Neuropsychologia xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Neuropsychologia

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

Genetic differences in emotionally enhanced memory

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ARTICLE INFO

Article history:
Received 19 July 2010
Received in revised form 28 October 2010
Accepted 9 November 2010
Available online xxx

Keywords:
Emotional memory
Episodic memory
Amygdala
Neurogenetics
Motivated attention

ABSTRACT

Understanding genetic contributions to individual differences in the capacity for emotional memory has tremendous implications for understanding normal human memory as well as pathological reactions to traumatic stress. Research in the last decade has identified genetic polymorphisms thought to influence cognitive/affective processes that may contribute to emotional memory capacity. In this paper, we review key polymorphisms linked to emotional and mnemonic processing and their influence on neuromodulator activity in the amygdala and other emotion-related structures. We discuss their potential roles in specific cognitive processes involved in memory formation, and review links between these genetic variants, brain activation, and specific patterns of attention, perception, and memory consolidation that may be linked to individual differences in memory vividness. Finally we propose a model predicting an influence of noradrenergic, serotonergic, and dopaminergic processes on emotional perception, as well as on memory consolidation and self-regulation. Outside of the laboratory, it is likely that real-life effects of arousal operate along a continuum that incorporates other "non-emotional" aspects of memory. For this reason we further discuss additional literature on genetic variations that influence general episodic memory processes, rather than being specific to emotional enhancement of memory. We conclude that specific neuromodulators contribute to an amygdala-driven memory system that is relatively involuntary, embodied, and sensorily vivid.

In the most famous passage from Marcel Proust's *À la Récherche de Temps Perdu* (translated as *In Search of Lost Time*, or *Remembrance of Things Past*), the narrator has bitten into a *madeleine*, a small cake dipped in tea, and experiences a wash of inexplicable joy. "Where could it have come to me from, this all-powerful joy?" he wonders. "I sensed that it was connected to the taste of the tea and the cake, but that it went infinitely far beyond it, could not be of the same nature. Where did it come from? What did it mean? How could I grasp it?" (Proust, 1913: 2002). In the pages to follow, Proust describes in great phenomenological detail the effortless and elusive qualities of his memory, distinguishing such seemingly automatic washes of memory from voluntary efforts at retrieval, and linking it to sensory experience. Proust described his emotional memory as involuntary, vivid and embodied, perhaps enabling his subsequent formidable recollection of contextual details concerning thoughts, perceptions, and happenings.

Proust was an outlier. Most people do not share his mnemonic capacity. On the other hand, some are particularly vulnerable to the effects of traumatic memory, as in post-traumatic stress disorder (PTSD). Such individual differences have tremendous implications for the understanding of normal human memory as well as pathological mnemonic reactions to traumatic stress, which can differ across individuals even when they are exposed to the same events. Some of this difference in capacity may be genetic. Research in the last decade has identified a number of common genetic variations thought to interact with life experience to influence the capacity for emotional memory. In this paper, we review some of these polymorphisms and their influence on neuromodulatory activity in the amygdala and other emotion-related structures. We then discuss their potential roles in specific cognitive processes involved in memory formation. Yet, although the division of memory into emotional vs. neutral is necessary for interpreting the role of genotype in memory formation, one limitation of this research is that it is largely based on laboratory manipulations designed to exploit effects of emotion on memory. In naturalistic human autobiographical memory a strict division between "emotional" and "non-emotional" memory is less clear. Outside of the lab, it is more likely that emotional effects on attention and memory operate along a continuum to facilitate retrieval of multifaceted mnemonic information, including perceptual, cognitive, and semantic information along with emotional information. We will therefore also discuss additional literature on genetic variations thought to influence general processes associated with episodic memory.

