Hippocampal structure predicts cortical indices of reactivation of related items

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ABSTRACT

One of the key components of relational memory is the ability to bind together the constituent elements of a memory experience, and this ability is thought to be supported by the hippocampus. Previously we had shown that these relational bindings can be used to reactivate the cortical processors of an *absent* item in the presence of a relationally bound associate (Walker et al., 2014). Specifically, we recorded the event-related optical signal (EROS) when presenting the scene of a face-scene pair during a preview period immediately preceding a test display, and demonstrated reactivation of a face-processing cortical area (the superior temporal sulcus, STS) for scenes that had been previously paired with faces, relative to scenes that had not. Here we combined the EROS measures during the same preview paradigm with anatomical estimates of hippocampal integrity (structural MRI measures of hippocampal volume and diffusion tensor imaging measures of mean fractional anisotropy and diffusivity) to provide evidence that the hippocampus is mediating this reactivation phenomenon. The study was run in a sample of older adults aged 55–87, taking advantage of the high amount of hippocampal variability present in aging. We replicated the functional reactivation of STS during the preview period, specific to scenes previously paired with faces. Crucially, we also found that this phenomenon is correlated with structural hippocampus integrity. Both STS reactivation and hippocampal structure predicted subsequent recognition performance. These data support the theory that relational memory is sustained by an interaction between hippocampal and cortical sensory processing regions, and that these functions may be at the basis of episodic memory changes in normal aging.

1. Introduction

It has long been known that, when a person recollects an event, s/he does not simply remember a recording of it but, rather, a reconstruction of multiple elements of that memory stored in various parts of the cortex (Norman and O'Reilly, 2003). During this reconstruction the same cortical processors that were active at the initial encounter are reactivated (Marr, 1971; Norman and O'Reilly, 2003; Johnson and Rugg, 2007; Rugg et al., 2008; Hofstetter et al., 2012). For example it has been shown that the areas of cortex that were used to process a face or a location are again active when a person is asked to remember those items (O'Craven and Kanwisher, 2000). This phenomenon is not specific to faces or locations but has been demonstrated across a wide range of stimulus types such as colors (Simmons et al., 2007), tools (Chao et al., 2002), and words (Johnson et al., 2009; Hofstetter et al., 2012), to name a few. Recently we and others were

able to show that not only individual items can be reactivated in the cortex, but that items can reactivate other relationally-bound items from the same event (Hofstetter et al., 2012; Staresina et al., 2012, 2013; Zeithamova et al., 2012; Oudiette et al., 2013; Walker et al., 2014). It has been hypothesized that the hippocampus is a critical structure in the process of storing and retrieving the multiple pieces of information constituting a relational memory (Cohen and Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum and Cohen, 2001; Norman and O'Reilly, 2003). Although the importance of the hippocampus in relational memory is supported by a large amount of data (Hannula et al., 2006; Konkel et al., 2008; Watson et al., 2013), its critical role in reactivating relationally bound items has yet to be demonstrated. In this paper we demonstrate this link by showing that variability in hippocampal volume and connectivity in normally aging older adults is highly correlated with the extent of reactivation of cortical representations and with a person's ability to reactivate related information.

For the purposes of this paper we define reactivation as the activation, during retrieval, of the same cortical processor(s) used during the initial presentation of that item. Furthermore, we are interested in reactivation of relationally-bound information. Some studies investigating reactivation used some type of semantic cue that was known to participants prior to the experiment (e.g., the name of the object) in order to elicit reactivation. In such cases, however, reactivation could simply be the result of a semantic association established over a long period of time, and not specifically linked to a particular episode. In the case of relational memory, instead, we are interested in reactivation of an associated item after the presentation of another item arbitrarily paired with it during a *single study episode*. Evidence for relational memory in this case would therefore come from demonstrating the reactivation of cortical processors related to the processing of one item elicited by the presentation of the episodically-paired second item, even in the physical absence of the first item. In this case, evidence for relational memory reactivation would come from finding that a particular item elicits activation of a cortical region not normally involved in its processing, but involved instead in the processing of a stimulus type that was paired with it in a single previous episode.

There are strong theoretical bases for the involvement of the hippocampus in relational memory. It is generally accepted that the hippocampus is important in the formation and retrieval of declarative memories (Cohen and Squire, 1980). The hippocampus is believed to relationally bind together and store arbitrary associations (Cohen and Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum and Cohen, 2001). A considerable body of empirical evidence demonstrates the critical role of the hippocampus in creating and storing flexible associations after just one exposure (Hannula et al., 2006, 2007; Konkel et al., 2008; Hannula and Ranganath, 2009; Warren et al., 2010; Zeithamova and Preston, 2010; Duff et al., 2013). Furthermore, it is thought that the hippocampus can then use these relational bindings to reactivate an item in the presence of a relationally bound associate (Cohen and Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum and Cohen, 2001; Norman and O'Reilly, 2003).

