that in comparison to rest, correlations between PCC seed regions and MD regions, pre-supplementary motor area and anterior insula, during the Navon global/local letter task (Navon 1977) became positive, with the degree of between network connectivity reflecting accuracy.

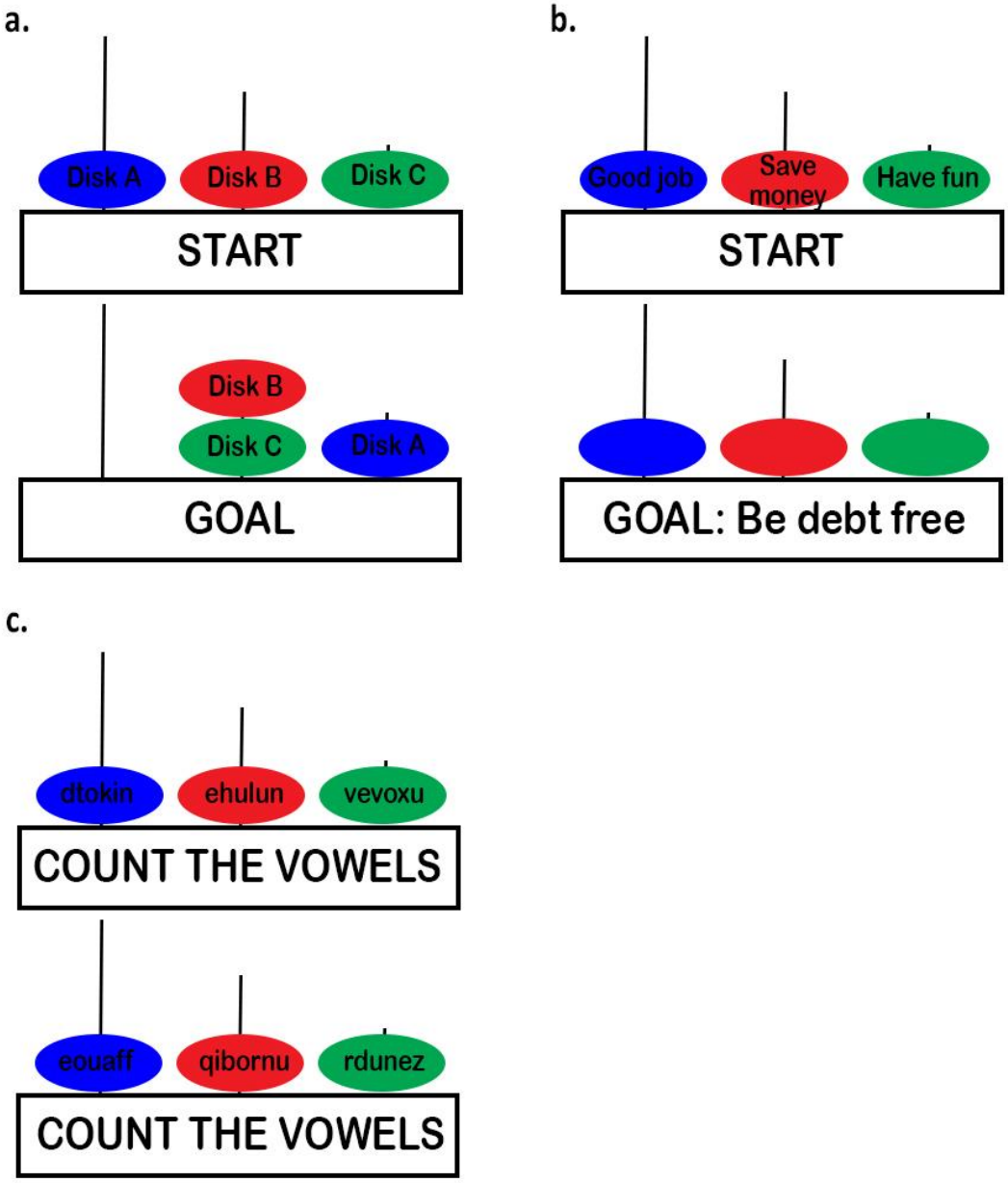

Figure 1.11. Task stimuli from Spreng et al. (2010). a. Visuo-spatial planning task – participants were asked the minimum number of moves it would take to change the starting configuration of disks to the goal configuration by moving one disk at a time. b. Autobiographical planning task – participants were asked to imagine a detailed plan to achieve the goal using the three points. c. Control task – participants were asked to count the vowels. Figure adapted from Spreng et al. (2010).

Other research assessing univariate activations also suggests the competitive relationship between 'task-positive' MD regions and 'task-negative' DMN is not as clear cut as has been previously suggested. Increased activity in DMN regions has been linked to external task performance and MD activations have even been associated with off-task cognition. Intriguingly, Christoff et al. (2009) implicated the MD network as well as the DMN in off-task mind wandering. In the event sampling study described above, Christoff et al. (2009) found regions of the MD network (as well as DMN

regions) that were more active immediately before probes where participants reported off-task thoughts compared to when participants reported on-task cognition. The researchers suggest that MD regions are not only important for maintaining focus during task control but also important for maintaining focus on self-generated, task-unrelated thoughts.

DMN has been linked to goal-related activity in a number of demanding cognitive control tasks. Spreng et al. (2014) found increases in DMN activity during a 2-back working memory task using famous faces rather than anonymous faces, mirroring a performance benefit for famous face matching. This finding also held after trial activity was split by reaction time. DMN activity was still greater during slower famous face matches than faster anonymous face matches, suggesting that the DMN activity during famous face matching represents more than just a difficulty effect. The researchers suggest that the DMN contributes to task performance when required to retrieve information from long term knowledge. Furthermore, in a series of studies, Smallwood et al. found increased DMN activation when participants were required to make decisions about stimuli presented in the previous trial compared to when making perceptual decisions about current stimuli (Smallwood et al. 2013; Konishi et al. 2015; Murphy et al. 2018). These researchers suggest that DMN activations during externally-directed tasks are due to retrieval of learnt information which is not available in the current environment. The content of retrieved information, they suggest, does not have to be rich and semantic in content in order to require DMN for retrieval (Murphy et al. 2018, 2019).

However, the role of the DMN in externally-focused tasks does not appear to be limited to memory retrieval. In a cued attention task, Hahn et al. (2007) asked participants to indicate the presence of a target as quickly as possible by button press. The target could be in one of four locations on the screen. Prior to the target's appearance, a cue was presented to the middle of the screen giving information about the upcoming target location. The cue varied in specificity from 'specific location' to 'uncued' by pointing to 1, 2, 3 or all 4 of the 4 target locations. Activity in core DMN and left pIPL was negatively related to reaction time for uncued trials when participants did not have prior information about the target location. These findings hint at a role for the DMN during task performance when attention is focused more broadly in the absence of top-down endogenous control.

Esterman et al. (2012) suggest a more complicated relationship between DMN univariate activity and task performance. From participant performance during a sustained attention task, the researchers identified two attentional states from reaction time variability data. The 'in the zone' state was characterized by periods of relatively stable reaction time and the 'out the zone' state was

characterized by periods of reaction time variability. While DMN activity was more associated with the less error-prone 'in the zone' state, further increases in DMN activation within this state were predictive of errors.

Finally, a study by Crittenden et al. (2015) implicated the DMN in externally-focused task switching. In this study, participants were asked to perform a yes/no task according to a rule cued by the colour of a frame surrounding the stimuli. Two tasks were associated with each of three stimulus domains (pictures, words and shapes). Tasks were presented sequentially in a pseudorandom order to create task stay trials (where the current task is the same as the previous task), within-domain switch trials (where the current task involves the same stimulus domain as the previous task) and between-domain switch trials (where the current task involves a different domain of stimulus compared to the previous task). Following Andrew-Hanna et al. (2010), Crittenden et al. (2015) divided the DMN into Core, Medial Temporal (MTL) and Dorsal Medial (dmPFC) subnetworks. Contrary to the common finding of decreased DMN activity during demanding, externally-focused cognition, Crittenden et al. (2015) found Core and MTL subnetworks to increase activity during the most demanding, between-domain switch trials (with the dmPFC subnetwork, if anything, showing the reverse). Furthermore, in all 3 subnetworks, multivoxel pattern analysis (MVPA) showed distinct activity patterns for different trial types, in particular for the three different stimulus domains. These findings suggest that DMN activity can be seen not only during internally-directed cognition, but also some aspects of external task switching when instruction cues call for retrieval and implementation of a new set of task rules. Similar suggestions of DMN activations during task transitions have also been found by Fox et al. (2005b). These researchers found transient activation at onset and offset of four different tasks in the posterior cingulate cortex, temporo-parietal junction, precuneus and posterior precuneus (inferior parietal lobe).

THESIS OVERVIEW

In the introduction so far I have discussed the importance of context for everyday cognition, and the developing role found for the DMN in representing such rich, meaningful contexts. We have also established that the DMN is not regularly associated with task control; instead, a set of frontoparietal brain regions known as the MD system have been robustly related to demanding task processes. Although early evidence showed that DMN activity is often anti-correlated with task-relevant MD activity, recent research suggests that DMN regions can co-activate with MD regions, and can contribute to external task processes under certain conditions. These findings that the DMN has

been implicated in representing rich contexts and can show task-related activations can lead one to hypothesize that the DMN should be important during contextual control. This thesis aims to better understand the contribution of the DMN in contextual control.

Chapter 2 considers why current studies of contextual control do not implicate DMN regions, and examines evidence for DMN activity during a new contextual control task. An fMRI experiment was designed to compare activity during contextual control in rich, meaningful scenes, in comparison to contextual control from arbitrary letter stimuli. In a direct contrast between contextual control using scenes versus letters, DMN regions of the posterior cingulate cortex, parahippocampus and posterior inferior parietal cortex are found to be active. MD regions show strong activity increases for both letter and scene stimuli. Further analyses aim to understand what task-related content is represented in these regions.

Chapter 3 asks whether regions beyond MD are necessary for adequate performance in more lifelike naturalistic tasks. As the DMN has been proposed to be important for context representation (Ranganath and Ritchey 2012; Baldassano et al. 2016, 2017), Chapter 3 examines whether DMN regions are particularly important for good performance in these naturalistic tasks. This neuropsychology experiment used behavioural data accumulated from brain lesioned patients across a series of naturalistic tasks and a standard IQ task. Patients showed marked performance impairment on naturalistic tasks, compared to matched controls, even after controlling for differences in IQ. While MD lesion volume was found be predictive of IQ, MD lesion volume was not predictive of naturalistic task performance. Interestingly, DMN lesion volume was not found to be related to patient performance in any task. Voxel based lesion symptom mapping analyses found no single region could predict naturalistic task impairment. Although problems of power are discussed, naturalistic tasks are suggested to utilize more distributed regions of the brain compared to standard executive tasks.

Chapter 4 aims to understand to what extent the DMN contributes to non-spatial executive tasks. Crittenden et al. (2015) suggest that in a hierarchically-structured task, DMN regions represent the broader task domain and respond with greater activation to larger task switches. However, these findings were confounded by differences in visual distinguishability. This chapter describes an fMRI experiment using a similar hierarchically-structured task set, but unconfounding visual differences, and with an additional comparison between rest and task states. Whilst replicating previous DMN task switch effects, large DMN increases for task restarts after rest were also found. These univariate findings were complemented by representation of broad task domain, but not specific tasks, in DMN

regions. The relationship between the role of the DMN in cognitive transitions and in context representation is discussed.

Chapter 5 assesses an alternative explanation for the switch effects of the previous chapter. The fMRI experiment presented in this chapter asks whether the activation of the DMN at cognitive transitions reflects changes in task rule retrieval difficulty instead of degree of task switch. To this end, this study directly manipulated the rule retrieval demands. Contrary to the retrieval account, increased retrieval demand led to reduced DMN activity, accompanied by increased activation in MD regions.

Finally in Chapter 6, the implications for these findings on DMN research and the cognitive control literature are discussed.

Chapter 2

Context-dependent decision making in naturalistic contexts

INTRODUCTION

As discussed fully in Chapter 1, context has been proposed to be important for guiding future action by representing situational constraints and simulating possible courses of events (Zacks et al. 2007). Due to its association with scene, episode and context representation (Hassabis and Maguire 2007; Baldassano et al. 2016, 2017; Chen et al. 2017), researchers have suggested that the DMN may play a key role in this context guided cognition (Bar 2007, 2009; Ranganath and Ritchey 2012). One specific theory suggests that DMN regions, particularly the posterior hippocampus, parahippocampus, retrosplenial cortex, posterior cingulate cortex and angular gyrus, make up a posterior medial system which is proposed to identify, construct and represent a situation model based on the current situational context along with its social, semantic and temporal associative relationships (Ranganath and Ritchey 2012). However, there is little direct evidence to implicate the DMN in context-dependent decision making. In fact, research into the neural correlates of contextual control often implicate prefrontal MD regions rather than the DMN (Koechlin et al. 2003; Badre and D'Esposito 2007, 2009; Badre and Nee 2018).

In these studies, contextual control is measured by tasks in which the rules to apply change depending on arbitrary stimulus properties. For example, in Koechlin et al. (2003), if the letter was green, participants were asked to make vowel/consonant judgements. When the letter was red, participants were asked to make upper/lowercase judgements (see Figure 1.6). Activity during these contextual control tasks is then contrasted with activity during an easier task where the stimulus-response mapping remains stable. Contextual control in these tasks tends to be restricted to the posterior dorsolateral prefrontal cortex and inferior frontal junction included in the MD system rather than in the DMN.

As the DMN often shows deactivations during demanding externally-focused tasks (McKiernan et al. 2003, 2006; Fox et al. 2005a; Kelly et al. 2008), it is perhaps unsurprising, from a 'task-negative' viewpoint, that the DMN has not been related to context-dependent decision making in these kinds of tasks. However, given that DMN regions are consistently found to be active during studies using naturalistic stimuli such as movies, scenes and personal events (e.g. Andrews-Hanna et al. 2010; Baldassano et al. 2016, 2017), an alternative suggestion is available. Rich, meaningful stimuli, often used when studying the DMN, allow access to semantic and social associations developed over time from other experiences of similar environments. For example, when two people in a movie enter a restaurant, from our own experiences we might have the prediction that the next thing that will happen will be that they will ask the waitress for a table. A suggestion made by several researchers is that the DMN is important for context-dependent decision making, but only when the context is associatively rich, allowing one to use past knowledge to make predictions about current and upcoming events (Zacks et al. 2007; Bar 2007, 2009; Ranganath and Ritchey 2012).

This experiment sought to directly compare activity during contextual decision making tasks using arbitrary cues and meaningful scenes. In this way, a 'task-negative' view of DMN function could be compared with the theory that the DMN is specifically important during meaningful context-dependent decision making. In line with previous theories, DMN regions were predicted to be active during context-dependent decision making with rich meaningful contexts compared to when using arbitrary cues (Zacks et al. 2007; Bar 2007, 2009; Ranganath and Ritchey 2012). As MD activity is associated with diverse task demands (Duncan and Owen 2000; Fedorenko et al. 2013), the MD network is predicted to be active for context-dependent decision making regardless of how meaningful the cues are. Furthermore, using multivariate representational similarity analysis (RSA) this experiment aims to further examine the task-related content represented in these regions of interest during both meaningful scene and arbitrary letter versions of the task.

METHODS

Participants

48 participants (29 female) between 18-35 years old, were recruited through the Medical Research Council Cognition and Brain Sciences Unit participant panel. All participants selected were right handed, native English speakers, with normal or corrected to normal vision and between 18-40 years old. Ethics approval was granted from the Cambridge Psychology Research Ethics Committee. 8

participants (4 female) were excluded from further analysis due to poor task performance (4) (50% or fewer correct trials on one or more task condition), excessive motion (3) or mid-task cancellation (1).

Task

Task events are illustrated in Figure 2.1. In order to give participants an immersive, ongoing task to focus on, participants were presented with emails and asked to categorise the email as either spam or not spam by left hand ring and middle finger button presses respectively. This task was non-speeded and the emails would remain on the screen until participants made a response. Equal numbers of spam and non-spam emails were presented to participants in a randomised order. The emails were presented on one of 4 backgrounds in blocks of 10 seconds. Half (20) of the participants received scene backgrounds (the scenes group) and the other 20 participants saw black backgrounds with two white letters displayed centrally at the top of the screen (the letters group). The 8 different backgrounds are presented in Figure 2.1.

At either at 2 or 6 seconds after the start of each 10 second block, a sound played and participants were asked to respond to the auditory stimulus as quickly as possible. Participants were told that the auditory task was the priority, so that usually, when a sound occurred, they would interrupt processing of the email, respond to the sound, then return to the email. In fact, however, sound and email responses were allowed in either order, with each email remaining until the response was given, and each sound remaining until either response or the end of the block. For both the scene and letters group, there were 4 context-dependent sounds (doorbell, phone, sneeze and alarm bell), which required participants to use the background information (scenes or letters) in order to decide which button to press, and one context-independent sound (birdsong), with the same response irrespective of context.

For the scenes group, each visual scene cued one of four situational contexts: alone in your living room in the middle of the day, alone in your bedroom having just woken up, studying with a friend in the evening waiting for pizza delivery, and working at school waiting for the end of the lesson. Participants were asked to use this situational information to decide whether they would “react to” or “ignore” context-dependent sounds. “React” was indicated by pressing a key with the ring finger of the right hand, while “ignore” was indicated with the right middle finger. The rules for each context are presented in Figure 2.1. In the living room, participants were told to react to the phone and doorbell. They were told to ignore the sneeze (no need to say anything as they were alone) and the alarm bell (alarm clock irrelevant in the middle of the day; in this case, “ignoring” was taken to mean simply switching the alarm off). Similar explanations were given for the other three contexts. In

the bedroom participants were told to react to the phone and alarm bell (signalling time to get up), but to ignore sneeze and doorbell. When studying at a friend's house participants were told to ignore phone call or alarm bell, but react to sneeze (e.g. apologise) and doorbell (answer the door for pizza). Finally, at school the participant was asked to ignore doorbell or phone, but to react to sneeze or alarm bell (indicating the end of the lesson).

For the letters group, participants were shown that each letter presented to the top of the screen corresponded to the first letter of one of the sounds (phone = P, doorbell = D, alarm bell = A, sneeze = S). When a sound played, if the beginning letter of the sound was present in the background letter pair then participants were asked to press to "react" to the sound. If the beginning letter of the sound was not present, then participants were asked to press "ignore". As shown in Figure 2.1, the background letters were paired such that the four pairs matched the rules for the scenes group (e.g. letter context PD = scene context living room).

The 10 second blocks were presented in a pseudorandom order. On 75% of blocks the background context changed and on 25% of the blocks it repeated. These background repeats as well as the jittered sound onset time were implemented to help separate fMRI responses to sound onset and background switch. The experiment consisted of 3 runs of 97 blocks. As transient DMN activity can accompany large cognitive transitions (Crittenden et al. 2015), the first block of each run (background context and sound randomized, sound onset at 6 seconds) was discarded from analysis. Following this first block, each run contained 24 blocks of each of the background contexts. Within each background, each context-dependent sound was played 4 times per run, and birdsong was played 8 times per run, with half of the sounds in each case presented at 2 sec and half at 6 sec after block onset. Each run also contained 30 s rest periods at the start and end.

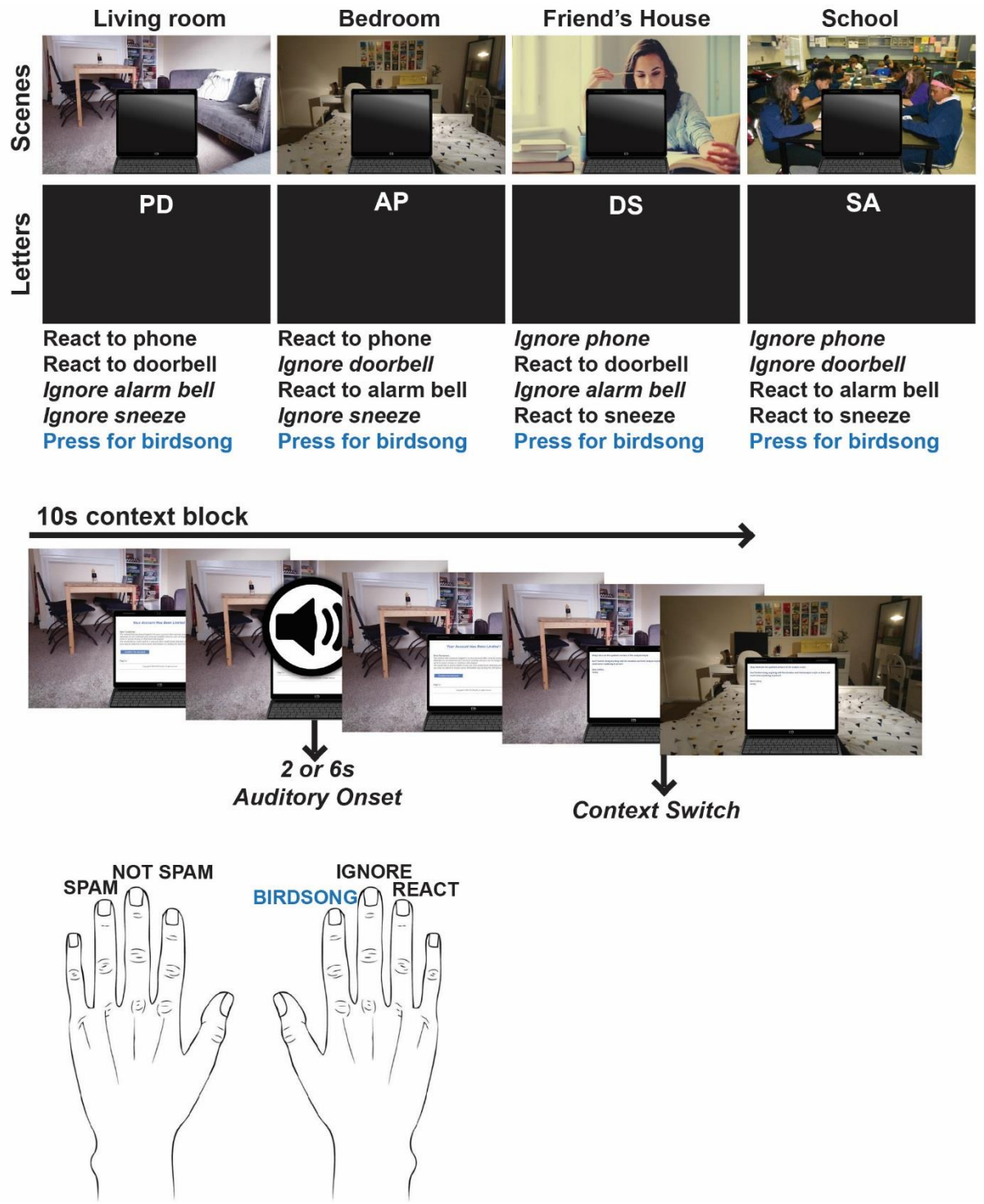

Figure 2.1. Task design. The ongoing task required participants to read emails and judge whether they were spam or not by left hand button press. Background scenes or letters were presented in 10 second blocks. On 75% of blocks, the background context was different from the previous context; on the other 25% of the blocks, the background context was repeated. An auditory stimulus played at either 2 or 6 seconds after the start of the block. Participants were asked to respond to the sound by right hand button press. For birdsong, the response button was fixed as the right index finger. Correct responses for the other 4 sounds were context-dependent. For the scenes group, each of the 4 visual

scenes indicated a situational context, with details of the place, what they would be doing, and the time of day. Using the situational information, participants were asked to judge whether they would ignore or react to the sounds. For the letters group, the experimenter showed participants that the first letter of each of the context-dependent sounds corresponded to each letter in the on-screen letter pairs. If the played sound matched one of the letters in the letter pair then participants were asked to press 'react' and if the letter cued by the sound was not present then participants were asked to press 'ignore'.

Three hundred spam and 300 non-spam email stimuli, stripped of personally identifiable details, were sourced from the first author's emails. To ensure participants were reading the emails rather than remembering their previous response to the same email, in each run a new set of 200 emails (100 spam and 100 non-spam) were used. Email stimuli were positioned centrally along the x-axis and below centre along the y-axis with the centre of the email positioned approximately 1.8 degrees of visual angle below the centre of the screen. In the scenes group, this positioning fit the emails inside of a superimposed laptop in order to convey the impression that the participants were checking their emails in each scene. Email stimuli measured approximately 7.5 (width) x 5.6 (height) degrees of visual angle. The letter cues were positioned centrally along the x-axis and above centre along the y-axis with the bottom edge 4.6 degrees of angle above central fixation. The letter stimuli measured approximately 2.3 (width) x 1.5 (height) degrees of visual angle. Scene stimuli spanned the entire screen (visual angle approximately 49 x 30 degrees). The experiment was controlled using Psychophysics Toolbox for MATLAB (Brainard 1997).

Training

Participants were carefully pre-trained to ensure good learning of the task rules. First, participants were introduced to the email task and learned the spam and non-spam button presses. Then participants were introduced to the sounds. First they heard the birdsong and learnt the corresponding button press. Then participants were asked to identify the 4 context-dependent sounds by name, and corrected if they had any difficulty. Participants were then introduced to each context and the associated task rules. For the scenes group, the experimenter elaborated on each of the contexts and explained why the response rules applied. For the letters group, the experimenter explained the match between the letter contexts and names of the context-dependent sounds. Participants were then presented with each sound in every context in a pseudorandom order and asked to say what button they would press. When the experimenter was sure that the participant had understood the task rules, participants moved on to complete a short 12 block practice version of the task outside of the scanner.

Data acquisition

Images were acquired using a 3 T Siemens Prisma magnetic resonance imaging (MRI) scanner, fitted with a 32-channel head coil. Functional MRI (fMRI) acquisitions used T2*-weighted multiband Echo-Planar Imaging (multiband acquisition factor 3 for 2.5 mm slices with no interslice gap, TR 1.1 s, TE 30 ms, flip angle 62°, voxel size 2 × 2 mm^2). T1-weighted multiecho magnetization-prepared rapid gradient-echo (MPRAGE) images were also obtained (TR 2.53 s, TE 1.64, 3.5, 5.36 and 7.22 ms, flip angle 9°, voxel size 1 mm^3).

Preprocessing

Images were preprocessed using automaticanalysis (version 4) (Cusack et al. 2015) and SPM 12 (Wellcome Department of Cognitive Neurology, London, UK) for Matlab (Mathworks). The sequence of preprocessing stages involved spatial realignment of the raw EPIs, slice-time correction to the middle slice, coregistration of the functional EPI images to the structural T1-weighted image, and normalization to the Montreal Neurological Institute (MNI) template brain. For the whole brain univariate analysis only, functional images were then spatially smoothed using a Gaussian kernel of 10 mm full-width at half-maximum (FWHM).

Regions of Interest

This study aimed to follow the DMN regions defined by Andrews-Hanna et al. (2010). As described in Chapter 1, Andrews-Hanna et al. (2010) established 20 DMN regions that can be grouped into core, MTL and dmPFC subnetworks. In Andrews-Hanna et al. (2010), these DMN regions were defined as 8mm spheres around the central coordinates presented in Table 2.1. Here these regions were expanded so as to encompass a full brain volume more representative of the typical DMN.

Table 2.1. Central MNI coordinates for DMN regions defined by Andrews-Hanna et al. (2010). Colour denotes subnetwork: yellow=core DMN, green=MTL DMN, blue=dmPFC DMN.

ROI	x	y	z
L PCC	-8	-56	26
R PCC	8	-56	26
L amPFC	-6	52	-2
R amPFC	6	52	-2
L HF	-22	-20	-26
R HF	22	-20	-26
L PHC	-28	-40	-12
R PHC	28	-40	-12

L Rsp	-14	-52	8
R Rsp	14	-52	8
L pIPL	-44	-74	32
R pIPL	44	-74	32
vmPFC	0	26	-18
L TPJ	-54	-54	28
R TPJ	54	-54	28
L LTC	-60	-24	-18
R LTC	60	-24	-18
L TempP	-50	14	-40
R TempP	50	14	-40
dmPFC	0	26	-18

The DMN ROIs, presented in Figure 2.2a, were generated using networks 10, 15, 16 and 17 from the liberal mask of the 17 network cortical parcellation reported in Yeo et al. (2011). Networks 15, 16 and 17 closely corresponded to the 3 DMN networks described by Andrews-Hanna et al. (2010), the MTL subnetwork, the dmPFC subnetwork and the core hubs. Network 10 was described by Yeo et al. (2011) as the orbital frontal-temporopolar network, containing temporopolar and orbital frontal regions. This network was included as it contained the ventromedial prefrontal cortex from Andrews-Hanna et al. (2010). These 4 networks were combined and smoothed with a 4mm FWHM Gaussian smoothing kernel and voxels with values > 0.5 after smoothing were retained. The combined network was then parcellated into 20 subregions by assigning each voxel to its closest DMN coordinate as defined by Andrews-Hanna et al. (2010). In cases where non-contiguous volumes were assigned to the same region, the volume that was closest to its Andrews-Hanna coordinate was chosen if its size was > 45 voxels, otherwise the next closest volume with > 45 voxels was chosen. To make all volumes bilateral, left and right volumes for each region (e.g. left and right posterior cingulate cortex) were concatenated to generate 11 bilateral regions: posterior cingulate cortex (PCC), anterior medial prefrontal cortex (amPFC), parahippocampus (PHC), hippocampus (HF), retrosplenial cortex (Rsp), posterior inferior parietal lobe (pIPL), ventromedial prefrontal cortex (vmPFC), lateral temporal cortex (LTC), temporo-parietal junction (TPJ), temporal pole (TempP) and dorsomedial prefrontal cortex (dmPFC).

Frontoparietal MD ROIs were taken from Fedorenko et al. (2013). MD regions (Figure 2.2b) included the posterior–anterior extent of the inferior frontal sulcus (pIFS, aIFS), a posterior dorsal region of lateral prefrontal cortex (pdLFC), inferior frontal junction (IFJ), anterior insula/frontal operculum (AI/FO), presupplementary motor area/dorsal anterior cingulate (preSMA/ACC), and intraparietal

sulcus (IPS). A template for these regions was downloaded from http://imaging.mrc-cbu.cam.ac.uk/imaging/MDsystem. Only the frontoparietal ROIs were selected.

Finally, as the MD volume AI/FO and the DMN volume vmPFC showed slight overlap, the region of overlap was removed from both ROIs.

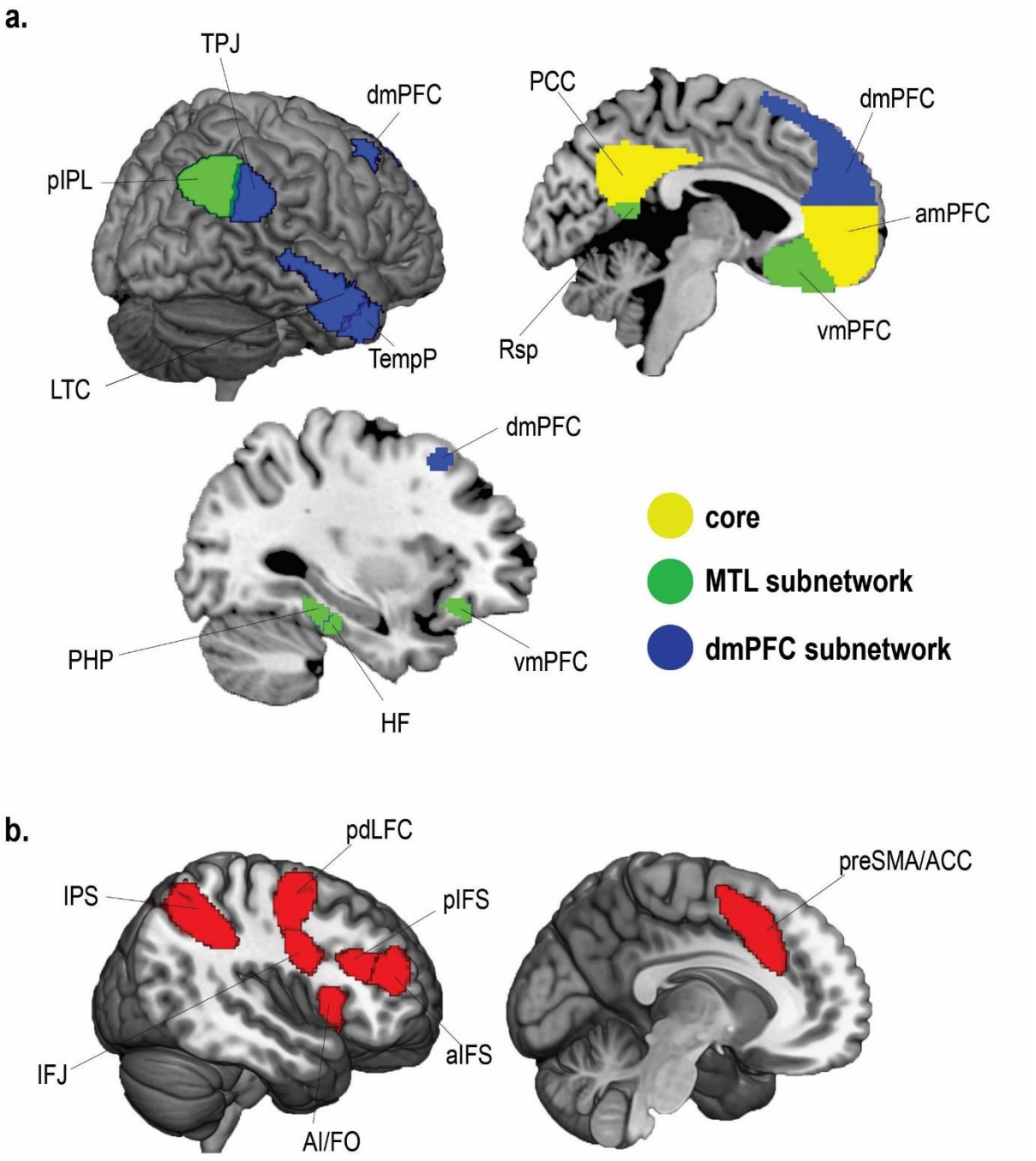

Figure 2.2. Regions of interest. a. DMN ROIs defined from networks 10, 15, 16 and 17 of the 17 network Yeo et al. (2011) parcellation and split into subregions by proximity to peak coordinates from Andrews-Hanna et al. (2010). PCC=posterior cingulate cortex, amPFC=anteromedial prefrontal cortex, HF=hippocampal formation, PHC=parahippocampus, Rsp=retrosplenial cortex, pIPL=posterior inferior

parietal lobe, vmPFC=ventromedial prefrontal cortex, LTC=lateral temporal cortex, TPJ=temporo-parietal junction, TempP=temporal pole, dmPFC=dorsomedial prefrontal cortex. b. frontoparietal MD ROIs from Fedorenko et al. (2013). AI/FO=anterior insula/frontal operculum, preSMA/ACC=pre-supplementary motor area/anterior cingulate cortex, pdLFC= posterior dorsolateral frontal cortex, IPS=inferior parietal sulcus, aIFS=anterior inferior frontal sulcus, pIFS=posterior inferior frontal sulcus, IFJ=inferior frontal junction.

