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

Eva Battaglini [a], Belinda J. Liddell [a], Pritha Das [b], Gin S. Malhi [b], Kim Felmingham [c], Richard A. Bryant [a, *]

[a] University of New South Wales, Sydney, Australia
[b] University of Sydney, Sydney, Australia
[c] University of Melbourne, Melbourne, Australia

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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

* Corresponding author. School of Psychology, University of New South Wales, NSW 2052, Australia.
E-mail address: r.bryant@unsw.edu.au (R.A. Bryant).

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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

be challenging. However, investigation of the neural processes underlying retrieval of intrusions may help to elucidate the processes that differentiate these memories from those which are deliberately recalled, and further studies are required to confirm and build upon the research conducted in this area thus far. Accordingly, this study investigated the neural correlates associated with intrusive retrieval of memories. Participants with high anxiety and stress levels (selected in order to increase the likelihood of experiencing intrusions) were initially presented with a film depicting traumatic scenes, which they viewed after completing a cold pressor task. This physiological stressor was designed to increase arousal during encoding of the negative films because augmented arousal increases occurrence of intrusions (Bryant, McGrath, & Felmingham, 2013). During subsequent fMRI scanning, participants were presented with brief neutral cues selected from the trauma film as a means of triggering intrusive memories of the aversive film content. Following scanning, participants were asked in detail about the frequency, content and characteristics of the intrusions that they experienced during scanning. In line with previous studies of intrusive and emotional memories, we hypothesised that retrieval of intrusions would involve greater activations in frontal regions of the brain, as well as amygdala, insula, hippocampus, precuneus and parietal cortex, relative to cues that did not trigger intrusions.

1. Method

1.1. Participants

Thirty-nine healthy participants (25 females, 14 males; mean age 22.85 years, $SD = 4.59$) were recruited via advertising at the University of New South Wales. Participants were initially screened using the anxiety and stress subscales of the Depression Anxiety Stress Scale (DASS21; Lovibond & Lovibond, 1995) to obtain a sample of participants with moderate levels of stress (range: 10–21; $M = 14.40$, $SD = 2.89$) and anxiety (range: 6–16; $M = 10.23$, $SD = 2.72$) (Henry & Crawford, 2005); these participants were selected to increase the likelihood of eliciting intrusions in the MRI. Participants were excluded if they had: current diagnosis or history of psychosis or bipolar disorder; history of serious brain injury or loss of consciousness for more than ten minutes; history of stroke or neurological disorder; severe non-correctable impairment of vision; impairment of hearing or hand movement; and current or previous heavy consumption of alcohol and other drugs (e.g. marijuana, heroin, cocaine, amphetamines). This study was approved by the Northern Sydney Area Health Service and University of New South Wales Human Research Ethics Committees, and all participants gave written informed consent prior to participating.

Nine participants were scanned but excluded from final analyses because they either did not report experiencing any intrusions during the scan ($n = 5$); had excessive movement during scanning ($n = 2$); inconsistent button press responses in the scanner ($n = 1$); or displayed artifacts on the scan arising from hair products used by the participant ($n = 1$). This left a final sample of 30 participants (19 female, 11 male, mean age 22.20 years, $SD = 4.28$).

1.2. Measures

Pre-scanning questionnaires. Before undergoing the scan, participants completed the following self-report questionnaires: Beck Depression Inventory - Second Edition (BDI-II; Beck, Steer, & Brown, 1996) to assess depression symptoms, State-Trait Anxiety Inventory (STAI; Spielberger, 1983) Trait Anxiety subscale to assess trait anxiety, and the Impact of Event Scale (IES; Horowitz, Wilner, & Alvarez, 1979) to assess the extent to which participants experienced intrusions in general (not specific to a traumatic event) over the previous week.

Post-scanning questionnaires. After scanning, participants completed a questionnaire assessing their perceptions of the stimuli. The questionnaire had four items: the questions 'How negative would most people find these?' and 'How positive would most people find these?' were presented regarding negative and neutral images, with the questions being asked separately for each image type. Responses were provided on a 10-point Likert-type scale (1 = *Not at all*, 10 = *Extremely*).

Participants also completed an intrusion questionnaire. This questionnaire was used to investigate the characteristics of the intrusions which the participant reported experiencing during their scan. Items included: 'How distressing did you find the image?', 'How vivid was the image?', 'How controllable was the image?' and 'How much did you mean to think about the image?' Responses were given on a 7-point Likert-type scale (1 = *Not at all*, 7 = *Extremely*). Participants completed these four items separately for each intrusion that they reported.

