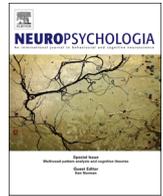




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Autobiographical memory in semantic dementia: New insights from two patients using fMRI



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ABSTRACT

Episodic autobiographical memory (EAM) consists of personal events embedded within a specific spatiotemporal context. Patients with semantic dementia (SD) generally show preserved recent EAMs, but a controversy remains concerning their ability to retrieve remote ones. Only one fMRI study examined remote autobiographical memory in SD through a longitudinal case study (Maguire, Kumaran, Hassabis, & Kopelman, 2010). Here, we propose a cross-sectional study to test the hippocampal-neocortical up-regulation hypothesis, through a multimodal approach (gray matter volume, activation, connectivity analyses), directly comparing recent and remote autobiographical memory retrieval and collecting data to assess phenomenological re-experiencing. EAM retrieval recruits a distributed network of brain regions, notably the hippocampus which is shown to be atrophied in SD, although some studies report no hippocampal atrophy in SD. Using fMRI, we examined recent and remote EAM retrieval in two SD patients with different profiles of hippocampal atrophy, compared to 12 healthy elders (HE). JPL presented severe bilateral hippocampal atrophy, while EP showed sparing of both hippocampi. Behaviourally, JPL was impaired at retrieving EAMs from both life periods and showed poorer use of visual mental imagery than HE, while EP retrieved memories which were as episodic as those of HE for both periods and relied on greater use of visual mental imagery than HE. Neuroimaging results showed that, for JPL, hyperactivations of the residual hippocampal tissue and of frontal, lateral temporal, occipital and parietal cortices did not efficiently compensate his autobiographical memory deficit. EP however presented hyperactivations in similar neocortical regions which appeared to be more efficient in compensating for atrophy elsewhere, since EP's EAM retrieval was preserved. Functional connectivity analyses focusing on the hippocampus showed how the residual hippocampal activity was connected to other brain areas. For JPL, recent autobiographical retrieval was associated with connectivity between the posterior hippocampus and middle occipital gyrus, while for EP, connectivity was detected between the anterior hippocampus and numerous regions (medial temporal, occipital, temporal, frontal, parietal) for both recent and remote periods. These findings suggest that intensification of hippocampal atrophy in SD strongly affects both recent and remote autobiographical recollection. Up-regulation of neocortical regions and functional hippocampal–neocortical connectivity within the autobiographical network may be insufficient to compensate the lifelong episodic memory deficit for patients with extensive hippocampal atrophy.

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1. Introduction

Semantic dementia (SD) is a variant of fronto-temporal dementia characterized by a gradual loss of semantic memory (Snowden, Goulding, & Neary, 1989), with progressive anomia and deterioration

of vocabulary (Neary et al., 1998). An asymmetrical atrophy of the lateral temporal lobe is generally observed (Hodges & Patterson, 2007) with an antero-posterior gradient, the highest changes located in its anterior portion (Desgranges et al., 2007). A relative preservation of episodic memory is observed, with intact recent and day-to-day memory, while a controversy concerning the recall of remote autobiographical memories persists. Some studies report a reversed temporal gradient with preservation of recent relative to remote memories (Graham & Hodges, 1997; Graham, Kropelnicki, Goldman, & Hodges, 2003; Graham, Patterson, & Hodges 1999; Hodges & Graham, 1998; Hou, Miller, & Kramer, 2005; Matuszewski et al., 2009; Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Piolino, Desgranges, et al., 2003; Snowden, Griffiths, & Neary, 1996). These patterns have been interpreted in favour of the standard theory of memory consolidation (Bayley & Squire, 2005; McClelland, McNaughton, & O'Reilly, 1995; Murre, 1996; Squire & Alvarez, 1997) which states that recent memories rely on the medial temporal lobe (MTL), while remote memories rely on neocortical regions, including the lateral temporal lobe. However, the standard theory does not distinguish between the two components (episodic and semantic) of declarative memory. Several studies on SD show impairments of the semantic aspects of autobiographical memory (e.g., names of acquaintances) which contrasts with relatively good recall of episodic autobiographical events (Duval et al., 2012; Piolino, Belliard, Desgranges, Perron, & Eustache, 2003). Some of these studies report a flat gradient showing a relative preservation of EAM across all life periods in SD (Maguire et al., 2010; McKinnon, Black, Miller, Moscovitch, & Levine, 2006; Moss, Kopelman, Cappalletti, De Mornay Davies, & Jaldow, 2003; Piolino, Belliard, et al., 2003; Westmacott, Leach, Freedman, & Moscovitch, 2001). These findings are consistent with the Multiple Trace Theory (MTT, Nadel & Moscovitch, 1997; Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006) which argues in favour of a permanent involvement of the MTL, in particular the hippocampus, in the retrieval of EAMs, whatever their remoteness. One possible explanation for the conflicting findings might be the degree of hippocampal atrophy, a crucial structure involved in EAM retrieval (for review, Viard, Desgranges, Eustache, & Piolino, 2012).