Univariate Analysis

Data for each participant were examined using the General Linear Model. Regressors were separately created for the auditory response for each combination of sound (doorbell, phone, alarm bell, sneeze, birdsong) by context (living room, bedroom, friends, school, or PD, AP, DS, SA). Each regressor was modelled as an event from stimulus onset to response, convolved with the canonical hemodynamic response function. Additional regressors were created to model the block onset for each combination of context switch type (context switch, context stay) by context (living room, bedroom, friends, school, or PD, AP, DS, SA). These block onset regressors were modelled as delta functions convolved with the canonical hemodynamic response function, positioned at the onset of the block. For the main analysis, the 30s rest blocks were modelled separately and then discarded from further analysis, so that the implicit baseline reflected the ongoing email task.

For each participant, mean beta values for each combination of sound and context, compared to implicit baseline, were extracted from each ROI using the MarsBaR SPM toolbox (Brett et al. 2002). These were averaged to give a single mean contrast of context-dependent sounds (doorbell, phone, alarm bell, and sneeze)>implicit baseline. A contrast was also constructed for context-independent birdsong>implicit baseline. To examine the effects of context-dependence between groups a mixed model ANOVA was constructed with context-dependence as the within-participant factor (context-dependent>implicit baseline and context-independent>implicit baseline) and group as the between participant factor (scenes and letters). For the first analysis, an additional factor of ROI was included for each network separately. Further ANOVAS examined the effect of context-dependence between groups for each ROI separately. A similar ANOVA was used in a whole brain voxelwise analysis, thresholded at $p < .05$ corrected for multiple comparisons using the false discovery rate (FDR).

Multivariate Analysis

To understand the representational content in DMN and MD regions, a representational similarity analysis (RSA) was performed, using linear discriminant contrasts (LDC, Nili et al. 2014) as the measure of dissimilarity between activation patterns. The LDC (also known as the “crossnobis”

estimator) is a cross-validated estimate of the squared Mahalanobis distance between two patterns, and expresses representational dissimilarity. True distances would be positively biased as noise adds dissimilarity between patterns of activity. The crossnobis distance is calculated using leave-one-run-out cross-validation to give a distance estimate which is distributed around zero for identical but noisy patterns, and is not positively biased. The analysis used the RSA toolbox (Nili et al. 2014), in conjunction with in-house software. This analysis was based on the same design matrix as the standard GLM described above. For each participant, voxelwise activity patterns were obtained for each ROI during auditory events for each combination of sound by context, resulting in 20 patterns for each run. Block onset activity for each combination of context and switch type was also modelled, but the results were not further examined. The LDC dissimilarity between pairs of response patterns (e.g. doorbell-bedroom and phone-bedroom) was calculated over pairs of runs or folds (i.e. 1-2, 2-3, 1-3). For each fold, one run was first assigned as the testing set (e.g. run 1) and the other as the training set (e.g. run 2). The pairs of patterns from the testing run (run 1) were projected onto the linear discriminant fit to the training run (run 2) and the difference between the projected patterns (distance along the discriminant) was calculated. This process was also carried out in reverse (e.g. run 2 patterns projected onto a linear discriminant fitted from run 1), and an average distance calculated across both directions and folds. To compare dissimilarities across ROIs of different sizes, the LDC values were normalised by dividing by the number of voxels in each ROI. This resulted in a 20x20 symmetrical representational dissimilarity matrix (RDM) for each ROI for each participant.

The model RDM for scene contexts (equivalent for letters) is shown in Figure 2.3. Blue squares correspond to different context-dependent sounds within the same context. Red squares correspond to the same context-dependent sounds in different contexts. Yellow squares correspond to different context-dependent sounds in different contexts. For all colours, correct response similarity (same = both ‘react’, or both ‘ignore’; different = one ‘react’, one ‘ignore’) is reflected by luminance, where darker colours equal same response and lighter colours equal different responses. Grey corresponds to dissimilarity measures within birdsong events or between birdsong and context-dependent sounds. Diagonal entries (black squares) are zero by definition as they do not reflect dissimilarities between different events. Based on this matrix, separate contrasts were used to examine coding of context, sound and response. Figure 2.3 also presents the examined contrasts. Contrasts were constructed just for the context-dependent sounds, where sounds, contexts and responses were balanced. If regions distinguish between contexts, dissimilarity should be greater for different sounds in different contexts (yellow) compared to in the same context (blue); and dissimilarity for different contexts should also be significantly greater than zero even when sound and response are the same (dark red). If regions can distinguish between sounds, dissimilarity should be greater for different sounds in different contexts (yellow) compared to the same sound in different contexts (red); and

dissimilarity for different sounds should also be significantly greater than zero even when context and response are the same (dark blue). If regions can distinguish between response type, dissimilarity should be greater for different responses (light colours) compared to the same response (dark colours), when other differences are matched. Contrasts were computed by averaging dissimilarity values across each colour for each ROI in each participant and then, for each ROI, performing t-tests of the contrast values against zero. The three contrasts for each decoding measure (context, sound and response) were averaged before performing these t-tests.

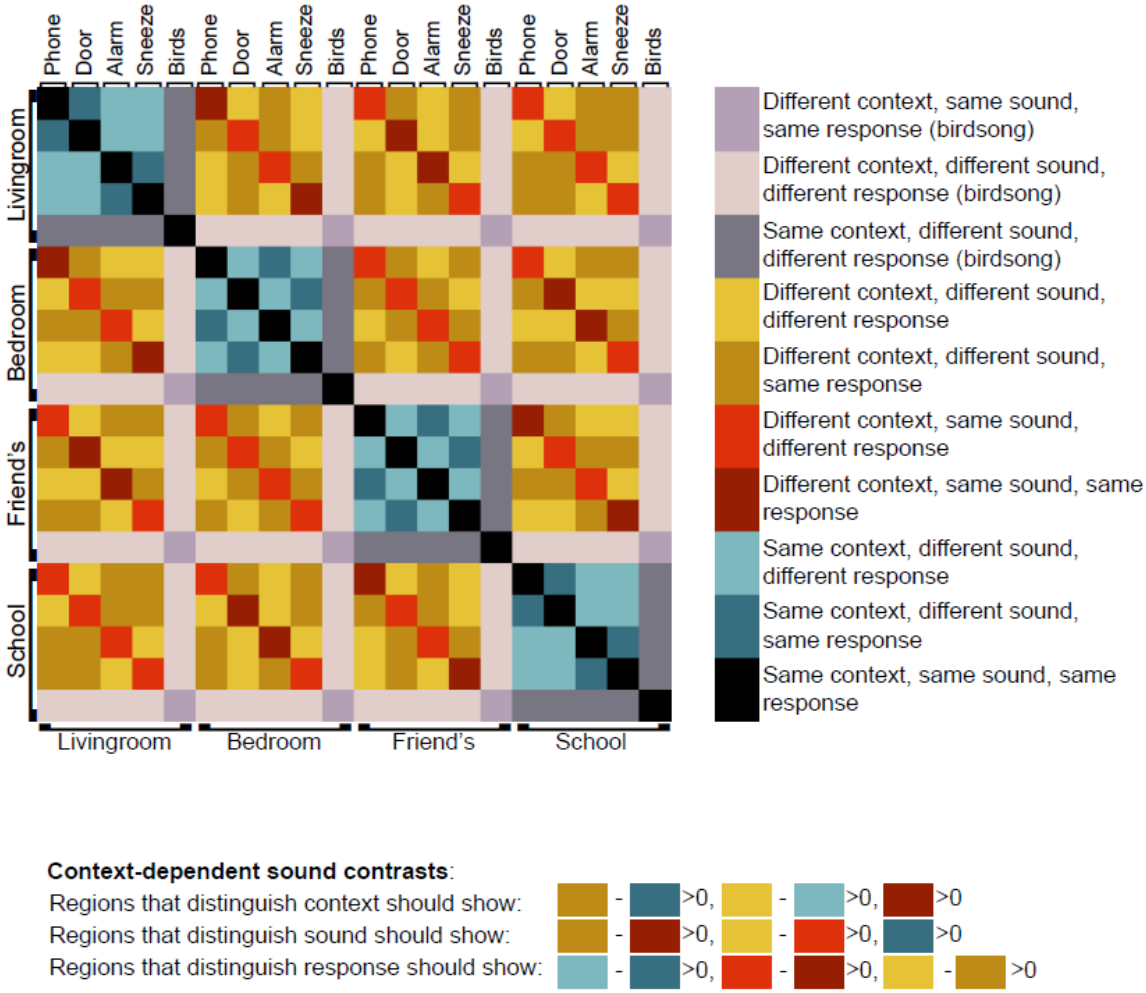

Figure 2.3. The model RDM matrix for the scene context group. Each square corresponds to dissimilarity between pairs of auditory events. Blue squares correspond to different context-dependent sounds within the same context. Red squares correspond to the same context-dependent sounds in different contexts. Yellow squares correspond to different context-dependent sounds in different contexts. For all colours, correct response similarity (same = both react, or both ignore; different = one react, one ignore) is reflected by luminance where darker colours equal same response and lighter colours equal different responses. Grey corresponds to dissimilarity measures between and within birdsong events. Diagonal entries (black squares) are zero by definition as they do not reflect dissimilarities between different events. Below the matrix are the contrasts used to examine

context, sound and response decoding. An equivalent matrix was constructed for the letter context group.

RESULTS

Behaviour

For the email task, independent samples t-tests found no difference between performance in the scene and letters groups, in either error (M_{scene}=14.2%, M_{letter}=14.9%, t(38)=0.31, p=0.76) or reaction time (M_{scene}=1.69s, M_{letter}=1.65s, t(38)=0.51, p=0.61).

Figure 2.4 presents performance broken down by groups and sound types. For proportion error and reaction time separately, a strong effect of sound type is seen. Participants made fewer errors and were faster to respond during context-independent (birdsong) trials compared to context-dependent sound trials. Participants also made more errors and were slower to respond to alarm bell trials compared to the other context-dependent sounds. A two-way mixed model ANOVA with group as the between-participant factor (scenes and letters) and sound type as the within participant factor (phone, door, alarm bell, sneeze and birdsong) confirmed these impressions. A significant main effect of sound type on proportion error (F(4,152)=12.25, p<0.01) and reaction time (F(4,152)=154.7, p<0.01) was found. Neither the effects of group (proportion error: F(1,38)=0.05, p=0.83; reaction time: F(1,38)=0.03, p=0.87), nor the interaction between group and sound type (proportion error: F(4,152)=0.46, p=0.77; reaction time: F(4,152)=1.25, p=0.29) was significant.

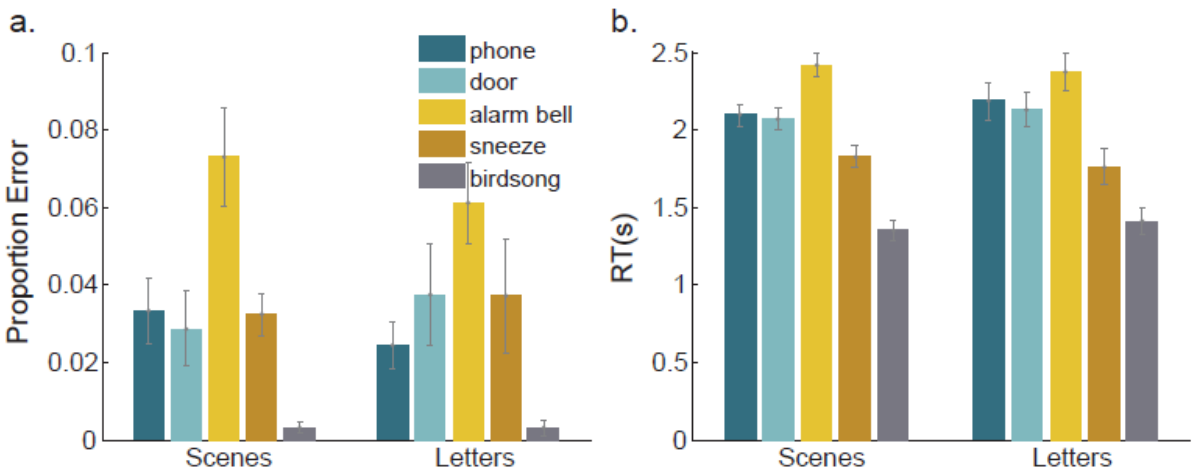

Figure 2.4. a. Proportion error and b. reaction time during auditory task performance for each group by sound type. Error bars show standard error of the mean across participants within each group.

Figure 2.5 presents auditory performance broken down by groups and task contexts. A two-way mixed model ANOVA with group as the between-participant factor (scenes and letters) and task context as the within participant factor (living room, bedroom, friend's and school) showed no main effect for either task context (proportion error: $F(3,114)=1.53$, $p=0.21$; reaction time: $F(3,114)=1.93$, $p=0.13$) or group (proportion error: $F(1,38)<0.01$, $p=0.96$; reaction time: $F(1,38)=0.01$, $p=0.91$). For proportion error, the interaction between group and task context was also not significant ($F(3,114)=2.20$, $p=0.09$). For reaction times, there was a significant interaction, ($F(3,114)=10.78$, $p<0.01$), reflecting relatively fast responses for the school task in the scenes group, but the opposite in the letters group.

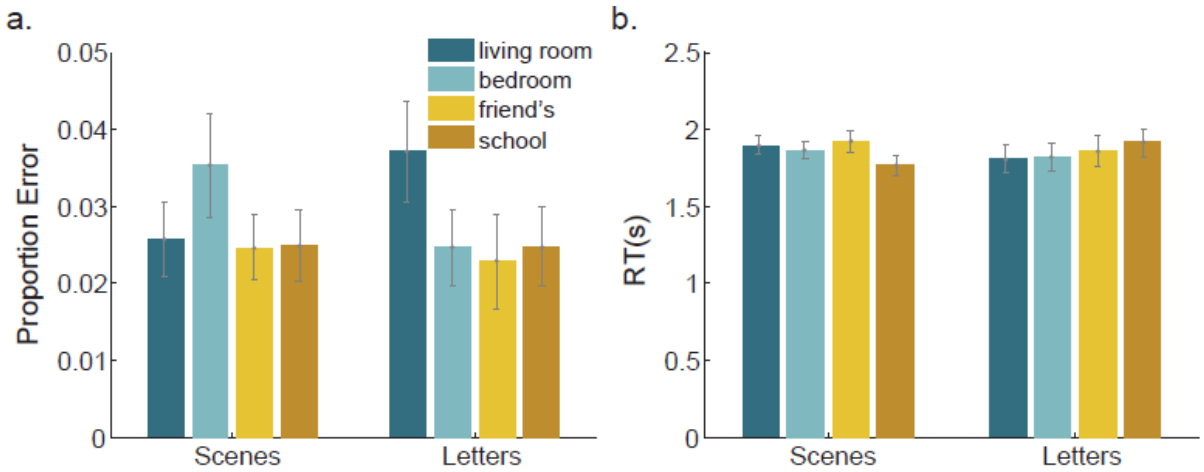

Figure 2.5. a. Proportion error and b. reaction time during auditory task performance for each group by context type. Error bars show standard error of the mean across participants within each group.

fMRI: Univariate

Regions of Interest

Separately for each DMN ROI, and for scene and letters groups, Figure 2.6 plots responses to context-dependent sounds (averaged across types) and the context-independent sound (birdsong). Across DMN regions, two distinct patterns of univariate activity can be seen. In the PCC, Rsp, PHC, HF, pIPL and TPJ a preference for scenes is shown, with this group difference particularly evident for context-dependent sounds. In the dmPFC, amPFC, vmPFC, LTC and temporal pole there is little evidence of a group effect; instead an effect of context-dependence is seen, with greater activity in the easier, context-independent condition compared to the context-dependent condition.

Data were examined using a three-way mixed model ANOVA with the factors of ROI, group and context-dependence. Significant main effects of ROI ($F(10,38)=10.21$, $p<0.01$), group ($F(1,38)=6.20$, $p<0.02$) and context-dependence ($F(10,38)=6.02$, $p<0.02$) were found, as well as significant

interactions between ROI and group ($F(10,38)=4.48$, $p<0.01$), ROI and context-dependence ($F(10,38)=5.09$, $p<0.01$), context-dependence and group ($F(1,38)=4.09$, $p=0.05$), and a significant three-way interaction between ROI, group and context ($F(10,38)=11.97$, $p<0.01$). For each individual ROI, two-way mixed model ANOVAs with the factors group and context-dependence were then performed. Multiple comparisons between ROIs were corrected for using the Bonferroni-Holm correction. The results, presented in Table 2.2, confirm the above impressions. Medial frontal and anterior temporal regions only showed an effect of context-dependence, significant after multiple comparison correction in vmPFC and LTC. In comparison, several posterior DMN regions (HF, PHC, Rsp, pIPL) showed a significant interaction between group and context-dependence with PHC and Rsp also showing a main effect of group. Also shown in Figure 2.6 are the results from t-tests of each contrast against baseline, also corrected for multiple comparisons across ROIs.

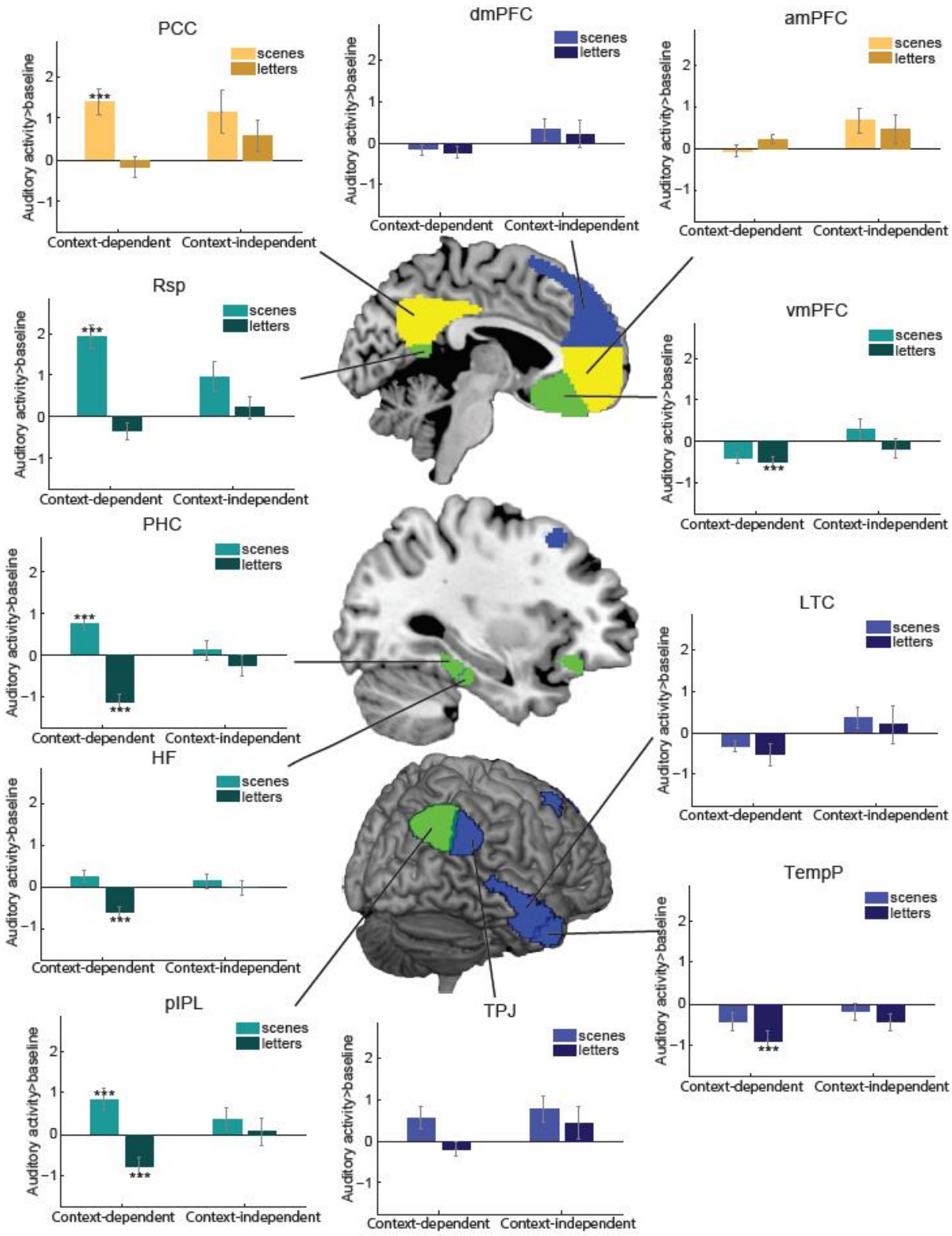

*Figure 2.6. Beta estimates for auditory events against implicit baseline in DMN ROIs, separated by context-dependence (context-dependent or context-independent) and group (scene or letter). Asterisks on bars indicate significant differences from baseline (single sample 2-tailed t-tests) after multiple comparison correction, *** = p<0.01*, ** = p<0.02, * = p<0.05*. Error bars show standard error of the mean across participants within each group. Colour indicates subnetwork: yellow = Core DMN, green = MTL DMN, blue = dmPFC DMN. PCC=posterior cingulate cortex, amPFC=anteromedial*

prefrontal cortex, HF=hippocampal formation, PHC=parahippocampus, Rsp=retrosplenial cortex, pIPL=posterior inferior parietal lobe, vmPFC=ventromedial prefrontal cortex, LTC=lateral temporal cortex, TPJ=temporo-parietal junction, TempP=temporal pole, dmPFC=dorsomedial prefrontal cortex.

Table 2.2. Results of two-way mixed model ANOVAs with a between-participant factor of group and a within-participant factor of context-dependence, for each ROI. Significant effects after Bonferroni-Holm multiple correction comparison across ROIs within each network (whole DMN, MD) are in bold. Colour indicates (sub)network: yellow = Core DMN, green = MTL DMN, blue = dmPFC DMN, plum = MD. PCC=posterior cingulate cortex, amPFC=anteromedial prefrontal cortex, HF=hippocampal formation, PHC=parahippocampus, Rsp=retrosplenial cortex, pIPL=posterior inferior parietal lobe, vmPFC=ventromedial prefrontal cortex, LTC=lateral temporal cortex, TPJ=temporo-parietal junction, TempP=temporal pole, dmPFC=dorsomedial prefrontal cortex, AI/FO=anterior insula/frontal operculum, preSMA/ACC=pre-supplementary motor area/anterior cingulate cortex, pdLFC= posterior dorsolateral frontal cortex, IPS=inferior parietal sulcus, aIFS=anterior inferior frontal sulcus, pIFS=posterior inferior frontal sulcus, IFJ=inferior frontal junction.

ROI	**Context-dependence**		**Group**		**Interaction**	
	F(1,38)	**P**	**F(1,38)**	**P**	**F(1,38)**	**P**
PCC	1.39	0.25	4.66	0.04	5.13	0.03
amPFC	7.62	0.01	0.02	0.90	1.91	0.18
HF	4.98	0.03	7.94	<0.01	**10.44**	**<0.01**
PHC	0.91	0.35	**16.92**	**<0.01**	**40.64**	**<0.01**
Rsp	1.73	0.12	**16.96**	**<0.01**	**25.96**	**<0.01**
pIPL	1.10	0.30	7.19	0.01	**14.33**	**<0.01**
vmPFC	**12.16**	**<0.01**	1.24	0.27	1.82	0.19
TPJ	3.99	0.05	2.24	0.14	0.88	0.35
LTC	**15.30**	**<0.01**	0.22	0.64	0.01	0.93
TempP	7.61	<0.01	1.68	0.20	0.71	0.41
dmPFC	7.27	<0.01	0.09	0.77	0.02	0.89
AI/FO	0.51	0.48	0.33	0.57	2.07	0.16
preSMA/ACC	0.13	0.72	0.51	0.48	3.64	0.06
IPS	3.08	0.09	0.68	0.41	**11.41**	**<0.01**
pdLFC	0.96	0.33	0.19	0.66	5.56	0.02
IFJ	2.99	0.09	<0.01	0.99	1.13	0.29

pIFS	0.82	0.37	0.21	0.65	0.47	0.50
aIFS	0.06	0.80	0.04	0.85	5.75	0.02

The same analyses were repeated for regions of the MD network. For each MD ROI, and for scene and letters groups, Figure 2.7 plots the BOLD response to context-dependent sounds and the context-independent sound. MD regions showed strong responses for all conditions of the auditory task compared to baseline email activity. For the letters group, as expected, response appeared stronger for the harder context-dependent sounds. Intriguingly, this result was eliminated or even reversed in the scenes group. Confirming these impressions, a three-way mixed model ANOVA between ROI, group and context-dependence showed a main effect of ROI ($F(6,38)=19.45$, $p<0.01$) and a significant interaction between ROI and context-dependence ($F(6,38)=6.12$, $p<0.01$). The interaction between group and context-dependence also trended towards significance ($F(1,38)=3.94$, $p=0.054$). Separate two-way mixed model ANOVAs for each ROI (Table 2.2) showed, after correcting for multiple comparisons across ROI, a significant interaction effect between group and context-dependence only in the IPS.

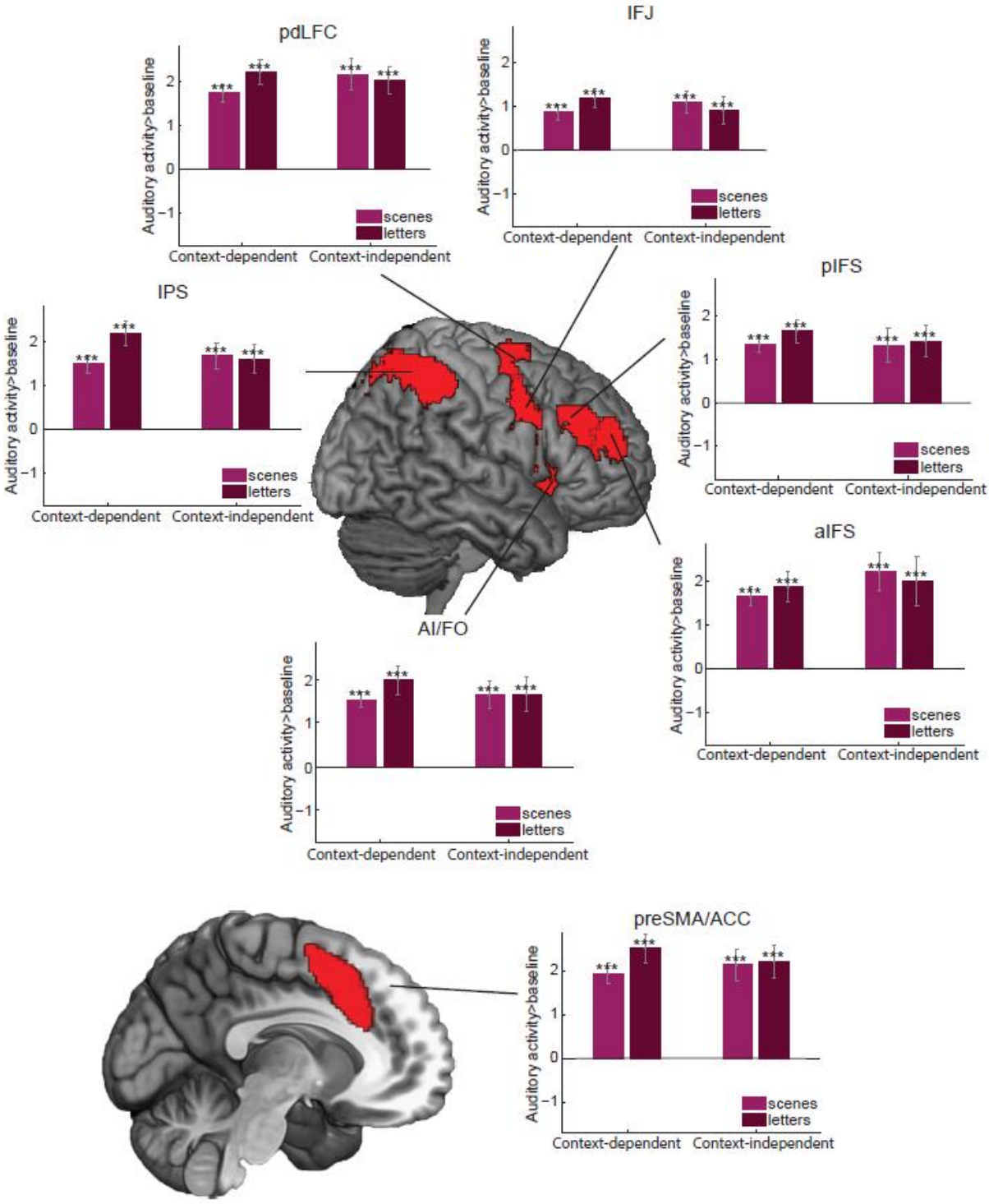

Figure 2.7. Beta estimates for auditory events against implicit baseline in MD ROIs, separated by *context-dependence (context-dependent or context-independent) and group (scene or letter). Format as in figure 2.6. AI/FO=anterior insula/frontal operculum, preSMA/ACC=pre-supplementary motor area/anterior cingulate cortex, pdLFC= posterior dorsolateral frontal cortex, IPS=inferior parietal sulcus, aIFS=anterior inferior frontal sulcus, pIFS=posterior inferior frontal sulcus, IFJ=inferior frontal junction.*

Whole brain

To supplement the ROI analyses, Figure 2.8 shows the results of a whole brain analysis for the interaction between group and context-dependence, thresholded at p<0.05, FDR corrected. In line with the ROI analysis, posterior DMN regions of PCC/Rsp, left PHC and left pIPL showed a stronger scene>letter contrast for context-dependent sounds compared to context-independent sounds (Figure 2.8, blue). This results was reversed in MD regions of IPS, IFJ, along with left extrastriate and right motor cortex, with a stronger letter>scene contrast for context-dependent sounds compared to context-independent sounds.

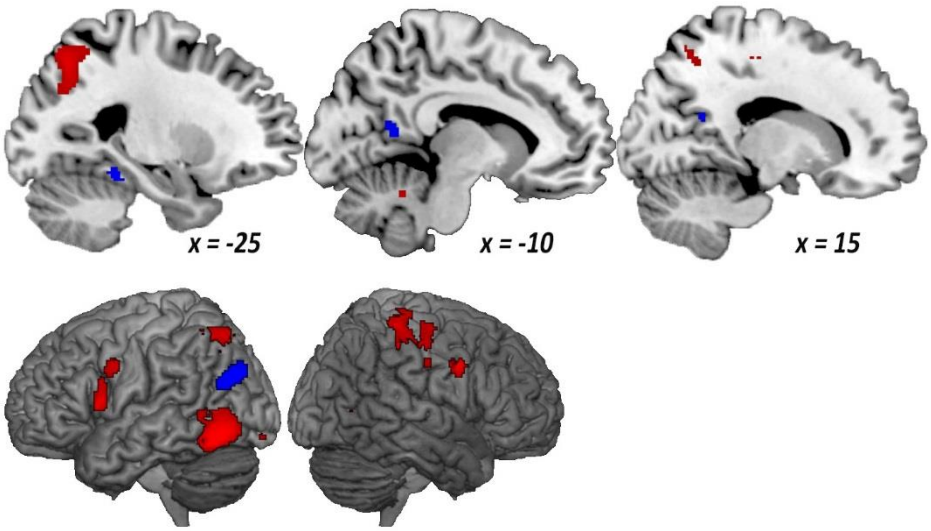

Figure 2.8. Whole brain results for the interaction of group by context-dependence (p<0.05, corrected by FDR). Blue colour voxels in which the scene>letter contrast is stronger in context-dependent sounds compared to context-independent sounds. Red colour represents voxels in which the letter>scene contrast is stronger in context-dependent sounds compared to context-independent sounds. The brain render shows a search depth of 8 voxels. Sagittal slices show x coordinate values in MNI space.

fMRI: Multivariate

To understand the representational content in DMN and MD regions, a representational similarity analysis (RSA) was performed. Separate contrasts were created to show multivariate discrimination of context, sound and response (see the Methods section and Figure 2.3). The analysis was conducted for just the context-dependent sounds. Results are shown in Figure 2.9 for each DMN ROI.

For context decoding, throughout much of the DMN, with the exception of anterior lateral temporal regions, a group effect is seen with scene context decoding much stronger than letter context decoding. To assess these effects, a two-way mixed model ANOVA with group as the between participant factor and ROI as the within participant factor was performed, finding significant main

effects of ROI ($F(10,38)=1.91$, $p<0.05$) and group ($F(1,38)=10.48$, $p<0.01$); the interaction, however, was not significant ($F(10,38)=1.78$, $p>0.05$). Figure 2.9 shows results of individual t-tests, comparing decoding level against chance (0) and independent-samples t-tests comparing between groups. Again, these t-tests were corrected for multiple comparisons across ROIs. They suggest significant context decoding for scenes in 8 of 11 regions of the DMN, weakest in lateral temporal lobe ROIs. Furthermore, in the Rsp, amPFC and pIPL, independent samples t-tests showed a significant difference between context decoding in the scene and letters group.

Several DMN regions also showed significant sound decoding. Decoding was disproportionately strong in the lateral temporal ROI, presumably due to its proximity to auditory cortex. Like context decoding, sound decoding also tended to be stronger in the scenes group than the letters group with all but the hippocampus showing significant sound decoding in the scenes group. To quantify these effects, data were examined using a two-way mixed model ANOVA with group as the between participant factor and ROI as the within participant. The analysis showed a significant main effect of ROI ($F(10,38)=29.10$, $p<0.01$). Neither the effect of group ($F(1,38)=2.24$, $p>0.05$, nor the interaction effect was not significant ($F(10,38)=1.43$, $p>0.05$). As this analysis could be being driven by the disproportionately strong results of the LTC, this two-way ANOVA was repeated with the LTC ROI removed. Again, a main effect of ROI was found ROI ($F(9,38)=5.08$, $p<0.01$); the effect of group was also now significant ($F(1,38)=4.15$, $p<0.05$) reflecting greater sound decoding for the scenes group in most DMN regions. This group effect was further demonstrated by the results of t-tests showing sound decoding only in the scenes group in the PHC, amPFC, vmPFC, and TempP. Independent samples t-tests further showed that sound decoding was stronger in the scenes group compared to the letters group in the pIPL.