Follow-up questionnaire. To measure the subsequent experience of intrusions, a modified version of the Impact of Event Scale (IES) was administered two days after scanning. The measure consisted of 4 items specifically referring to intrusive recollections of the images presented during the scan ('Any reminder brought back feelings of it'; 'Other things kept making me think about it'; 'I thought about it when I didn't mean to'; 'Pictures about it popped into my mind'); each item was rated on a 5-point Likert-type scale (0 = *Not at all*, 4 = *Extremely*). Participants completed these items separately for neutral clips and negative scenes from the trauma film.

1.3. Experimental task and design

Stimuli. Stimuli were 20 film clips, of between ten and 120 s in duration. Ten negative (mean length 48 s, SD = 30.47 s) and ten neutral film clips (all 20 s in duration) were included. The negative film clips were taken from commercially available films, and contained highly negative and aversive content such as graphic scenes of violence and surgery footage (e.g. scenes from an educational film demonstrating the anatomy of the brain, including the removal of the skull cap of a cadaver to expose the brain and meninges; scenes depicting a riot involving two opposing gangs, including shots of injured gang members lying on the ground in the aftermath). Ten negative film clips were selected because this was considered to be the maximum number which could be shown, given time constraints and the cumulative impact on the participant of viewing distressing film content. Ten film clips containing emotionally neutral content were also used. These were taken from the website http://www.youtube.com, and consisted of abstract animations of shapes and patterns. These neutral clips acted as a visual perceptual control, which contained no emotional content. The duration of the neutral clips was shorter than the negative clips in order to avoid loss of participant attention to the potentially less interesting neutral content.

Each of the 20 clips was also edited into a shortened version, or cue, that was two seconds in duration. Each film cue showed only emotionally neutral content, regardless of the nature of the full version of the clip. These were designed to trigger intrusive memories of the negative content of the originally encoded film clips. Cues taken from negative clips were selected in order to be as neutral as possible (i.e. not including items seen during intrusive elements of the clip), and the content of the cues typically came prior to the intrusive element of the clip.

Experimental Protocol. Participants completed the pre-scanning

questionnaires the day before scanning. On the day of scanning, the baseline saliva sample was collected. Participants then completed the cold pressor task. This involved placing their forearm into very cold water (1–2 °C) and keeping it immersed for 90 s. This task is a commonly used laboratory stressor, which has been found to activate the sympathetic nervous system (Velasco, Gomez, Blanco, & Rodriguez, 1997) and hypothalamic-pituitary-adrenal (HPA) axis (Bulliner et al., 1984). After completing the cold pressor task, participants viewed the full versions of the film stimuli, played on a computer monitor. Between film clips, a black screen was presented for four seconds. Participants were instructed to pay attention to the screen, and avoid averting their eyes.

After watching the full versions of the film clips, participants underwent an fMRI scan. Scanning commenced between 22 and 28 min after viewing the film clips. During this scan, they viewed the short (two second) neutral cue sections of the film clips, with each cue being followed by a fixation cross for 10 s. After viewing the cue and fixation cross, a screen would appear prompting the participant to press a button in order to rate how they felt while watching the film cue that had just been presented, on a 4-point scale (1 = *Not negative at all*, 4 = *Extremely negative*). No reference was made in these instructions to the full versions of the film clips viewed prior to scanning, in order to avoid priming the participants to recall the full clips. A mixed block/event design was used, consisting of five negative blocks (containing two film cue events from negative clips per block) and five neutral blocks (containing two film cue events from neutral clips per block). Blocks were presented in a pseudorandomized order. Stimuli were presented via a computer monitor set up at the end of the scanner bore nearest to the participant's head. The films were then viewed by the participant via a small adjustable mirror positioned outside of the head coil, in front of the participant's eyes. Presentation of stimuli was controlled via a computer running Presentation® software (Version 14.7, Neurobehavioral Systems, www.neurobs.com), which also recorded button-press responses.

After scanning was completed, participants completed a brief qualitative interview regarding their experience of intrusions during scanning. Participants were asked 'What was going through your mind during the scan?' If any mention was made of the film clip stimuli beyond what was depicted in the two-second cues, participants were then asked which clips were recalled, and whether the recall was deliberate or intrusive, i.e. 'Did you remember this clip deliberately? Or did it just pop into your head without you meaning for it to?' Participants then completed the intrusion questionnaire for each film clip that they reported recalling intrusively during the scan. They also completed a copy of the stimuli questionnaire, with reference to the film clips generally.

