Autobiographical memory in semantic dementia: A longitudinal fMRI study

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ABSTRACT

Whilst patients with semantic dementia (SD) are known to suffer from semantic memory and language impairments, there is less agreement about whether memory for personal everyday experiences, autobiographical memory, is compromised. In healthy individuals, functional MRI (fMRI) has helped to delineate a consistent and distributed brain network associated with autobiographical recollection. Here we examined how the progression of SD affected the brain's autobiographical memory network over time. We did this by testing autobiographical memory recall in a SD patient, AM, with fMRI on three occasions, each one year apart, during the course of his disease. At the outset, his autobiographical memory was intact. This was followed by a gradual loss in recollective quality that collapsed only late in the course of the disease. There was no evidence of a temporal gradient. Initially, AM's recollection was supported by the classic autobiographical memory network, including atrophied tissue in hippocampus and temporal neocortex. This was subsequently augmented by up-regulation of other parts of the memory system, namely ventromedial and ventrolateral prefrontal cortex, right lateral temporal cortex, and precuneus. A final step-change in the areas engaged and the quality of recollection then preceded the collapse of autobiographical memory. Our findings inform theoretical debates about the role of the hippocampus and neocortical areas in supporting remote autobiographical memories. Furthermore, our results suggest it may be possible to define specific stages in SD-related memory decline, and that fMRI could complement MRI and neuropsychological measures in providing more precise prognostic and rehabilitative information for clinicians and carers.

1. Introduction

Semantic dementia (SD) is a variant of fronto-temporal dementia. This progressive pathology is characterised initially by asymmetric atrophy of the anterior temporal lobes (Hodges & Patterson, 2007). It involves a range of symptoms that includes anomia, deterioration of expressive and receptive vocabulary, and a deficit in semantic memory (Hodges & Patterson, 2007; Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989). Whilst these features are typically observed, there is less agreement about whether memory for personal everyday experiences, autobiographical memory, is compromised.

SD patients have been reported to show better preservation of recent relative to remote autobiographical memories (Graham & Hodges, 1997; Graham, Kropelnicki, Goldman, & Hodges, 2003; Hou, Miller, & Kramer, 2005; Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Piolino et al., 2003; Snowden, Griffiths, & Neary,

1996). This pattern has been interpreted as support for the standard consolidation model of memory (Squire, 1992), where remote memories, dependent on the neocortex, are impaired because of the deleterious effect of SD on the integrity of temporal neocortex. By contrast their preserved recent memories have been held to reflect the relatively normal operation of the hippocampus in the early stages of the disease, or more uniform impairments across all time periods later in the disease. As such, SD patients are suggested to complement amnesic patients with selective hippocampal damage who are reported to have impaired recent but intact remote autobiographical memories (Hodges & Patterson, 2007; Nestor et al., 2002). The reverse temporal gradient observed in SD patients has been questioned, however, as findings from other studies have failed to confirm such a pattern, and instead report preserved recent and remote autobiographical memories in the early stages of the disease (McKinnon, Black, Miller, Moscovitch, & Levine, 2006; Moss, Kopelman, Cappalletti, De Mornay Davies, & Jaldow, 2003; Westmacott, Leach, Freedman, & Moscovitch, 2001). The lack of consistent findings may reflect the limited number of autobiographical memories tested in some studies (as few as 5 – McKinnon et al., 2006), the difficulty of assessing retrieval in SD where expressive speech can be variably compromised, and the stage in the disease process at which patients are tested (Matuszewski

et al., 2009). The integrity of the hippocampus also needs to be considered, as not only lateral and anterior neocortical tissue is compromised in SD, but the hippocampus and medial temporal lobes are also affected to a variable degree even early in the course of the disease (Chan et al., 2001; Galton et al., 2001). Thus, as with cases of amnesia, the status of autobiographical memory in SD and the neural substrates that support it remain controversial.

In healthy participants our understanding of the neural basis of autobiographical memory has been enhanced by the use of fMRI, which has helped to delineate the brain networks involved and the response profile of the hippocampus. Recollecting memories of personal past experiences has been shown to rely on a distributed set of brain regions that includes the hippocampus (more often on the left), parahippocampal gyrus, lateral temporal cortices, posterior parietal cortex, retrosplenial cortex, posterior cingulate cortex, precuneus, thalamus, the medial prefrontal cortex, and cerebellum (Maguire, 2001; Svoboda, McKinnon, & Levine, 2006). These findings are highly consistent across studies (Svoboda et al., 2006), are evoked by verbal (e.g. Maguire & Frith, 2003) or photographic (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004) stimuli, and are robust even for single participants (Maguire, Vargha-Khadem, & Mishkin, 2001). Moreover, the majority of fMRI studies of autobiographical memory retrieval have documented hippocampal involvement irrespective of whether memories were formed recently or remotely in the distant past (Svoboda et al., 2006). By contrast, whilst there are numerous reports of structural MRI and resting state FDG-PET and SPECT in SD (e.g. Desgranges et al., 2007; Diehl et al., 2004; Nestor, Fryer, & Hodges, 2006), there is a dearth of fMRI memory studies involving SD patients.

In patients with brain lesions, several investigations have emphasised the contribution of right-sided lateral temporal and frontal lobe pathology in producing retrograde amnesia (Bright et al., 2006; Buccione, Fadda, Serra, Caltagirone, & Carlesimo, 2008; Kopelman, Stanhope, & Kingsley, 1999; Markowitsch et al., 1993; O'Connor, Butters, Miliotis, Eslinger, & Cermak, 1992; Ogden, 1993). This partial discrepancy with the fMRI findings in healthy participants, where left-sided activations are more prominent (Maguire, 2001; Svoboda et al., 2006), makes it interesting to know what would happen to fMRI activity patterns during autobiographical recollection when the hippocampi and temporal neocortex, particularly on the left, are atrophied. One possibility is that residual hippocampal tissue would still be activated during autobiographical retrieval, or that right fronto-temporal or other cortical regions would be recruited if the hippocampi were malfunctioning.