A similar ANOVA for response decoding showed only a significant effect of ROI ($F(10,38)=2.87$, $p<0.02$); the group effect ($F(1,38)=1.52$, $p>0.05$) and the interaction ($F(10,38)=0.86$, $p>0.05$) were both non-significant. After correcting for multiple comparisons, t-tests showed significant response decoding in the PCC and dmPFC for the scenes group only.

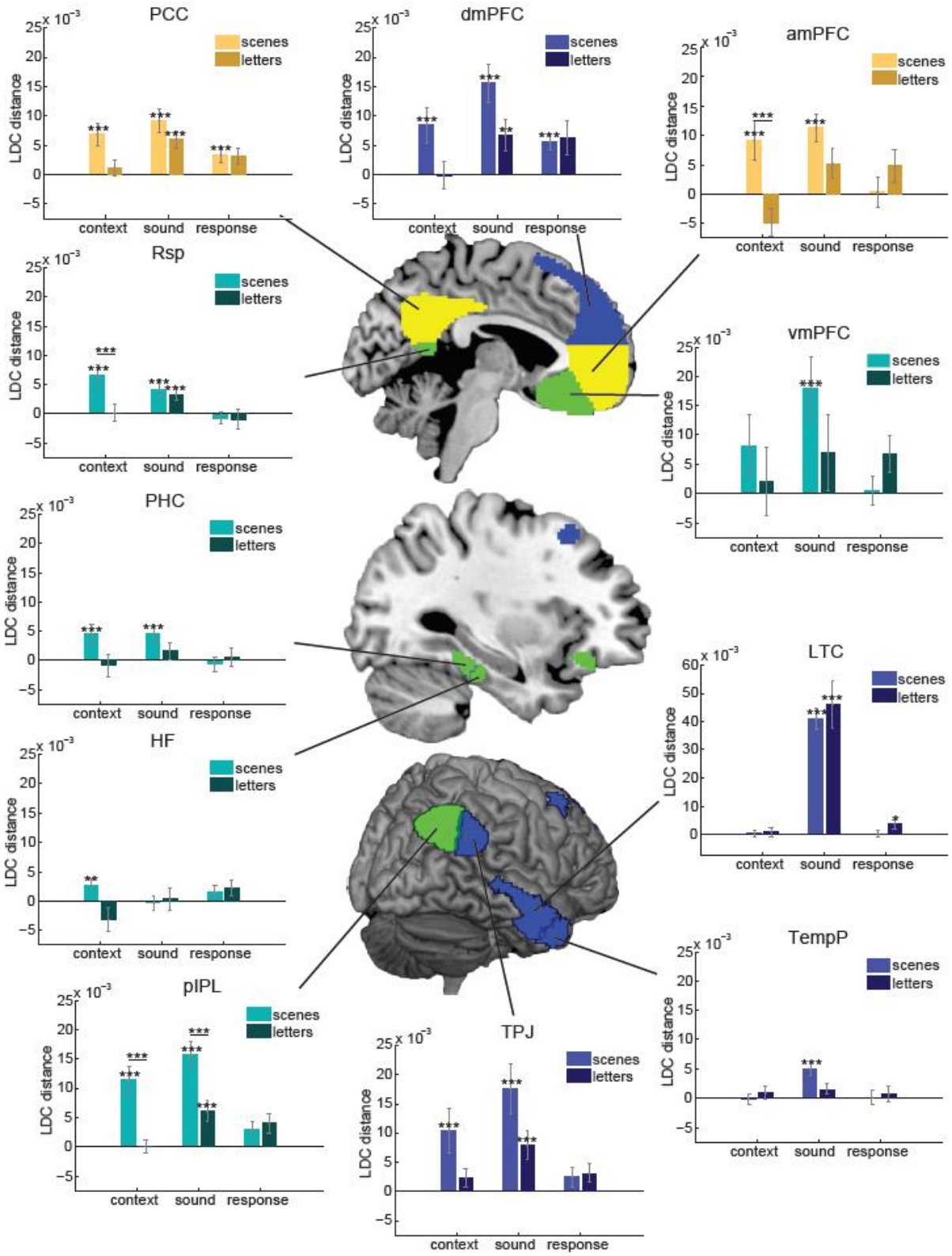

*Figure 2.9. Representational dissimilarity for task features by group in DMN ROIs. Y-axis is an LDC distance measure of discrimination. For full details of how task feature dissimilarity measures were computed, see Methods and Figure 2.3. Asterisks on bars indicate significant above chance decoding (single sample 1-tailed t-tests). Lines indicate significant group differences (independent samples 2-tailed t-tests). All t-tests we corrected for multiple comparisons by Bonferroni-Holm correction across ROIs. *** = p<0.01, ** = p<0.02, * = p<0.05. Error bars show standard error of the mean across*

participants within each group. Colour indicates subnetwork: yellow = Core DMN, green = MTL DMN, blue = dmPFC DMN. PCC=posterior cingulate cortex, amPFC=anteromedial prefrontal cortex, HF=hippocampal formation, PHC=parahippocampus, Rsp=retrosplenial cortex, pIPL=posterior inferior parietal lobe, vmPFC=ventromedial prefrontal cortex, LTC=lateral temporal cortex, TPJ=temporo-parietal junction, Temp-Pole=temporal pole, dmPFC=dorsomedial prefrontal cortex.

Figure 2.10 presents similar results for MD ROIs. Again, a two-way mixed model ANOVA was constructed for each type of information, with group as the between participant factor and ROI as the within participant factor.

For context decoding, a few MD regions, especially the IPS, showed strong scene context decoding compared to letter context decoding. The results from the a two-way mixed model ANOVA reflected this, finding significant main effects of ROI ($F(6,38)=10.25$, $p<0.01$) and group ($F(1,38)=7.57$, $p<0.01$), along with a significant interaction ($F(6,38)=6.85$, $p<0.01$). Additional t-tests, corrected for multiple comparisons, revealed significant context decoding for scenes in IPS and IFJ.

For sound decoding, all regions showed strong sound decoding with few differences between groups. Again, decoding was particularly strong in IPS. Reflecting these observations, the two-way mixed model ANOVA revealed significant main effects of ROI ($F(6,38)=10.68$, $p<0.01$), while the effect of group ($F(1,38)=0.85$, $p>0.05$) and the interaction were not significant ($F(6,38)=0.54$, $p>0.05$). Even after correcting for multiple comparisons, t-tests showed significant sound decoding for both sound and letters groups across all MD regions.

Response decoding was particularly strong in IPS with a trend towards stronger response decoding in the letter condition across most MD regions. The two-way mixed model ANOVA showed a significant effect of ROI ($F(6,38)=7.67$, $p<0.01$); however, the group effect ($F(1,38)=2.92$, $p>0.05$) and the interaction ($F(6,38)=1.55$, $p>0.05$) were not significant. T-tests showed that response decoding for the scenes group was limited to the IPS, while pdLFC also showed response decoding in the letters group.

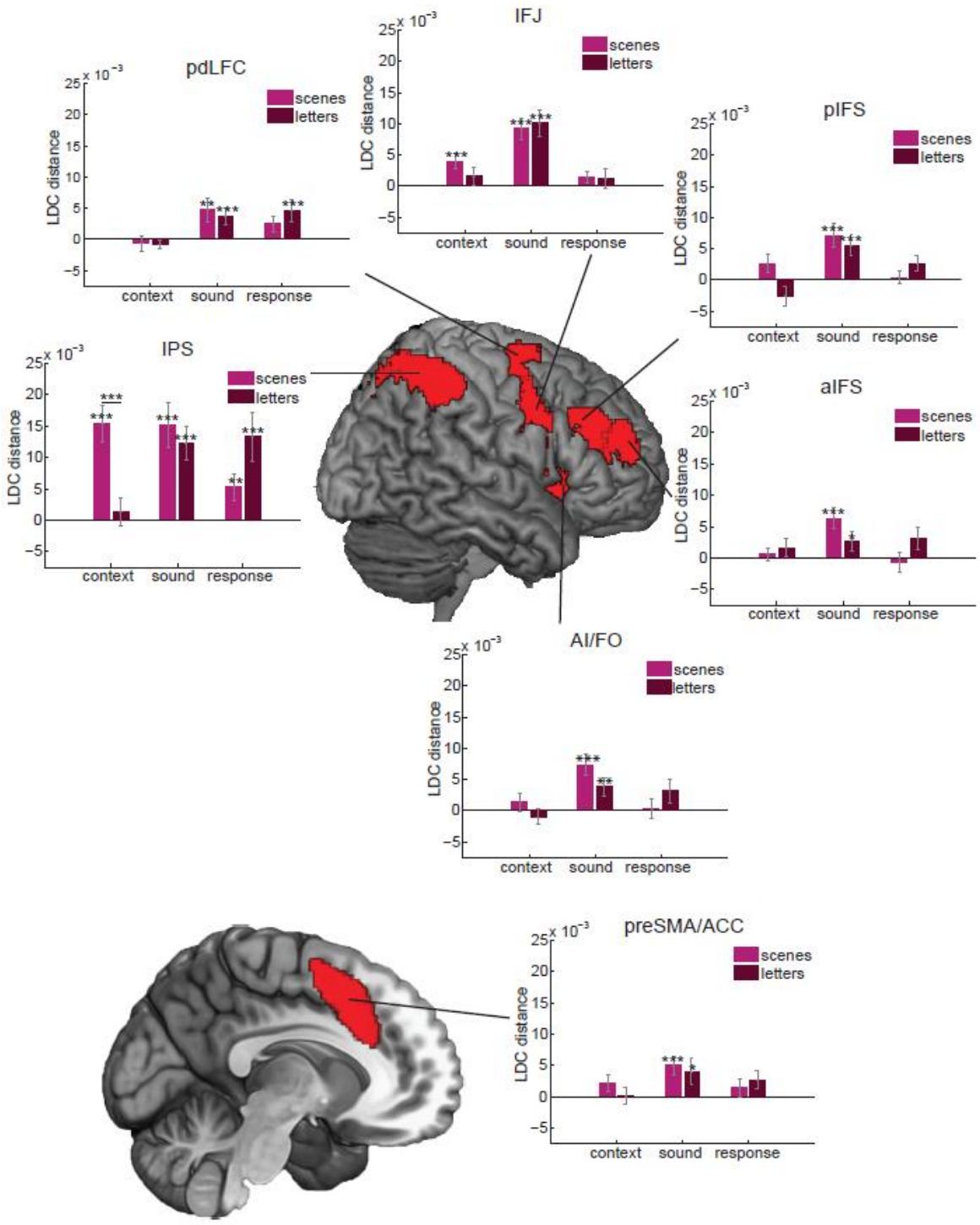

Figure 2.10. Representational dissimilarity for task features by group in MD ROIs. Format as in figure 2.9. AI/FO=anterior insula/frontal operculum, preSMA/ACC=pre-supplementary motor area/anterior cingulate cortex, pdLFC= posterior dorsolateral frontal cortex, IPS=inferior parietal sulcus, aIFS=anterior inferior frontal sulcus, pIFS=posterior inferior frontal sulcus, IFJ=inferior frontal junction. For full details of how task feature dissimilarity measures were computed, see Methods and Figure 2.3.

DISCUSSION

This experiment aimed to test the theory that the DMN is associated with contextual decision making in lifelike contexts. To test this, activity during decision making using lifelike scenes was directly compared with activity during decision making using arbitrary letter cues. In comparison to DMN regions which were hypothesised to show sensitivity for lifelike contexts, the MD system was hypothesised to be active for all demanding tasks, regardless of the context type.

Despite minimal behavioural differences between groups, substantial effects of group were found in neural responses of the two networks of interest. In DMN regions, two distinct patterns of univariate responses were identified. Firstly, replicating the standard 'task-negative' DMN effect (McKiernan et al. 2003, 2006; Fox et al. 2005a), medial prefrontal and anterior lateral temporal DMN regions showed greater activity for context-independent decisions compared to the more difficult context-dependent decisions regardless of group. A group of posterior DMN regions, however, were also sensitive to context type. In line with theories emphasising the importance of DMN regions in constructing and representing scenes, events and situation models (Bar 2007, 2009; Hassabis and Maguire 2007; Ranganath and Ritchey 2012), these posterior DMN regions showed greater activation for scenes compared to letters. Furthermore, contrary to the 'task-negative' viewpoint, in the scenes group, activity in these regions was stronger for more difficult context-dependent decisions compared to context-independent decisions. These findings suggest that some DMN regions are important for contextual decision making in meaningful, lifelike contexts.

Interestingly, the dissociation between DMN regions appear to not follow the segmentation of the DMN found from resting state functional connectivity by Andrews-Hanna et al. (2010) and Yeo et al. (2011). These posterior DMN regions instead make up the components of the posterior medial system described by Ranganath and Ritchey (2012). The posterior medial system, consisting of the posterior hippocampus, parahippocampus, retrosplenial cortex, posterior cingulate and posterior inferior parietal lobe, is proposed to play a primary role in the construction and representation of a situation model. These situation models are thought to hold information about the broad features of the current situation and relevant information associated with these situational features. Evidence from the multivariate analyses also suggests that a broader set of DMN regions can represent features of a task situation. Specifically, several DMN ROIs showed decoding of both context and sound information, especially in the scenes group.

As posterior DMN regions have been repeatedly linked to visual scene perception (Epstein and Kanwisher 1998; Bird and Burgess 2008), one might wonder whether DMN activity during context-dependent decision making in the scenes group is simply related to visual scene perception, necessary only during context-dependent trials, rather than also representing contextual associations required to make context-dependent decisions. Although a definitive answer would require further experiments with non-visual contexts, several aspects of the findings suggest that this may not be the entire story. While the univariate results, found typical 'scene perception' regions of the PHC, several additional regions - Rsp, HF, PCC and pIPL - showed selective responses to scene-based decisions. In representational similarity analysis, even more extensive DMN regions were found to encode scene information, including amPFC, dmPFC and TPJ. Furthermore, many DMN regions showed decoding of sound type as well as context, and across these regions, sound representation was also enhanced in the scenes group. As well as contributing to visual scene perception, these results suggest also that in scene-based decision making DMN regions are involved in representing multiple aspects of the cued context, using such integrated information to control appropriate behaviour.

Research from the cognitive control literature would suggest that MD regions are important for task control across a diverse range of task demands (Duncan 2010, 2013; Badre and Nee 2018). In line with these theories, MD regions showed a strong increase in activity during auditory decision making events compared to the baseline email task in both scene and letters groups. However, unlike previous findings (Koechlin et al. 2003; Badre and D'Esposito 2007), and contrary to the typical increases in MD activity with increased task demands (Fedorenko et al. 2013), MD regions did not show a predicted increase in activity with the more demanding context-dependent decisions compared to context-independent decisions. Instead, the IFJ, identified in the whole brain analysis only, and the IPS showed an interaction between context-dependence and stimulus type. Activity in these regions showed a stronger effect of context-dependence in the letters group compared to the scenes group. Importantly, this interaction was the reverse of that shown in posterior DMN regions in which activation increased for context-dependent sounds compared to context-independent birdsong in the scenes group. This finding might suggest that, during context-dependent decision making, with rich meaningful contexts, DMN regions can 'take over' control functions from MD regions.

At first glance, the context decoding results for MD regions, showing no letter context decoding, seem contrary to the univariate results showing the relative importance of MD regions for letter-based decisions. However, in the letters group, the context-dependent task did not require representation of the entire letter pair on any given trial. Instead, when a sound was played, the

participant simply needed to check whether its first letter was included in the letter pair at the top of the screen. As the letter searched for was related to the played sound, letter processing may largely have been reflected in our measure of sound decoding.

Linking together research on contextual control and situation models, these findings suggest that posterior DMN regions can play a role in context-dependent decision making, only when the context is a more meaningful scene compared to a more abstract association. With a meaningful spatial context, posterior DMN regions, similar to the posterior medial network described by Ranganath and Ritchey (2012), showed increased activation for context-dependent decisions compared to context-independent decisions, while the reverse pattern was observed for an arbitrary letter context. Consistent with previous findings, the MD system appears to have a more general function, important for auditory decisions with both context types. Intriguingly, a possible interpretation of the findings is that, during meaningful contextually dependent decision making, these networks interact, with posterior DMN regions potentially ‘taking over‘ control functions, reflected in a reduction in MD activity. Depending on context, either DMN or MD regions may play a prominent role in selection and control of appropriate behaviour.

Chapter 3

Naturalistic task performance in brain damaged patients

INTRODUCTION

The results from Chapter 2 suggested that task performance utilised additional brain regions when using more meaningful stimuli compared to using abstract task rules. Similar findings have also been reported in the neuropsychology literature. While brain lesioned patients' IQ scores have been found to fully explain the variance in a number of other executive tasks (Roca et al. 2010), Shallice and Burgess (1991) found naturalistic tasks were more sensitive in capturing patient impairment compared to standard executive tasks. Frontal lobe patients were asked to perform a number of executive tasks and two complex naturalistic tasks: the six element task and the multiple errands task. In the six element tasks participants were asked to maximise their score on three sets of two tasks within a 15 minute time period. Within each task, the problems became increasingly difficult so the optimal strategy was to spend an equal amount of time on each task. In the multiple errands task, which took place in a pedestrian precinct, participants were asked to complete eight lifelike tasks. These included shopping for certain items, being present at a scheduled time and finding out the price of tomatoes. Participants were also given several additional rules, for example, that they must buy something from any shop they enter. Although the patients showed no differences from controls on standard measures of executive function, they performed significantly worse on the naturalistic tasks. Patients undertook fewer of the six element tasks, spending longer on each task and, despite memory for the rules, made more rule breaks, failed more tasks and made more inefficient planning decisions in the multiple errands task.

In a direct comparison with Cattell IQ scores, Roca et al. (2010) also found frontal lesion patient impairment in several naturalistic tasks including the hotel task (a version of the six element task) and the faux pas task where participants were asked to make judgements about the social correctness of certain events. While impairments in other executive tasks could be explained by deficits in fluid IQ, deficits in these more naturalistic tasks could not be fully accounted for by fluid IQ scores.

A recent movement in neuroscience has been to understand the functional roles of large-scale brain networks rather than individual brain regions. In line with this goal, Woolgar et al. (2010, 2018) tested 80 patients with focal brain lesions on a fluid intelligence task, the Cattell Culture Fair (Cattell 1971). Patient MD lesion volume, as well as total lesion volume and lesion volume in language specific regions, were then correlated with patient scores of fluid IQ. Complementary to imaging findings (Duncan 2006; Bishop et al. 2008), only MD lesion volume was found to be predictive of fluid IQ, suggesting that the MD network is necessary for IQ. However, as naturalistic task performance cannot fully be explained by fluid IQ scores, it is possible that a different brain network might be responsible for naturalistic task performance.

Further analyses from Roca et al. (2011) particularly implicated the anterior PFC in naturalistic task impairment. Roca et al. (2011) split the patient group into those with and without anterior PFC lesions. Only the patient group with anterior PFC lesions showed deficits compared to controls in the hotel and faux pas tasks. The anterior prefrontal cortex contains both lateral and medial subregions that have been linked to several functional roles indicating a role in naturalistic task performance. The anterior lateral PFC has been implicated in multi-tasking, representation of alternative choices and prospective memory (Daw et al. 2006; Benoit et al. 2011; Boorman et al. 2011; Boschin and Buckley 2015). The anterior medial PFC, on the other hand, is often implicated in social reasoning (Gilbert et al. 2007), often as part of the larger DMN (Frith and Frith 2003).

As seen in the previous chapters, the DMN has also been related to a number of naturalistic tasks including navigation (Spiers and Maguire 2007; Howard et al. 2014; Javadi et al. 2017, 2018), episodic memory recall (Diana et al. 2007; Hayama et al. 2012) and meaningful context dependent decision making (Chapter 2). As the previously outlined studies have focused purely on frontal patients, it is unclear to what extent whole brain networks, such as the DMN, are necessary for good performance in complex, naturalistic tasks. This study aimed to understand how networks of brain regions rather than regions within a single lobe contribute to cognitive function. Thirty four brain damaged patients and 30 non-brain damaged controls were tested on the Cattell IQ test as well as three more naturalistic tasks. Importantly, these patients had brain lesions to different cortical regions, not exclusively frontal regions. The naturalistic tasks were designed to measure different aspects of lifelike experience including time management and social reasoning. By using such different naturalistic tasks, the secondary aim of this research was to understand to what extent different naturalistic task elements depend on overlapping or different cognitive processes.

METHODS

Patients

34 patients were tested from the Cambridge Cognitive Neuroscience Research Panel at the MRC Cognition and Brain Sciences Unit. Patients were selected on the basis of having chronic, focal lesions from mixed aetiology excluding traumatic brain injury, and aged between 18-80 years. There were no other formal exclusion criteria for region of lesion or specific cognitive deficit. Two patients were unable to complete more than 1 task so have been excluded from further analysis. 30 non-brain damaged control participants were also tested. Control patients were age and years of education matched to the patient group. There were no significant differences between the age of patients (mean=58.4, SD=15.3) and controls (mean=56.2, SD=17.5) ($t(28)=0.039$, $p=0.97$) or the years of education of patients (mean=13.9, SD=2.33) and controls (mean=14.3, SD=3.65) ($t(28)=0.171$, $p=0.87$).

Testing

Participants were given a battery of computer-based and other tasks described below. The test battery was completed in a single session lasting around 90-120 minutes. The battery consisted of 7 tasks, presented in the following order: Cattell, situations, *frames*, hotel 1, *concurrent discrimination*, switch length, hotel 2, *background*. This chapter will focus only on the Cattell, situations, hotel and switch length tasks, as remaining tasks did not focus on naturalistic decision making and time management. For one patient, the battery was split into two shorter sessions. Computer-based tasks were given on a Dell 1280x1024 resolution laptop.

Tasks

Cattell

Participants were given the standardised version of the Cattell Culture Fair, Scale 2 - Form A (Cattell, 1971) which contained four timed subtasks (series completion, odd one out, matrices, topological relations). At the start of each subtask, the experimenter read aloud the rules to the participant and went through 3 examples with them. Total correct scores were calculated and then converted into IQs from the standardised table of norms ("Institute for Personality and Ability Testing" 1973). To match the rest of the data set, IQ scores were inverted such that higher numbers would correspond to poorer performance.

Situations

While the faux pas task tested patients' understanding of social appropriateness, a large overlap has been found between brain regions implicated in social reasoning and a number of other cognitive functions including establishing broad contexts (Ranganath and Ritchey 2012; Baldassano et al. 2016) and event narratives (Baldassano et al. 2017). The situations task was designed to test social and non-social decision making in real-life vignettes. During the task, participants were shown 12 short stories and after each story asked one social judgement question, one emotion judgement question and one executive judgement question. An example story and question set is presented in Figure 3.1. For each item participants were first shown the story text and asked to read through the story. After reading, participants were asked to press a button. With the story text still present on the screen the questions were then presented one by one along with 3 possible answers each. The answer options were designed such that one was correct, one was very incorrect and the third was plausible but less optimal than the correct option. Participants were asked to respond as quickly as they could using buttons "1", "2" or "3" on the keyboard, corresponding to the 3 possible answers. The order of story presentation was randomised and the order in which the questions were presented was pseudorandomised such that each type of question (social, feeling and executive) were presented equally first, second and third. The position of the correct answer was counterbalanced across question types such that it appeared in positions 1, 2 and 3 on an equal number of trials. As presented in the Results section, the preliminary analyses assessed group effects against question type. For the main analyses scores were then averaged across question types to create scores of proportion error and median reaction time for correct trials.

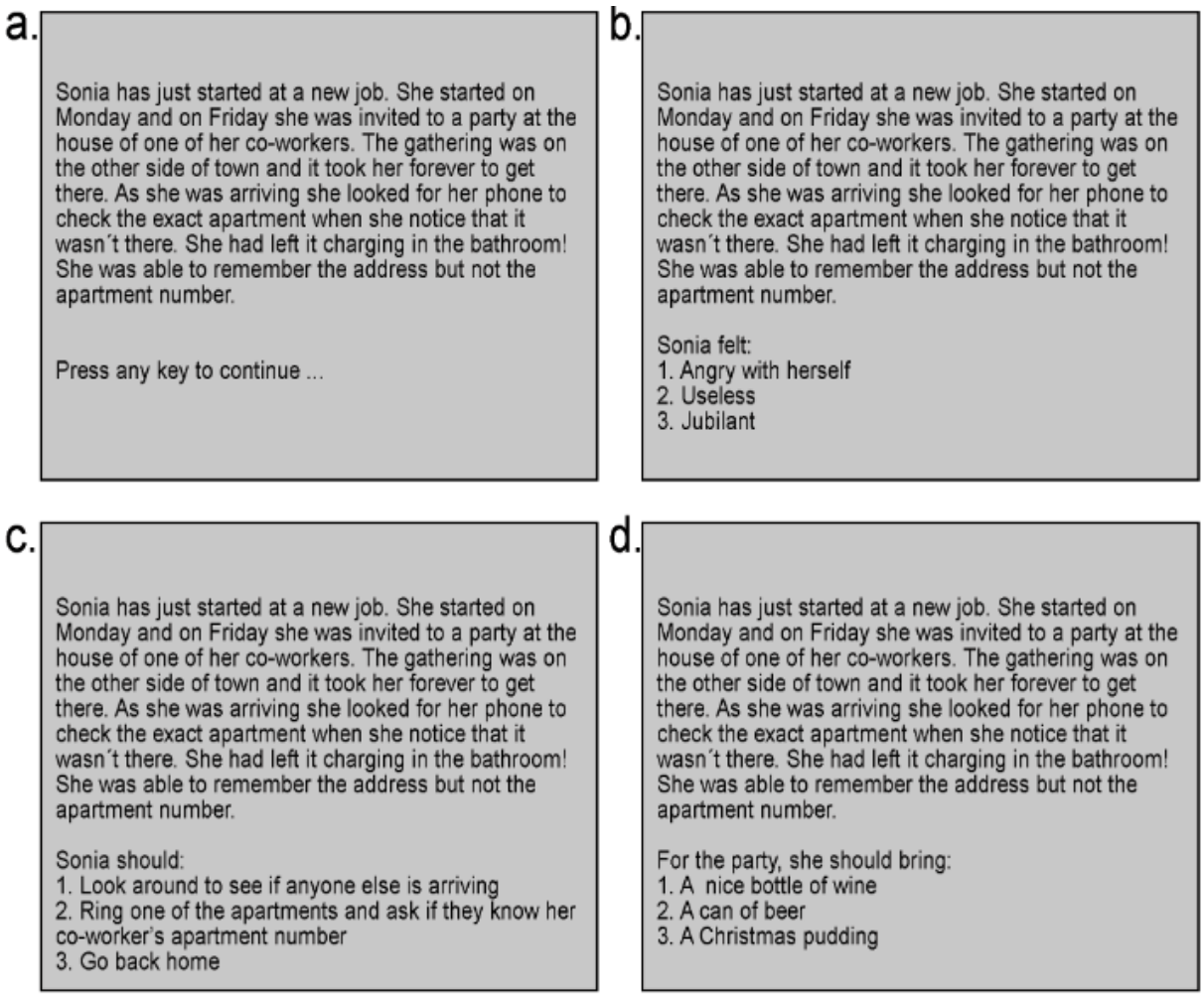

Figure 3.1. An example item in the situations task. a. Participants first read the story at their own pace before pressing any key to continue. Participants were then presented with a feeling question (b), an executive question (c) and a social question (d), in counterbalanced order. The questions were self-paced and the story remained on the screen throughout the question phase.

Hotel

Following Roca et al. (2010, 2011) participants were also tested on a version of the hotel task. An example of the hotel task layout is presented in Figure 3.2. Participants were asked to imagine they were in a job interview for a position at a hotel and were asked to try 3 different hotel tasks, each one involving sorting a stack of sheets of papers. Participants were shown each of the tasks and told to try and do some of each of them. Participants were told that they would have 9 minutes to complete the task and that it would be impossible to finish any of them completely in the time limit. To keep track of the time participants were given a clock. Throughout the task the clock was turned away from the participants but participants could choose to check it at any time before returning it to its backward-facing position.

Participants were given two variants of the task which varied the form of an interruption added to the subtasks. The order of the two variants was counterbalanced across participants with two other tasks performed in between the two variants. The addition of these interruptions follows from (Manly et al. 2002) who found patients performed no worse than controls on the hotel task when given an additional auditory alert designed to break participants' focus on the current task and reorient them to the overall goal of the experiment. The aim of the different interruption types used in this version of the hotel task was to test whether there was a differential benefit between reorienting participants' attention away from the subtask towards either another aspect of the task (internal interruption) or the broader external environment (external interruption). In the internal interruption condition a yellow sheet of paper was placed after every 7 task items in each subtask. Participants were told to place the yellow item in the same pile that they sorted the previous item. In the external interruption condition a written instruction, directing participants to perform an action directed towards an aspect of the participants' environment, was placed after every 7 task items in each subtask. Participants were asked to follow the written instruction (e.g. point to a window) and then place the instruction sheet to the side.

There were two sets of 3 tasks for each of the hotel versions. The set of tasks paired with each interruption condition was counterbalanced across participants. Set A consisted of sorting conference name tags by alphabetical order, sorting invoices into piles according to the vendors, and sorting bills into piles according to customer name. Set B consisted of sorting staff meeting name tags by alphabetical order, sorting restaurants lists into piles by their location, and sorting spa receipts into piles by treatment.

Preliminary analysis showed no differences between interruption types. However, there was evidence that participants (especially controls) improved their strategy when performing the task for the second time. Accordingly, scores were based on summed deviation from optimal time (180 seconds) across the 3 subtasks of the first version performed.

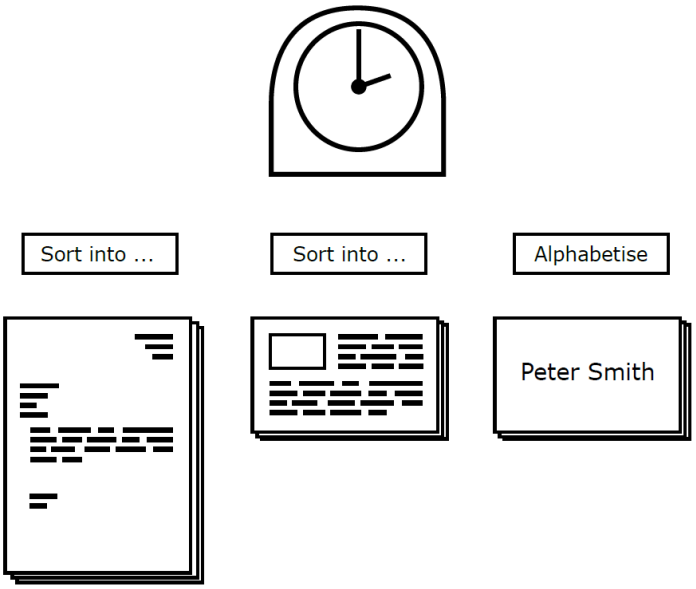

Figure 3.2. Experimental set up for the hotel task. Note that the clock was facing away from the participants except when explicitly checked.

Switch length

One of the differences between the hotel task and standard executive tasks is that in the hotel task there are extended periods of time where participants are continuing the same task at their own pace. It is possible deficits in hotel task performance are due to patients becoming absorbed in a subtask and losing track of the overall goal. The switch length task was designed to test whether patients are particularly impaired at task switching after longer rather than shorter periods of time. Task events are illustrated in Figure 3.3. For each trial, participants were presented with a picture to the left of the screen and a word with a letter missing on the right of the screen. Participants were required to make yes/no judgements on one of these stimuli based on a task rule cued by a central shape. If the rounded corners of the cue pointed towards the left then participants were asked to do the picture task. If the rounded corners of the cue pointed towards the right then participants were asked to do the word task. Changes in the cue were designed not to be too salient so that participants would need to remember to actively attend to the cue in order to know what task to do rather than being alerted by a salient change. The two tasks used were taken from Crittenden et al. (2015). For pictures, the decision was whether the item would fit in a shoebox; for words, it was whether addition of a letter ‘a’ in the blank position would create a real word. Participants were asked to make a “yes” or “no” response, by left or right keypress respectively, based on the task specified by the cue shape. Performance was self-paced, with the imperative stimuli remaining until a key was pressed, and participants were asked to respond as quickly as possible without making mistakes. An inter-trial interval (ITI) of 1.5 seconds followed each response.

Pilot studies revealed that switch performance continued to decline with an increase in the number of previously repeated trials until around 12 trials, after which performance remained similar. Accordingly, trials of the same task were repeated in blocks of 4, 6 or 12 trials with switch length presented in a pseudorandom order. This allowed for 4 switch conditions: stay trials (task trials preceded by the same task), switch 4 trials (task switch after 4 of the same task), switch 6 trials (task switch after 6 of the same task), and switch 12 trials (task switch after 12 of the same task). The experiment consisted of 1 run of 182 trials with a break in the middle of the run. The run contained 4 blocks of each length for each task (plus an additional final block of 6 trials) creating 152 stay, 8 switch 4 trials, 8 switch 6 trials, and 8 switch 12 trials. The entire task lasted approximately 18 minutes.

Before the start of the task, participants were shown 2 trials on paper and asked which task they would do given the cue shape and what button they would press in response to the cued stimulus. Participants continued with the main task only when the experimenter was satisfied that the participant understood the cue and remembered the button presses.

There were equal numbers of “yes” and “no” trials for each combination of task and switch type. At the task switch trial and the first stay trial after a task switch, correct answers for the word task and the picture task were always different. For all other stay trials, the correct response for the cued task was randomised so that it was the same as the uncued task on half of the trails and different on the other half of the trials.

To capture the effect of switch length on switching performance, scores were calculated as the difference between proportion error for switch 12 trials – switch 4 trials and, for correct trials only, the difference between median reaction time for switch 12 trials – switch 4 trials.

Each stimulus was positioned either side of fixation with 3.6 degrees of visual angle from stimulus centre to fixation. Each stimulus fit into a rectangle measuring approximately 6.0 (width) x 4.5 (height) degrees of visual angle. The cue was presented centrally measuring approximately 1.4 x 1.4 degrees of visual angle. The experiment was controlled using Psychophysics Toolbox for MATLAB (Brainard, 1997).

