Medial prefrontal–hippocampal connectivity during emotional memory encoding predicts individual differences in the loss of associative memory specificity

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A B S T R A C T

Emotionally charged items are often remembered better, whereas a paradoxical loss of specificity is found for associative emotional information (specific memory). The balance between specific and generalized emotional memories appears to show large individual differences, potentially related to differences in (the risk for) affective disorders that are characterized by 'overgeneralized' emotional memories. Here, we investigate the neural underpinnings of individual differences in emotional associative memory. A large group of healthy male participants were scanned while encoding associations of face-photographs and written occupational identities that were of either neutral ('driver') or negative ('murderer') valence. Subsequently, memory was tested by prompting participants to retrieve the occupational identities corresponding to each face. Whereas in both valence categories a similar amount of faces was labeled correctly with 'neutral' and 'negative' identities, (gist memory), specific associations were found to be less accurately remembered when the occupational identity was negative compared to neutral (specific memory). This pattern of results suggests reduced memory specificity for associations containing a negatively valenced component. The encoding of these negative associations was paired with a selective increase in medial prefrontal cortex activity and medial prefrontal–hippocampal connectivity. Individual differences in valence-specific neural connectivity were predictive of valence-specific reduction of memory specificity. The relationship between loss of emotional memory specificity and medial prefrontal–hippocampal connectivity is in line with the hypothesized role of a medial prefrontal–hippocampal circuit in regulating memory specificity, and warrants further investigations in individuals displaying 'overgeneralized' emotional memories.

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1. Introduction

Emotional events can be pervasively engrained in memory, as demonstrated by vivid recollections of flashbulb-memories (Brown & Kulik, 1977) or intrusive memories of patients with post-traumatic stress disorder (Brewin, Gregory, Lipton, & Burgess, 2010). Indeed, an emotional enhancement effect is reliably found experimentally when probing memory for items like faces, objects, scenes, words or movie clips that are charged with a negative emotional valence compared to neutral items (Bradley, Greenwald, Petry, & Lang, 1992; Cahill & McGaugh, 1995; Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann, Ely, Grafton, & Kilts, 1999; Talmi & Moscovitch, 2004). However, a somewhat different picture emerges when

memory is tested beyond isolated items, probing memory for associated items or spatiotemporal context. While memory for negative items themselves is enhanced compared to neutral items, memory for associated items or associated context is impaired (Bisby & Burgess, 2014). Even when an impaired memory for associative detail is found, the subjective sense of vivid recollection can be increased (Rimmele, Davachi, Petrov, Dougal, & Phelps, 2011).

The paradoxical modulatory effect of emotion on memory is reminiscent of the so-called 'weapon-focus' effect reported in the eye-witness literature, whereby a perceived item of negative valence (such as a weapon) impairs witnesses' ability to identify the perpetrator carrying the gun (peripheral associated information) (Christianson & Loftus, 1991; Migueles & Garcia-Bajos, 1999; Steblay, 1992). It has thus been argued that emotional valence might enhance the likelihood that the theme or gist of an event is remembered at the expense of memory for specific details (Adolphs, Tranel, & Buchanan, 2005). Recently, it has been

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postulated that emotionally arousing items attract particular attention, thereby enhancing binding of its constituting elements. At the same time, the association of the central object with contextual information and other objects is weakened (Mather, 2007). These two tenets are not contradictory, but are rather shown to complement each other in explaining the emotional memory paradox. When comparing encoding of negative versus neutral material, detailed memory is preserved for particularly those objects that are central, whereas memory for the non-emotional background becomes less detailed (Kensinger, Garoff-Eaton, & Schacter, 2007). Similarly, when encoding emotional material, the increased subjective sense of recollection is found to be related to an enhanced memory for the what, where and when of a specific emotional item, whereas peripheral details and associations to other items occurring at the same time are poorly remembered (Bisby & Burgess, 2014; Rimmele, Davachi, & Phelps, 2012; Rimmele et al., 2011). While an emotionally arousing picture impairs memory for the background pattern, it does not impair item recall, item recognition, or location memory of another central picture or object and its features (Erk et al., 2003; Mather, Gorlick, & Nesmith, 2009; Touryan, Marian, & Shimamura, 2007). Emotional items also impair memory for the specific association among them. For instance, one study found that recognition memory for negative word-pairs was found to be impaired compared to neutral or positive word pairs, and this was expressed primarily as an increased false alarm rate for re-arranged negative word pairs (Pierce & Kensinger, 2011). Notably, the hit rate for negative words demonstrated decreased forgetting across the one week consolidation period, but this finding was paralleled by a similar increase in the false alarm rate. Thus, while the emotional valence boosts item recall and item recognition, it reduces memory specificity for associations and background context.

