



Using fMRI to understand event construction in developmental amnesia



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ABSTRACT

Recently, neuroimaging and patient-lesion methods have been combined to explain anomalies such as patients' intact performance on tasks on which they would be predicted to perform poorly. In some cases, preserved performance has been attributed to activation of residual tissue within the damaged region. However, activation of remnant tissue can also occur in relation to impaired performance and, thus, may not necessarily correspond to successful recruitment. To constrain these neuroimaging interpretations, what is needed is a paradigm with closely matched conditions that yields intact and impaired performance in the same patient. We investigated this in H.C., an amnesic person with congenital abnormalities of the hippocampus and its connections, who was scanned during remembering and imagining, abilities known to depend on the hippocampus. Specifically, we examined whether differences in activation and/or functional connectivity would explain H.C.'s compromised ability to construct events relating to herself in autobiographical memory (SELF condition) and events relating to personally familiar others (FAMILIAR condition) versus her intact ability to construct events relating to unknown others (UNFAMILIAR condition). Despite behavioral dissociations in H.C., the pattern of activation and functional connectivity supporting her performance was strikingly similar to that of controls across conditions. Most notably, like controls, H.C. showed robust hippocampal activation and functional connectivity to the hippocampus, both when her performance was intact and impaired. Across all conditions, H.C. activated several extra-hippocampal regions to a greater extent than did controls, and modest differences were observed in functional connectivity between extra-hippocampal regions. Taken together, these findings urge caution when drawing conclusions about the functional integrity of a structurally compromised brain region even when it is activated and/or co-activated with other regions.

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1. Introduction

Functional MRI (fMRI) of healthy individuals and patient-lesion methods are often viewed as complementary in answering questions about brain-behavior relations, each contributing unique information that the other method is lacking. fMRI studies identify the set of brain regions that support task performance, whereas patient-lesion studies isolate the structures that may be critical. Morris Moscovitch embraced the use of patient and neuroimaging methods as a means to test theoretical frameworks for which he is famous. For example, as predicted by Multiple Trace Theory (Nadel

and Moscovitch, 1997; Moscovitch et al., 2005), Moscovitch and colleagues found evidence in individuals with hippocampal damage of impaired autobiographical episodic memory for a lifetime of events (e.g., Gilboa et al., 2005; Rosenbaum et al., 2005, 2008; Viskontas et al., 2000) and obtained complementary findings with fMRI of equivalent hippocampal activation during recent and remote autobiographical remembering in healthy adults (Addis et al., 2004a; Gilboa et al., 2004; Hirshhorn et al., 2012; McCormick et al., 2010; Robin et al., 2015; Ryan et al., 2001). At the same time, he has acknowledged that patients may show intact performance on tasks on which they would be predicted to perform poorly (Rosenbaum et al., 2014b) due to reorganization and/or compensatory processes (Cabeza and Dennis, 2013). To investigate these hypotheses, researchers, including Morris Moscovitch, have begun to harness the power of combining functional neuroimaging and patient-lesion methodologies (e.g., Addis et al., 2007; Gilboa et al.,

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2009; Rosenbaum et al., 2007). In honor of Morris Moscovitch's festschrift, we present a study illustrating how, despite the value of marrying methods to understand brain-behavior relations, findings of intact and impaired event construction in single neurological cases are not always easily informed by functional neuroimaging.

Converging evidence indicates that the hippocampus, known for its role in autobiographical episodic memory, is also critical for imagining events (for a review, see Schacter et al., 2012). fMRI studies consistently show that hippocampal activation increases when healthy individuals recall past episodes and imagine novel events, and lesion work has demonstrated that patients with hippocampal damage produce impoverished descriptions of both types of events (Andelman et al., 2010; Kwan et al., 2010; Race et al., 2011; but see Hurley et al., 2011). However, few studies have combined fMRI and patient-lesion methods to examine event construction in individuals with hippocampal amnesia.

The few studies that have adopted a combined approach in hippocampal amnesia were primarily conducted to explore unexpected instances of preserved performance (Maguire et al., 2001; Mullally et al., 2012, 2014; but see Hayes et al., 2012). The goal of these studies was to investigate whether intact performance in the presence of hippocampal system compromise might be due to 1) activation of residual hippocampal tissue or 2) reliance on extra-hippocampal regions. The former explanation appeared to account for the preserved performance in two individuals with hippocampal amnesia. For instance, Jon, a well-characterized developmental amnesic case, showed activation of residual hippocampal tissue in relation to autobiographical memories that he was able to recall (Maguire et al., 2001). Likewise, case P01, an individual with adult-onset hippocampal amnesia, showed activation of residual hippocampal tissue in relation to intact scene construction (Mullally et al., 2012). By contrast, in another study examining Jon's preserved ability to generate fictitious and future experiences (Maguire et al., 2010), residual hippocampal tissue was not found to be activated, leading the authors to conclude that extra-hippocampal regions likely support Jon's construction of these events (Mullally et al., 2014). Similarly, the adult-onset amnesic case V.C. showed intact retrieval of personal and general facts in the absence of residual hippocampal activation (Maguire et al., 2005). Because V.C.'s behavioral performance was similar to that of controls, hippocampal activation observed in controls was interpreted as unessential to personal and general fact knowledge.