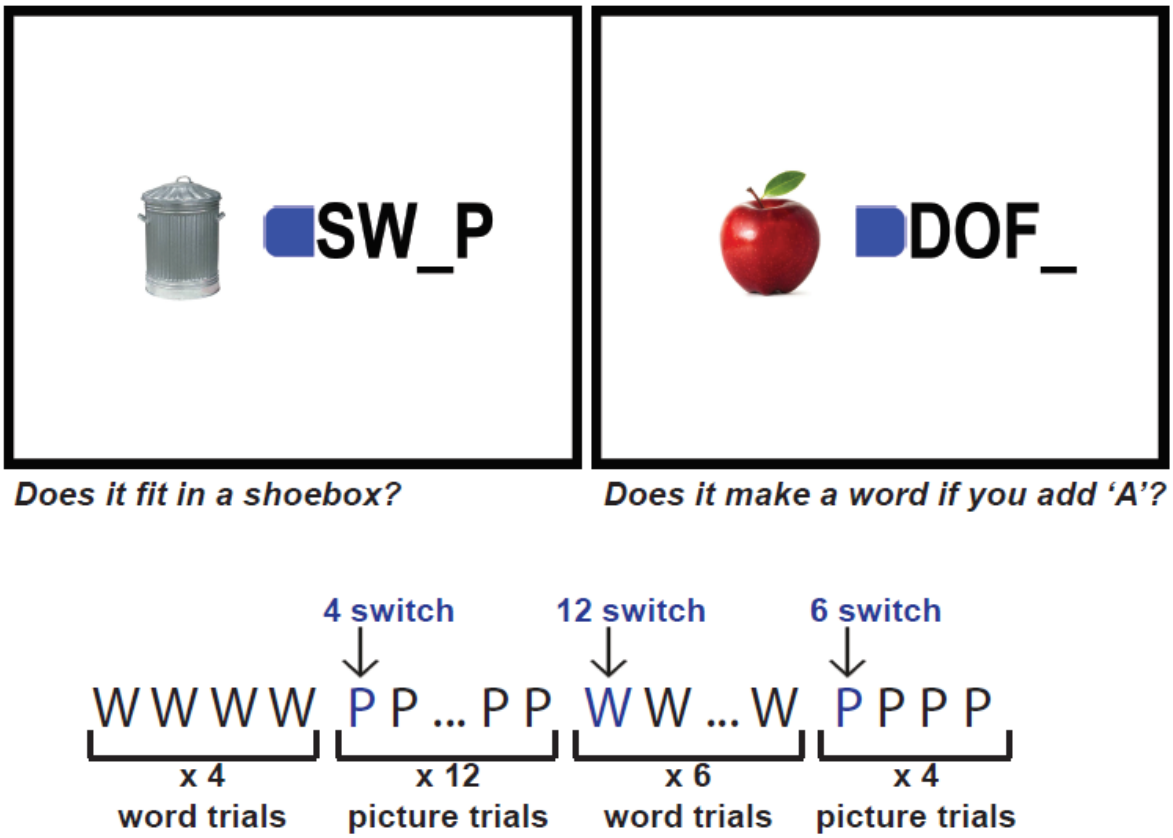

Figure 3.3. Task design for the switch length task. Pictures were presented to the left of the screen with words containing a blank space presented to the right of the screen. Participants were either cued to do the left hand picture task or the right hand word task depending on the direction of the rounded curves of the central blue square. The cued task alternated in blocks of 4, 6 or 12 repeating trials, creating switch trials which varied by number of trials of the previous task (switch 4, switch 6 and switch 12 trials). Note the blue task cue is not to scale with the rest of the task image; it has been enlarged so that the curved edges are visible.

Neuroradiological Assessment

MRI T1 and T2 structural scans were taken for all patients. Lesions were traced on structural images by a neurologist, blind to the experimental results, using MRIcron (Rorden and Brett 2000) before normalising to MNI space using SPM5 software (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) with cost-function masking to mask the lesion from the calculation of the normalization parameters (Brett et al. 2001).

Regions of Interest

DMN and MD network volumes were generated by combining the individual ROI volumes used in Chapter 2 (see Figure 2.2). The resulting MD network and DMN regions of interest (ROIs) are presented in Figure 3.4.

A final "Other" region of interest was also included to test for a performance deficit in patients associated with regions beyond those in the DMN and MD. The Other region was created using custom scripts for SPM 12 (Wellcome Department of Cognitive Neurology, London, UK). First a whole grey matter volume was created by concatenating all grey matter regions included in the AAL Atlas (Tzourio-Mazoyer et al. 2002). Then grey matter included in the MD or DMN, and all grey matter 5mm or less from these volumes, was excluded. As an additional occipital-temporal region is sometimes associated with the MD network but also strongly related to visual processing, this region, presented also in Figure 3.4, was also excluded. Remaining grey matter was assigned to the Other ROI.

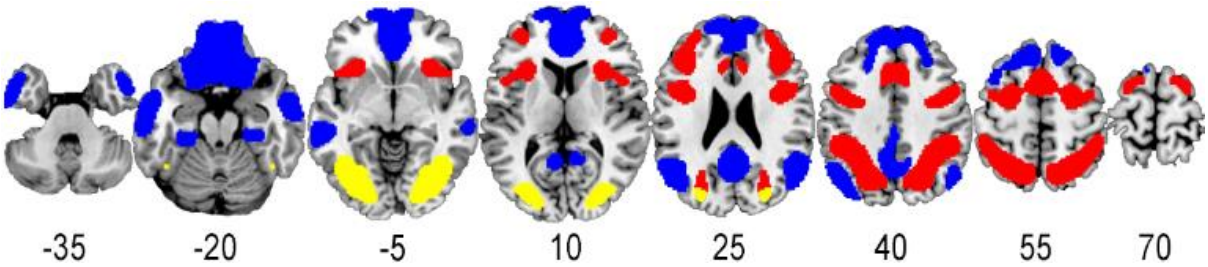

Figure 3.4 ROI volumes for MD network (red), DMN (blue) and the excluded occipital-temporal region (yellow). Horizontal slices show z coordinates in MNI space.

Volume of damage in each network was then calculated for each patient. Table 3.1 presents patient lesion volume for DMN, MD and Other ROIs.

Table 3.1. Patient demographics, task completion information and lesion volumes in ml for three regions of interest.

Sex	**Cattell**	**Situations**	**Hotel**	**Length**	**DMN**	**MD**	**Other**
M	y	y	y	n	10.42	17.58	17.62
M	y	y	y	y	26.85	12.04	11.89
F	y	y	y	y	8.93	7.78	24.39
M	y	y	y	n	27.94	6.72	4.74
M	y	y	y	y	8.46	26.82	20.52
F	y	y	y	y	6.30	15.17	6.97
M	y	y	y	y	7.60	0.00	14.70
M	y	y	y	y	6.81	0.02	0.40
F	y	y	y	y	2.32	3.08	3.20
M	y	y	1st only	n	26.28	7.86	11.98

F	y	y	y	y	4.46	8.62	4.35
M	y	y	y	y	33.00	1.57	5.08
F	y	y	y	y	4.64	2.66	23.87
M	y	y	y	y	0.32	8.28	12.88
M	y	y	y	y	7.08	8.74	8.74
M	y	y	y	y	0.00	9.17	17.90
F	y	y	y	y	2.23	14.27	5.09
F	y	y	y	y	1.70	0.00	7.70
F	y	y	y	y	4.90	0.00	12.48
M	y	y	y	y	4.54	10.10	5.75
M	y	y	y	y	45.29	21.00	10.64
F	y	y	y	y	8.73	5.57	3.71
M	y	y	y	y	0.50	16.50	19.19
M	y	y	y	y	0.03	12.04	11.57
F	y	y	y	y	0.00	0.10	28.64
M	y	y	y	y	1.46	0.00	3.82
M	y	y	y	y	5.96	0.00	6.77
F	y	y	y	y	1.39	18.46	0.22
M	y	y	y	y	11.14	3.10	14.89
M	y	y	y	y	0.24	14.67	0.61
M	y	y	y	y	0.18	0.43	0.32
M	y	y	y	n	0.00	16.01	20.14

Correlations between lesion volumes are shown in Table 3.2. Lesion volumes in the 3 ROIs were not significantly related.

Table 3.2. Correlations (Pearson's r) between lesion volumes in each region of interest.

	DMN	**MD**	**Other**
DMN		0.141	-0.057
MD			0.141

RESULTS

Situations Task

For the situations task, a central question was whether patients were particularly impaired at judgements of social appropriateness as tested by the Faux Pas task in Roca et al. (2010) or whether patient impairment extended to different types of situational judgement. To test this question for each dependent variable (proportion error and reaction time) a two-way mixed model ANOVA was performed with the between-participant factor of group (patient or control) and the within-participant factor of question type (executive, feeling, social). Mean scores for each question type for each group are presented in Table 3.3. For both participant error and reaction time measures there was a significant main effect of group (Error: $F(1,60)=7.47$, $p<0.01$; RT: $F(1,60)=10.9$, $p<0.01$), question type (Error: $F(2,120)=15.32$, $p<0.01$; RT: $F(2,120)=91.83$, $p<0.01$) and a significant interaction (Error: $F(2,120)=3.10$, $p<0.05$; RT: $F(2,120)=4.03$, $p<0.05$). The interaction effect seemed to be related to patient performance in the feeling questions. Patients were particularly inaccurate at the feelings questions compared to controls, however patients also showed the least reaction time impairment at the feelings questions compared to controls. It is possible that this interaction effect is a consequence of a speed-error trade-off in the patient group for the feeling questions. As all question types suggest patient impairment compared to controls, for the following analyses, performance was collapsed across question type to create a mean error and mean reaction time score.

Table 3.3. Means and standard deviations (SD) for patient and control error and reaction time for each question type in the situations task.

	Error				**RT (s)**			
	Patients		**Controls**		**Patients**		**Controls**	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*RT*
Executive	0.19	0.12	0.15	0.10	12.71	6.65	8.48	2.35
Feeling	0.21	0.10	0.08	0.08	7.96	4.85	5.33	1.61
Social	0.10	0.09	0.09	0.09	10.86	6.05	7.05	1.82

Differences between patients and controls

Table 3.4 presents mean and standard deviation scores for each task measure for patients and controls separately. Mean scores show marked differences between patients and controls. A one-way ANOVA for each performance measure was performed in order to assess the significance of these patient control differences. As expected, the patient group performed significantly worse across all but one measure compared to controls (Table 3.5).

Table 3.4. Mean scores and standard deviation (SD) for patients and controls in the 6 task measures.

	Patients		**Controls**	
	Mean	*SD*	*Mean*	*SD*
IQ	-96.0	21.9	-107	14.8
Hotel TD (sec)	335	277	158	109
Situations Proportion Errors	0.17	0.08	0.12	0.05
Situations RT (sec)	10.5	5.69	6.95	1.66
Switch 12 - 4 Proportion Errors	0.08	0.17	0.02	0.11
Switch 12 - 4 RT(sec)	0.66	0.91	0.002	0.36

Following Roca et al. (2010), to test whether the behavioural deficit in patients could be accounted for by IQ, between-group ANCOVAs were performed with IQ as the covariate. Table 3.5 shows the results from the standard ANCOVA model (regression lines relating performance score to IQ constrained to have the same slope in the two groups). As calculated from the corresponding variance terms of the ANCOVA, within-group correlations with IQ (r) are also presented. For all but one score a positive correlation with IQ was found. However, unlike the previous results with classical executive tasks (Roca et al. 2010), patient-control differences were still significant once the effect of IQ was partialled out.

Table 3.5. G*roup differences between patients and controls before accounting for differences in IQ (ANOVA) and after accounting for differences in IQ (ANCOVA). Bold values represent significant effects (p<0.05). d.f = degrees of freedom, F = F-value, P = p-value, r = within-group Pearson's correlations with IQ.*

	ANOVA			**ANCOVA**			
	d.f	*F*	*P*	*d.f*	*F*	*P*	*r*
IQ	**(1,60)**	**5.07**	**0.028**	-	-	-	-
Hotel TD	**(1,60)**	**10.78**	**0.002**	**(1,59)**	**6.53**	**0.013**	**0.336**
Situations Errors	**(1,60)**	**7.47**	**0.008**	**(1,59)**	**4.47**	**0.039**	0.263
Situations RT	**(1,60)**	**10.86**	**0.002**	**(1,59)**	**6.15**	**0.016**	**0.407**
Switch 12 - 4 Errors	(1,56)	2.77	0.101	(1,55)	3.29	0.075	0.123
Switch 12 - 4 RT	**(1,56)**	**13.27**	**<0.001**	**(1,55)**	**11.57**	**0.001**	0.101

As a direct comparison with Roca et al. (2010) these analyses were re-run for the 14 patients (12 for the switch length task) whose lesions were restricted to the frontal lobe. The results for the one-way ANOVAs and ANCOVAs are presented in Table 3.6. In line with Roca et al. (2010), our results show frontal lesion patient impairment in the hotel task which is not fully accounted for by differences in IQ score. This was also the case for situation task reaction time and reaction time difference in the switch length task. After accounting for IQ, group differences in situation judgement accuracy were eliminated, though this was likely due to the small sample size.

Table 3.6. Group differences between frontal-only patients and controls before accounting for differences in IQ (ANOVA) and after accounting for differences in IQ (ANCOVA). Bold values represent significant effects (p<0.05). d.f = degrees of freedom, F = F-value, P = p-value, r = average within-group Pearson's correlations with IQ.

	ANOVA			**ANCOVA**			
	d.f	*F*	*P*	*d.f*	*F*	*P*	*r*
IQ	**(1,42)**	**4.57**	**0.038**	-	-	-	-
Hotel TD	**(1,42)**	**15.11**	**<0.001**	**(1,41)**	**10.89**	**0.002**	0.209
Situations Errors	**(1,42)**	**4.72**	**0.036**	(1,41)	1.97	0.168	**0.364**
Situations RT	**(1,42)**	**11.64**	**0.001**	**(1,41)**	**7.67**	**0.008**	0.264
Switch 12 - 4 Errors	(1,40)	1.26	0.268	(1,39)	1.94	0.171	0.183
Switch 12 - 4 RT	**(1,40)**	**13.27**	**<0.001**	**(1,39)**	**14.33**	**<0.001**	0.162

Effects of lesion volume

The next analysis examined the relationship between behavioural scores and lesion volumes. This analysis was restricted just to the patient group.

Following Woolgar et al. (2010, 2018), we asked first whether IQ was predicted by volume of MD lesion. Scatterplots relating IQ to ROI lesion volumes are shown in Figure 3.5. To account for multiple comparisons (ROIs), significance threshold for correlations was set to p<0.017, one-tailed. Consistent with Woolgar et al. (2010, 2018), patient IQ was found to be significantly related to MD lesion volume (r=0.533, p<0.001). There was no relationship between DMN lesion volume (r=-0.214, p=0.120) and IQ or Other lesion volume and IQ after correcting for multiple comparisons (r=0.346, p=0.026).

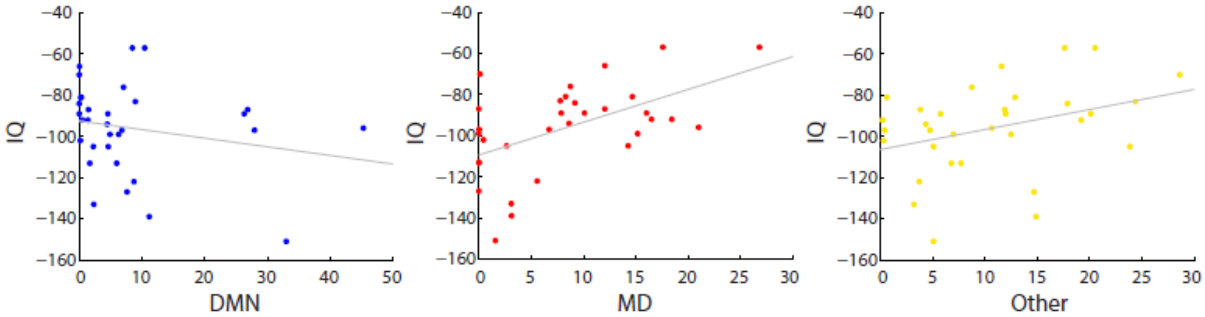

Figure 3.5. Correlations between DMN, MD and Other lesion volume and IQ score.

As 9 of the current patients were also tested in Woolgar et al. (2010), the analysis just of MD lesion volume was re-run with those 9 patients excluded. The results continued to show a significant positive correlation between MD lesion volume and IQ (r=0.388, p=0.034).

These analyses were then repeated for all behavioural measures. The results of these correlations are presented in Table 3.7. Except for IQ, no performance measure was significantly related to lesion volume in either MD nor DMN regions. Lesion volume in the Other ROI was correlated just with the RT score (switch 12 - 4) from the switch length task.

Table 3.7. Correlations (Pearson's r) between lesion volume and performance. Significant values (one-tailed, correcting for multiple comparisons across 3 ROIs) are shown in bold.

	DMN	**MD**	**Other**
IQ	-0.214	**0.533**	0.346
Hotel TD	-0.060	0.233	0.114
Situations Errors	-0.154	0.281	0.111
Situations RT	0.093	0.270	0.333
Switch 12 - 4 Errors	-0.124	-0.151	-0.216
Switch 12 - 4 RT	0.052	-0.190	**0.563**

Between task correlations

To test whether the naturalistic tasks were related to each other, between-task correlations were performed separately in patient and control groups. Table 3.8 presents the r-values for these correlations with patient group correlations in the top triangle and control group correlations in the bottom triangle. The r-values in bold represent significant (p<0.05) correlations. Only in the patient group were any measures significantly related to one another. Partially matching the results in Table

3.5, IQ score was related to hotel time deviation from optimum and situations RT. The only other significant correlation was between situations RT and the RT difference score from the switch length task.

Table 3.8. Between task correlations (Pearson's r) for patients (top triangle) and controls (bottom triangle). Bold values represent significant two-tailed correlations (p<0.05).

	IQ	**Hotel TD**	**Situation Errors**	**Situation RT**	**Switch 12-4 Errors**	**Switch 12-4 RT**
IQ		**0.420**	0.249	**0.459**	-0.184	0.207
Hotel TD	0.030		0.230	0.306	-0.330	-0.012
Situations Errors	0.296	-0.081		0.345	-0.197	-0.235
Situations RT	0.234	0.155	0.034		0.079	**0.431**
Switch 12 - 4 Errors	-0.003	0.227	0.357	-0.149		-0.209
Switch 12 - 4 RT	-0.202	0.016	-0.215	-0.027	-0.022	

Residual patient impairment

In accordance with Roca et al. (2010), in order to assess the degree to which the residual task impairment, after accounting for the effects of IQ, was related to lesions in the three regions of interest, the standardized residual scores, calculated from the ANCOVAs, were averaged across tasks. For the four patients who had not completed the switch length task, their average residual score was generated from the three tasks they had completed. Mean patient residual scores were then correlated with DMN, MD and Other lesion volume. After correcting for multiple comparisons, average residual was not correlated with volume of damage in any ROI, with the strongest correlation for Other (r=0.305). To demonstrate that the relationship between Other lesion volume and residual impairment is not related to a particular region, Figure 3.6 shows the lesions of the 6 patients with the greatest residual impairment after accounting for IQ.

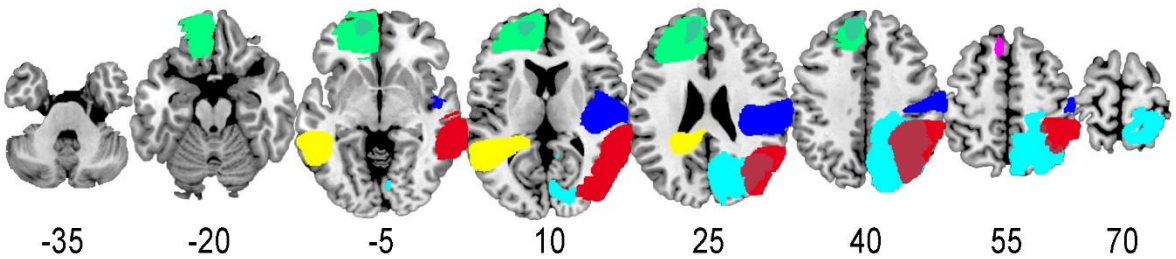

Figure 3.6. Lesion overlap for the patients with the greatest residual impairment after accounting for differences in IQ. Each colour (yellow, pink, green, cyan, lilac, white) represents a different patient's lesion.

DISCUSSION

This study aimed to understand the degree to which naturalistic task performance relies on brain regions additional to those usually implicated in executive task function.

Compared to controls, patients were found to show behavioural impairment in IQ score and across four out of five of the naturalistic task measures. IQ scores have found to be highly predictive of task performance in standard executive tasks (Miyake et al. 2000; Duncan 2006; Roca et al. 2010); consistent with this, patient IQ score was found to correlate with hotel task and situation task performance. However, in line with Roca et al. (2010), patient performance in these naturalistic tasks was worse than would be predicted from IQ scores, suggesting that the completion of the hotel, situations and switch length tasks may require additional cognitive processes beyond those captured by measures of fluid IQ.

While MD lesion volume was found to correlate with IQ score, replicating Woolgar et al. (2018), lesion volume in the MD network was not found to be significantly related to any naturalistic task measure. DMN lesion volume was also not found to be related to performance in any of the tasks. Instead, lesion volume in grey matter regions outside of MD and DMN regions was found to be significantly related to reaction time for task switch trials after 12 compared to 4 task repeats. The lack of significant correlations between patient impairment and lesion volume across the three regions of interest could perhaps indicate that naturalistic task performance requires a diverse range of cognitive processes, thus recruiting multiple brain regions. Consistent with this theory, residual patient impairment, after accounting for the variance in IQ, was not found to be specific to any particular region. Unlike Roca et al. (2010, 2011) who tested only frontal lesioned patients and found that patients with the greatest residual impairment showed lesion overlap in the anterior prefrontal cortex, the findings reported here suggest that naturalistic task deficits can be related to many different cortical regions. Although it is unclear what precise regions are important for naturalistic task performance after accounting for IQ, further correlation analyses revealed that this residual patient impairment was particularly correlated with grey matter lesion volume in regions outside of the MD and DMN. Future studies with a much larger patient sample and greater participant lesion overlap will be required in order to find specific regions related to naturalistic task performance.

Perhaps contrary to the results of Chapter 2, DMN lesion volume was not found to be related to performance in any of the naturalistic task measures used here. One possibility is that the

distribution of DMN lesion volumes, with most patients having very small and only 5 showing very large DMN lesions. This clustering of DMN lesion volume across patients may have made it difficult to find a relationship between the DMN and behavioural performance. Alternatively, it is also possible that the DMN is not necessary for these tasks. Looking at the broader DMN imaging literature, perhaps these results are less surprising. The hotel and switch length tasks primarily require prospective memory, time management and self-interruption/inhibition. These functions are usually more related to the anterior PFC (Burgess et al. 2003; Benoit et al. 2011; Volle et al. 2011) and the MD network (Stiers et al. 2010; Fedorenko et al. 2013) rather than the DMN. The situations task however, does seem more related to the DMN function. As discussed in Chapter 1, reading similar scenarios and making judgements about how the subject of the story would behave in false belief imaging tasks was found to activate the DMN (Frith and Frith 2003; Amodio and Frith 2006). Other studies have found increased DMN activation when asked to construct events from memory and imagination (Addis et al. 2007, 2009; Andrews-Hanna et al. 2010). Perhaps, as imaging suggests, the DMN is involved in representing the scenarios in the situations task. This scenario representation, however, may not be performance-limiting. Instead, multiple brain systems may be required in order to effectively judge how the characters would respond.

These results suggest that performance of complex, naturalistic tasks requires additional cognitive processes beyond those captured by IQ. Consistent with Woolgar et al. (2010), lesion volume in MD regions could reliably predict impairments in IQ; however, neither the MD network nor the DMN were found to be related to naturalistic task impairment. The results instead suggest that naturalistic task performance may depend on multiple cognitive processes and cortical regions extending beyond the MD network and DMN.

Chapter 4

The role of the default mode network in cognitive transitions

INTRODUCTION

The results from Chapter 2 implicated posterior DMN regions in making context-dependent decisions in an externally-focused task using lifelike scenes compared to using arbitrary letter cues. In accordance with these findings, several recent papers show the importance of the DMN in representing scene information. Robin et al. (2018) used multivoxel pattern analysis to uncover which features of events could be distinguished by activity patterns in the DMN. In the scanner, participants were presented with a person, object and location and asked to imagine an event incorporating those features. Each feature was presented multiple times in new combinations. The researchers found that imagined events could be distinguished by location when object and person features were kept constant in the hippocampus, parahippocampus, posterior medial cortex and anterior medial prefrontal cortex. In comparison, fewer regions were able to distinguish between imagined events when person or object differed but the location was maintained. Furthermore, direct comparisons of classifier performance for location, object and person features showed greatest classification accuracy in location discrimination, suggesting these regions primarily represent scene information.

However, some studies suggest DMN regions may be important during non-spatial externally-focused tasks by representing the broad features of task contexts as well as spatial contexts. In Schuck et al. (2016) participants were presented with overlapping face/house stimuli and asked to make old/new judgements based on the currently relevant category. Participants were asked to change category (house or face) after making a different age judgement from the previous trial (old -> new or new -> old). The researchers found that posterior medial cortex, anterior medial prefrontal DMN regions and MD regions of presupplementary motor area, anterior middle frontal gyrus and inferior parietal sulcus could distinguish the currently relevant category. Furthermore, the same DMN regions and inferior parietal sulcus also represented information about the previous category. Similarly, as described fully in Chapter 1, Crittenden et al. (2015) also found DMN regions were

sensitive to task context. Univariate contrasts showed increased DMN activity in Core and MTL DMN subnetworks with task switches to a more dissimilar task context. Multivoxel pattern analysis (MVPA) extended these findings showing that activity patterns in DMN regions could distinguish between the three different stimulus domains but not finer-grained task distinctions. However, in Crittenden et al. (2015) task dissimilarity was confounded by visual stimulus similarity and, as the task cue was presented simultaneously with the imperative stimuli, it was impossible to distinguish whether DMN regions were representing broad task contexts or visual differences in stimulus domain.

This study aimed to further the findings from Crittenden et al. (2015) in several ways. First, to replicate the finding of DMN activation increases during large task switches, thus supporting a role for the DMN in cognitive control. Second, to compare switch-related DMN activity to the usual profile of DMN activation during rest, by adding short rest trials. The addition of a rest condition thirdly allowed the comparison of task-switch DMN activity with a larger cognitive transition from rest to task. In line with Crittenden et al. (2015) and against a 'task-negative' hypothesis, increases in DMN activity are predicted to follow both 'task-negative' switches from task to rest as well 'task-positive' switches from rest back to task. And finally, by separating the task cueing phase from the imperative stimulus onset this study aimed to find evidence for the representation of broad task context in DMN regions when the degree of visual dissimilarity is kept similar across each task type.

METHODS

Participants

28 participants (13 female), between 18-29 years old, were recruited through the Medical Research Council Cognition and Brian Sciences Unit volunteer panel. All participants were right handed, native English speakers, with normal or corrected to normal vision, and normal colour vision. Ethics approval was granted from the Cambridge Psychology Research Ethics Committee. 4 participants (3 female) were excluded from further analysis due to technical error (3) or participant non-compliance (1).

Task

Task events are illustrated in Figure 4.1. Participants were required to make same/different judgements on pairs of simultaneously presented stimuli based on a task rule. There were 3 stimulus domains with 2 task rules associated with each (male/female and old/young for face stimuli;

skyscraper/cottage and inside/outside view for building stimuli; first letter and last letter for word stimuli). A further rest condition was added in which there was no task for participants to complete.

Trials of the seven tasks (including rest) were presented in a pseudorandom order. This allowed for 6 switch conditions: rest switch (rest trials preceded by task trials), rest stay (rest trials preceded by rest trials), restart (task trials preceded by rest trials), between-domain switch (task trials preceded by different-domain task trials), within-domain switch (task trials preceded by same-domain task trials) and task stay trials (task trials preceded by the same task).

Each trial was split into 2 phases. In the 2 second cue phase, a coloured frame was presented. Each colour corresponded to a task or rest trial as represented in Figure 4.1. In the execution phase of task trials, two stimuli would appear and the coloured frame would turn black. Participants were asked to make a “same” or “different” response, by left or right keypress, based on the task specified by the colour of the frame in the cue period. There were equal numbers of “same” and “different” trials in each task and switch type. Performance was self-paced, with the imperative stimuli remaining until a key was pressed, and participants were asked to respond as quickly as possible without making mistakes. Which button corresponded to “same” and “different” was counterbalanced across participants. An inter-trial interval (ITI) of 1.75 seconds followed each response. To improve isolation of brain activity associated with cues – the main focus of the study – 33% of trials were catch trials, with no execution phase. Instead of an imperative stimulus, catch trials had an additional 1.2 seconds of ITI, matched to the average response time in a behavioural pilot study. This same additional ITI also followed the cue phase of rest trials.

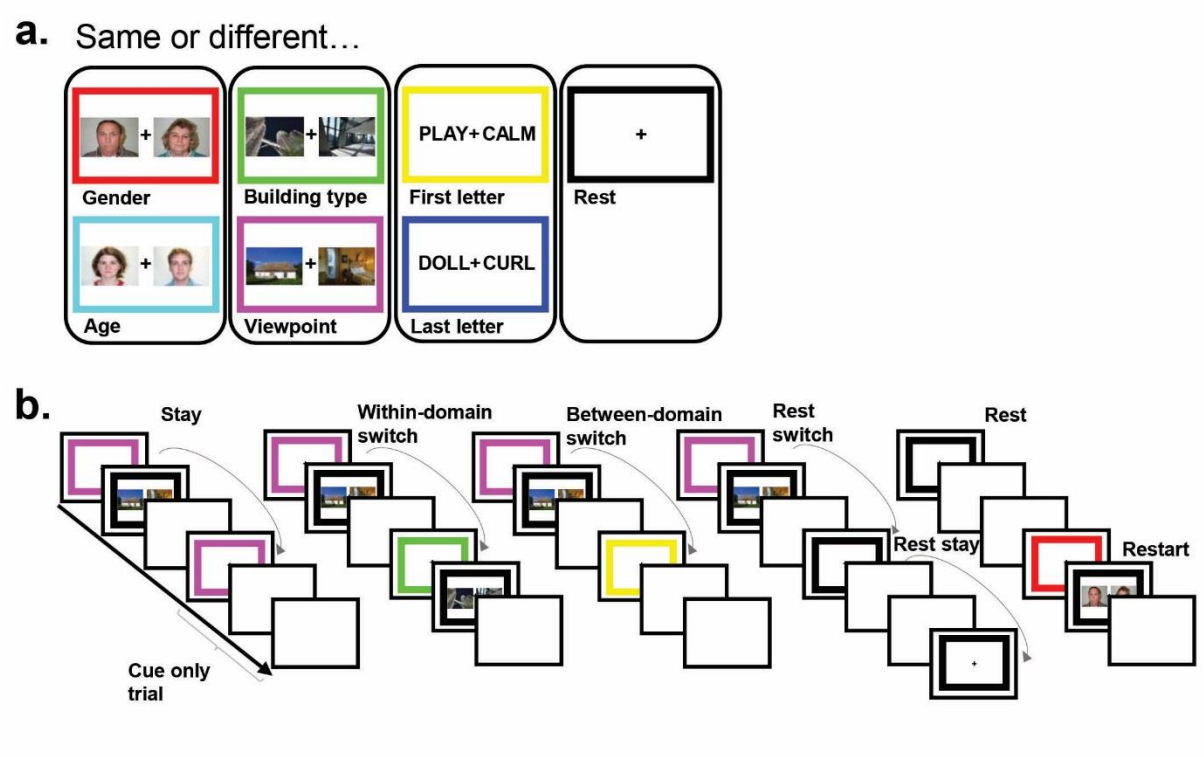

Figure 4.1. Task design. Participants were required to make same/different judgements on pairs of stimuli based on a task rule. Each task rule was cued by the frame colour, learnt by participants in a training session prior to scanning. a. Each of the six tasks and their associated frame colour. There were 3 stimulus domains with 2 task rules associated with each. An additional black frame cued rest trials in which there was no upcoming task to complete. b. Experimental design. Each trial consisted of a 2 second cue phase in which the coloured frame specifying the task rule for the upcoming trial (or rest trial) was presented, followed by an execution phase (until response) or a 1.2 second delay, followed by a 1.75 second inter-trial interval. 'Cue-only trials' refer to task trials where there was no execution phase. The tasks were presented in a pseudorandom order creating 6 switch conditions: task stay trials (task trials preceded by the same task), within-domain switch (task trials preceded by same domain task trials), between-domain switch (task trials preceded by different domain task trials), rest switch (rest trials preceded by task trials), rest stay (rest trials preceded by rest trials) and restart (task trials preceded by rest trials).

The experiment consisted of 3 blocks of 217 trials each. Each block contained 36 task stay, 36 within-domain switch, 36 between-domain switch, 36 rest switch, 12 rest stay and 24 restart trials. Of the task stay, within-domain switch and between-domain switch trials, 24 contained a task execution stage and 12 were catch trials. All restart trials were full trials, including task execution. There were equal numbers of each task type for each of the task switch conditions (task stay, within-domain switch, between-domain switch and restart). In addition to the above main trials, each block contained the first trial (switch type undefined), and 36 dummy trials (trials following catch trials).

Dummy trials were all full trials, equally split between task types, and discarded from further analysis.

Stimuli were sourced from Wikimedia Commons and the Park Aging Mind Laboratory face database (Minear and Park 2004). Each stimulus was positioned either side of the fixation with 3.6 degrees of visual angle from stimulus centre to fixation. Each stimulus measured approximately 6.0 (width) x 4.5 (height) degrees of visual angle. The experiment was controlled using Psychophysics Toolbox for MATLAB (Brainard, 1997).

Training

Participants were carefully pre-trained to ensure good learning of task rules. First, they were shown pairs of stimuli from each domain and asked to make same/different judgements according to each of the six task rules. Participants were then asked to learn the colour of frame associated with each task rule using self-paced pen and paper memory tests. Participants were then introduced to rest trials and catch trials. To ensure fluid retrieval of task rule by frame colour, a series of coloured frames was presented on a monitor and participants were asked to name aloud the corresponding task rule. This portion of the training was complete when participants completed two cycles of frame colours without making a mistake. Finally, participants were given a practice block of the task. They were asked to use the cue period to prepare for the upcoming task. In the first 14 trials response feedback was given. The last 19 trials had no feedback and identical timings to the main task. Training lasted around 20 minutes, after which participants were moved into the scanner for their 3 task runs of approximately 20 minutes each. Before each run, participants were asked again to describe the rule associated with each cue colour.

