J. Behav. Ther. & Exp. Psychiat. 58 (2018) 60–67

Contents lists available at ScienceDirect

Journal of Behavior Therapy and Experimental Psychiatry

journal homepage: www.elsevier.com/locate/jbtep

An investigation of potential neural correlates of intrusive retrieval of distressing memories

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ARTICLE INFO

Article history:
Received 23 April 2016
Received in revised form
3 August 2017
Accepted 12 August 2017
Available online 15 August 2017

Keywords:
Intrusive memories
Neuroimaging
fMRI
Retrieval

ABSTRACT

Background and objectives: Despite the prevalence of intrusive memories across psychological disorders, little is known about the neural networks that underpin this form of memory. This study used functional magnetic resonance imaging (fMRI) to identify neural circuits associated with the retrieval of intrusive memories.

Methods: Participants with moderate levels of anxiety (N = 30) underwent a cold pressor task to induce a physiological stress response, after which they viewed 10 neutral and 10 negative film clips. In a method designed to induce intrusive memories, participants then completed an fMRI scan in which they viewed short (2 s) depictions of neutral components from the original film clips.

Results: There were no significant differences in activations during intrusion and non-intrusion responses. Exploratory analyses comparing intrusive responses to neutral stimuli found the insula, inferior frontal gyrus, precuneus, right cerebellum and bilateral supplementary motor area were uniquely activated during experience of intrusions (compared to the neutral cue baseline), whereas no significant activations were in response to negative scenes that did not trigger intrusions.

Limitations: This study did not compare the different neural processes implicated in intrusive and intentional emotional memories. The limited intrusions that could be elicited in the scanning environment restricted the number of trials that could be employed.

Conclusions: Although no differences in neural activations were observed between intrusive and non-intrusive responses, the observation of precuneus involvement is consistent with models that propose that intrusive memories are impacted by the extent to which there is contextual integration of the relevant memories.

Unwanted intrusive memories occur across a wide variety of psychological disorders, including posttraumatic stress disorder (PTSD) (Bryant, O'Donnell, Creamer, McFarlane, & Silove, 2011), depression (Reynolds & Brewin, 1999), health anxiety (Muse, McManus, Hackmann, Williams, & Williams, 2010), agoraphobia (Day, Holmes, & Hackmann, 2004) and social anxiety (Hackmann, Clark, & McManus, 2000). These unwanted intrusions can cause distress and disruption in the lives of those who experience them.

Different theories have attributed intrusive memories to impairment of consolidation that would typically allow incorporation of new encoded information into autobiographical memory (Conway & Pleydell-Pearce, 2000; Brewin, Gregory, Lipton, & Burgess, 2010), or to excessive monitoring of suppressed memories, resulting in their reoccurrence (Klinger, 1996; Wenzlaff & Wegner, 2000). Other theories propose that situational cueing plays a primary role in the experience of intrusions, with intrusive memories being recalled associatively, initiated by situational cues (Berntsen, 2010; Foa, Steketee, & Rothbaum, 1989).

Despite the prevalence and clinical impact of intrusions, the neural mechanisms that underlie the development and experience of intrusive memories are not well understood. This is in part due to the spontaneous nature of intrusions, which are difficult to capture through experimental manipulation. Some insight into neural

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http://dx.doi.org/10.1016/j.jbtep.2017.08.004
0005-7916/

mechanisms that may underpin intrusive memories may be gleaned from neuroimaging studies of the neural correlates of emotional memories. Given that intrusive memories typically relate to highly emotional events, it is possible that neural regions critical to the retrieval of emotional memories, such as the hippocampus (Smith, Stephan, Rugg, & Dolan, 2006), amygdala and medial prefrontal cortex (mPFC), are also involved in the involuntary retrieval of such memories (Dolcos, Denkova, & Dolcos, 2012). Consistent with this proposal is evidence that retrieval of traumatic memories has been found to activate the mPFC (namely the anterior cingulate cortex (ACC)), amygdala, insula and temporal cortices in individuals with PTSD (Hamaan, 2001). Intrusions are also likely to be associated with disruptions to the hippocampus because of its involvement in retrieving contextual information (Eichenbaum, 2000). The orbitofrontal cortex may also be activated due to emotional processing (Kringelbach, 2005; Rolls, 2000), or due to emotion regulation processes (Golkar et al., 2012). The lateral prefrontal cortex (lPFC), precuneus and parietal regions may also be involved as part of a network that underpins search processes associated with memory retrieval (Buchanan, 2007). Although neuroimaging research on autobiographical memory points to these networks potentially being implicated in the involuntary retrieval of memories, the specific circuitry associated with intrusive retrieval has not been studied in detail. Accordingly, the current study aimed to map the neural correlates associated with unintentional memory retrieval.

