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Research report

Episodic future thinking is impaired in the behavioural variant of frontotemporal dementia

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ABSTRACT

Remembering the past and imagining the future are complex endeavours proposed to rely on a core neurobiological brain system. In the behavioural variant of frontotemporal dementia (bvFTD), regional patterns of brain atrophy affect medial prefrontal and temporal cortices of this core network. While autobiographical memory impairments have been documented in bvFTD, it remains unknown whether the ability to imagine future events is also compromised. Here, we investigated episodic future thinking in 10 bvFTD patients and contrasted their performance with Alzheimer's disease (AD, $n = 10$) and healthy matched Control ($n = 10$) participants. Participants were asked to remember 3 events from the previous year and to envisage 3 possible events that could occur in the next year. Both patient groups showed equivalent episodic detail performance for the retrieval of past events and the simulation of possible future episodes. Patients with bvFTD, however, showed additional impairments for the generation of external (non-episodic) details irrespective of condition. Voxel-based morphometry analyses revealed divergent neural correlates of episodic past and future thinking performance specific to each patient group. Atrophy in the posterior cingulate cortex was implicated in the disruption of past and future thinking in AD. In contrast, in bvFTD, disruption of past retrieval correlated with atrophy in medial prefrontal regions, whereas future thinking deficits were associated with atrophy of frontopolar, medial temporal regions including the right hippocampus, and lateral temporal and occipital cortices. Our results point to the involvement of multiple brain regions in facilitating retrieval of past, and simulation of future, events. Damage to any of these key regions thus adversely affects the ability to engage in personally relevant mental time travel.

1. Introduction

The ability to withdraw from the current moment to mentally travel backwards and forwards in subjective time has been shown to rely on the integrity of a common core neurobiological network (Addis et al., 2009a; Botzung et al., 2008; Okuda et al., 2003; Spreng et al., 2009; Szpunar et al., 2007). The engagement of these core brain regions facilitates the

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simulation of alternative events and perspectives, distinct from stimulus-driven behaviour (Buckner and Carroll, 2007; Spreng and Grady, 2010), and likely confers an adaptive advantage to humans in their daily lives (Suddendorf et al., 2009).

Much of our understanding regarding the capacity for remembering the past and imagining the future stems from functional neuroimaging studies in healthy individuals. It is now firmly established that key components of the core network that reliably activate during past autobiographical retrieval and self-referential future simulation include the medial temporal lobes, notably the hippocampus, the frontal poles, and midline core regions including the posterior cingulate cortex (PCC), and lateral parietal and temporal regions (Addis et al., 2009a; Andrews-Hanna, 2012; Okuda et al., 2003; Szpunar et al., 2007). While striking neural overlap has been observed between past and future thinking, direct comparisons between past and future tasks in several studies have revealed important differences in terms of the neural activity specific to each temporal condition. In particular, imagining future events has been shown to recruit the hippocampus and frontopolar cortex to a greater extent than recollecting past events (Addis et al., 2007; Okuda et al., 2003; Szpunar et al., 2007). Such discrepancies between past and future thinking likely reflect the more intensive nature of episodic future simulation in terms of the demands placed on the hippocampus to flexibly recombine disparate elements together to create a novel simulation in the future, relative to the recollection of past events that have already occurred (Schacter and Addis, 2007). In parallel with studies investigation the simulation of future events, exploration of the capacity to construct spatially contiguous scenes has been advanced as a core mechanism underlying past retrieval, future imagination, and spatial memory processes. Again, across neuroimaging studies, activation of the same network of regions including the hippocampus, parahippocampal gyrus, retrosplenial cortex, posterior parietal cortex, ventromedial prefrontal cortex (PFC), and middle temporal cortices is reliably demonstrated when healthy individuals visualise a new fictitious experience (Hassabis et al., 2007a; Hassabis and Maguire, 2007; Summerfield et al., 2010).