When investigating the brain basis of the emotional modulation of memory, a distinction is thus warranted between memory for the central item and memory for associated information and spatiotemporal context. Corroborating this distinction is the finding that damage to the amygdala, a brain region deemed to be essential for emotional modulation of memory (McGaugh, 2004; Phelps, 2004), impairs gist memory while retrieval of associated detail is preserved (Adolphs et al., 2005). Individual differences in emotion-modulated item memory can be related at the neural level with activity in the amygdala and other medial temporal lobe (MTL) regions, as well as their mutual connectivity (Dolcos, LaBar, & Cabeza, 2004; Hamann et al., 1999; Kilpatrick & Cahill, 2003; Murty, Ritchey, Adcock, & LaBar, 2010; Ritchey, Dolcos, & Cabeza, 2008). The neural mechanisms underlying the emotional regulation of memory specificity are, however, less clear. In general, there is a wide set of regions implicated in the retrieval of associative detail in both cued recall and source memory tasks, including the medial prefrontal cortex (mPFC), posterior midline, bilateral parietal and medial temporal regions (Hayama, Vilberg, & Rugg, 2012; Vilberg & Rugg, 2014). Particularly, the mPFC has been found to respond also to emotional valence and arousal (Geday, Gjedde, Boldsen, & Kupers, 2003; Geday, Kupers, & Gjedde, 2007; Phan et al., 2003), to social and self-referential processing (Gusnard, Akbudak, Shulman, & Raichle, 2001; Mitchell, Banaji, & Macrae, 2005; Mitchell, Neil Macrae, & Banaji, 2005) and emotion regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Quirk & Beer, 2006). Connectivity between the mPFC and amygdala have been found to be important for regulating emotions (Banks et al., 2007; Quirk & Beer, 2006). Recent findings have converged in implicating the mPFC also in the integration of information in pre-existing knowledge structures, so-called schemas that appear to be memories generalized over several episodes (Lewis & Durrant, 2011; Van Kesteren, Ruiter, Fernández, & Henson, 2012). Thus, it can be suggested that the mPFC plays a critical role in assimilating

generalized memories that are less specific to an individual episode. A recent study in mice has added critical support for this hypothesis by revealing mPFC–hippocampal connectivity mediates specificity of emotional memories. However, it remains to be tested whether this interaction is also involved in regulating emotional associative memory in humans. Interestingly, a recent study in mice revealed that specific thalamic nuclei regulate the specificity of emotional memories by modulating mPFC–hippocampal connectivity (Xu & Südhof, 2013). Thus, connectivity between mPFC and hippocampus appears critical in regulating emotional associative memory specificity, but this remains to be tested in humans.

Here, we investigate the neural mechanisms related to the modulation of associative memory specificity by emotional item valence. Individual differences in neural mechanisms might be particularly interesting when informing future research into extreme impairments in emotional memory specificity found in clinical populations (Foa, Gilboa-Schechtman, Amir, & Freshman, 2000; Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 2000; Watkins, Vache, Verney, & Mathews, 1996). We explore these individual differences here in a normal population using a memory encoding task where faces need to be associated with occupational identities. This task has been frequently used in the literature to elucidate individual variation in associative memory (Dominique & Papassotiropoulos, 2006; Erk et al., 2010, 2011; Werner et al., 2009). Here, we added a manipulation of emotional valence of the occupational identity labels to allow us to look at individual differences in emotional associative memory. Specifically, a large group of young healthy men were scanned while encoding associations of individual faces and either neutral (e.g., 'driver') or negative (e.g., 'murderer') occupations, and were asked later to identify the particular neutral and negative occupational identity associated with each particular face. Broadly, this laboratory task resembles a line-up situation where a victim needs to identify a villain from a range of other identities. Memory performance is operationalized on a general, gist-level (a face is associated with an occupational identity from the correct valence-category but not the exact occupational identity) and a specific, detailed level (the specific face–occupational identity association is remembered correctly). A loss of memory specificity can be expected for those associations that consist of negative occupational identities, potentially mediated by interactions of MTL regions with the mPFC.

2. Materials and methods

2.1. Participants

One-hundred-twenty young healthy male volunteers in the age range of 18–31 (mean age 21.9; SD = 2.63) provided informed consent to participate in the study. All subjects were right-handed and pre-screened to exclude a history or current status of psychiatric, neurological or endocrine disorder, and to exclude the consumption of illicit drugs or medications affecting the central nervous or endocrine systems at any point over the past six months. The study was conducted in accordance with guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, The Netherlands) and the declaration of Helsinki. To ensure that all subjects in the final sample understood and performed the task correctly, we removed those participants from further analysis that performed extremely poorly. The threshold was set at two items correct, where the items were counted correct when both valence + identity was correct. Two items corresponds to the number of items that can be expected to be guessed correctly if subjects were fully aware of the valence of each face and completed every item of the test (32 faces, 16 negative