Evidence of hippocampal atrophy is now well documented in SD, even in the early stages of the disease (Acosta-Cabronero et al., 2011; Boxer et al., 2003; Chan et al., 2001; Davies, Graham, Xuereb, Williams, & Hodges, 2004; Desgranges et al., 2007; Good et al., 2002; Lehmann et al., 2010; Nestor, Fryer, & Hodges, 2006; Rosen et al., 2002; van de Pol et al., 2006), although there remains a variability with some patients presenting no hippocampal atrophy (Mummery et al., 2000). Despite such hippocampal atrophy, SD patients are still able to retrieve autobiographical memories, at least to a greater extent than patients with Alzheimer's disease (AD; Hodges, 2013; Irish et al., 2011). Two observations can explain such discrepancies: a rostro-caudal gradient is observed in SD, with atrophy mainly localized in the anterior part of the hippocampus, while in patients with Alzheimer's disease, atrophy is located all along the axis of the hippocampus (Chan et al., 2001; Davies et al., 2004; for review, Hornberger & Piguet, 2012). Moreover, the limbic-diencephalic network (precuneus, posterior cingulate cortex), important in autobiographical memory (Maguire, 2001; Svoboda, McKinnon, & Levine, 2006), is affected in AD (Hodges, 2013) which may explain their greater difficulty in retrieving autobiographical memories compared to SD (Nestor et al., 2006; Piolino, Desgranges, et al., 2003).

Studies on remote autobiographical memory in SD are scarce and only one fMRI study examined remote autobiographical memory in a patient suffering from SD (Maguire et al., 2010). In this longitudinal case study, the patient was examined on three separate occasions (years 1, 2 and 3), with an episodic autobiographical recall task during fMRI scanning, followed by a debriefing session, performed each time.

At year 1, despite atrophy in the left hippocampus and left anterior temporal neocortex, the quality of the patient's recollection was similar to that of a single age-matched control subject and the "classic" autobiographical network (medial prefrontal and lateral temporal cortices, medial temporal lobe, medial parietal and retrosplenial cortices, occipital areas) was activated. Neuropsychological testing showed that he was impaired on a semantic fluency task and scored poorly on a verbal memory test (story recall), possibly reflecting his semantic and language difficulties. At year 2, with atrophy starting to involve the contralateral areas (right hippocampus, right anterior temporal neocortex and right temporal pole, right cerebellum), his autobiographical memory gradually lost in specificity and recollective (i.e., episodic) quality and other neocortical areas were up-regulated (ventromedial and ventrolateral prefrontal cortices, right lateral temporal cortex and precuneus). Neuropsychological testing showed his naming difficulties became more pronounced and impairments in comprehension more evident. At year 3, there was significant atrophy of both temporal lobes, including both hippocampi (more extensive on the left) and right cerebellum, coinciding with a collapse of his autobiographical memory. Moreover, he became more withdrawn with increased word-finding difficulties, paraphasias and comprehension problems. By modelling the effects of memory remoteness parametrically, Maguire et al. (2010) found no changes in the brain network according to the age of memories, ranging from adolescence to the recent year. Memories from different life periods were however not directly compared to one another, rich re-experiencing via phenomenological scales was not probed and functional hippocampal-neocortical connectivity was not studied.

Here, in the same vein as Maguire et al.'s (2010) pioneer study, we examined the effects of hippocampal atrophy on the integrity of the brain activity recorded by means of fMRI during EAM retrieval. We expected to confirm this previous work using a cross-sectional approach in a pathology which is scarcely studied with fMRI, not only to bring support to Maguire et al. (2010) findings, but also to confirm these results with a different paradigm and different patients. Moreover, we also expected to complement this previous work in a number of relevant ways, especially by adding further evidence regarding the hippocampal-neocortical regulation hypothesis in SD, via activation and connectivity analyses, and collecting numerous behavioural data to assess the degree of phenomenological re-experiencing (episodic quality, emotional intensity, valence, mental visual imagery, state of consciousness, repetition) in two SD patients with different profiles of atrophy: one had bilateral anterior hippocampal atrophy and the second had relatively preserved hippocampi. These patients were scanned while retrieving EAMs from two different life periods (recent and remote), ranging as far as childhood to the recent year. We examined whether or not a deficit in autobiographical memory recall in SD was present depending on the degree of atrophy and remoteness of memories. We recorded functional activations and performed connectivity analyses focusing on the hippocampus to show how the residual hippocampal activity was connected to other brain regions and if these connections had a compensatory effect in the two patients. Based on prior work in our laboratory (Piolino et al., 2004, 2008; Viard et al., 2007, 2010) in line with MTT, we predicted that hippocampal atrophy would affect recent and remote EAM retrieval, while a (relative) preservation of the hippocampus would permit EAM retrieval, whatever memory remoteness. Based on Maguire et al. (2010) prior fMRI study in SD, we expected that, in the presence of atrophied regions within the autobiographical memory network, different processes might be observed: either activation in residual tissue, up-regulation of areas within the network or recruitment of additional brain areas. We expected that hippocampal atrophy would severely impair connectivity to other regions (e.g., neocortical) preventing rich autobiographical recollection, while intact hippocampi would continue to be functionally connected to the rest of the autobiographical network.

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