One of the difficulties encountered when studying the neural substrates of intrusive memories in clinical populations, such as PTSD, is that observed responses may be associated with many of the contributing symptoms, rather than intrusions per se. It is for this reason that studies have attempted to understand the mechanisms underpinning intrusive memories across a range of paradigms using healthy analogue samples (Cheung, Garber, & Bryant, 2015; Hagenaars, Brewin, van Minnen, Holmes, & Hoogduin, 2010). Experimentally induced intrusions may be achieved by providing individuals with neutral cues that have become associated with target memories. This approach is supported by findings that intrusions in PTSD can be triggered by associated non-traumatic stimuli (Hackmann, Ehlers, Speckens, & Clark, 2004), which have been temporally related to the target memory (Ehlers & Clark, 2000). Hence, employing neutral cues that have been previously associated with the target memory is a potentially useful method of triggering intrusions during a scanning session, minimizing difficulties relating to the unpredictable nature of these memories.

Few previous studies have used neuroimaging methods to investigate intrusions. A PET study (Hall, Gjedde, & Kupers, 2008) presented healthy participants with images, followed by a repeat presentation of the same images paired with cue words. To ensure explicit memory for image-word associations, participants then generated sentences, including cue words, describing image content. During PET scanning, participants recalled images associated with cue words (voluntary condition), or semantically categorized cue words (involuntary condition – modelling intrusions of the images). Participants were not told that cues in the involuntary condition would provoke intrusions, but indicated after scanning whether they had recalled images associated with the cues. Compared to a control condition, voluntary and involuntary recall were associated with regional cerebral blood flow (rCBF) increases in the posterior cingulate gyrus, left precuneus, and right parahippocampal gyrus. Involuntary recall was specifically associated with increased rCBF in the left dlPFC, and voluntary recall with increased rCBF in the right dlPFC and left precuneus. However, this study did not distinguish between involuntary recall of emotional and neutral stimuli. Since intrusions generally include strong emotional content, this study can be seen as lacking an important aspect of clinical intrusions.

In another study healthy participants viewed a film including negative and neutral scenes during an fMRI scan, and completed an intrusion diary for seven days post scan (Bourne, Mackay, & Holmes, 2013). The encoding of negative scenes associated with subsequent intrusions was compared to negative scenes that did not become intrusive, as well as to neutral scenes. Encoding of negative content that subsequently became intrusive was associated with increased activation in the amygdala, ventral occipital cortex, rostral ACC, inferior frontal gyrus and medial temporal gyrus. These regions have been broadly associated with emotional processing, mental imagery, threat processing, and flagging of salient events to be remembered. However, by focusing on the encoding stage of intrusions, this study did not investigate the neural correlates of retrieval of intrusive memories.

In a clinical study, flashback memories were triggered during an fMRI scan using personalized trauma-relevant word cues (Whalley et al., 2013). Flashbacks, compared to ordinary episodic trauma memories, were associated with increased activity in the insula, motor and sensory areas, and with decreased activation in the parahippocampal gyrus, midbrain, precuneus and posterior cingulate cortex. These findings suggest that the neural circuitry underlying PTSD flashbacks is distinct from autobiographical memory, involves increases in dorsal visual processing, and results in decreased activity in regions associated with memory contextualization.

A recent study has investigated the retrieval of intrusions in a healthy population (Clark, Holmes, Wollrich, & Mackay, 2016). In this study, participants viewed traumatic film footage while undergoing an fMRI. Following this first scan, participants returned to the scanner, and completed another scan. During this second scan, they responded with a button press when they experienced an intrusive memory of the trauma film. fMRI data from this group was compared to that of a control group, who underwent a scan during which they randomly pressed a button. Compared to the control group, the intrusions group exhibited greater activation bilaterally in the superior and middle frontal regions, and also in the left inferior frontal gyrus and bilateral operculum.

In addition, imaging studies have used symptom provocation in participants with PTSD to investigate the neural bases of intrusion retrieval in a clinical population. A meta-analysis (Sartory et al., 2013) of 19 symptom provocation studies (with a total of 274 PTSD patients) found that compared to control participants, the response of PTSD patients to trauma-related stimuli showed greater activation in the mid-line anterior cingulate cortex, retrosplenial cortex, precuneus, right middle frontal gyrus, superior parietal lobe, left precentral gyrus and angular gyrus. PTSD patients showed decreased activation compared to controls in the superior and middle temporal gyri, postcentral and mid-occipital gyrus. Comparing trauma-relevant stimuli with the control condition, PTSDs had greater activation in the mid-line pregenual and retrosplenial cortex and precuneus, bilateral amygdala, midoccipital and angular gyrus. Activation seen in the midline retrosplenial cortex and precuneus in response to symptom provocation was interpreted as suggesting enhanced self-referential processing and retrieval of autobiographical memory in PTSDs. This enhanced processing was interpreted as coming at the expense of attending to the presented stimuli, since trauma-exposed controls showed greater activation in auditory and visual association areas.

The relative paucity of neuroimaging studies is likely due to the difficulties inherent in capturing this phenomenon in the magnetic resonance imaging (MRI) context. Unintentional retrieval is a defining characteristic of intrusions, and triggering such memories at sufficient frequency that one requires in an MRI experiment can