Here we examined whether or not there was a temporal gradient in autobiographical memory recall in the context of SD, as have previous studies. However, we extended this previous work in a number of ways. Given the well-established brain network known to support autobiographical memory retrieval in fMRI studies of healthy participants (Maguire, 2001; Svoboda et al., 2006), we sought to ascertain the effect of SD on this network. Would the remnant tissue in regions of atrophy be active? Would there be evidence of compensatory mechanisms? Moreover, as well as contributing novel insights from a 'snapshot' view of SD at one point in time, we examined how the progression of SD affected the brain's autobiographical memory network. We did this by testing an SD patient with fMRI on three separate occasions, each one year apart, during the course of his disease. In this way we hoped to provide new information to aid the understanding of the effect of SD-related temporal lobe atrophy on autobiographical memory, and to explore the mechanisms of change through time, a relatively neglected topic to date but one of prognostic and theoretical significance. Overall, therefore, our findings might provide important information for clinicians and carers, whilst also informing key theoretical debates about the role of the hippocampus and

neocortical areas in supporting remote autobiographical memories.

We charted the effect of SD on the autobiographical memories of patient AM. He was in effect his own control as we compared his performance over successive years. We employed a paradigm similar to that used by Gilboa et al. (2004) who tested healthy participants. As well as activating the classic autobiographical memory network, this paradigm had a number of advantages for our purpose. First, the stimuli were selected without the knowledge of the participant, in our case by AM's wife of fifty years. Second, the stimuli were photographs, which reduced reliance on AM's compromised verbal skills. Longitudinal testing in this case was only possible because of the unusually large reservoir of photographs accrued by AM's family over many decades. Thus during each year's fMRI scan we were able to test recall for many different autobiographical memories (i.e. 75 unique events in total over the course of the study, none of which was repeated), ranging from recent events to those that had occurred remotely in the past.

2. Methods

2.1. Case history

AM, a 70-year-old right-handed retired merchant seaman with 9 years of formal education, was first seen in the St Thomas's Neuropsychiatry and Memory Disorders Clinic in November 2001. At that time AM and his wife reported progressive memory loss over the last 2–3 years, particularly involving remembering peoples names, difficulty in word-finding, and difficulties in comprehension such that AM would occasionally "go blank" in conversation. He also had some difficulty with conceptual tasks, such as following instructions, but he could do home repairs using well-practised skills. AM reported that he had great difficulty in remembering telephone messages, but memory for day-to-day episodes was relatively well preserved. AM had noticed that he sometimes recalled the names of people and objects after a long latency period. There was no known family history of dementia. AM had been treated for depression on two occasions in the past but was not depressed during this study.

During this initial presentation, AM was fully orientated in time and place and could give an excellent account of recent news events, e.g. the then recent invasion of Afghanistan, although he could not remember the name of the World Trade Centre. He knew that he had been to France on a day trip the week before, and he was able to describe accurately what he had done there. He was able to name high frequency items, such as jacket, sleeve, cuff, and watch, but not low frequency items such as a lapel, watch face, buckle, or skirting board. On formal neuropsychological testing AM showed relatively well preserved IQ and executive function, as measured on the Modified Card-sorting test (Table 1). However, he could name only 4 items correctly out of 30 on the Graded Naming Test. He scored poorly on a verbal memory test for stories (WMS-R Logical Memory) possibly reflecting his semantic and language difficulties, whilst on the WMS-R Visual Reproduction subtest he scored at the 72nd percentile for immediate recall, and at the 66th percentile for delayed recalled. On the Recognition Memory Test he recognised 41 out of 50 words correctly, and 37 out of 50 faces. On FAS verbal fluency AM scored 27. Further investigations revealed preserved reading of regular and irregular words and non-words, and preserved mental calculation (see Cappelletti, Butterworth, & Kopelman, 2006). On the Autobiographical Memory Interview (Kopelman, Wilson, & Baddeley, 1990), he showed a recency effect in recalling personal semantic facts and a U-shaped curve in retrieving autobiographical incidents.

Standard blood tests were normal, and an MRI brain scan showed focal atrophy of the left temporal lobe involving the lateral, inferior and medial temporal structures including the left hippocampus. There was only minor atrophy in the right temporal lobe and at the frontal poles. A diagnosis of progressive fluent aphasia was made within the context of a fronto-temporal ('semantic') dementia, involving predominantly focal left temporal lobe atrophy.

AM was monitored over the next 6 years – Table 1 summarises his neuropsychological test scores. His mental state fluctuated somewhat, and he would tend to be more confused in the early morning and in the late evening than in the middle of the day. Over the course of 2002, there was a slow deterioration, and Mrs AM noticed that her husband had increasing difficulty in understanding certain words such as 'garden' and 'hobby'. She also reported that his conversation had become more stereotyped, and he liked to keep to familiar themes and repetitive stories (usually about football matches). Otherwise he would tend to go silent in company. However, AM retained excellent recall of recent events. In 2003, his wife reported further deterioration, and AM would commonly comment "I can't remember what that means." He often had difficulty understanding conversation, when something was said for the first time, and he often repeated himself. He made a number of interesting semantic errors saying "radio rings" for telephone, "rubbish plants" for weeds, "letters" for words, "bread" for potatoes, "company" for football team, and