1.4. Image acquisition

fMRI data was collected using a Siemens Trio 3 Tesla scanner (Siemens, Erlangen, Germany) located at the University of Sydney's Advanced Research and Clinical Highfield Imaging (ARCHI) facility. Data was collected using gradient echo echo-planar imaging to depict BOLD activity. Twenty-nine brain slices were acquired parallel to the AC-PC line (4 mm thick with 1 mm gap; effective thickness 5 mm), 64 × 64 matrix: TR 2sec, TE 32 ms, FOV of 240 mm.

1.5. Image analysis

All fMRI data processing and analyses were performed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

The images underwent slice-time correction, realignment, reslicing, and normalisation to the EPI template provided by SPM8. Images were smoothed with an 8 mm full-width half-maximum Gaussian kernel. Data was manually checked for alignment with the AC-PC line, and screened for excessive movement across scans (greater than 3 mm or greater than 2° rotation).

1.6. Data analysis

An event-related analysis was used to investigate the patterns of brain activation which occurred during trials where participants reported experiencing intrusions, with scene cues that triggered an intrusive memory being modelled separately from cues that were not associated with an intrusion. Responses on the post-scan intrusion questionnaire were used to index intrusions vs. cues not associated with an intrusion. Each modelled event included the two second cue, and the first six seconds of the 10 s fixation (eight seconds total duration for each event). The primary contrast of interest was intrusions > negative scene cues (no intrusion), which indexed BOLD signal changes related specifically to negative intrusions. Other contrasts included intrusions > neutral scene cues (no intrusion), and negative scene cues (no intrusion) > neutral scene cues (no intrusion). One sample t-tests were conducted between conditions at the whole brain level. Following previous studies of the neural basis of intrusive memories, comparisons were conducted using a cluster based significance threshold of $p < 0.05$ FWE, and a cluster threshold of 10 contiguous voxels (Bourne et al., 2013; Clark et al., 2016).

2. Results

2.1. Behavioural analyses

Mean scores on the pre-scanning questionnaires are presented in Table 1. The mean score on the STAI trait anxiety subscale ($M = 48.57$, $SD = 4.74$) indicates moderate levels of trait anxiety. The mean BDI-II score ($M = 22.80$, $SD = 10.93$) is suggestive of moderate levels of depressive symptoms (Beck, Steer, & Garbin, 1988). Participants' IES scores ($M = 22.00$, $SD = 11.20$) were moderate, but well below cutoff scores predictive of PTSD (Creamer, Bell, & Failla, 2003).

The data was inspected for missed trials. No participant included in the final sample missed more than one trial. Participants rated the negative films ($M = 8.20$, $SD = 1.10$) as significantly more likely to be perceived as negative than the neutral films ($M = 1.50$, $SD = 1.01$) ($t(29) = 27.33$, $p < 0.005$), whilst also finding the neutral films ($M = 4.40$, $SD = 2.70$) more positive than the negative films ($M = 1.73$, $SD = 1.01$) ($t(29) = 5.07$, $p < 0.005$) (Table 2).

In the post-scanning intrusions questionnaire, participants reported experiencing intrusions of between two and eight of the negative film clips while they were in the scanner (mean number of intrusions = 4.77, $SD = 1.72$)., with skewness = 0.213 ($SE = 0.427$) and kurtosis = −0.918 ($SE = 0.833$). Table 3 presents mean scores on post-scanning intrusions questionnaire items. These scores indicate that participants found their intrusions moderately distressing ($M = 4.48$, $SD = 1.81$), highly vivid ($M = 5.39$, $SD = 1.40$), only moderately controllable ($M = 4.15$, $SD = 1.65$), and low on

Table 1
Pre-scanning questionnaire scores.

Measure	Mean	*SD*
BDI-II	22.80	10.93
STAI	48.57	4.74
IES	22.00	11.20
VVIQ	54.41	9.35

Table 2
Post-scanning stimuli questionnaire scores (1 = Not at all, 10 = Extremely).

Item	Mean	*SD*
How negative would most people find these? (negative images)	8.2	1.10
How negative would most people find these? (neutral images)	1.50	1.01
How positive would most people find these? (negative images)	1.73	1.01
How positive would most people find these? (neutral images)	4.40	2.70

Table 3
Post-scanning intrusion questionnaire scores (1 = Not at all, 7 = Extremely).