While only a handful of fMRI studies have examined unexpected instances of intact remembering/imagining in hippocampal amnesic patients, even fewer fMRI studies have examined activation patterns in relation to compromised performance. In one study, K.C., an adult-onset amnesic case with bilateral hippocampal damage and a profound inability to recollect past events, showed activation of what little remained of his hippocampus during a house recognition task on which he performed poorly (Rosenbaum et al., 2007). In other patient work, a person with semantic dementia and severe bilateral hippocampal atrophy demonstrated activation within right posterior hippocampus despite impoverished recall of recent memories (Viard et al., 2013). Taken together, these studies suggest that activation of damaged tissue may not necessarily correspond to successful recruitment or performance.

To constrain these neuroimaging interpretations, what is needed is a paradigm with closely matched conditions that yields intact and impaired performance in the same patient. In the current study, we had the rare opportunity to systematically compare the neural correlates of compromised versus intact event construction in a single case. We examined this in H.C., a young woman with developmental amnesia and structural compromise to

the extended hippocampal system (Olsen et al., 2013; Rosenbaum et al., 2011, 2014a; Vargha-Khadem et al., 1997, 2003). Specifically, we examined whether differences in activation and/or functional connectivity would explain H.C.'s compromised ability to construct events relating to herself in autobiographical episodic memory (SELF condition) and events relating to personally familiar others (FAMILIAR condition) versus her intact ability to construct events relating to unknown others (UNFAMILIAR condition; Rabin et al., 2013).

2. Materials and methods

2.1. Participants

2.1.1. H.C.

H.C. is a right-handed woman with 13 years of education. We tested H.C. twice, at 20 and 23 years of age (using different stimuli), for consistency purposes. Only the second session is reported here because it was subsequently discovered that the events in the SELF condition during H.C.'s first testing session were rehearsed prior to scanning, making the results of that condition difficult to interpret. Manual segmentation of H.C.'s hippocampus and surrounding medial temporal lobe (MTL) cortices revealed smaller hippocampal volumes by approximately 30% bilaterally compared with demographically matched controls. This difference in volume was limited to the hippocampal formation and equally distributed across the subfields and the anterior-posterior axis (Olsen et al., 2013). A more recent detailed examination of H.C.'s MRI scans revealed neuroanatomical abnormalities that are highly suggestive of disruption occurring very early in gestation. In addition to the previously reported smaller hippocampal volumes, there is also evidence of abnormal development of the extended hippocampal system, including aplasia of the mammillary bodies, atrophy of the anterior thalamic nuclei bilaterally, hypogenesis of the fornices, and abnormal hippocampal shape and orientation (Rosenbaum et al., 2014a).

H.C.'s neuropsychological profile has been well-documented (Rosenbaum et al., 2011). Her IQ is in the average range and she shows intact performance in non-mnemonic, cognitive domains, including attention, executive function, language, and visuospatial processing (Rosenbaum et al., 2011). She has impaired memory for personal life events and public event details but relatively intact personal and semantic memory (Rosenbaum et al., 2011). Of relevance to the present investigation are previous experimental measures of H.C.'s future thinking and social cognition abilities. H.C. demonstrates impaired episodic prospection (Kwan et al., 2010; but see Hurley et al., 2011), but is capable of making other types of future-regarding decisions (Kwan et al., 2013). She performs normally on standard tests of theory of mind (Rabin et al., 2012), and her social network is average in size (Davidson et al., 2012).

2.1.2. Control participants

Eighteen right-handed, healthy women with normal or corrected-to-normal vision and no reported history of neurological or psychiatric illness served as controls (mean age=19.3 years, $SD=1.2$; mean education=13.3 years, $SD=1.1$; this is the same group of controls reported in Rabin and Rosenbaum, 2012 and Rabin et al., 2013). Participants gave informed written consent in accordance with the ethics committees at York University and Baycrest.

2.2. Stimuli

A real-world family photos test was employed in the current

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