Data acquisition

Images were acquired using a 3 Tesla Siemens Prisma magnetic resonance imaging (MRI) scanner, fitted with a 32-channel head coil. Functional magnetic resonance imaging (fMRI) acquisitions used T2*-weighted multiband Echo-Planar Imaging (multiband acquisition factor 3 for 2.5mm slices with no interslice gap, TR 1.1s, TE 30ms, flip angle 62 degrees, voxel size 2 x 2mm). T1-weighted multiecho magnetization-prepared rapid gradient-echo (MPRAGE) images were also obtained (TR 2.53 s, TE 1.64, 3.5, 5.36 and 7.22 ms, flip angle 9°, voxel size 1 mm^3).

Preprocessing

Images were preprocessed using automaticanalysis (version 4) (Cusack et al. 2015) and SPM 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom) for Matlab (Mathworks).

The sequence of preprocessing stages involved spatial realignment of the raw EPIs, slice-time correction to the middle slice, co-registration of the functional EPI images to the structural T1-weighted image, and normalization to the Montreal Neurological Institute (MNI) template brain. For univariate analysis, functional images were then spatially smoothed using a Gaussian kernel of 10mm full-width at half-maximum. No smoothing was used for multivariate analysis.

Regions of Interest

To stay as close as possible to the DMN subnetworks defined by Andrews-Hanna et al. (2010), DMN ROIs were generated as 8mm radius spheres around peak coordinates from that study. DMN ROIs are shown in Figure 4.2a. Due to the position of the bounding box, some voxels surrounding Andrews-Hanna et al.'s (2010) original peak temporal pole coordinates were not measured; to amend this, the temporal pole volumes as used in Crittenden et al. (2015) were each dilated in volume by 2 voxels. Frontoparietal MD ROIs were taken from Fedorenko et al. (2013). MD regions (Figure 4.2b) included the posterior-anterior extent of the inferior frontal sulcus, a posterior dorsal regions of the lateral frontal cortex, inferior frontal junction, anterior insula/frontal operculum, pre-supplementary motor area/ dorsal anterior cingulate, and intraparietal sulcus. A template for these regions can be downloaded from http://imaging.mrc-cbu.cam.ac.uk/imaging/MDsystem. By using the version which separates each ROI, only frontoparietal ROIs were selected.

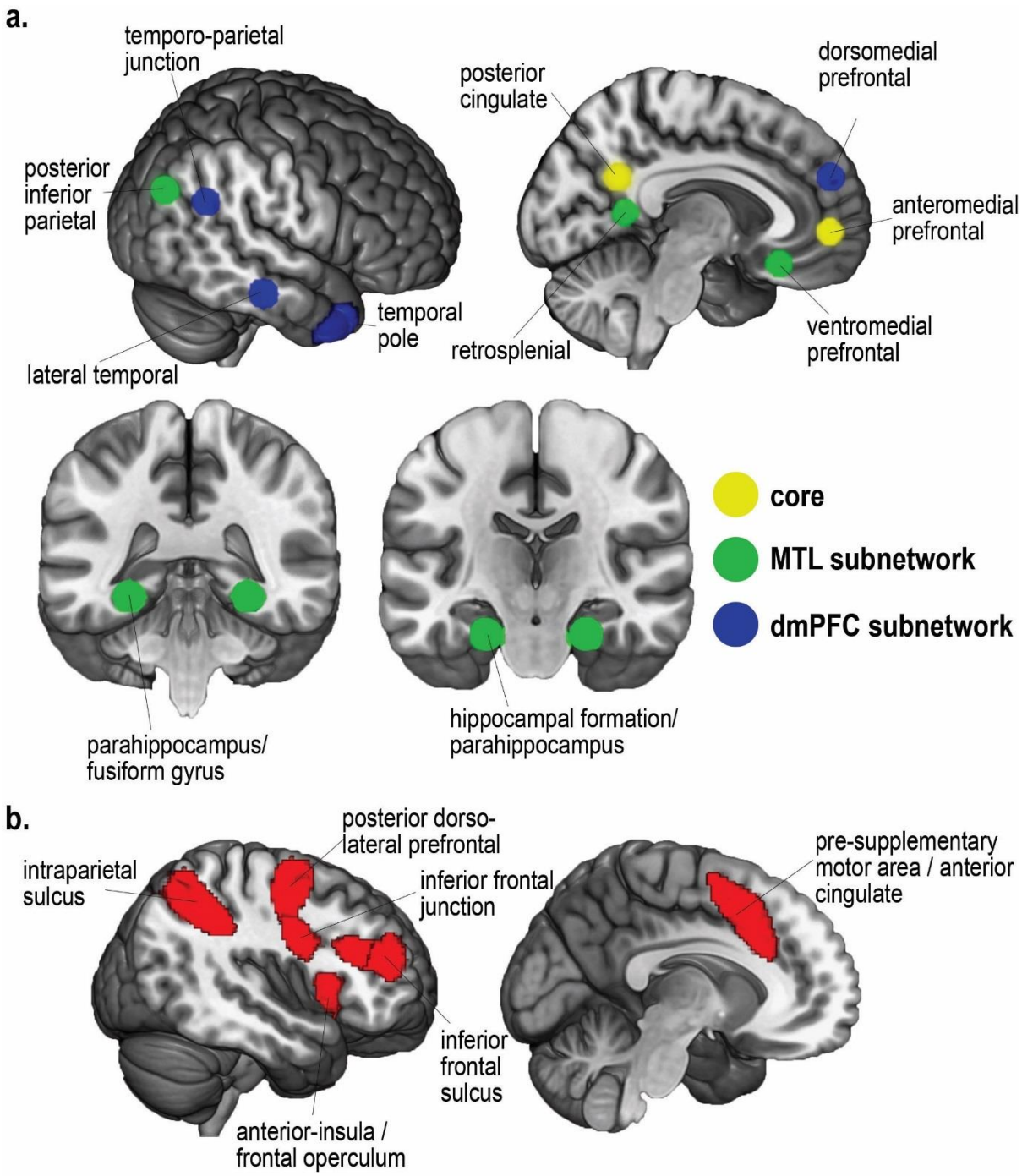

Figure 4.2. Regions of interest. a. DMN ROIs from peak coordinates presented in Andrews-Hanna et al. (2010). b. MD ROIs from Fedorenko et al. (2013).

Univariate analyses

Data for each participant were examined using the General Linear Model. Regressors were separately created for each combination of switch condition (task stay, within-domain switch, between-domain switch, restart, rest switch, rest stay, dummy) by task type (gender, age, building type, viewpoint, first letter, last letter) by task phase (cue, execution). Response type (same or different) was also separated for execution phase regressors. Incorrect trials were modelled separately and discarded.

Dummy trials were also excluded from further analysis. Each regressor was modelled as a delta function convolved with the canonical hemodynamic response function, positioned at the onset of the cue periods and the middle of each execution period. Except for the restart condition, use of 33% trials with no execution phase meant that regressors could be well separated for cue and execution phases. Average contrast values were extracted for each ROI for each participant using the MarsBaR SPM toolbox (Brett et al. 2002), and contrast values were then averaged across ROIs for each DMN subnetwork. A similar analysis was also carried out for univariate activity in the MD network.

Multivariate analyses

Multivoxel pattern analysis (MVPA) was performed using the Decoding Toolbox (Hebart et al. 2015). As with the univariate analysis, each regressor was modelled as a delta function convolved with the canonical hemodynamic response function, positioned at the onset of the cue period and the middle of each execution period. Incorrect trials were removed. MVPA then examined rule discrimination in patterns of cue phase activity, using the same ROIs as for univariate analysis. Prior to pattern analysis, beta values were Z-scored across tasks within each voxel of the ROI. Separate pairwise classifications were performed for each of the 15 possible task pairs (e.g. age vs. building type). Classification was carried out using a linear support vector machine (LIBSVM; Fan et al. 2005) and a leave-one-run-out approach, with the classifier trained on data from two runs and tested on the third, and results averaged over the three possible left-out runs. Classification accuracy (CA) minus chance (50%) was generated for each classification pair, for each ROI and participant. The CA for each subnetwork was then computed from the average CA across ROIs in the subnetwork. Again, a similar analysis was also carried out for the MD network.

Finite Impulse Response Model

To examine restart activity against a stable resting baseline, this analysis focused on occasions in which 4 rest trials appeared in a row, followed by restart. This analysis used a Finite Impulse Response model (FIR) model, where each trial was split into 4 parts (1.2375s bins), extending from the onset of the first rest to 9.9 seconds after restart. The execution phases for each task switch type (task stay, within-domain switch, between-domain switch, and restart) were modelled as before, such that activation related to task execution was regressed out of the implicit baseline and FIR rest/restart estimates. Each execution regressor was modelled as a delta function convolved with the canonical hemodynamic response function, positioned in the middle of each execution period. The remaining implicit baseline contained inter-trial periods as well as responses to all other cue events (i.e. stay, within-domain switch, between-domain switch, and remaining rest and restart cues).

Average contrast values were extracted for each ROI for each participant using the MarsBaR SPM toolbox (Brett et al. 2002), and contrast values were then averaged across ROIs as before.

RESULTS

Behavioural switch costs

Participants performed with an average of 95.9% correct responses (SD = 0.03). Paired-sample t-tests showed that responses were significantly faster for task stay trials (1217ms) compared to within-domain switch trials (1373ms, $t(23) = 4.87$, $p < 0.01$), between-domain switch trials (1348ms, $t(23) = 3.97$ $p < 0.01$), and task restarts (1239ms, $t(23) = 4.22$, $p < 0.01$). In contrast to the results of Crittenden et al. (2015), there was no significant difference between within- and between-domain switches. This is likely due to the introduction of a 2 second switch cue before the onset of the imperative stimulus making this design less sensitive to behavioural switch costs but allowed for estimation of switch-related activity independent of stimulus and execution effects.

Increased DMN activity on rest trials

Given the interest in cognitive switching, the fMRI analyses focused largely on cue-related activity, with activity for task execution removed (see Materials and Methods). The first analysis tested for the typical "task-negative" characteristic of the DMN, with stronger activity during rest compared to task. To this end, for each DMN subnetwork, cue activity was compared in rest and task trials, the latter defined as the mean of task stay, within-domain switch and between-domain switch trials. For all univariate analyses, average contrast values for each region of interest (ROI) were extracted, and contrast values were then averaged across ROIs within each subnetwork (see Materials and Methods). Figure 4.3 shows average contrast values for rest switch>task and rest stay>task. There were significant increases in activity during rest switch compared to task in all DMN subnetworks (core: $t(23) = 3.88$, $p < 0.01$; MTL: $t(23) = 4.86$, $p < 0.01$; dmPFC: $t(23) = 3.00$, $p < 0.01$), and for rest stay compared to task in the core and MTL subnetworks (core: $t(23) = 4.05$, $p < 0.01$; MTL: $t(23) = 4.96$, $p < 0.01$), but not in the dmPFC subnetwork ($t(23) = 1.41$, $p > 0.05$). Additional t-tests revealed increased activity in rest stay compared to rest switch trials only in core and MTL subnetworks (core: $t(23) = 2.48$, $p < 0.05$; MTL: $t(23) = 3.94$, $p < 0.01$; dmPFC: $t(23) = 0.36$, $p > 0.05$). To compare subnetworks, a two-way repeated measures ANOVA was run with factors contrast (rest stay>task stay, rest switch>task stay) and DMN subnetwork (core, MTL, dmPFC). While the effect of contrast was not significant ($F(1,23) = 3.81$, $p >0.05$), significant main effects of subnetwork ($F(2,46) = 15.86$, $p < 0.01$) and a significant interaction effect were found ($F(2,46) = 11.11$, $p < 0.01$).

For comparison, Figure 4.3 also shows average contrast values for rest switch>task and rest stay>task in MD regions. MD regions showed significantly greater activity during task than switches to rest ($t(23) = 2.18$, $p < 0.05$), but showed no significant differences between rest stay compared to task ($t(23) = 2.78$, $p > 0.02$).

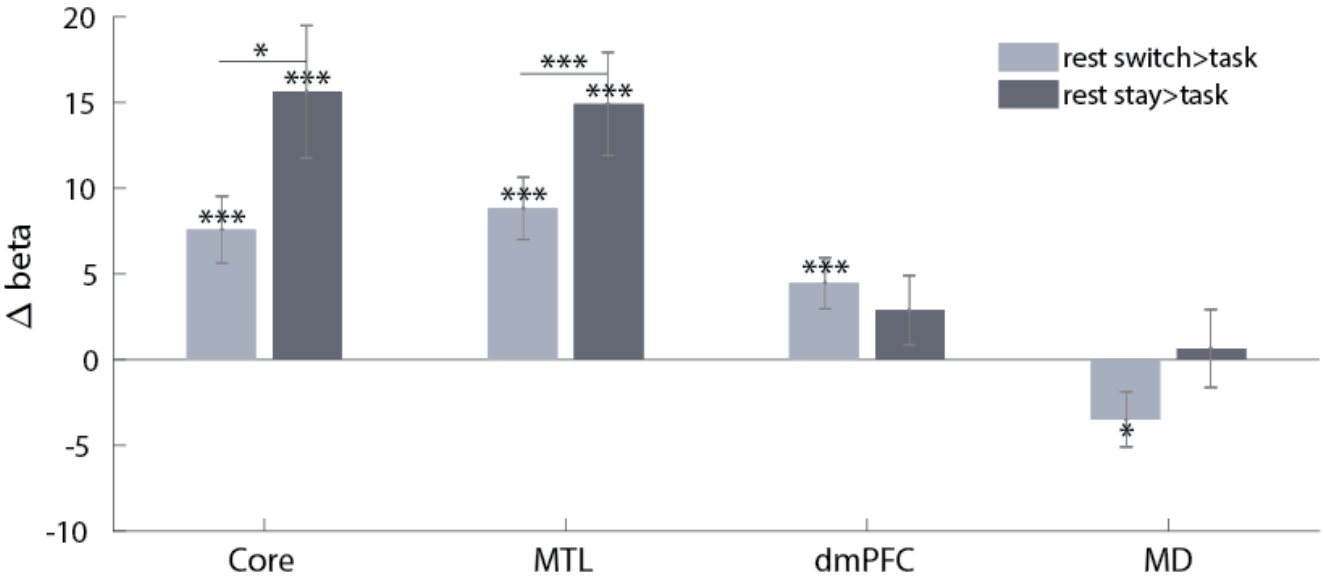

*Figure 4.3. Contrasts of rest compared with task activity in each DMN subnetwork and the MD network. Significant (P < 0.05) increases in rest activity compared with task, as well as paired t-tests between contrasts within DMN subnetworks, are indicated with *P < 0.05, **P < 0.02, ***P < 0.01. Error bars show standard error of the mean across participants.*

Increased DMN activity for large task switches

Second, this study aimed to replicate the results of Crittenden et al. (2015), showing increased activity in core and MTL subnetworks for between-domain switch trials. Figures 4.4a-c show the effects of switch condition on cue period activity in each DMN subnetwork. Core and MTL DMN subnetworks showed increased activity for between-domain switches compared to both within-domain switches (core: $t(23) = 2.17$, $p < 0.05$; MTL: $t(23) = 2.23$, $p < 0.05$) and task stay trials (core: $t(23) = 2.38$, $p < 0.05$; MTL: $t(23) = 2.44$, $p < 0.05$). In line with trends reported by Crittenden et al. (2015), the dmPFC subnetwork showed the opposite effects of switch type, with decreased activity for between-domain switches compared to within-domain switches ($t(23) = 2.20$, $p < 0.05$). Within-domain switch trials were not significantly different from task stay trials.

In a supplementary analysis, no significant effects of switch type were found during the execution phase for core and MTL DMN subnetworks, while the dmPFC subnetwork showed decreased activity for between-domain switch trials compared to within-domain switch ($t(23) = 2.54$, $p < 0.02$) and task stay ($t(23) = 3.07$, $p < 0.01$).

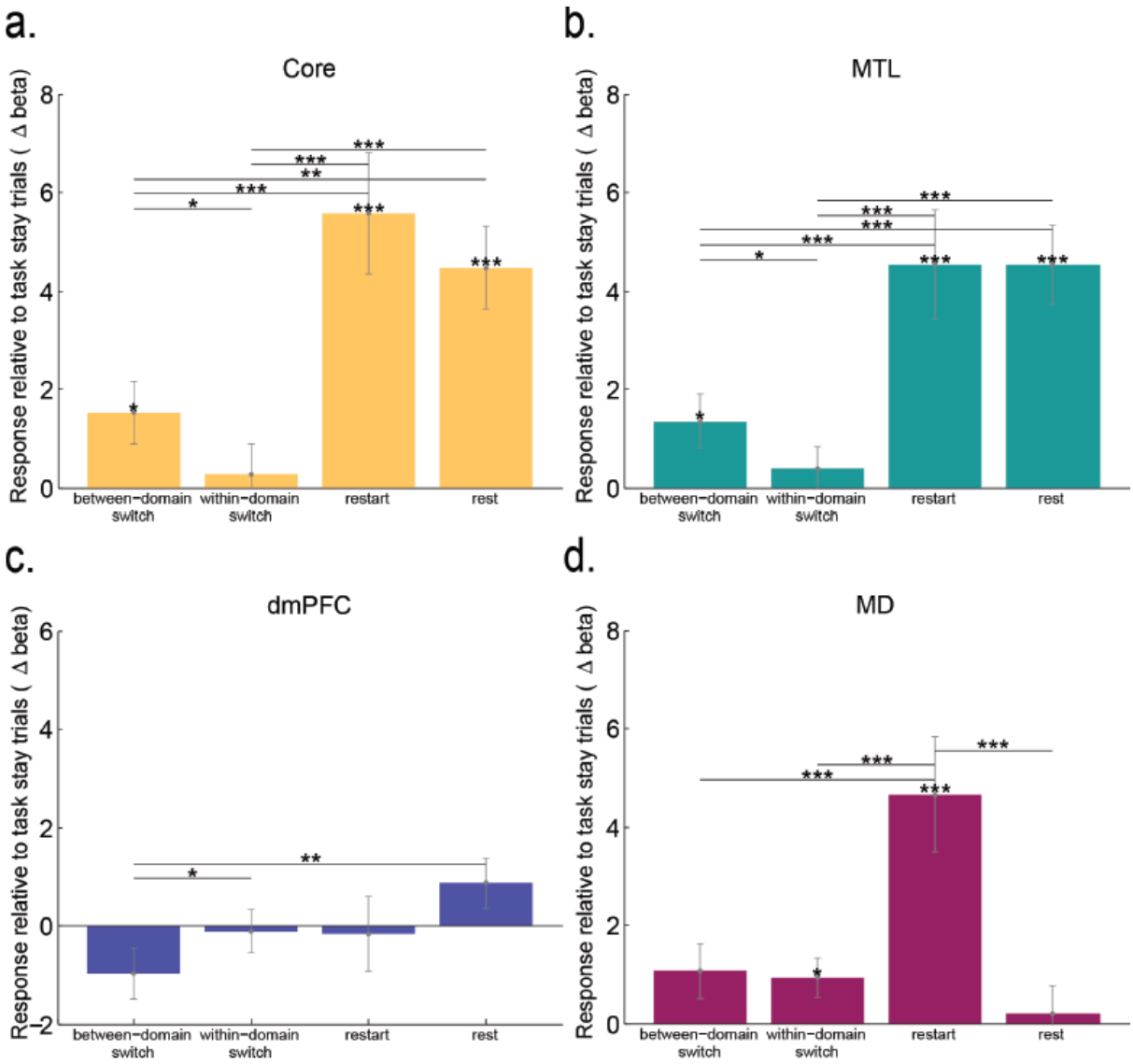

*Figure 4.4. Contrasts of between-domain switch, within-domain switch, restart and rest compared with task stay trials for each DMN subnetwork and MD regions. ((a) Core DMN, (b) MTL DMN, (c) dmPFC DMN, (d) MD). Significant (P < 0.05) increases in activity compared with task stay, as well as paired t-tests between contrasts within (sub)networks, are indicated with *P < 0.05, **P < 0.02, ***P < 0.01. Error bars show standard error of the mean across participants.*

Large increases in DMN activity for task restarts

Finally this research aimed to examine DMN activity at task restarts, i.e. activity on trials where participants switched back from rest to task. For each DMN subnetwork, Figures 4.4a-c also show the

contrast values for restart>task stay, with rest>task stay (mean of rest stay and rest switch trials) added for comparison. For core and MTL, but not dmPFC, subnetworks, t-tests revealed increased activity during both restart (core: $t(23) = 4.53$, $p < 0.01$; MTL: $t(23) = 4.05$, $p < 0.01$; dmPFC: $t(23) = 0.23$, $p > 0.05$) and rest (core: $t(23) = 5.31$, $p < 0.01$; MTL: $t(23) = 5.65$, $p < 0.01$; dmPFC: $t(23) = 1.72$, $p > 0.05$) compared to task stay.

This design allowed for separation of cue and execution-related activity in task stay, within-domain switch and between-domain switch trials. This was achieved by including cued task trials without an execution phase, reducing the covariance between the two task phases. However, all restart trials were full trials including an execution phase. As such, this design could not separate cue and execution components in this condition. To check the conclusions in relation to restart-related activity, the analyses were repeated using beta values from whole trials (defined as the average beta values of both cue and execution phases of restart and task stay trials). These analyses similarly found increased activity for restart compared to task stay activity in core and MTL DMN subnetworks (core: $t(23) = 5.07$, $p < 0.01$; MTL: $t(23) = 5.98$, $p < 0.01$) and increased activity during rest compared to task stay in the core DMN subnetwork ($t(23) = 5.62$, $p < 0.01$). MTL rest activity was not greater than whole task stay trial activity. In the dmPFC DMN subnetwork, rest activity was greater than task stay ($t(23) = 6.07$, $p < 0.01$) but restart was not.

Component ROIs within each subnetwork

Figures 4.5-4.7 show the above contrasts plotted for individual ROIs in each DMN subnetwork. Core DMN subnetwork regions showed similar patterns of response across rest and restart contrasts, although the task switch response was driven by PPC and absent in amPFC. Within the MTL subnetwork, all regions responded strongly to rest, the task switch response was driven by Rsp and PHC, and the restart response was seen everywhere except the posterior intraparietal lobe. The dmPFC subnetwork show less convergence across individual ROIs, consistent with its weak effects overall.

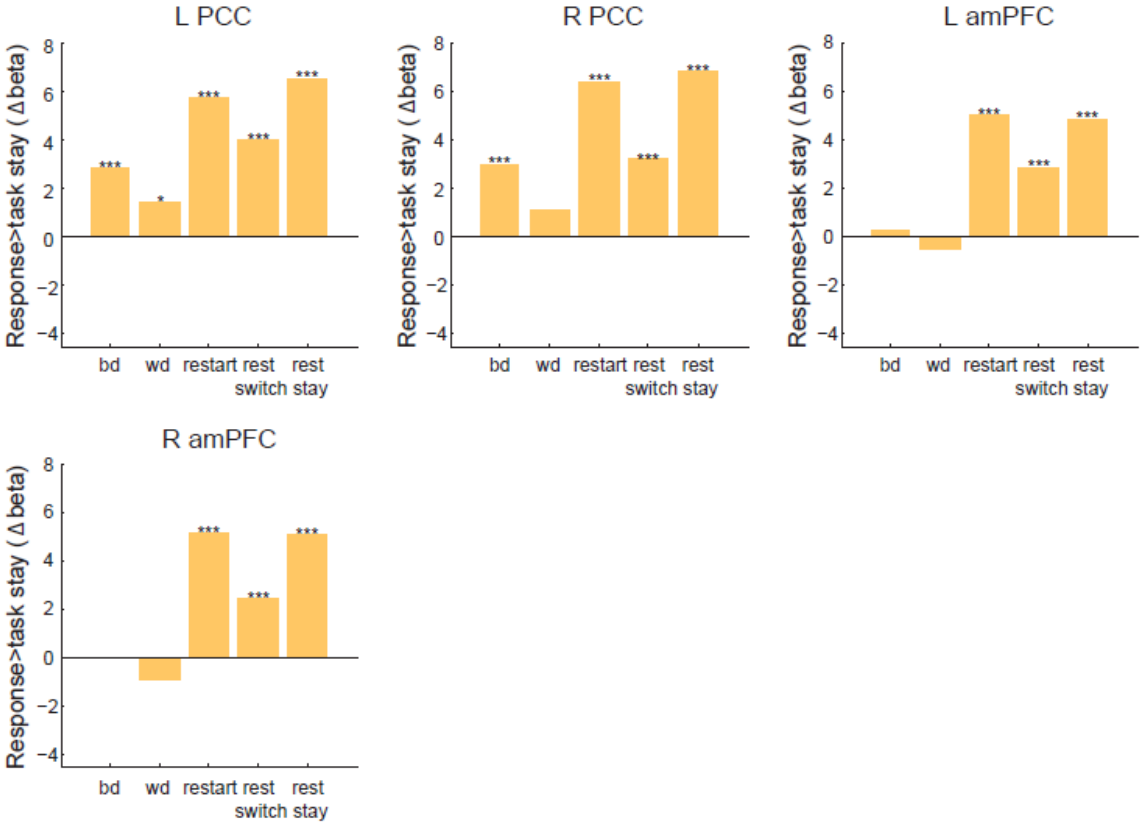

*Figure 4.5. Contrasts of between-domain switch (bd), within-domain switch (wd), restart, rest switch and rest stay relative to task stay trials for each ROI in the Core DMN subnetwork. Significant increases in activity compared to stay are indicated with * = p < 0.05, ** = p < 0.02, *** = p < 0.01. L PCC = left posterior cingulate cortex, R PCC = right posterior cingulate cortex, L amPFC = left anteromedial prefrontal cortex, R amPFC = right anteromedial prefrontal cortex.*

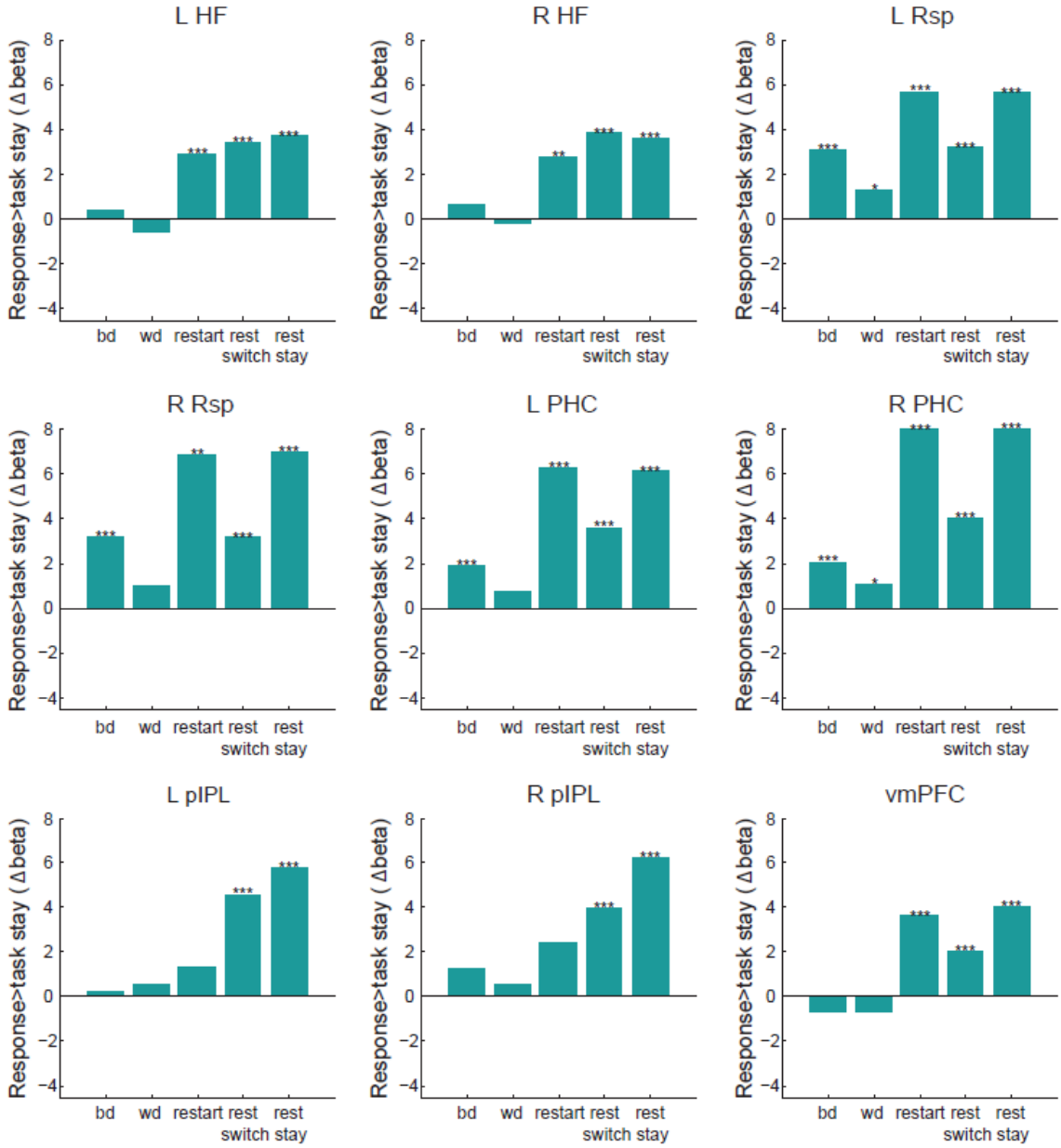

*Figure 4.6. Contrasts of between-domain switch (bd), within-domain switch (wd), restart, rest switch and rest stay relative to task stay trials for each ROI in the MTL DMN subnetwork. Significant increases in activity compared to stay are indicated with * = p < 0.05, ** = p < 0.02, *** = p < 0.01. L HF = left hippocampal formation/parahippocampus, R HF = right hippocampal formation/parahippocampus, L Rsp = left retrosplenial, R Rsp = right retrosplenial, L PHP = left parahippocampus/fusiform gyrus, R PHP = right parahippocampus/fusiform gyrus, L pIPL = left posterior inferior parietal lobe, R pIPL, right posterior inferior parietal lobe, vmPFC = ventromedial prefrontal cortex.*

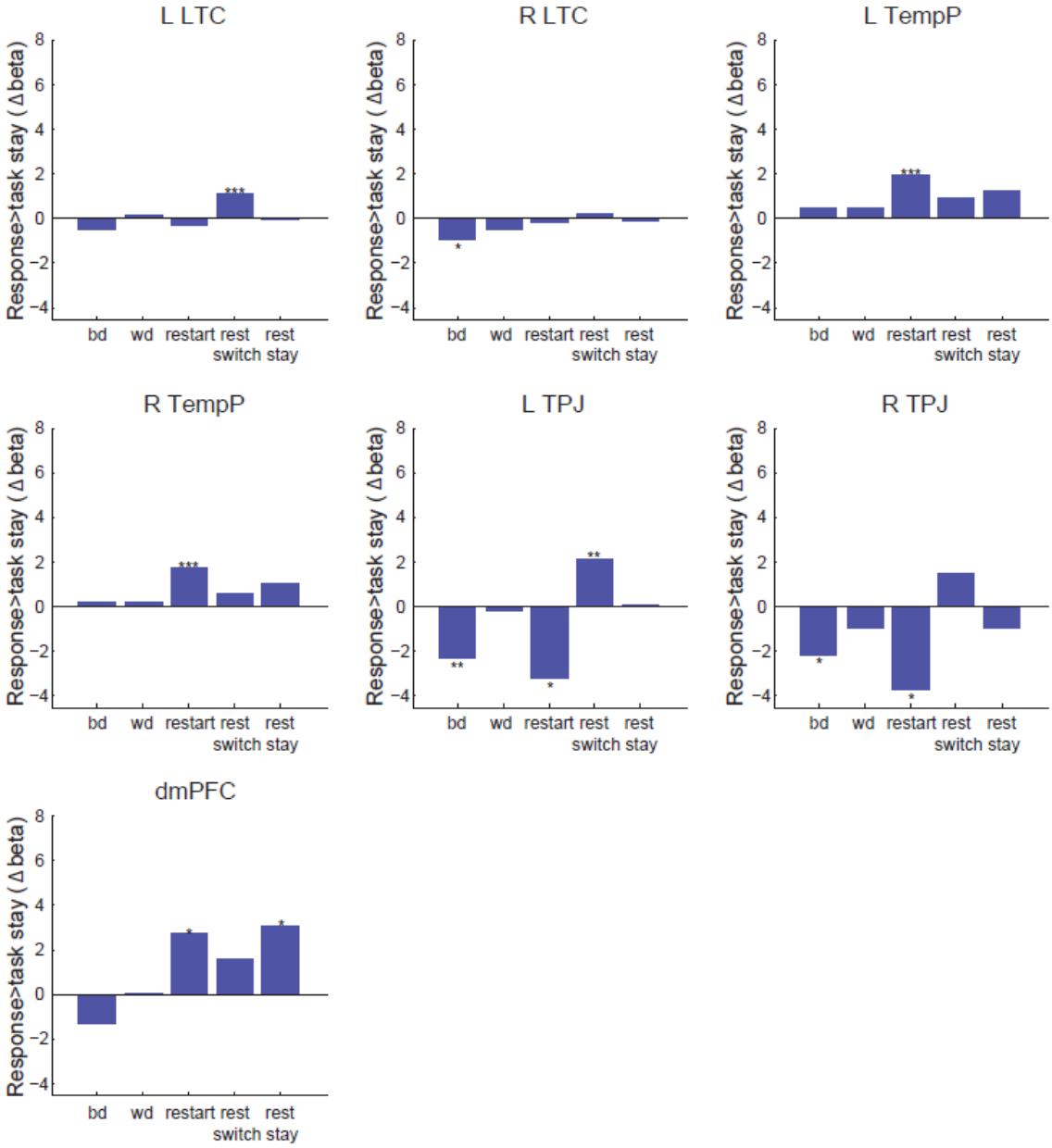

*Figure 4.7. Contrasts of between-domain switch (bd), within-domain switch (wd), restart, rest switch and rest stay relative to task stay trials for each ROI in the dmPFC DMN subnetwork. Significant increases in activity compared to stay are indicated with * = p < 0.05, ** = p < 0.02, *** = p < 0.01. L LTC = left lateral temporal cortex, R LTC = right lateral temporal cortex, L TempP = left temporal pole, R TempP = right temporal pole, L TPJ = left temporo-parietal junction, R TPJ = right temporo-parietal junction, dmPFC = dorsomedial prefrontal cortex.*

MD activity across trial types

For comparison with the DMN data (Figures 4.4a-c), Figure 4.4d shows contrasts of different trial types with task stay for the MD network. As in core and MTL subnetworks, t-tests showed greater MD activity for restart ($t(23) = 3.95$, $p < 0.01$). MD activity was also greater in within-domain switch

trials ($t(23) = 2.29$, $p > 0.05$) compared to task stay trials. Between-domain switch activity was not significantly different from task stay activity although there was also no difference between responses to within-domain switches and between-domain switches. In contrast to Core and MTL DMN subnetworks, the response on rest trials was not significantly greater than on task stay trials. Again, a supplementary analysis showed no significant effects of switch type during task execution.