We (Walker et al., 2014) were able to show evidence for reactivation in a study using a face-scene preview paradigm. In this paradigm, unique face and scene exemplars (novel and never repeated in the course of the study) are presented together at encoding. At test, for each trial, a scene is presented ahead of the test display (scene preview). We found that scene previews that were previously studied with a face showed reactivation of the same face processing regions found to be active when encoding those faces. Crucially, such reactivation was not found for novel scenes not previously paired with faces. We termed this type of reactivation "relational reactivation." Using a similar paradigm, Hannula and Ranganath (2009) had participants study pairs of faces and scenes and then tested the participants using a three-forced-choice recognition task to identify which face went with a scene, with a scene preview immediately prior to the test display. They found that hippocampal activity was related to later performance during the scene preview but not during the actual test display. Taken together these two studies lead to the prediction that hippocampal activity is associated with reactivating the face that was originally paired to the scene.

Others have reported similar evidence of hippocampal mediation of the relational reactivation process (Hofstetter et al., 2012; Staresina et al., 2012, 2013; Zeithamova et al., 2012; Gordon et al., 2014). These studies show increased functional connectivity between the hippocampus and other parts of the medial temporal lobe (MTL) thought to be responsible for specific processing of stimuli during retrieval. Zeithamova et al. (2012) were able to show a correlation between activity in the anterior MTL and an overall pattern of reactivation in the ventral visual stream when a participant was imagining a related item, indicating the possibility of an association between hippocampal activity and the overall pattern of reactivation. Similarly, Gordon

et al. (2014) also found a correlation between hippocampal activity and reactivation of patterns of activity associated with people and places.

The current study extends previous research by examining whether structural hippocampal integrity is associated with the degree of reactivation of paired memory representations in the cortex. There is a strong link between hippocampal volume (controlling for intracranial volume) and overall relational memory performance (Maguire et al., 2000; Erickson et al., 2009; Chaddock et al., 2010). Furthermore, measures of water diffusion in the hippocampus such as fractional anisotropy (FA) and mean diffusivity (MD), both thought to index white matter integrity, have also been linked to overall and associative memory ability. Specifically, individuals with high mean FA and low MD in the hippocampus perform better across a range of memory tasks (Charlton et al., 2006; Carlesimo et al., 2010), although not everyone has found a link between mean FA and memory performance (Carlesimo et al., 2010). Here we examined whether hippocampal structure, as measured through hippocampal volume, mean FA, and MD, was associated with the ability to relationally-reactivate representations in the cortex. In order to maximize hippocampal variability we chose to use older adults in our study. As people age, their hippocampi starts to atrophy, and there is also evidence of white matter degradation (Raz et al., 2005; Walhovd et al., 2005; Charlton et al., 2006). These changes create greater variability in both hippocampal size as well as white matter measures among adults, especially older adults. Older adults are also known to show decline in episodic memory, albeit with a large variability across individuals (Morcom et al., 2003; Buckner, 2004; Duverne et al., 2009; Fabiani, 2012). It is this greater variability that we harnessed to test whether hippocampal structure is associated with the ability to relationally reactivate items in the cortex.

To observe reactivation we employed a modified version of the paradigm used by Walker et al. (2014). In this paradigm participants study pairs of faces and scenes and then are tested on those pairs using a yes/no recognition task. As in the paradigm employed by Hannula et al. (2006), Hannula and Ranganath (2009), the critical aspect is that prior to every test display there is a scene preview. However, in our paradigm, instead of having only old scenes, some of the scenes are novel (i.e., never studied with a face before). By contrasting old scenes that were previously paired with a face and novel scenes that were never paired with a face, we can examine the extent to which participants are reactivating the face representation areas during the scene preview. In order to examine both the temporal and spatial dynamics of that reactivation we used the event related optical signal (EROS, Gratton and Fabiani, 2010). This technique uses a combination of temporal and spatial resolution to determine not only "where" activity is taking place but also "when" the activity is taking place, allowing investigators to examine the order of activation of various areas of the brain, instead of just establishing that those areas were active during a particular trial type.

In this experiment participants studied pairs of faces and scenes, first viewing either a face or a scene individually followed by the pair together (see Fig. 1). At test, participants were given an old/new recognition test for each of the face-scene pairs, each preceded by a scene preview. We found activity during scene previews in the posterior superior temporal sulcus (STS). The STS is an area known to be part of the network involved in processing faces, being shown to be active during both general face processing (Puce et al., 1998, 2003; Grill-Spector et al., 2004; Fairhall and Ishai, 2007) as well as in social judgments about a face (Puce et al., 1998; Hoffman and Haxby, 2000). It is also easily accessible by our imaging technique (which has limited penetration inside the head). The activity was greater for "old" scene previews compared to new or "novel" scene previews (which had no face associated with them), and was elicited in the *same region that was activated by faces presented alone* during the study phase (localizer) even though no faces were present. Critically, this reactiva-