Item	Mean	*SD*
How distressing did you find this image?	4.48	1.81
How vivid was the image?	5.39	1.40
How controllable was the image?	4.15	1.65
How much did you mean to think about the image?	2.53	1.37

intentionality of recall ($M = 2.53$, $SD = 1.37$).

2.2. Imaging analyses

The primary contrast of interest in this study was intrusions > negative scene cues (no intrusion). This contrast investigated regions that were specifically engaged to negative triggers that were associated with intrusions, relative to activation present when viewing clips corresponding to negative scenes that did not trigger an intrusion. No significant activations were seen for this contrast.

In the wake of the non-significant differences between intrusive and non-intrusive cues, we conducted exploratory analyses to determine possible patterns associated with intrusive retrieval. Specifically, we followed Bourne et al. (2013)'s approach in which the contrasts (a) intrusions > neutral scene cues and (b) negative scene cues (no intrusion) > neutral scene cues were compared. That is, regions of brain activation which occurred in the intrusions > neutral scene cues contrast but not in the negative scene cues (no intrusion) > neutral scene cues contrast were interpreted as reflecting the neural correlates of intrusions. We emphasise that this is a secondary analysis that does not directly address the primary hypothesised differences between intrusive and non-intrusive conditions. For the contrast intrusions > neutral scene cues, significant clusters of activation were present in the bilateral supplementary motor area, anterior insula, inferior frontal gyrus, precuneus and right cerebellum (Table 4, Fig. 1). These regions were not active in the negative scene cues (no intrusion) > neutral scene cues contrast, where no significant clusters survived thresholding. Thus, these key regions appeared to be exclusively active during the reported experience of intrusions during reminders of the aversive clips, relative to reminders of the neutral clips.

3. Discussion

The prediction of distinct neural activations between intrusive and non-intrusive conditions was not supported. Secondary analyses indicated that the insula, inferior frontal gyrus, precuneus, right cerebellum and bilateral supplementary motor area were uniquely activated during the retrieval of intrusive memories to cues for negative scenes (compared to neutral cue baseline). The unique contribution of these findings is that they shed light on neural processes implicated in retrieval, as distinct from encoding, of intrusive memories. It important, however, to emphasise that the results reported are not a result of directly comparing conditions of interest, and so can only be viewed as an initial, exploratory investigation of this phenomenon. No significant activations were present when comparing intrusions to a negative cue baseline.

The regions that were activated have previously been partially implicated in the formation of intrusions, both theoretically and experimentally. Experimentally, the findings of this study partially support those of Clark et al. (2016), with both studies observing that intrusive memory recall was associated with activity in the left inferior frontal gyrus and bilateral frontal operculum. The findings of this study also lend partial support to Brewin and colleagues' (2010) theoretical neurocognitive model of intrusions, which implicates regions including the insula and precuneus as underlying intrusive retrieval.

When considering the role of emotional processing in the experience of intrusions, activation in the precuneus may be related to the retrieval of emotional memories, with previous research indicating its involvement in search processes involved in memory retrieval (Buchanan, 2007). Although this literature is based on intentional search efforts for memories, it is possible that the same region is implicated in involuntary retrieval, as proposed by Brewin et al.'s neural model (2010). Cerebellar activation is consistent with emotional processing, as well as the regulation of emotional expression (Sacchetti, Scelfo, & Strata, 2009; Stoodley, 2012; Turner et al., 2007).

We recognize that the occurrence of intrusions may also involve inhibition processes, which would accord with models of intrusions that posit that attempted suppression can lead to an increased likelihood of a memory becoming intrusive (Wenzlaff & Wegner, 2000). The possibility of inhibitory activity being present may also be supported by the activation seen in the inferior frontal gyrus, which has been associated with cognitive control and behavioural suppression (Depue, 2012; Depue, Curran, & Banich, 2007), as well as with integration of sensory and emotional/motivation information, allowing for decisions to be made about potential responses, including suppression (Kringelbach & Rolls, 2004). The supplementary motor area is involved in motor control and planning, but this region may also be implicated in cognitive control and the selection of appropriate action in emotional contexts (Kober et al., 2008), functions which are relevant to inhibitory activity. These functions may occur in association

Table 4
Intrusions > Neutral scenes, whole brain, FWE 0.05.