To compare effects of switch magnitude in DMN and MD, two two-way repeated measures ANOVAs were run, with factors contrast (between-domain switch>task stay, within-domain switch>task stay) and network (core, MD in the first analysis; MTL, MD in the second). The ANOVA comparing core DMN with MD activity found no significant main effects of contrast or network, but a significant interaction ($F(1,23) = 5.05$, $p < 0.05$). Results were similar in the ANOVA comparing MTL DMN with MD, with no significant main effects of contrast or network, but a significant interaction ($F(1,23) = 6.56$, $p < 0.02$). The results show that the effect of switch magnitude was greater in DMN subnetworks than in MD.

Increased activity at task restart is distinct from prolonged rest activity

A potential concern over restart activity is that, in part, it might reflect carry-over from the preceding rest, either because of sustained neural activity, or a prolonged haemodynamic response. To examine activity at restart in more detail, and in particular to compare restart against a stable resting baseline, instances in which at least 4 rest trials occurred in a row were selected (data available for all 24 participants; mean of 3.88 instances per participant). Using a Finite Impulse Response model (see Materials and Methods), activity in 1.2375s time bins (4 bins/trial) across the run of 4 rests and into the following restart was estimated.

The results are shown in Figure 4.8. Across all 3 DMN subnetworks, the results suggest a peak of activity following restart. At least after long rests, in other words, a restart drives stronger DMN activity than the rest trials themselves. To compare restart with the immediately preceding rest, average activity across the 3 bins corresponding to 3.7125 to 7.425 seconds after restart (bins 20-22) and the 3 corresponding bins for the final rest (bins 16-18) was computed. A two-way repeated measures ANOVA with the factors DMN subnetwork (core, MTL and dmPFC) and trial (restart, rest) showed a main effect of trial that fell just short of significance ($F(1,23) = 3.86$, $p = 0.062$), along with a significant interaction ($F(1,23) = 4.17$, $p < 0.05$). The restart effect appeared largest in the MTL subnetwork. Significant increases in response to restart compared to rest in the MD network were also found ($t(23) = 3.46$, $p < 0.01$).

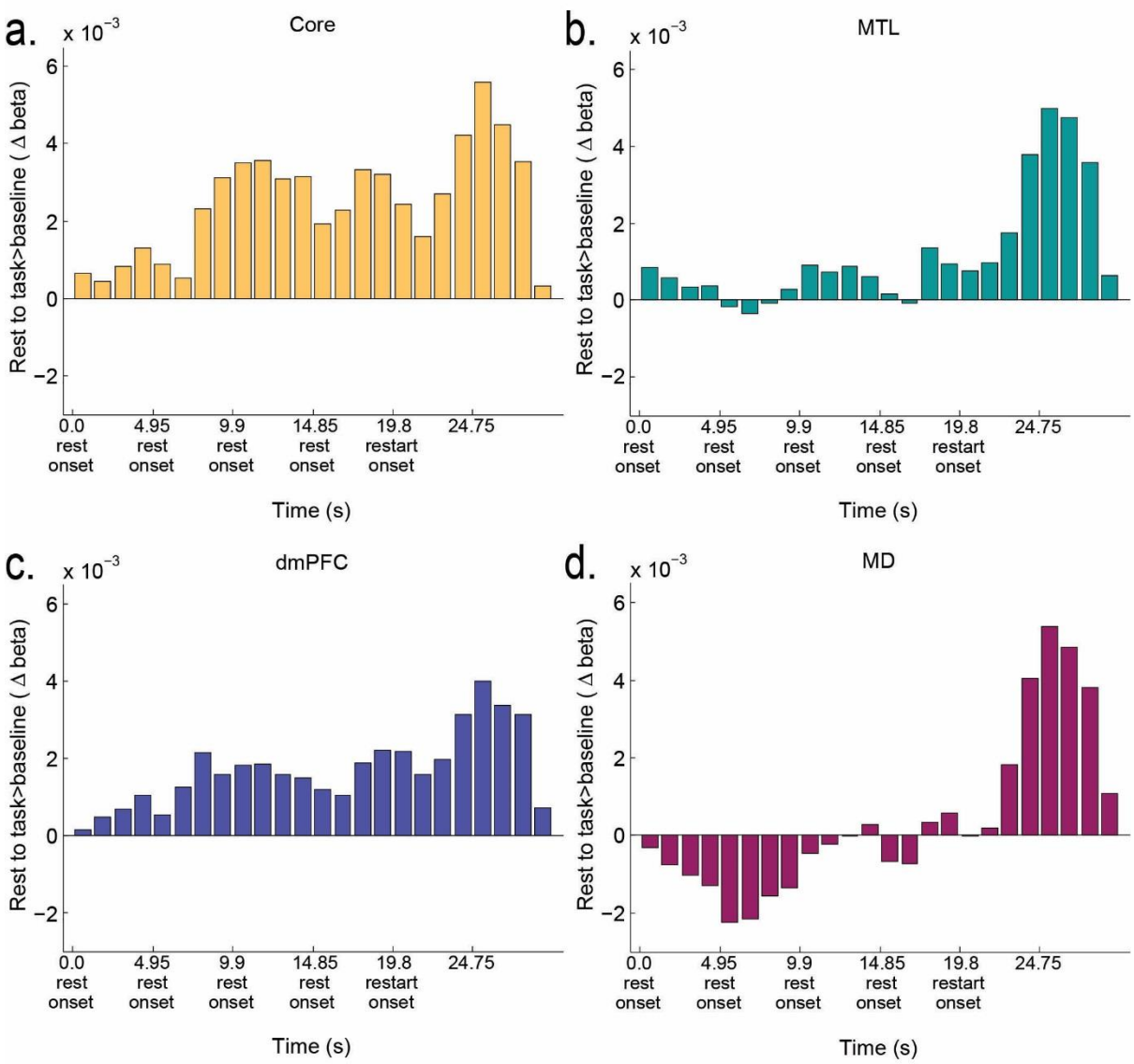

Figure 4.8. Finite impulse response beta activity estimates in 1.1 second time bins during repeated rest trials before task restart for each DMN subnetwork and the MD network. (a. Core DMN, b. MTL DMN, c. dmPFC DMN, d. MD). Restart onset occurs at bin 19.

Individual voxels in DMN and MD regions show sensitivity to both rest and between-domain task switches

To investigate whether voxels within the same regions were sensitive to rest as well as to the between-domain task switches, for each participant in each ROI the proportion of voxels showing above threshold responses to rest>task, between-domain switch>task stay, and to both rest>task and between-domain switch>task stay contrasts, at the threshold value of $p < 0.05$, uncorrected were calculated. All (sub)network regions showed some voxels sensitive to both rest and between-domain switches with a large proportion of between-domain switch sensitive voxels also sensitive to rest (core: 18.3%, MTL: 26.9%, dmPFC: 11.7%, MD: 10.8%).

DMN and MD activity patterns distinguish task domains

Multivariate analyses were also carried out to establish whether DMN cue period activity could distinguish between different task types. For each task pair (e.g. age vs. building type), a support vector machine (LIBSVM; Fan et al. 2005) was trained to discriminate the two tasks, based on voxelwise activity patterns in each DMN ROI separately (see Materials and Methods). Classification accuracy (CA) was assessed using a leave-one-run-out procedure, and expressed as accuracy minus chance (50%). The CA for each subnetwork was then computed from the average CA of each ROI in the subnetwork.

Separately for within- and between-domain task pairs, Figure 4.9 shows mean values of CA minus chance for each DMN subnetwork, along with results of a similar analysis for the MD network. Although mean classification accuracies were low, T-tests showed classification accuracy significantly above chance for between-domain task pairs in all DMN subnetworks as well as the MD network (core: $t(23) = 2.99$, $p < 0.01$; MTL: $t(23) = 3.95$, $p < 0.01$; dmPFC: $t(23) = 2.93$, $p < 0.01$; MD: $t(23) = 3.84$, $p < 0.01$). Only in MD regions was classification accuracy of within-domain task pairs significantly above chance ($t(23) = 4.42$, $p < 0.01$). Paired t-tests revealed a significant increase in classification accuracy for between-domain task pairs compared to within-domain task pairs in core and MTL subnetworks (core: $t(23) = 2.59$, $p < 0.02$; MTL: $t(23) = 3.38$, $p < 0.01$). A two-way repeated measures ANOVA was also carried out with the factors network (DMN, MD) and task pair similarity (within-domain, between-domain). Data were averaged over core, MTL and dmPFC subnetworks to obtain DMN values. Significant main effects of network ($F(1,23) = 8.86$, $p < 0.01$) and similarity ($F(1,23) = 4.86$, $p < 0.05$) were found, as well as a significant interaction ($F(1,23) = 4.85$, $p < 0.05$).

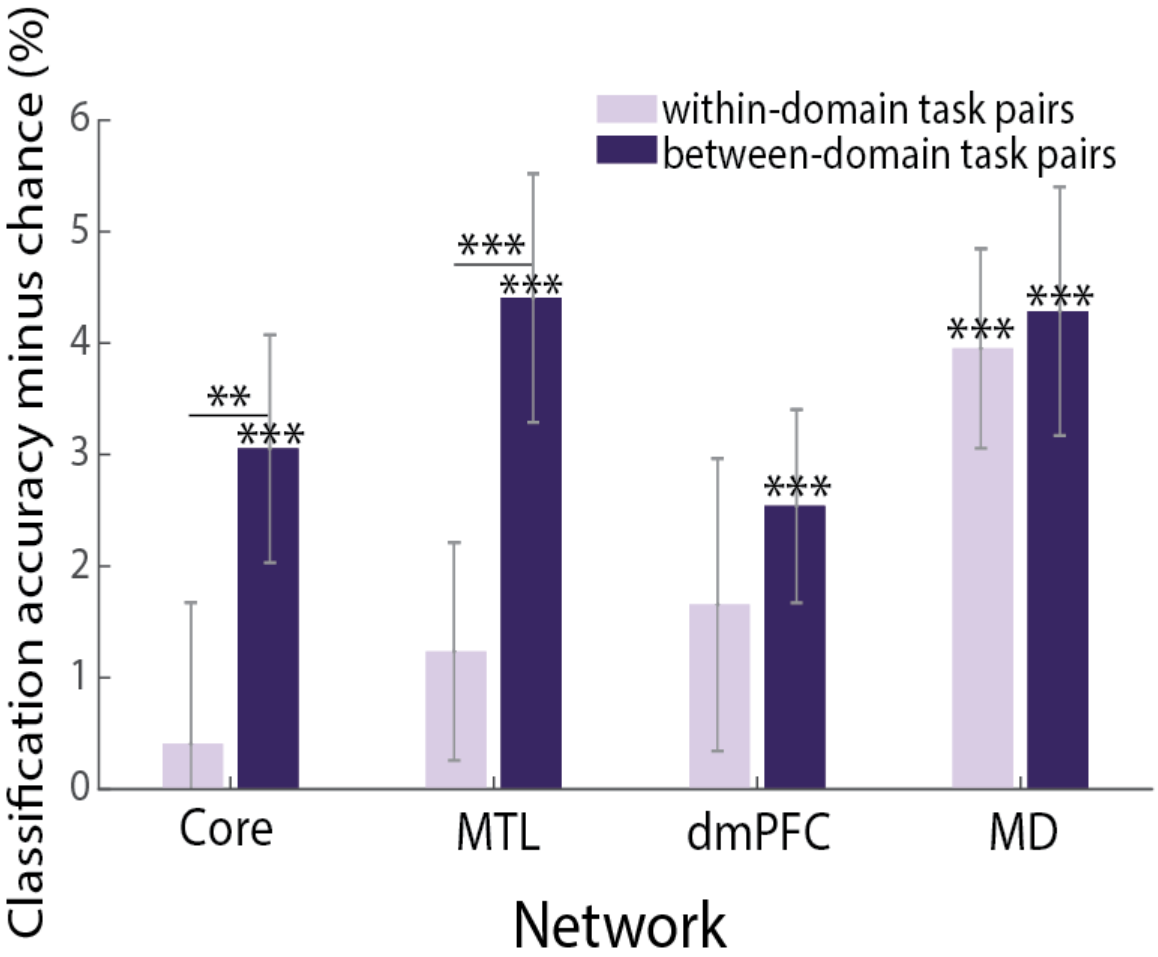

*Figure 4.9. Average classification accuracies minus chance for within-domain (light bars) and between-domain (dark bars) task pairs for each DMN subnetwork and the MD net-work. Significant classification accuracy above chance (p < 0.05), as well as significant paired t-tests between within-domain task pairs and between-domain task pairs, are indicated with * = p < 0.05, ** = p < 0.02, *** = p < 0.01. Error bars show standard error of the mean across participants.*

DISCUSSION

This study aimed to extend a prior suggestion, that regions of the DMN can play a role in externally-directed task switching, and further, to test whether the DMN represents the broad task category in the absence of the imperative stimuli which previously caused a visual confound. In accordance with Crittenden et al. (2015), the results confirm the role of the DMN in cognitive transitions. Increased activity was found in core and MTL subnetworks for a large change of task domain but not for a within-domain task change. In line with prototypical findings, increased DMN activity on rest trials compared to task was also shown. Perhaps most striking, core and MTL subnetworks were also

strongly active during the transition back from rest to task, with further analyses showing some overlap between voxels most active for rest and those showing task switch effects. Additionally, results from the multivariate analysis found DMN activity patterns during the cue period could distinguish between broad task domains, even in the absence of the imperative stimulus, but not finer-grained discriminations. On the other hand, activity in MD regions could distinguish on a finer scale between all six tasks.

These results hold several implications for theories of DMN function. Inconsistent with theories suggesting a role for the DMN in processes directed away from the current external environment (e.g. self-projection, Buckner and Carroll 2007), the current findings show DMN switch-related activity changes in the context of an external task. Substantial activity at task restart is directly inconsistent with these theories. As established in the Introduction, the DMN is often implicated in representing broad features of a current scene, episode or context, including spatial surroundings (e.g. Hassabis and Maguire 2007, 2009; Ranganath and Ritchey 2012), time (e.g. Addis et al. 2007, 2009; Andrews-Hanna et al. 2010), and social aspects of self and others (Frith and Frith 2003; D'Argembeau et al. 2005) etc. This has been called a "situation model" by Ranganath and Ritchey (2012) and is proposed to guide current cognition by constraining what kind of behaviour is currently possible, desirable or permitted (see also Zacks et al. 2007; Bar, 2007,2009). The current results also suggest a role for the DMN in implementation and control of current cognition, beyond its importance in imagining contexts different from the current moment. Furthermore, as well as its more established role in the construction of broad spatial environments (Hassabis and Maguire 2007, 2009), in accordance with Crittenden et al. (2015) and Schuck et al. (2016), the current results also implicate the DMN in representing broad task contexts.

Throughout the task, I suggest, DMN switching effects are caused by a constant waxing and waning of the relative prominence of context representation. DMN activity is strong at rest, perhaps because little else competes for cognitive resources. Sometimes this DMN context representation may be internally constructed through engagement in self-generated thought, but equally, representation of current surroundings may simply be strengthened. At the task restart, one possibility is that a broad task context is constructed, in order for the new task components to be bound to and supported against competing alternatives. As we progressively become embedded in the operations of a focused task, the broader task context representation may recede, perhaps because it becomes less relevant and is suppressed through selective attention. This weakening of context representations could correspond to the experience of "losing ourselves" in ongoing activity, and to well-known anti-correlations between task-negative and task-positive regions (Fox et al. 2005a; Kelly et al. 2008).

With a major switch to a new task, however, the broad task context may need to be updated, again leading to increased DMN activation.

At cognitive transitions, new behavioural rules must be implemented. In part, these rules are retrieved from memory, as in the present study. As DMN activity is often found during episodic retrieval, it could be argued that activity at transitions also reflects retrieval demand. Although context representations are important in retrieving or establishing new rules, DMN activity even for short rest trials suggests that retrieval itself is not a necessary condition for increasing DMN activity. There are also retrieval tasks, such as N-back, which show no DMN activity (Owen et al. 2005). Though some aspects of "retrieval" are evidently linked to the DMN, more is needed to establish which types or aspects of retrieval are most relevant.

Intriguingly, in the current data, DMN regions showed some task-related patterns of activity similar to those of MD regions, with strong increases at between-domain switches and restart. These results match occasional previous reports that DMN and MD activity are not necessarily anti-correlated (Christoff et al. 2009; Spreng et al. 2010; Gerlach et al. 2011; Dixon et al. 2017; Margulies and Smallwood 2017). In line with studies implicating MD activity in task set implementation (Dosenbach et al. 2006; Duncan 2010, 2013; Crittenden et al. 2016), it is plausible that during task restarts DMN and MD regions work together. During task restarts, DMN regions could be responsible for representation and assessment of the broad cognitive context, enabling the MD network to implement a specific task set. During large switches to a different task domain in particular, the broad task context may need to be updated in order to double-check the task constraints relating to this large switch. These suggestions match the broad proposal that DMN and MD systems play complementary roles in the organisation of complex, goal-directed behaviour (Margulies and Smallwood 2017). Despite these similarities, DMN and MD networks also showed important differences. While DMN showed increased activity only for large, between-domain task switches, even small, within-domain switches recruited MD regions. The current MVPA results were consistent with this distinction, indicating MD activity was able distinguish on a finer scale between all six tasks while only relatively coarse task representations were found in the DMN.

As task restart trials always followed rest trials, one possibility is that high DMN activity at restart could reflect slow decay of neural activity, or simply a prolonged haemodynamic response, following rest. However, the results from the FIR model for long rest runs tell against this possibility. In all DMN subnetworks, the data show that, following restart, activity increased beyond the level established during the preceding rest (Figure 4.8). These results show that restart itself recruits strong DMN activity. This finding is also supported by Fox et al. (2005b) who found transient task onset activity in

DMN regions including the posterior cingulate, precuneus and temporo-parietal junction across 4 different tasks. Rest activity also showed a transient component, with a peak at rest onset followed by decay as rest continued. The current data, as well as Fox et al. (2005b), strongly link DMN activity to cognitive transitions from rest to task as well as task to rest.

In line with the findings of Andrews-Hanna et al. (2010) and Crittenden et al. (2015), these results show substantial differences between DMN subnetworks. While activity was very similar for core and MTL subnetworks, the dmPFC network behaved quite differently, with reduced activity on switch trials, and only modest increase for rest trials. Like core and MTL subnetworks, however, the dmPFC subnetwork did show MVPA encoding of task domain. Whilst being consistent with Crittenden et al. (2015), the activity pattern in the dmPFC subnetwork is difficult to interpret. Andrews-Hanna et al. (2010) suggested that dmPFC subnetwork regions might be important for self-referential and social cognitive processes, which have been found to share considerable neural overlap (Saxe et al. 2006; Lombardo et al. 2010). One possibility is that, in a study like ours, reinstatement of social context has little involvement in cognitive transitions; potentially it is more important in everyday events, in which social context may be richer and more variable.

In summary, these results have highlighted the importance of the DMN in cognitive transitions, extending our understanding of DMN function from its well-established role in internally-focused representations to externally-focused tasks also. Just as the DMN encodes internally-generated scenes, episodes or contexts, these results suggest the DMN also encodes current contexts. Though many previous accounts have emphasised spatial, temporal, and social aspects of a cognitive environment, such as the setting for an autobiographical memory, the current results suggest that contexts might also include broad task structure. While the DMN may be important for representing broad contextual information at times of uncertainty, brought about by large environmental changes, the MD system appears to be responsible for implementation and control of specific task sets over prolonged periods of task performance. Once a task set is established, broad contextual information becomes less relevant and hence may recede, along with DMN activity.

Chapter 5

The effect of rule retrieval on activity in the default mode network

INTRODUCTION

Evidence from the Chapter 4, in combination with the results of Crittenden et al. (2015), suggests that the DMN is important for cognitive transitions in externally-directed tasks. For core and MTL subnetworks, switching to tasks of a different domain was found to show increased activation compared to switching to a task of the same stimulus domain or repeating the same task. Furthermore, activity in core and MTL subnetworks also increased with a switch from task to rest, but also with a switch from rest back to task (see also Fox et al. 2005b). The evidence suggested that the DMN – at least the core and MTL components – represents cognitive contexts or situation models (see also Zacks et al. 2007; Bar 2007, 2009; Ranganath and Ritchey 2012). Though many previous accounts have emphasised spatial, temporal, and social aspects of a cognitive environment, such as the setting for an autobiographical memory, evidence from Chapter 4 suggests that contexts might also include broad task structure. To explain the involvement of DMN in cognitive transitions, Chapter 4 proposes that, through a series of similar task trials, representation of the broader task context progressively fades, as attention is increasingly focused on the specific task at hand. With switch to a substantially new line of activity, however, representation of the broad task context might be updated, perhaps to allow specific task components to be bound to and supported against competing alternatives.

This study aimed to test an alternative account of these findings. Although DMN activity is well known in the context of episodic recollection (Hayama et al. 2012; Vilberg and Rugg 2012), some authors have proposed a broader role in information retrieval. Spreng et al. (2014) found increases in DMN activity during a 2-back working memory task using famous faces compared to anonymous faces, suggesting that the DMN contributes to task performance when this requires retrieval from long term knowledge. In a series of studies, Smallwood et al. found increased DMN activation when participants were required to make decisions about stimuli presented in the previous trial compared to perceptual decisions about current stimuli (Smallwood et al. 2013; Konishi et al. 2015; Murphy et

al. 2018). They suggest that DMN activations during externally-directed tasks are due to retrieval of information which is not available in the current environment. Along similar lines, it could be argued that DMN activation during transitions to more dissimilar tasks in Crittenden et al. (2015) and the results of Chapter 4 are simply an effect of memory retrieval demand. For example, in repeat trials, participants simply have to retrieve the same colour-rule information as retrieved on the previous trial. Retrieval might also be easy on within-domain switch trials if participants have formed a strong association between the two colours associated with the same stimulus domain. In this case, when the colour switches but the stimulus domain remains the same, participants can simply switch to the other rule of this domain. Retrieval demands are likely higher on between-domain switch trials and restarts following rest, where such short-cuts are not possible.

In the previous studies (Crittenden et al. 2015; Chapter 4) effects of rule retrieval difficulty and degree of switch were inseparable. The current study was developed in order to examine rule retrieval directly. To this end, retrieval demand was manipulated by varying the number of alternative rules in the task set. Additionally, it was examined whether switches in stimulus domain continue to increase DMN activity in a setting substantially simpler than the Crittenden et al. (2015) and Chapter 4 tasks. Activity in the three sub-networks of the DMN were compared with a set of typically task-related "multiple-demand" (MD) regions. These regions typically show increased activity with increased task difficulty (Duncan and Owen 2000; Duncan 2010, 2013; Fedorenko et al. 2013) and include parts of the inferior frontal sulcus, dorsal prefrontal cortex, inferior frontal junction, anterior insula, presupplementary motor area and intraparietal sulcus. Against the suggestion that activity might reflect rule retrieval, these results show increased MD activity but decreased DMN activity with increased retrieval demand.

METHODS

Participants

46 participants (27 female), between 18-35 years old, were recruited through the Medical Research Council Cognition and Brian Sciences Unit volunteer panel. All participants selected were right handed, native English speakers, with normal or corrected to normal vision, and between 18-40 years old. The experiment was con-ducted in accordance with ethics approval granted from the Cambridge Psychology Research Ethics Committee. 4 participants (2 female) were excluded from further analysis due to poor task performance (n=1), excessive motion (n=2) or mid-task cancellation (n=1).

Task

Task events are illustrated in Figure 5.1. Participants were presented with either written words, or pictures of animals, and asked to press one of 8 buttons depending on the category of item that was presented. Half (21) of the participants were asked to classify 6 types of animal (bird, fish, insect, mammal, mollusc, reptile) and identify which of 2 vowels was used in the word stimuli (A, E). The other (21) participants had to classify 2 types of animal (bird, mammal) and identify which of 6 vowels was used in the word stimuli (A,E,I,O,U,Y). Within each group, the response mappings were counterbalanced such that 2-choice responses were made with index fingers for half of the participants, and with little fingers for the other half. Figure 5.1a shows the possible response mappings for the group with a 6-choice word task.

Each stimulus remained until a button press was made. Participants were asked to respond as quickly as possible without making mistakes. An inter-trial interval (ITI) of 2 seconds followed each response, with a fixation cross presented in the centre of the screen.

The two stimulus domains were presented in pseudorandom order. This generated four conditions that crossed the number of response options (2 or 6) with whether the stimulus domain repeated or switched: 2-choice domain-stay (a 2-choice stimulus following another), 2-choice domain-switch (switch from a 6-choice stimulus to a 2-choice stimulus), 6-choice domain-stay (a 6-choice stimulus following another) and 6-choice domain-switch (switch from a 2-choice stimulus to a 6-choice stimulus). The experiment consisted of a single block of 145 trials. Each block contained 36 trials of each condition, plus the first trial of the block (switch type undefined) which was discarded from further analysis. In Table 5.1, the total number of analysed trials is further broken down by whether, on successive trials, responses were the same (response stay), responses were different but from the same hand (hand stay), or from different hands (hand switch).

Table 5.1. Number of trials per response choice number, domain switch type and response switch type.

		Response Stay	**Hand Stay (Response Switch)**	**Hand Switch (Response Switch)**
2 Choice	Domain Stay	18	0	18
	Domain Switch	0	18	18
6 Choice	Domain Stay	6	12	18
	Domain Switch	0	18	18

The experiment was controlled using Psychophysics Toolbox for MATLAB (Brainard 1997). Stimuli were presented on a screen located at the back of the scanner, made visible to participants via a mirror mounted on a 32 channel head coil. All stimuli were presented on a white background in the centre of the screen, sized to fit snugly inside a rectangle measuring approximately 6.0 (width) x 4.5 (height) degrees of visual angle. The word stimuli were presented in black upper case and varied from 3 to 6 letters long. All word stimuli and picture stimuli were chosen to be familiar and recognisable to the participants as developed through behavioural pilots. For each participant there was a pool of 48 word stimuli and 48 picture stimuli. There were 24 stimuli for each of the 2 choice categories and 8 stimuli for each of the 6 choice categories. For example, for a participant with the 6 choice word task there would be 24 mammal pictures, 24 bird pictures, 8 A-words, 8 E-words, 8 I-words, 8 O-words, 8 U-words and 8 Y-words. Within each stimulus category, the exact stimulus presented on a given trial was selected at random but always different from the previously presented stimulus.

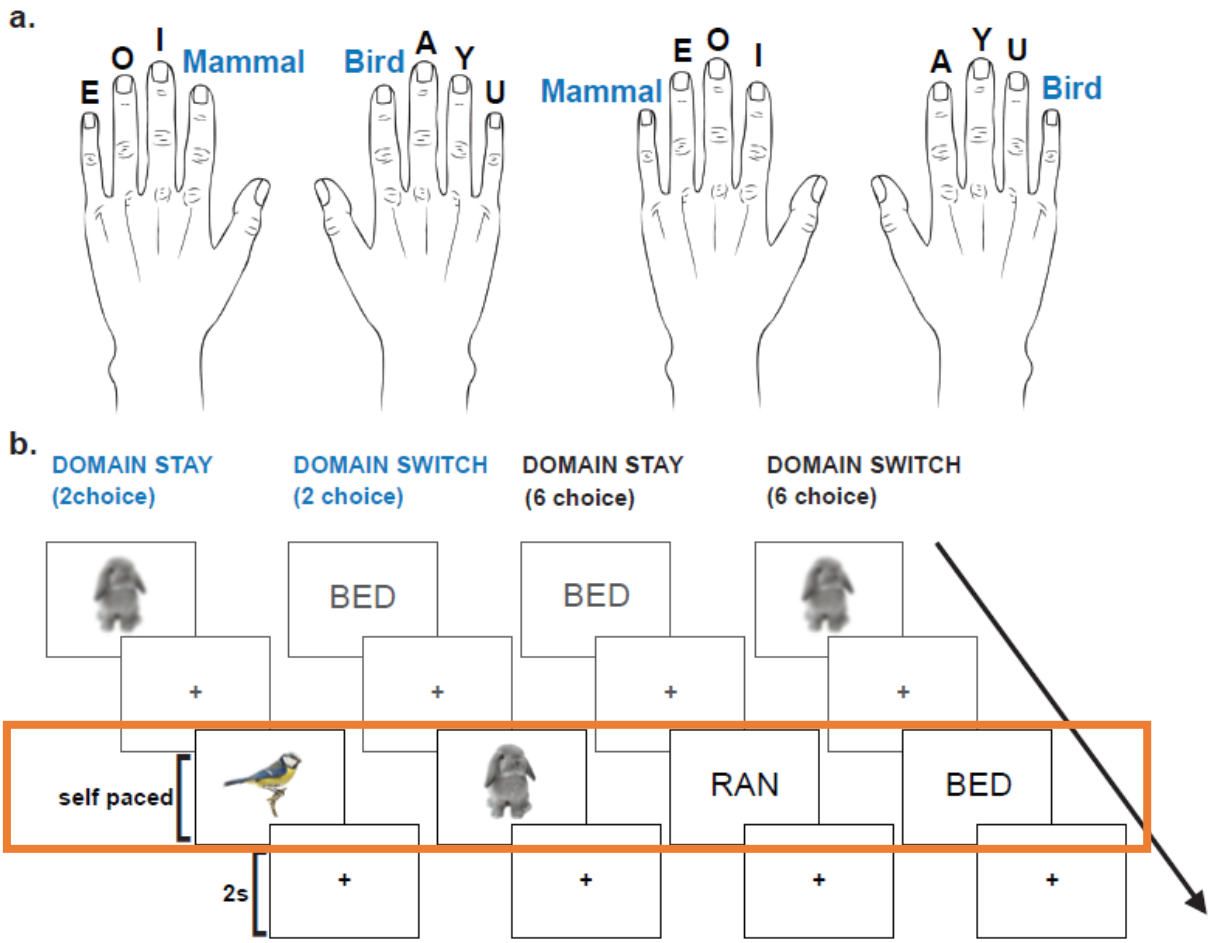

Figure 5.1. Task design, illustrated for the group with a 6-choice word task. a. The two possible category-response mappings. b. Example trials for each combination of choice number (2 or 6) by domain switch condition (switch or stay). The orange box specifies the current trial. Each trial was followed by a 2 second inter-trial interval.

Training

Participants were carefully pre-trained to ensure good learning of button presses. To encourage separation of the two task domains, participants were first presented with the 2-choice response rules and then asked to repeat them from memory. Next, participants were presented with the 6-choice response rules and asked to repeat them from memory. After learning the 2-choice and 6-choice rules separately, participants were shown one exemplar from each response category in a random order and asked which finger they would use to respond. This process was repeated twice. At the second run-through, all participants got all responses correct. Finally, participants performed a short practice block of 36 trials (9 from each combination of 2/6 choice x domain stay/switch) outside the scanner.

Data acquisition

Images were acquired using a 3 T Siemens Prisma magnetic resonance imaging (MRI) scanner, fitted with a 32-channel head coil. Functional MRI (fMRI) acquisitions used T2*-weighted multiband Echo-Planar Imaging (multiband acquisition factor 3 for 2.5 mm slices with no interslice gap, TR 1.1 s, TE 30 ms, flip angle 62°, voxel size 2 × 2 mm in plane). T1-weighted multiecho magnetization-prepared rapid gradient-echo (MPRAGE) images were also obtained (TR 2.25 s, TE 2.99 ms, flip angle 9°, voxel size 1 mm3).

Preprocessing

Images were preprocessed using automaticanalysis (version 4) (Cusack et al. 2015) and SPM 12 (Wellcome Department of Cognitive Neurology, London, UK) for Matlab (Mathworks). The sequence of preprocessing stages involved spatial realignment of the raw EPIs, slice-time correction to the middle slice, coregistration of the functional EPI images to the structural T1-weighted image, and normalization to the Montreal Neurological Institute (MNI) template brain. To match the experimental methods used in Chapter 4, functional images were then spatially smoothed using a Gaussian kernel of 10 mm full-width at half-maximum.

Regions of Interest

To stay as close as possible to the experimental methods used in the Chapter 4 study the same ROIs were used, as presented in Figure 4.2. The DMN ROIs (Figure 4.2a) are comprised of 8 mm radius spheres around peak coordinates from Andrews-Hanna et al. (2010). The DMN ROIs are clustered into core, MTL and dmPFC subnetworks based on the functional connectivity and univariate activity results from Andrews-Hanna et al. (2010). Consistent with the findings in Chapter 4, due to the

position of the bounding box, some voxels surrounding the Andrews-Hanna et al. (2010) temporal pole peak were not measured; to compensate for this, the temporal pole ROIs were each expanded in radius by 2 voxels. Frontoparietal MD ROIs (Figure 4.2b) were taken from Fedorenko et al. (2013), including the posterior–anterior extent of the inferior frontal sulcus, a posterior dorsal portion of the lateral prefrontal cortex, inferior frontal junction, anterior insula/frontal operculum, presupplementary motor area/dorsal anterior cingulate, and intraparietal sulcus. Volumes were downloaded from http://imaging.mrc-cbu.cam.ac.uk/imaging/Mdsystem using the separate-ROI version and selecting only the frontoparietal ROIs.

Analysis

fMRI data for each participant were examined using the General Linear Model. Regressors were separately created for each combination of choice number (6, 2) by domain switch condition (domain stay, domain switch) by response switch type (response stay, hand stay, hand switch). Each regressor was modelled as a rectangular function from stimulus onset to response, convolved with the canonical hemodynamic response function. Given that participant accuracy was very high (mean 98.3%), the original GLM did not exclude error trials. To check for any effect of error trials, in a follow-up GLM (not presented) each error trial was modelled separately and excluded from further analysis. This model produced almost identical results to those presented here.