Patient studies have proved particularly illuminating for our appreciation of specific brain structures that may not only be active but essential for envisaging the future. Importantly, patients with hippocampal damage, and therefore impaired episodic memory, have been shown to display severe difficulties in the imagination of detailed and coherent future events (Andelman et al., 2010; Hassabis et al., 2007b; Race et al., 2011) suggesting a fundamental role for the hippocampus in future thinking. In accord with these findings, studies investigating the neurodegenerative conditions of Mild Cognitive Impairment (Gamboz et al., 2010) and Alzheimer's disease (AD) (Addis et al., 2009b; Irish et al., 2012a) have also pointed to the possible crucial role for episodic memory in the simulation of future events. Recently, however, spared capacity for the simulation of future events in patients with bilateral hippocampal damage (Squire et al., 2010), and intact scene construction ability in adults (Maguire et al., 2010), and children (Cooper et al., 2011; Hurley et al., 2011), with developmental amnesia, has led to the proposition that residual functioning hippocampal tissue (Maguire et al., 2010; Mullally et al., 2012), or spared semantic representations of the world (Hurley et al., 2011; Maguire et al., 2010) may mitigate against the effects of hippocampal damage. In congruence with this idea, recent studies now point to the pivotal role of semantic memory in facilitating the constructive simulation of personally relevant future events (Duval et al., 2012; Irish et al., 2012a, 2012b).

Further patient studies suggest that disruption to any node of the core network will impinge dramatically on the capacity for future thinking. Severe impairments in the simulation of novel events have been documented following thalamic lesions which disrupt prefrontal cortical connectivity (Weiler et al., 2011), and in patients with Parkinson's disease in which disruption of fronto-striatal pathways is evident (de Vito et al., 2012). Importantly, this latter study suggests that executive dysfunction, as a consequence of frontal lobe atrophy, is an important factor in future thinking deficits in Parkinson's disease, and accords well with the observation of increased frontopolar activity when healthy individuals think about their futures (Okuda et al., 2003).

The neurodegenerative condition of the behavioural variant of frontotemporal dementia (bvFTD) offers an excellent opportunity to study the impact of damage to primarily medial prefrontal regions of the brain on self-projection to the past and future (Irish et al., 2012c; Zhou et al., 2010). bvFTD is associated with atrophy residing typically in frontoinsular cortices, including the medial and orbital prefrontal cortices (Seeley, 2008), which begins to encroach into lateral and medial temporal regions with disease progression (Rabinovici et al., 2007). Neuropsychological data point to severe impairments in executive function, decision-making, planning, perspective taking, and mentalising to consider the thoughts and feelings of others via theory of mind in bvFTD (Irish et al., 2012c; Piguet et al., 2011). A number of studies have demonstrated that autobiographical memory retrieval is severely compromised in bvFTD (Irish et al., 2011a; Matuszewski et al., 2006; Piolino et al., 2003), which in turn has been attributed to executive (Matuszewski et al., 2006) and frontal lobe (Piolino et al., 2007) dysfunction. Importantly, however, no study, to our knowledge, has explored the capacity for episodic future thinking in this cohort.

The aims of this study were twofold; firstly, we wished to investigate the extent to which future simulation is compromised in bvFTD using a well-established paradigm, and secondly, we sought to explicate the neural correlates of the proposed self-projective deficits in bvFTD using whole-brain voxel-based morphometry (VBM). We contrasted the performance of bvFTD patients with that of age- and disease-matched AD patients, in which episodic memory deficits represent the hallmark clinical feature (Irish et al., 2011b; McKhann et al., 2011). We hypothesised that equivalent deficits would be observed across past and future conditions in both AD and bvFTD, but that these impairments would be mediated by divergent patterns of neural atrophy. Specifically, we predicted that a largely posterior network including medial temporal and posterior parietal regions, including the PCC, would underpin the impoverished future thinking performance of AD patients. In contrast, we proposed that a largely anterior network centred on the anteromedial prefrontal