Region	MNI coordinates of peak activation (x, y, z)	Cluster size	Cluster *p* corr	Voxel *p* uncorr	*t*
Supplementary motor area L	−9 11 59	432	<0.001	<0.001	9.91
Insula L	−27 23 -41	178	<0.001	<0.001	8.73
Insula R	33 23 -4	112	<0.001	<0.001	6.78
Inferior frontal gyrus, opercular part L	−39 20 32	235	<0.001	<0.001	8.56
Inferior frontal gyrus, opercular part R	48 17 32	43	<0.001	<0.001	7.70
Precuneus R (cluster extends to Precuneus L)	6 -67 41	67	<0.001	<0.001	6.59
Cerebellum R	45 -58 -31	43	<0.001	<0.001	7.70
Cerebellum R	27 -85 -25	41	<0.001	<0.001	6.28

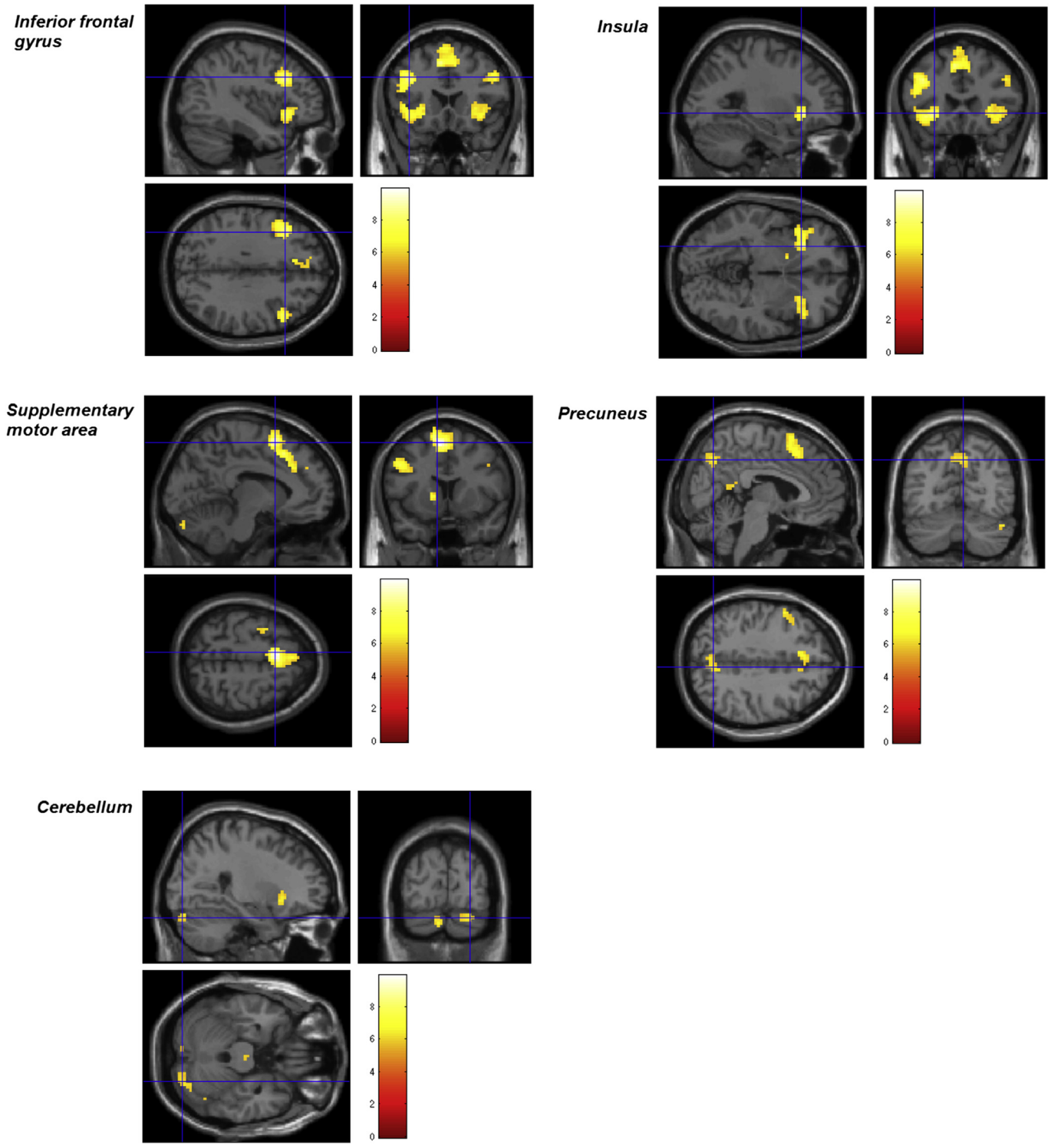

Fig. 1. Regions of BOLD activation during the contrast Intrusions > Neutral scenes, FWE 0.05. Crosshairs indicate peak activity in the cluster described in the legend.

with intrusions either because they play a contributing role in the experience of intrusive memories or they are an immediate response to the intrusive memory. It is not clear in this study the extent to which emotional regulation processes may have impacted the activations observed because we did not directly index potential regulatory responses.