Beta weight images were subtracted for the contrasts 6-choice>2-choice, 2-choice>6-choice, domain switch>domain stay, and domain stay>domain switch. As shown in Table 5.1, there were no domain-switch, response-stay trials, or 2-choice, domain-stay, hand-stay trials, and therefore no regressors for these conditions. A number of steps were taken in order to ensure that each contrast was balanced accordingly. For the contrast of 6-choice>2-choice (and 2-choice>6-choice) domain-stay, hand-stay, 6-choice trials were excluded, averaging regressors for the remaining 4 trial types in 2- and 6- choice conditions (Table 5.1). To examine domain switch effects, only hand switch trials were used as these were matched for 2- and 6- choice (Table 5.1). To check on domain switch effects specific to a response choice condition, switch contrasts were run separately for 2- and 6-choice regressors.

For the ROI analysis, mean contrast values were extracted from each ROI for each participant using the MarsBaR SPM toolbox (Brett et al. 2002), and contrast values were then averaged across ROIs for each DMN subnetwork and for the whole MD network. Additionally, the same contrasts were examined in a whole brain voxelwise analysis, thresholded at $p < .05$ corrected for multiple comparisons using the false discovery rate (FDR).

RESULTS

Behavioural Performance

Average accuracy was 98.3%, and average RT 0.95s. Independent samples t-tests showed no significant effect of 6-choice domain (6-choice animal or 6-choice word) (accuracy: $t(40)=1.97$, $p=0.055$, RT: $t(40)=1.07$, $p=0.290$) so results are collapsed across these groups.

Figure 5.3 shows error rate and reaction time for domain-switch type by response-switch type for 2-choice and 6-choice trials separately. Error rate was low across all conditions, while reaction times for 6-choice trials appeared slower than 2-choice trials.

To test for an effect of choice number paired-samples t-tests were performed. To ensure equal numbers of domain switch trials and hand switch trials in 2 and 6 choice measures, the four trial types that were present across both choice levels were selected: domain stay, response stay; domain switch, hand stay; domain stay, hand switch; domain switch, hand switch (Table 5.1). Trials within each of the four trial types were first averaged, before averaging across switch conditions. Paired-sample t-tests showed that responses were significantly faster for 2-choice trials than 6-choice trials ($t(41)=10.05$, $p<0.001$) but there was no effect of choice number on accuracy ($t(41)=0.09$, $p=0.926$).

To examine domain switch effects while controlling for response switch and choice number effects, the analysis was restricted to hand switch trials only (see Table 5.1). A two-way ANOVA with within-subject factors of choice number (2,6) and domain switch type (domain stay, domain switch) was performed for accuracy and reaction time data. For accuracy, there were no significant effects of choice number ($F(1,41)=2.78$, $p=0.103$), domain switch type ($F(1,41)=1.40$, $p=0.243$) or an interaction ($F(1,41)=2.46$, $p=0.124$). For reaction time, there was a significant main effect of choice number ($F(1,41)=72.03$, $p<0.001$), domain switch type ($F(1,41)=21.79$, $p<0.001$) and a significant interaction ($F(1,41)=24.36$, $p<0.001$). Paired-samples t-tests showed responses were significantly faster for domain stay compared to domain switch trials in the 2-choice condition ($t(41)=7.00$, $p<0.001$) but not the 6-choice condition ($t(41)=1.30$, $p=0.201$).

In summary, behavioural results show that the manipulation of retrieval difficulty by choice number was effective, and that switches of stimulus domain increased RT in the 2-choice but not the 6-choice conditions.

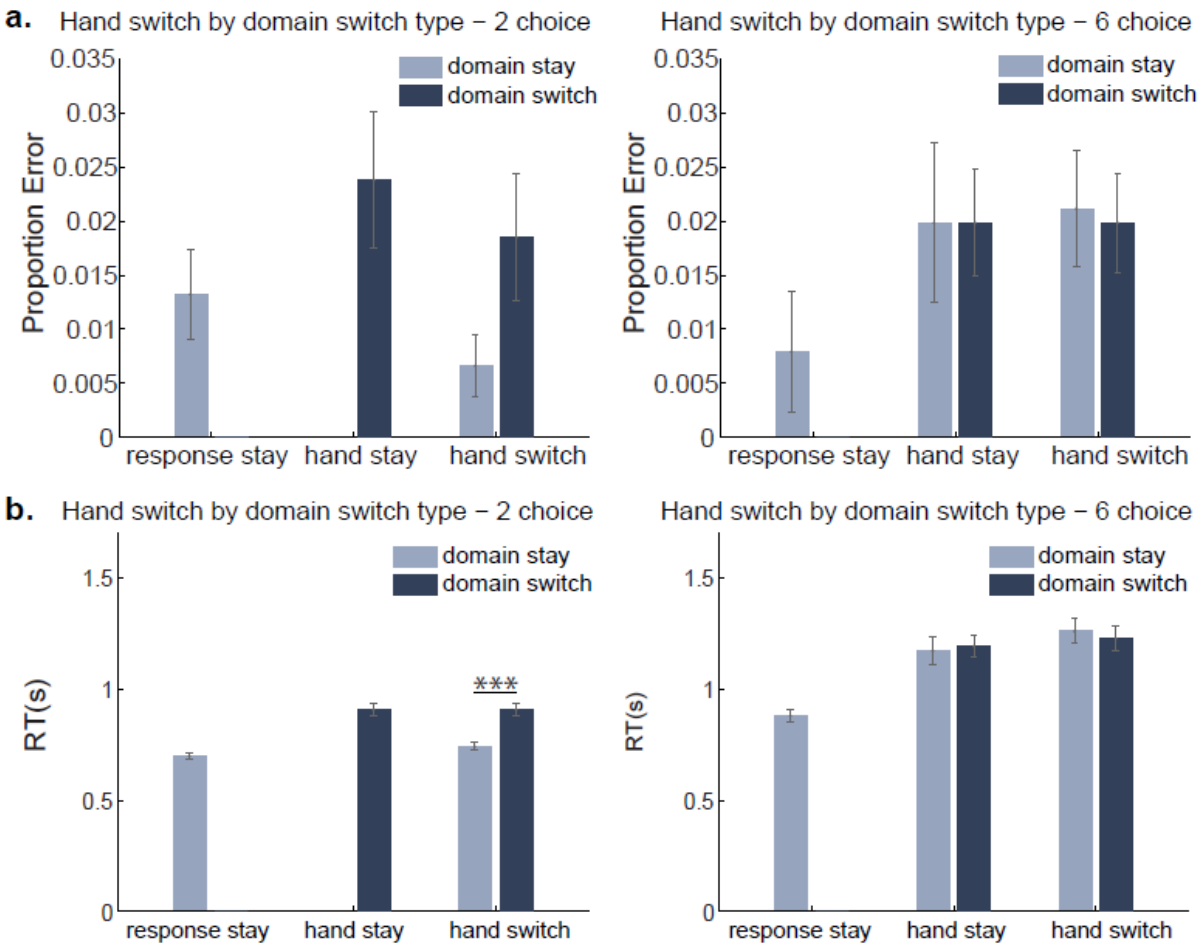

*Figure 5.3. Mean proportion of errors (a) and reaction times (b) for trials of each domain switch type by response switch type, plotted separately for 2-choice and 6-choice conditions. Significant 2-tailed paired t-tests between domain switch types are indicated with *** = p<0.01. Error bars show standard error of the mean between participants.*

ROI analysis

To examine the effects of retrieval difficulty, the primary analysis compared brain activity for 2- and 6-choice tasks. For this purpose, the average beta values over the four trial types that were present across both choice levels were used: domain stay, response stay; domain switch, hand stay; domain stay, hand switch; domain switch, hand switch (Table 5.1). Differences in mean beta value for 2- and 6-choice tasks are shown in Figure 5.4.

Results were clear cut. For DMN regions, activation was greater in 2-choice than in 6-choice. This difference was significant in core and dmPFC subnetworks (core: $t(41)=3.16, p<0.01$, dmPFC: $t(41)=2.70, p<0.01$). In the MTL subnetwork, there was no significant effect of choice number ($t(41)=0.78, p=0.44$). These results rule out the hypothesis that DMN activity increases with the number of choice alternatives during rule retrieval. In contrast, MD regions showed significantly greater activity for the more difficult 6-choice compared to 2-choice trials ($t(41)=3.17, p<0.01$).

Additional t-tests revealed significant differences in contrast values between MD network regions and all three DMN subnetworks (core: t(41)=4.54,p<0.001; MTL: t(41)=3.43,p<0.001; dmPFC: t(41)=5.16,p<0.001). A finer breakdown by individual regions within each (sub)network showed largely consistent results, though with variable significance across regions (see Figure 5.5).

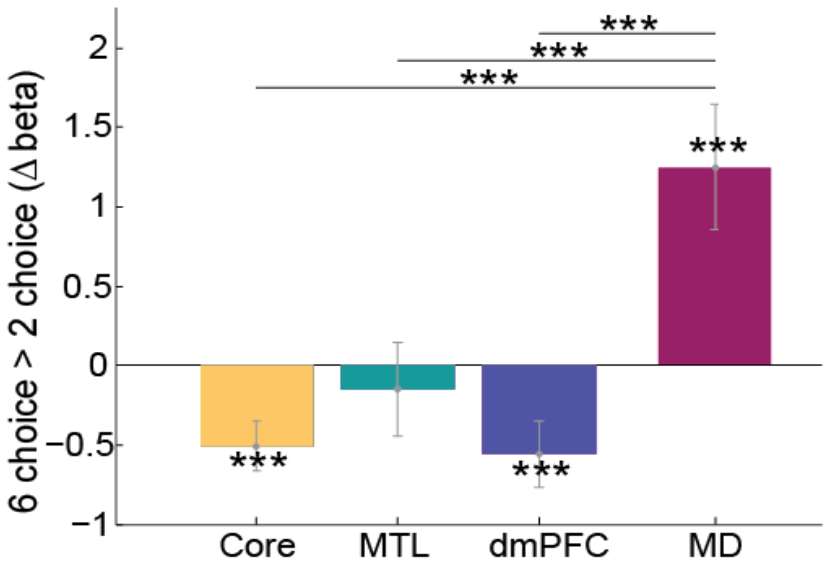

*Figure 5.4. Contrasts of choice number in each DMN subnetwork and the MD network. Significant changes in activity with choice number as well as paired t-tests between subnetworks are indicated with * = P<0.05, ** = p<0.02 and *** = p<0.01. Error bars show standard error of the mean between participants.*

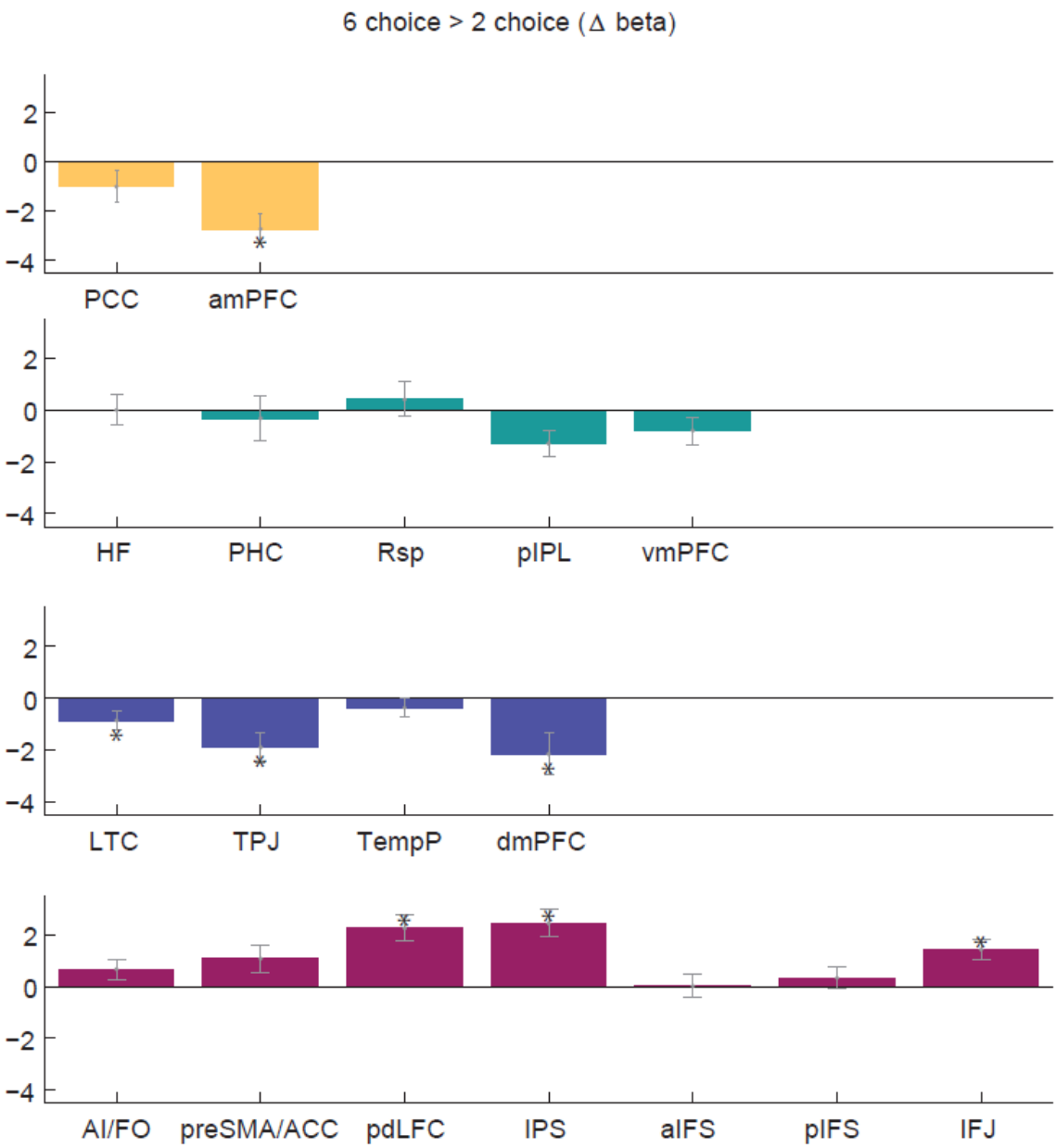

Figure 5.5. Contrasts of choice number for individual regions of interest within in each DMN subnetwork and the MD network. Significant changes in activity with choice number are indicated with an asterisk (p < .05, corrected for the number of regions within each (sub)network by Holm-Bonferroni). Error bars show standard error of the mean between participants. Yellow = core DMN, green = MTL DMN, blue = dmPFC DMN, purple = MD. PCC=posterior cingulate cortex, amPFC=anteromedial prefrontal cortex, HF=hippocampal formation, PHC=parahippocampus, Rsp=retrosplenial cortex, pIPL=posterior inferior parietal lobe, vmPFC=ventromedial prefrontal cortex, LTC=lateral temporal cortex, TPJ=temporo-parietal junction, TempP=temporal pole, dmPFC=dorsomedial prefrontal cortex, AI/FO=anterior insula/frontal operculum, preSMA/ACC=pre-supplementary motor area/anterior cingulate cortex, pdLFC=posterior dorsolateral frontal cortex, IPS=inferior parietal sulcus, aIFS=anterior inferior frontal sulcus, pIFS=posterior inferior frontal sulcus, IFJ=inferior frontal junction.

Effects of domain switching were next examined. For this purpose, mean beta values on domain switch vs domain stay trials were compared, restricting analysis just to hand switch trials (see Table 5.1). A two-way ANOVA with within-subject factors of choice number (2,6) and domain switch type (domain stay, domain switch) for each (sub)network type was constructed. Reflecting the previous analyses, core, dmPFC and MD (sub)networks showed a significant main effect of choice number (core: $F(1,41)=6.20$, $p<0.02$; dmPFC: $F(1,41)=8.02$, $p<0.01$; MD: $F(1,41)=11.55$, $p<0.01$). However, no subnetworks showed a significant main effect of domain switch type (Core: $F(1,41)=1.13$, $p=0.293$; MTL: $F(1,41)=1.82$, $p=0.185$; dmPFC: $F(1,41)=0.571$, $p=0.454$; MD: $F(1,41)=0.610$, $p=0.439$) or a significant interaction (Core: $F(1,41)=1.37$, $p=0.248$; MTL: $F(1,41)=1.39$, $p=0.251$; dmPFC: $F(1,41)=1.56$, $p=0.219$; MD: $F(1,41)=1.18$, $p=0.284$) (see Figure 5.6). Separate t-tests also showed no significant effect of switching for either 2- or 6-choice tasks. When the analysis was repeated collapsing across all DMN regions rather than separating by subnetwork, again there was a significant main effect of choice number ($F(1,41)=5.45$, $p<0.05$), but no main effect of domain switch type ($F(1,41)=1.16$, $p=0.289$) nor interaction ($F(1,41)=2.19$, $p=0.146$). Additional analyses for individual regions also did not show significant domain switch effects or interaction effects (see Figures 5.7-5.10).

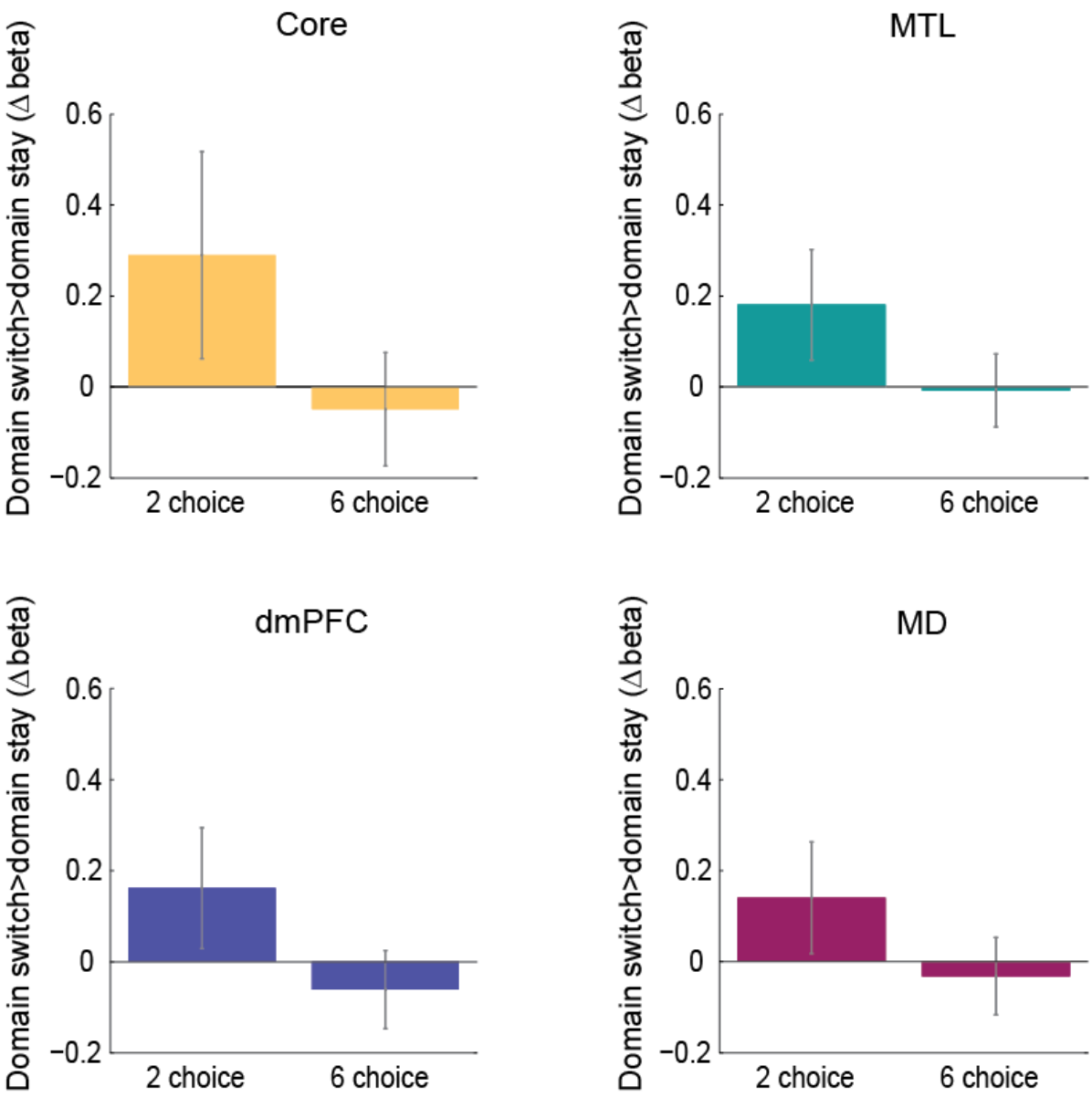

Figure 5.6. *Contrasts of domain switch effects by choice number in each DMN subnet-work and the MD network. No significant (P<0.05) effects of domain switch type were found. Paired t-tests showed no significant differences between domain switch effects for 2-choice and 6-choice trials. Error bars show standard error of the mean between participants.*

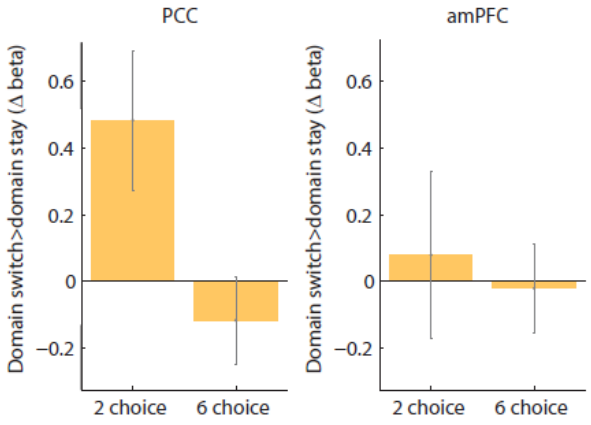

Figure 5.7. Contrasts of domain switch effects by choice number for individual ROIs within the Core DMN. After correcting for multiple comparisons within subnetworks using the Holm-Bonferroni correction, t-tests showed no significant effects of domain switch type for either 2-choice or 6-choice trials. Paired t-tests also showed no significant differences between domain switch effects for 2-choice and 6-choice trials. Error bars show standard error of the mean between participants. PCC=posterior cingulate cortex, amPFC=anteromedial prefrontal cortex.

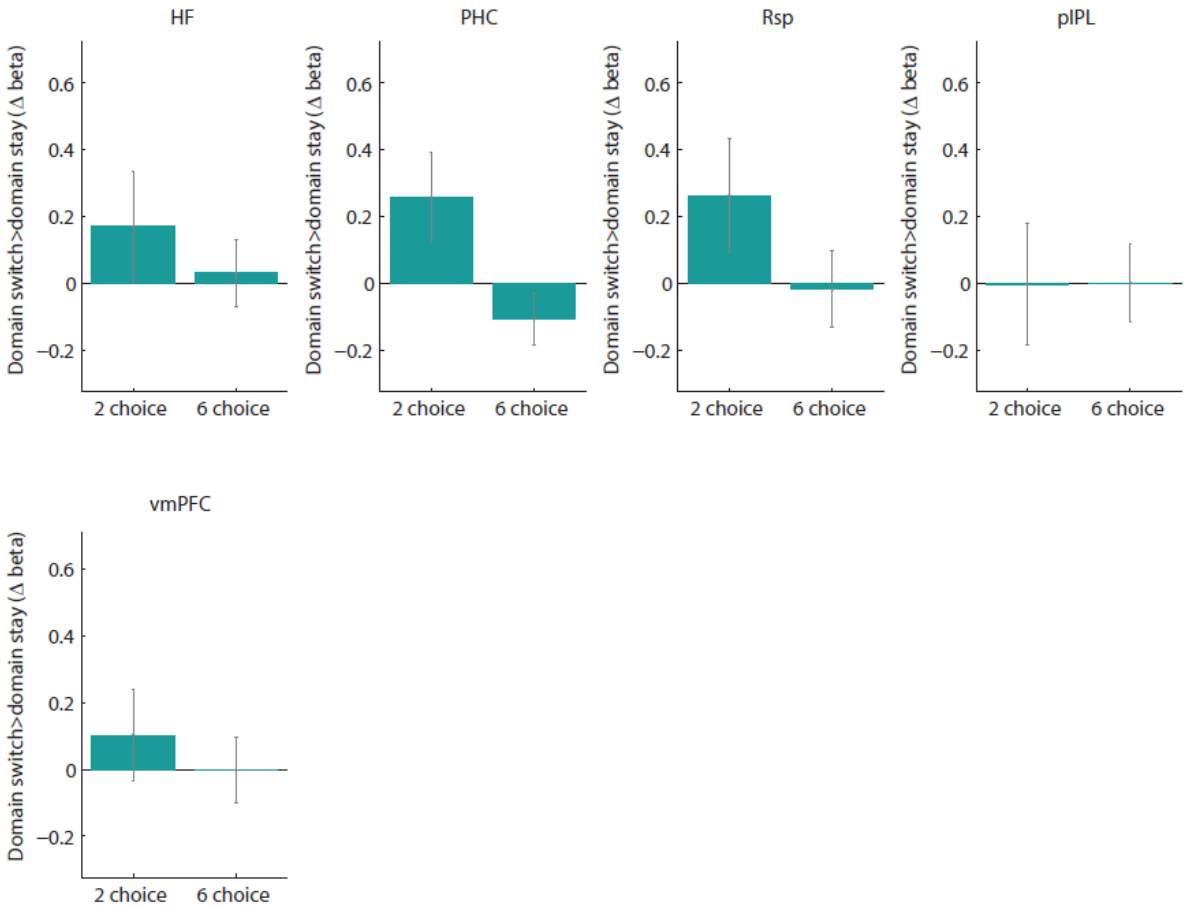

Figure 5.8. Contrasts of domain switch effects by choice number for individual ROIs within the MTL DMN. After correcting for multiple comparisons within subnetworks using the Holm-Bonferroni

correction, t-tests showed no significant effects of domain switch type for either 2-choice or 6-choice trials. Paired t-tests also showed no significant differences between domain switch effects for 2-choice and 6-choice trials. Error bars show standard error of the mean between participants. HF=hippocampal formation, PHC=parahippocampus, Rsp=retrosplenial cortex, pIPL=posterior inferior parietal lobe, vmPFC=ventromedial prefrontal cortex.

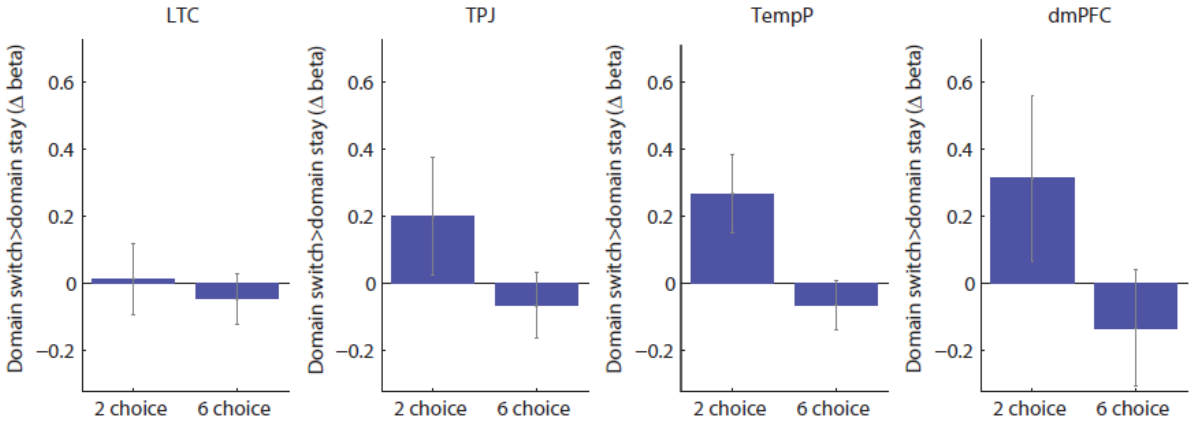

Figure 5.9. Contrasts of domain switch effects by choice number for individual ROIs within the dmPFC DMN. After correcting for multiple comparisons within subnetworks using the Holm-Bonferroni correction, t-tests showed no significant effects of domain switch type for either 2-choice or 6-choice trials. Paired t-tests also showed no significant differences between domain switch effects for 2-choice and 6-choice trials. Error bars show standard error of the mean between participants. LTC=lateral temporal cortex, TPJ=temporo-parietal junction, TempP=temporal pole, dmPFC=dorsomedial prefrontal cortex.

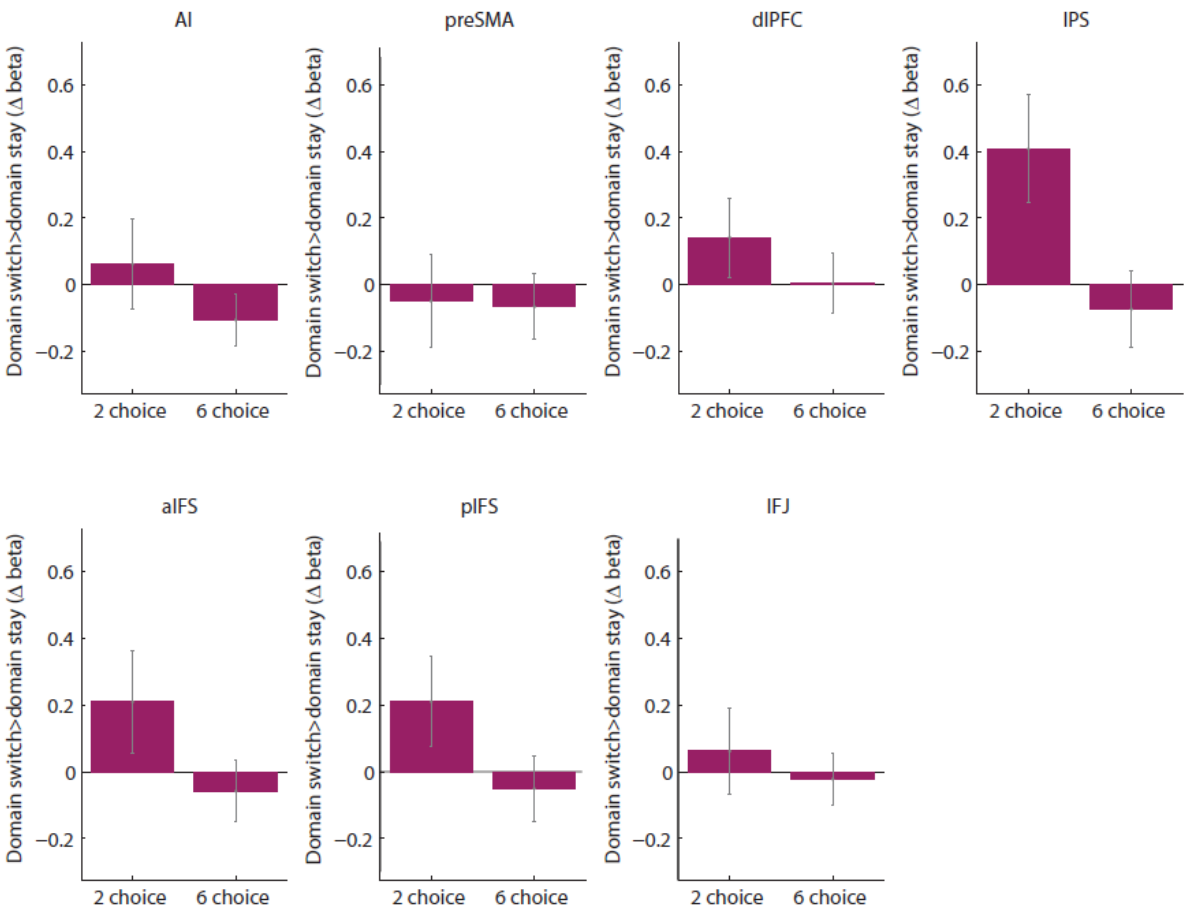

Figure 5.10. Contrasts of domain switch effects by choice number for individual ROIs within the MD network. After correcting for multiple comparisons within subnetworks using the Holm-Bonferroni correction, t-tests showed no significant effects of domain switch type for either 2-choice or 6-choice trials. Paired t-tests also showed no significant differences between domain switch effects for 2-choice and 6-choice trials. Error bars show standard error of the mean between participants. AI/FO=anterior insula/frontal operculum, preSMA/ACC=pre-supplementary motor area/anterior cingulate cortex, pdLFC=posterior dorsolateral frontal cortex, IPS=inferior parietal sulcus, aIFS=anterior inferior frontal sulcus, pIFS=posterior inferior frontal sulcus, IFJ=inferior frontal junction.

Whole brain analysis

Figure 5.11 shows the results of the whole brain analysis for the contrasts of 6-choice>2-choice and 2-choice>6-choice, thresholded at $p<0.05$, corrected for false discovery rate. In line with the ROI analysis, several MD network regions were found to be more active for 6-choice compared to 2-choice trials, including the anterior insula, inferior prefrontal and dorsal prefrontal cortex, intraparietal sulcus and pre-supplementary motor area. Stronger activity in the 6-choice task was also seen in a number of other regions, including precuneus, sensorimotor cortex, occipitoparietal cortex and regions in the basal ganglia. In contrast, greater activity in 2-choice than 6-choice was prominent across much of the DMN, including dorsomedial prefrontal, anteromedial prefrontal,

ventromedial prefrontal and lateral temporal cortex, posterior cingulate, hippocampus, and temporo-parietal junction.

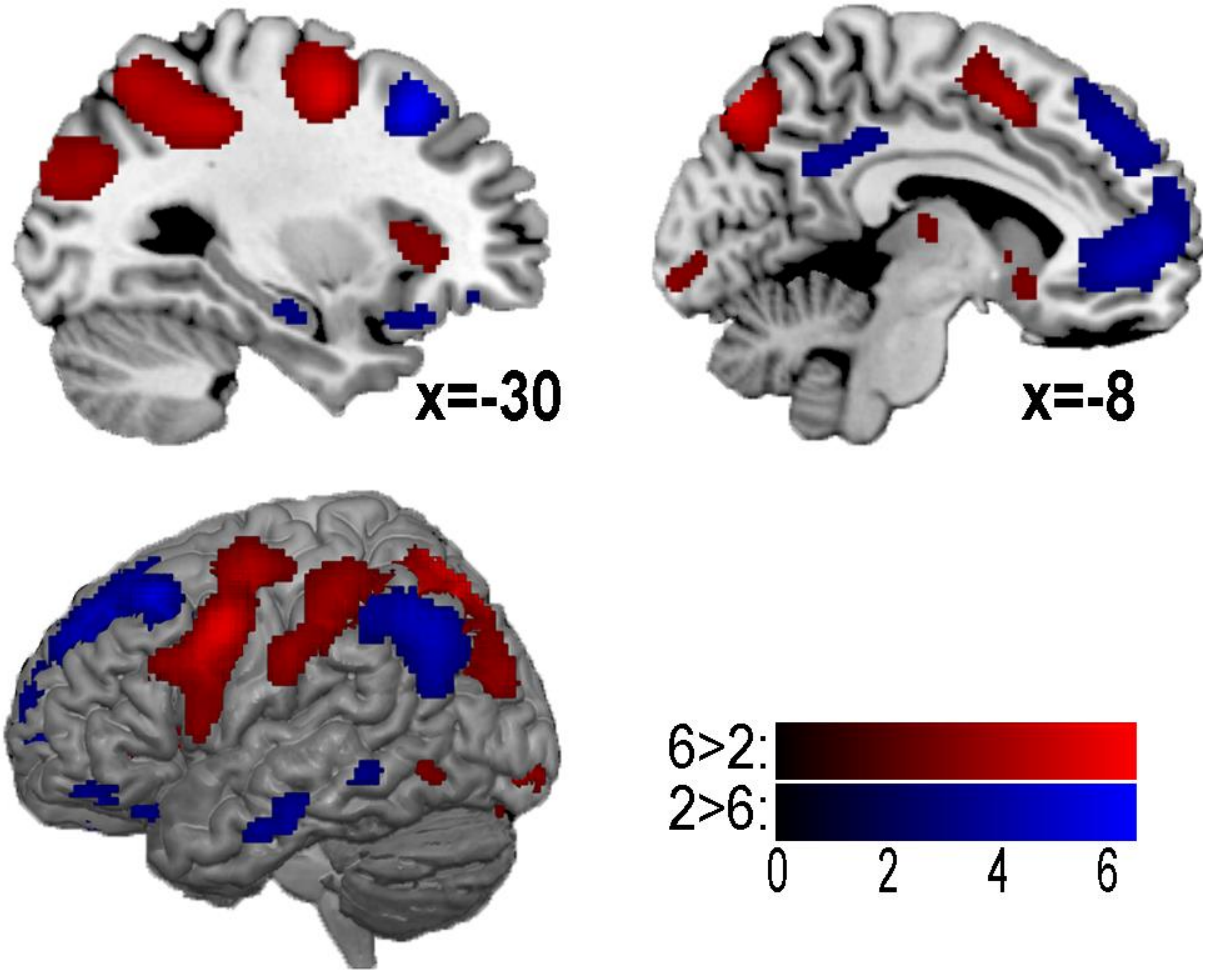

Figure 5.11*. Whole brain contrast values for choice number presented with an FDR corrected threshold of p<0.05, plotted in MNI space. The red colour scale represents 6 choice>2 choice. The blue colour scale represents 2 choice> 6 choice. Brain render shows search depth of 12 voxels. Medial slices show x coordinate values.*

At the whole brain level, no significant effects of domain switch vs domain stay were found for either 2 choice or 6 choice tasks, or when combined across choice number.

DISCUSSION

The primary aim of this study was to test whether increased difficulty of rule retrieval is associated with increased DMN activity. To achieve this, the number of alternative rules in a task set was manipulated. This manipulation had a large effect on behaviour with participants performing significantly slower for 6-choice trials compared to 2-choice trials. However, DMN activity, at least in

core and dmPFC regions, showed deactivation with increased retrieval difficulty. This rules out the retrieval difficulty hypothesis and instead matches many cases of deactivation with increasing task difficulty (McKiernan et al. 2003, 2006; Fransson 2006; Leech et al. 2011). Other studies have also looked at manipulating the number of alternatives or response mapping retrieval demands (Badre and D'Esposito 2007; Crittenden and Duncan 2014). These studies found increased activity in dorsal premotor cortex, intraparietal sulcus and pre-supplementary motor area for increased number of response buttons and do not report any DMN-related activity. Replicating these findings, activity in MD regions was found to increase with retrieval difficulty. This is consistent with many previous results showing that MD activity increases with task difficulty (Duncan 2010, 2013; Fedorenko et al. 2013) and working memory demands (Cohen et al. 1997; Owen et al. 2005).

As stated in the introduction, DMN activity has been linked to different aspects of retrieval (e.g. Smallwood et al. 2013; Konishi et al. 2015; Murphy et al. 2018), but especially to episodic recollection. Tulving (1985) outlined three key properties of episodic memory: a subjective sense of time (a feeling of mental time travel), connection to the self (self-relevance), and autonoetic consciousness (the cognitive ability to mentally project oneself to an imagined time and place). Particularly supporting these ideas, DMN regions have been found to show increased activity with increased self-relevance, vividness of the remembered episode, and self-projection (Andrews-Hanna et al. 2010; Richter et al. 2016). Rule retrieval is not deeply personal, nor does it require mental projection back to a time and place. In the previous study, instead of simply representing broad task context alone, DMN activity during large cognitive transitions might reflect the integration of broad task features to one's personal situational context (i.e. in an MRI scanner, doing a task) which are preferentially activated in the DMN. Perhaps for these reasons, the role of the DMN in memory retrieval does not extend to retrieval of task rules but does extend to a role in large cognitive transitions. It remains unclear, however, what constitutes a broad compared to a specific task rule and why only the broad but not specific aspects of task rules appear to be represented in DMN.

Given the negative relationship between DMN activity and retrieval demand, in isolation the current results could be interpreted in line with the common view of the DMN as task-negative, showing deactivation with increasing demand of an externally-focused task. However, a large body of work suggests that the relationship between the DMN and task related processes is more complex. For example, during a sustained attention task, DMN activity was positively related to a state of reaction time stability in which participants made fewer errors, however, within this state, further increases in DMN activation were predictive of errors (Esterman et al. 2012). Similarly, Sormaz et al. (2018) found that DMN activity reflected the level of detail during working memory maintenance in a 1-back task despite reduced univariate activity compared to the 0-back version (see also Murphy et al. 2019).

Further studies have also found that DMN regions represent task information. For example, the results from Chapter 4 showed that patterns of activity in DMN regions could distinguish between upcoming task domains (see also Crittenden et al. 2015). Similarly, Schuck et al. (2016) found that DMN activity patterns could be used to decode between different task contexts (house or face judgements). Thus it seems that many aspects of the DMN response are associated with active task processing, even in the absence of overall increases in univariate activity.

A secondary goal of this research was to see whether domain switches cause increased DMN activation in a much simpler task setting than used previously (Crittenden et al. 2015; Chapter 4). In this task the results do not show domain switch effects in DMN regions. Of course, this lack of DMN switch effect is not unusual: DMN domain switch effects are not typically reported in experiments when one is switching between just two tasks (Kimberg et al. 2000; Yeung et al. 2006). The lack of switch effects in the current study may help understand the switch-related DMN activity found in previous tasks (Crittenden et al. 2015; Chapter 4). Perhaps this activity is stronger in a more elaborate cognitive setting, in which parts of the task are hierarchically chunked and there is switching from one broad task context to another. Changes in broad task context may require integration of the new task context with one's current situational context, whereas local task changes may not require such large-scale reconfiguration of task representation.

Unlike core and MTL DMN subnetworks, the dmPFC subnetwork more consistently shows activity decreases with difficulty, even during large domain switches (Crittenden et al. 2015; McKiernan et al. 2003, 2006; Fransson 2006; Leech et al. 2011; Chapter 4). In the present study, the effect of rule retrieval was observed in core and dmPFC subnetworks, but not the MTL subnetwork. It remains to be understood what specific task demands cause these dissociations between subnetwork regions as opposed to their usual functional correlation, although some principles have been proposed (e.g. Andrews-Hanna 2012). Evidence from Poerio et al. (2017) also shows functional dissociations between DMN subnetworks. These researchers found that connectivity between superior frontal gyrus (including the dmPFC) and MTL regions was negatively related to task performance requiring external engagement, including the Tower of London task and encoding facts in stories. These results suggest that good performance in tasks of this sort may require a trade-off between different DMN subnetwork regions.

In summary, the difficulty of rule retrieval was not found to satisfactorily explain the findings from the previous chapter and of Crittenden et al. (2015). Instead, it can be concluded that these DMN activations are a genuine effect of large switches, at least in complex, hierarchical settings. If the DMN represents context, as much evidence suggests (Zacks et al. 2007; Ranganath and Ritchey 2012;

Baldassano et al. 2016; Milivojevic et al. 2016; Chen et al. 2017), these findings (Crittenden et al. 2015; Chapter 4) indicate that this may include broad task structures, established after a large cognitive switch. Further work should address the detail of DMN context representations, and their fluctuations during cognitive maintenance and transition.

Chapter 6

Discussion

Context is critical for cognition; for example, it allows one to infer the meaning of ambiguous words and make predictions about upcoming events on the basis of past experiences in similar contexts. While several researchers suggest a role for the DMN in representing the broad associative context, including spatial, social and temporal elements (Hassabis and Maguire 2007; Ranganath and Ritchey 2012), there is little direct evidence of a role for the DMN in contextual control of ongoing behaviour. This thesis aimed to address this question through a series of tasks designed to require reference to the broader context. The results were compared with 'task-positive' MD regions in order to understand the interaction between the two, often negatively related, networks during contextual control.

In Chapters 2 and 3, meaningful, naturalistic stimuli were used in order to test for the components of cognitive control in more life-like settings than typical cognitive control tasks. The findings suggest that performance of life-like naturalistic tasks involves more than just MD regions. Unlike for abstract executive tasks (Roca et al. 2010), Chapter 3 showed that differences in IQ scores, related to MD lesion volume, could not explain the difference in behavioural performance between patients and controls for more naturalistic tasks. Instead, poor patient behavioural performance for the naturalistic tasks was associated with regions of the cortex beyond the DMN and MD network. The results from the imaging study in Chapter 2 also find differences in brain activity dependent on whether the task rules were arbitrary or lifelike and meaningful. While MD regions showed strong responses to the task, MD activity was greater for decisions requiring the arbitrary rules compared to the meaningful rules despite few measured difference in behavioural difficulty. On the other hand, posterior DMN regions were found to be more active when making decisions using more meaningful spatial contexts. These findings suggest performance of complex, naturalistic tasks demands additional cognitive processes, requiring the function of additional brain regions beyond those usually associated with executive control.

While DMN regions were not found to be necessary for making situational judgements in Chapter 3, evidence from Chapter 2, in addition to other research (Ranganath and Ritchey 2012; Baldassano et al. 2016, 2017; Milivojevic et al. 2016; Chen et al. 2017) suggests that DMN regions may be important

for representing broad situational features. Chapter 2 showed that the majority of DMN regions, in the meaningful scene condition, represented information about the current spatial context and the current sound. As described by Ranganath and Ritchey (2012), these features of the episode may be bound together to create a situation model for the current event.

Furthermore, results from Chapters 4 and 5 suggest that DMN regions may also be sensitive to broad task contexts. Chapter 4 found increased DMN activity at large cognitive transitions between dissimilar tasks. Alongside this sensitivity to large switches, multivariate decoding analyses revealed that DMN regions were sensitive to broad task category but not to finer-grained task details. Chapter 5 showed that these univariate switch effects could not be fully explained by differences in rule retrieval difficulty across switch conditions. Instead, I suggest, in line with others (Ranganath and Ritchey 2012; Baldassano et al. 2016, 2017; Milivojevic et al. 2016), that the DMN represents context including broad task contexts established after large cognitive switches.

These findings, I believe, highlight three important factors of DMN function. First, the DMN is not necessarily 'task-negative' and is important for task-related processes. Second, the DMN is important for representing current situational contexts as well as imagining and remembering contexts that differ from the perceptual present. And third, that contextual information represented in the DMN is not limited to visual scenes but can also include broader task information.

The DMN is not 'task-negative'

While many papers have also emphasised the importance of the DMN in tasks requiring memory recall and episodic simulation (Addis et al. 2007, 2009; Diana et al. 2007; Smallwood et al. 2013; Spreng et al. 2014), these findings have led to an emphasis on DMN function in non-executive, internally-focused processes, often in competition with 'task-positive' regions (Fox et al. 2005a; Kelly et al. 2008). However, several recent papers suggest that the DMN can also be important for executive task performance (Hahn et al. 2007; Crittenden et al. 2015; Schuck et al. 2016). The findings here lend further support to this theory.

Chapter 2 showed that difficult context-dependent decisions were associated with increased activity in posterior DMN regions compared to context-independent decisions, when the context comprised of more meaningful scenes. Additionally, complementing the work of Crittenden et al. (2015), the results from Chapter 4 found that core and MTL DMN subnetworks showed increased activity during

large task switches compared to the easier stay trials. Most strikingly, these regions also showed activation peaks when shifting back to task after rest. As demonstrated in Chapter 5, this switch-related DMN activity could not simply be explained by differences in rule retrieval difficulty alone. The multivariate results from Chapters 2 and 4 further suggest the involvement of DMN regions in task performance, finding that task-relevant information was represented in several DMN regions. Such task-related decoding has also been found by Schuck et al. (2016) and Crittenden et al. (2015).

The DMN and perception

While it is commonly argued that the key role of the DMN is in representing internally constructed simulations distinct from the current environment (Buckner and Carroll 2007; Andrews-Hanna 2012), other evidence suggests that the DMN may also represent the current environmental context too. Firstly, the perceptuo-mnemonic hypothesis (Buckley et al. 2001) posits that MTL regions are not only contributing to mnemonic processes but are a continuation of visual processing pathways, with regions along the visual processing stream encoding more and more complex percepts by binding coarse visual features into more and more complex feature conjunctions. Whereas in primary visual cortex line orientation is represented, MTL regions were proposed to represent detailed objects, faces and scenes. This hypothesis was tested using a visual oddity task where participants were asked to identify the odd scene, face or object in 4 simultaneously presented images. The odd one out could not be detected by simple feature differences as all the images were presented at different viewpoints. The researchers found that amnesic patients with MTL lesions, either restricted to the hippocampus or extending to nearby MTL regions including the perirhinal cortex and parahippocampus, showed significant impairment in perceptual processing of scenes (Lee et al. 2005). Amnesic patients with additional MTL damage extending beyond the hippocampus additionally showed impairment in face and object oddity. In a complementary fMRI study, the researchers identified regions of the posterior hippocampus and parahippocampus were particularly related to scene oddity compared to face or size oddity judgements (Lee et al. 2008). These studies therefore suggest that MTL DMN regions of the hippocampus and parahippocampus are important for immediate visual perception of scenes as well as their more established role in memory.

More recently, multivariate imaging techniques have revealed the importance of DMN regions in the perceptual processing of and memory for movie scenes. Chen et al. (2017) found patterns of activity in several DMN regions, including posterior medial cortex, medial prefrontal cortex and parahippocampus were more similar during watching and recall of the same scenes compared to

different scenes. Furthermore, during movie watching these regions also showed scene-specific patterns of activity across different participants, further implicating DMN regions in the perception of scenes. Consistent with this finding, the results from Chapter 2 also showed decoding of the current scene in 8 out of 11 DMN regions.

Instead of interpreting DMN as processing purely 'internal' information, I suggest that the DMN represents rich contexts integrating information available from the current environment with information retrieved from long-term memory. What features make up this contextual representation are discussed more fully below.

What constitutes a 'broad context'?

While some researchers have found that DMN regions predominantly represent the visual spatial context of imagined events (Robin et al. 2018), the results of this thesis suggest that the representational content of the DMN may be much richer, plausibly containing multisensory, social, temporal and even broad task elements. Evidence from Chapter 2 shows that DMN regions represent task information gained from the visual scene as well as auditory sound type while the results from Chapter 4 suggest that in complex, hierarchical tasks, DMN regions can represent broad task context. Several past findings provide more direct evidence for this theory, suggesting that the DMN regions may lie at the top of a processing hierarchy, representing the most abstracted, complex information, integrated across time and modalities (Margulies et al. 2016; Baldassano et al. 2017).

As described in the previous section, MTL regions are thought to be a continuation of the visual processing stream, found to be important specifically for perceptual processing of complex objects, faces and scenes but not more simple, single feature perceptual differences (Lee et al. 2005, 2008). Similarly, relational memory theory (Cohen and Eichenbaum 1993) also suggests that MTL regions, especially the hippocampus, are important for remembering associations between spatial, temporal and object features rather than memory for single items. Konkel et al. (2008) tested hippocampal and medial temporal lobe amnesic patients on several types of relational memory within one task. In a study phase, participants were presented with 3 novel items sequentially, each at a new spatial location. In the test phase items were again presented in triplets. To test spatial relational memory, participants were asked whether the items were presented in the same or different locations as the study phase. To test for temporal relational memory, participants were asked whether the items were presented in the same or different order to the study phase. To test for item associative

memory, participants were asked whether items presented were from the same or different triplets. While both groups of amnesics showed impairments for all relational memory conditions, the hippocampal amnesics were not impaired on a standard item memory task where participants were asked whether the items were old or new. Along with evidence from perceptual oddity tasks (Lee et al. 2005, 2008), these findings therefore suggest that MTL regions are important for both perception and memory of complex relational information.

Furthermore, while life-like context representation may often be dominated by spatial information (Robin et al. 2018), other research suggests, in line with the results from Chapter 4, that contexts represented in DMN regions do not necessarily have to be spatial in nature. As discussed in Chapter 4, Crittenden et al. (2015) and Schuck et al. (2016) also found that patterns of activity in DMN regions could represent the current non-spatial task context. Research on grid cells further suggests that DMN regions can provide contextual structure for multiple domains of stimuli. Although grid cells are strongly implicated in representing the spatial structure of the environment (Doeller et al. 2010; Jacobs et al. 2013; Kraus et al. 2015), Constantinescu et al. (2016) recently found that grid-cell-like hexagonally symmetric responses in the entorhinal cortex and ventromedial prefrontal cortex could also represent conceptual knowledge structures, such as the neck:legs ratio in an artificial 'bird space' indicating that grid-like codes in these regions can also represent abstract conceptual information.

Research from Baldassano et al. (2017) suggests that regions beyond the MTL integrate information over time and sensory domains, during the encoding and recollection of narrative events. Using the same movie watching and recollection dataset as Chen et al. (2017), Baldassano et al. (2017) tested the degree to which patterns of activity across regions of the cortex were stable across time. Compared to sensory regions in which patterns of activity were stable only for short periods of time, around 15s, patterns of activity in the MTL, as well as the posterior medial cortex and angular gyrus were found to be remain stable often for over one minute. Changes in activity pattern, especially in posterior medial cortex and angular gyrus, were found to correspond to perceived boundaries between events, suggesting that stable responses in these regions might be important for representing the constant gist or context of an event. Baldassano et al. (2017) also found similar patterns of DMN activity for each scene when participants listened to audio-descriptions of a television series compared to when viewing the show; this was despite the scene durations being different in each presentation modality. In contrast, early sensory regions did not show similarities between patterns of activity during audio-visual and auditory only versions of the television show. Thus the researchers concluded that the posterior medial cortex and angular gyrus are important for representing the broad gist of events, regardless of input modalities.

Research from Margulies et al. (2016) further highlights a role for the DMN in representing heteromodal, abstracted information. Margulies et al. (2016) tested the similarity of functional connectivity patterns across the cortex in order to look for macroscale organisation in human brain connectivity. The researchers found that the maximum variance in connectivity patterns was described by a gradient from unimodal regions, serving primary sensory or motor functions, to regions of transmodal cortex, thought to represent abstract heteromodal concepts. This principle gradient captured the spatial organisation of the 7 functional connectivity networks identified by Yeo et al. (2011). As shown in Figure 6.1, the DMN is at the top of this gradient with executive-control networks such as MD in between the DMN and sensory control networks. This topographical organisation of the cortex, Margulies et al. (2016) suggest, indicates a role for the DMN in tasks requiring a rich representation of stimuli, more related to a stimulus' abstract meaning rather than its immediate sensory properties. In support of this, Murphy et al. (2018) found that variance in brain activity during a decision making task driven by conceptual information held in memory was captured by this principle gradient with increased activity from sensorimotor regions to transmodal regions.

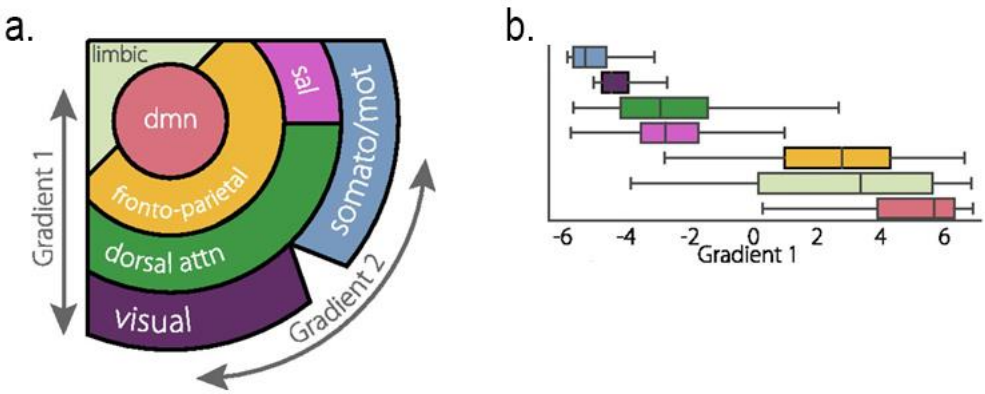

Figure 6.1. Figure adapted from Margulies et al. (2016). a. A schematic of the spatial relationships of the 7 resting state networks identified by Yeo et al. (2011) across the principle gradient, from sensorimotor to transmodal cortex, and a second gradient defining sensory and motor modalities. b. Principle gradient values for the seven Yeo et al. (2011) networks ordered by the mean value, with higher values indicating more abstract, heteromodal representations. dmn = default-mode network; dorsal attn = dorsal attention network; sal = salience network; somato/mot = somatosensory/motor network.

DMN Subnetworks

Although to a first approximation DMN regions tend to behave similarly, e.g. in their response to rest versus task, the findings from this thesis have uncovered several dissociations across DMN regions. As identified using resting state functional connectivity, Andrews-Hanna et al. (2010) and Yeo et al. (2011) suggest that the DMN can be parcellated into 3 subnetworks. These include the core hub of anterior medial prefrontal cortex and posterior cingulate cortex; a Dorsal Medial subnetwork including the dorsomedial prefrontal cortex and lateral temporal regions; and a Medial Temporal subnetwork including the parahippocampus, hippocampus, retrosplenial cortex, posterior inferior parietal lobe and sometimes ventromedial prefrontal cortex. The results from Chapter 4 also showed differences in DMN activity which roughly followed these subnetwork divisions. Core and Medial Temporal subnetwork regions showed increased activation for large task switches whereas Dorsal Medial subnetwork regions showed the reverse pattern. Univariate DMN activity in Chapter 2, however, did not follow the same subnetwork divisions. Instead, the results suggest an anterior-posterior division. Anterior regions appeared to consistently respond to task difficulty, showing decreased activity for the more difficult version of the task. During the arbitrary letter version of the task, posterior regions showed the same pattern of activity, however, during the meaningful scene version of the task, a reverse effect of difficulty was found with posterior DMN regions showing increased activation for the more difficult context-dependent condition. It is important to speculate what these differences across DMN regions might suggest.

Firstly, it is reasonable to propose that each DMN region is, to some extent, functionally specific. This speculation is supported by many examples throughout the literature. As discussed in detail in Chapter 1, the hippocampus, parahippocampus, retrosplenial cortex and posterior cingulate cortex have been strongly linked to spatial memory and navigation (Kumaran and Maguire 2005; Byrne et al. 2007; Javadi et al. 2017, 2018) as well as episodic memory (Scoville and Milner 1957; St. Jacques et al. 2011; Richter et al. 2016). Although the precise mechanism is yet to be fully elucidated, Byrne et al. (2007) and Bird and Burgess (2008) suggest that these regions may work together to translate between an egocentric viewpoint and allocentric spatial maps in order to best store knowledge of spatial relations for navigation but also to imagine a space from a first person perspective. An alternative, but perhaps compatible, suggestion is that these regions identify and represent a situation model including representing the spatial context but also storing information about the sequence of events (Ranganath and Ritchey 2012).

More anterior medial and lateral temporal DMN regions, on the other hand, have been associated more with social and semantic cognition. For example, Kumaran and Maguire (2005) found that the dmPFC subnetwork and core DMN regions showed increased activation during a task where participants were required to make decisions on the basis of social relations between people.

Furthermore, a meta-analysis Andrews-Hanna et al. (2014) found that social cognition terms such as 'mentalizing', 'theory of mind' and 'social' were primarily related to the dmPFC subsystem of the DMN. Similar regions have also been associated with semantic cognition. DMN regions of the temporal pole, middle temporal gyrus/LTC and angular gyrus/TPJ are thought to be components of a semantic network, along with other regions outside of the DMN including the ventral temporal pole, posterior temporal cortex, inferior frontal gyrus, SMA, IPS and aIFS (Binder et al. 2009; Jackson et al. 2016). Although a full discussion is beyond the scope of this thesis, semantic knowledge is likely associated with contextual control. As previously discussed, a situation model is proposed to represent the gist of the one's current situation along with related associative information. In line with this suggestion, Lanzoni et al. (2019) found that emotional cues and especially spatial contexts biased retrieval of conceptual information for polysemic words, enhancing participants' performance when the context cued the correct semantic concept and impairing participants' performance when the context cued the incorrect semantic concept. As the angular gyrus has been found to contribute to semantic integration (Bonnici et al. 2016; Price et al. 2016), it may play a particularly important role in accessing conceptual information associated with the current situation.

Why these more social/semantic DMN regions do not appear to be sensitive to context-dependent decision making in Chapter 2 or broad task context in Chapter 4 is still an outstanding question. This may be because there was relatively more requirement in these tasks to identify the broad situation/context, rather than social/semantic details, a role more specifically linked to the MTL and posterior DMN regions in Ranganath and Ritchey's (2012) posterior medial system. Furthermore, in Chapter 2, participants may have relied on an episodic strategy, imagining themselves in their own bedroom, living room etc. This process of transporting oneself into a first person spatial perspective has again been most related to more posterior DMN regions (Byrne et al. 2007; Bird and Burgess 2008). The use of rich social or semantic information relating to particular aspects of the environment may be relatively less important in this task. Other tasks concentrating on the use of semantic knowledge to aid decision making have instead been found to be associated with dmPFC subnetwork, in particular the angular gyrus and LTC, rather than MTL subnetwork DMN regions (Murphy et al. 2018), demonstrating that these regions can be important in task control if the task demands are weighted more towards semantic knowledge. A study directly comparing the relative recruitment of different DMN regions in situational judgements differentially weighted towards semantic control, spatial contextual control and social control may help to further develop these suggestions, perhaps using a method similar to the situations task in Chapter 3.

Given that different DMN regions seem to contribute to different cognitive processes, the question remains as to why these regions are so regularly found to be functionally and anatomically

connected? Several clues can be gained from identifying tasks that do homogeneously activate the full DMN. These tasks are mostly personal, episodic tasks (Addis et al. 2007, 2009; Szpunar et al. 2009) and usually involve imagination or recollection of lifelike events, requiring rich knowledge of the world including knowledge of spatial locations, social rules and an understanding of temporal patterns of events. This rich understanding of the world is critically important in daily life, however experimental studies rarely aim to capture this richness due to a requirement for experimental control. It is typically during these artificial, controlled experiments where we seek to understand specific cognitive functions that we see this separation within the DMN. Perhaps the use of life-simulator games, or the situations task in Chapter 3, where participants are able to make decisions based on their rich knowledge of the world with minimal constraints will be useful for ascertaining to what extent the full DMN contributes to decision making in a life-like environment.

The DMN and non-human animals

Due to the types of tasks with which the DMN is implicated, most of the experiments reported so far have used human participants. A question not yet addressed in this thesis is whether non-human animals also show evidence of a Default Mode Network and, if so, is it likely that the DMN of non-human animals is also representing their broad situational context in a similar way? Several papers suggest that, at the functional connectivity level, there is evidence for a corresponding DMN in monkeys. Using seed-based functional connectivity in monkeys, Vincent et al. (2007) found that the monkey posterior midline seed revealed similar DMN regions to those in humans including the Rsp, pIPL and HF. Furthermore, Mantini et al. (2011) found that activity in monkey DMN regions showed typical decreases in activity with increasingly demanding tasks.

Further evidence supports some functional overlap between DMN regions in monkeys and in humans. As described in detail in the introduction, it has been well established that posterior DMN regions in non-human animals are also important for spatial memory and navigation (O'Keefe and Dostrovsky 1971; Ono et al. 1991; Logue et al. 1997; Vann and Aggleton 2002; Bohbot et al. 2006). Most relevant to the current thesis, research by Barack et al. (2017) and Arsenault et al. (2018) further implicates the DMN in monkeys in context-dependent switching. Barak et al. (2017) showed that activity in posterior cingulate cortex of monkeys is sensitive to task context during a switching task. In this patch foraging task monkeys were shown a blue square on one side of the screen and a grey bar on the other side of the screen. To get a reward monkeys had to saccade to the blue square. Each time the monkeys chose to saccade to the blue square, the amount of reward received would

reduce. If monkeys chose the grey square (to leave the patch) monkeys would have to wait a period of time, denoted by the length of the grey bar, before entering a new patch. On arrival into a new patch the reward amount was reset to maximum and a new waiting time would be set. Activity in posterior cingulate cortex regions predicted patch departure, with increased firing rates ramping up from around 15 seconds before patch departure. This effect appeared only to be present when leaving poor reward environments compared to high reward environments. These findings suggest that DMN regions in monkeys, or at least the PCC, are also sensitive to non-spatial contexts and that these contexts can have an influence on switching behaviour, with posterior cingulate switch activity modulated by context. Further emphasizing the importance of the DMN in cognitive transitions, Arsenault et al. (2018) tested macaque monkeys whist performing a selective attention task in an fMRI scanner. In the task, monkeys were presented with two shapes, one to the left and one to the right of fixation. Of the stimuli one was task-relevant and one was task-irrelevant. Monkeys were rewarded for pressing a button when the task-relevant shape was grey rather than white. On successive trials the task-relevant shape would either stay in the same position or switch to the other side of the screen. Monkey DMN regions were found to show increased activity for trials where spatial attention was required to switch position compared to when spatial attention was maintained on the same location. Thus, research from the monkey literature support the findings from Chapter 4, suggesting a role for the DMN in cognitive transitions.

While it is important to note that some aspects of DMN function are more difficult to establish through non-human animal studies, and it remains a contentious issue as to whether non-human animals have true autonoetic awareness (Tulving, 1985), non-human animals have also been found to show an 'episodic-like' performance in memory and planning tasks (Clayton et al. 2001; Kornell et al. 2007; Raby et al. 2007). Such designs may allow future researchers to examine the extent to which DMN regions are related to 'episodic-like' memory and future planning in animals as well as humans.

MD and DMN

Echoing earlier findings, this research indicated the importance of the MD system for satisfying diverse task demands (Duncan and Owen 2000; Fedorenko et al. 2013). In Chapter 2 the MD network showed increased activity during the time pressured auditory task compared to the baseline email task. In Chapter 4, MD regions showed increased activity for task switches compared to rest and task repeats. And in Chapter 5, the same regions showed increased activity with increased rule retrieval

difficulty. The neuropsychology results of Chapter 3 further showed that MD lesion volume was related to patient IQ, a measure highly predictive of performance on other executive tasks.

As noted in the Introduction, the DMN and MD are often found to be negatively correlated, with MD implicated in 'task-positive' processes and DMN in 'task-negative' processes (McKiernan et al. 2003, 2006; Fedorenko et al. 2013). While the results of Chapter 5 were consistent with this, finding increased activity in MD regions for the more difficult task and the reverse pattern in the DMN, other results from the thesis suggest a more complicated relationship between the DMN and MD systems.

Firstly, the integrity of the MD system alone is not sufficient to explain differences in task performance in more naturalistic tasks. In line with the results of Roca et al. (2010), the results from Chapter 3 showed that patient impairment in the situations task, hotel task and block switching task could not be predicted by MD lesion volume alone. Impairment in task switching in the switch length task was instead related to grey matter lesions beyond MD and DMN regions.
Furthermore, the results from Chapter 2 suggest that, in some naturalistic tasks, the involvement of the MD system may be reduced. Chapter 2 showed that, while the MD system was recruited for auditory task performance, the relative activity level of MD regions for context-dependent decision making using more meaningful contexts was reduced compared to decisions using arbitrary letter rules. Instead, context-dependent decision making using meaningful stimuli was related to enhanced activity in posterior DMN regions, perhaps suggesting that recruitment of other regions beyond the MD system can alleviate requirements for MD input. While this finding is still consistent with a negative correlation between DMN and MD regions, it suggests that the MD system may not always be the 'task-positive' influence.

As developed in the introduction, results from functional connectivity can also show a positive relationship between DMN and MD regions during goal-directed task performance. Spreng et al. (2010) found increased functional connectivity between the DMN and FPN during an autobiographical planning task, suggesting that DMN regions can couple with MD regions to support goal-directed cognition. In this thesis, however, the contribution of the DMN alongside the MD network was found to not be limited to internally-focused autobiographical tasks. The results from Chapter 4 suggest that during more externally-focused tasks both MD and DMN regions are sensitive to large changes in task. I suggest that DMN regions may be most important after large changes because they require the updating of, or reference to, broad situational knowledge. As suggested by previous research (Dosenbach et al. 2006; Duncan 2010, 2013; Crittenden et al. 2016), MD regions may be more important for implementation of specific task rules, showing increased activity for even small changes in task. The MVPA results from Chapter 4 were consistent with this distinction,

indicating that MD activity was able distinguish on a finer scale between all six tasks while only relatively coarse task representations were found in the DMN.

In summary, I suggest that the MD system and DMN can work together during goal-directed task performance but only during tasks that require reference to a broad knowledge structure. While this knowledge structure usually contains associative knowledge of real-world situations in order to recall past experience, simulate future scenarios and understand other people's actions, it may also represent broad task contexts for tasks with hierarchical rule structures. The results from Chapter 4 also suggest how these networks may interact over time. While the DMN may be important for representing broad contextual information at times of uncertainty, brought about by large environmental changes, the MD system appears to be responsible for implementation and control of specific task sets over prolonged periods of time. Once a task set is established, the broad contextual information becomes less relevant and hence may recede, along with DMN activity.

Conclusions

In summary, the results described above suggest that DMN regions can represent the broad features of an ongoing cognitive episode, be it the gist of a scene from a movie or the current cognitive task. While such context representations are important during mind wandering, and internal thought processes distinct from the current environment, the DMN may also represent the current environmental context during task-related cognition.

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