It is important to note that there were a lack of significant results when comparing activation during the experience of intrusions with that when negative cues were viewed without the experience of intrusions. There are several issues that could have contributed to this, including methodological issues relating to eliciting and measuring intrusions (e.g. there are difficulties inherent in eliciting intrusions or determining when an intrusion starts and ends without priming participants to recall the negative stimulus; relying upon participant self-report may be problematic if participants have difficulties distinguishing between intrusive and

deliberate recall, in addition to the issue of accuracy of retrospective reporting), statistical power, and the use of a healthy participant sample. Larger powered studies with clinical samples that are prone to intrusions are needed in order to more effectively investigate intrusive recall. The paucity of prior studies addressing neural networks associated with intrusions in healthy samples hindered accurate power analysis prior to this study to determine the optimal sample size. It is also possible that the lack of significant results for the main contrast of interest occurred because intrusive and non-intrusive memory processes do not recruit differing neural networks. This possibility is worthy of consideration, but cannot be clarified by the current study.

There were no significant differences observed when comparing cues for negative scenes that failed to trigger intrusions with neutral scene cues. A possible explanation for this is that when not experiencing intrusions, participants were not recalling the full versions of film clips containing aversive content. Cues presented during the scan consisted of neutral scenes, regardless of the emotional content of the full version of the clip. Thus, if no memory of the full film was recalled, it is possible that strong negative affective response was absent, leading to a lack of difference in activation.

There are several methodological limitations to this study. Intrusions are inherently difficult to capture in an imaging context, given their spontaneous and unpredictable nature. At this time there are no robust methods for experimentally inducing intrusive memories with sufficient reliability to achieve desired occurrence of intrusions to readily study them in an MRI environment. Typical event-related designs use many more events than were used in this study, however this requires being able to elicit more intrusive memories. Another possible limitation is the lack of precision with which we measured whether an intrusion occurred at a particular point during scanning. This could have been achieved by having participants press a button when they experienced an intrusion, and press it again when the intrusion concluded (Mitchell et al., 2007). We decided against using such methods because we considered it more important to avoid priming effects which may have occurred if participants were told to monitor their thoughts for intrusions. The potential cost of this approach is that we relied on participants' retrospective memory to index intrusions, which may lead to lower accuracy. One of the procedural challenges in studying neural processes underpinning intrusions is the inherent difficulty in delineating between spontaneous occurrence of unwanted memories and intentional retrieval. Arguably a more reliable way to study intrusions is to focus on memories that are assessed over time as having intrusive qualities (Clark et al., 2016; Whalley et al., 2013), which may increase the likelihood of them occurring in the scanning context. However, even this approach does not ensure that they are experienced as intrusive on each trial during an fMRI session. In addition, we did not control for participants' attention to the film. In future studies, eye fixation measures could be used to confirm that participants were attending to the film clips. We also note that the intrusive-neutral contrasts were potentially confounded by the use of film stimuli to induce intrusions and abstract shapes as the neutral stimuli; these different types of stimuli raise the possibility that stimulus complexity, affective quality, or other associated features could explain distinct neural responses. Finally, this study did not assess the neural systems underlying intrusive vs. deliberate retrieval. A deliberate retrieval condition (where participants deliberately recall the content of a negative scene upon presentation of a cue) would clarify whether results seen were due to intrusiveness, or associated with emotional recall more generally.

This novel study provides preliminary evidence that the retrieval of intrusions is related to activations in brain regions associated with emotional processing and regulation. Viewing of cues which did not trigger intrusions activated regions associated with visual processing, normal memory retrieval, and contextual processing. This result accords with models that propose that contextual integration of a memory prevent that memory from being experienced intrusively (Brewin et al., 2010; Conway & Pleydell-Pearce, 2000; Ehlers & Clark, 2000). However, the current study did not determine whether deliberate retrieval occurred when intrusions were absent, and further research is needed to confirm this finding. The unique results of this exploratory study, which utilised a novel cueing paradigm to provoke intrusions, provide some useful insights into the neural underpinnings of intrusions, and point to potential directions for future neuroimaging research in the understanding of intrusive memories.

Conflicts of interest

No authors are declaring a conflict of interests.

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