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doi:10.1016/j.neuropsychologia.2010.11.010

A few studies reliably linking common genetic polymorphisms to personality traits or cognitive processes have been large, well-replicated association studies that link gene and behavior through the use of genome-wide screens (e.g., Papassotiropoulos et al., 2006). However, much research investigating associations between targeted polymorphisms and behaviors has been hampered by inconsistent results and failure to replicate, as revealed by recent meta-analyses (Barnett, Scoriels, & Munafo, 2008; Munafo et al., 2009). Effect sizes are small due to the contribution of multiple genes to a given trait or behavior (Butcher et al., 2004; Plomin, Owen, & McGuffin, 1994), sample sizes are often inadequate, and there are high levels of noise due to the many intervening factors between gene and behavior (Munafo, Durrant, Lewis, & Flint, 2009). In contrast, brain activation patterns elicited by laboratory tasks provide a mid-level phenotype between genotype and behavior, and in some cases have relatively robust relations with both (Canli, 2008). An *endophenotype approach* takes advantage of the greater sensitivity of brain imaging techniques to both genetic variation and behavior. We propose an endophenotypic approach to investigate links between genetic variations, patterns of brain activation, and specific aspects of memory formation and recall. Examining the role of specific genetic polymorphisms, which influence activity of key neuromodulators on brain activation patterns, can allow us to develop a finer-grained taxonomy of processes that influence emotional memory. Ultimately, a *behavioral epigenetic* approach can be used to look at the emergence of such patterns in development in interaction with life experience, which modulates gene expression and sculpts neural circuitry.

Before discussing neurochemical and genetic influences on emotionally enhanced perception and memory, however, we will begin by clarifying terminology used throughout the paper. First, when we talk about *emotional memory*, we refer specifically to long term, episodic memories of emotionally arousing events. *Episodic memory* is characterized by subjectively "re-living" events (Tulving, 2001). Formation of emotional memories crucially involves amygdala modulation of other brain regions subserving memory, including the hippocampus and prefrontal regions (Cahill & McGaugh, 1998; McGaugh, McIntyre, & Power, 2002; Roozendaal, McEwen, & Chattarji, 2009). *Encoding* an emotional event involves processing initial sensory information as a coherent construct that is later remembered. We will propose that specific processes associated with encoding of emotional memories may include greater allocation of attentional resources to an emotional event (Anderson, 2005) as well as enhancement of perceptual vividness (Cahill & Anderson, 2009). When referring to *attentional* processes potentially implicated in encoding emotional events, we are referring to a form of selective attention, or selection bias, driven by the motivational salience of an object or event. Such selective attention is thought to be mediated by an emotional saliency network (Barrett & Bar, 2009; Seeley et al., 2007), which includes the amygdala and orbitofrontal cortices. Such salience-driven selective attention is often demonstrated via an advantage for emotional stimuli in capturing limited attentional resources necessary for an item to enter awareness (Anderson, 2005; Anderson & Phelps, 2001; Lim, Padmala, & Pessoa, 2009), and in "motivated attention" studies finding increased visual cortex activation for emotionally salient visual stimuli (Bradley et al., 2003; Padmala & Pessoa, 2008; Pessoa, Kastner, & Ungerleider, 2002). When we refer to *perceptual vividness*, we are referring to the subjective experience of visual clarity (Cahill & Anderson, 2009). For example, perceptual vividness can be measured by estimation of the relative clarity with which images are perceived when they are partially obscured by visual noise.

Emotional memory formation also includes short and long-term memory *consolidation* processes: short-term consolidation involves a cascade of molecular processes necessary for the formation of new synaptic connections and structural change of existing ones that takes place over the course of hours (Frankland & Bontempi, 2005). In humans, it is still not known precisely when in time consolidation processes can be dissociated from encoding. Long-term consolidation processes involve reorganization of large-scale neural systems supporting memory (Frankland & Bontempi, 2005). Finally, a complete taxonomy of mnemonic processes should include specific qualities of episodic memory at the time of memory *retrieval*, or recall, as well. These include memory for specific objects vs. the context of the experience, temporal vs. spatial detail, and degree of emotional vividness (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002).

1. Genetic influences on emotional memory

It is well established that the amygdala plays a central role in both encoding and retrieval of emotional memories (Hamann, 2001; LaBar & Cabeza, 2006; Sharot, Delgado, & Phelps, 2004). Recent research suggests genetic differences influence patterns of amygdala activation during perceptual and mnemonic processing. In this review we will focus on four polymorphisms: (1) a deletion variant of the *ADRA2b* gene, which influences activity of adrenoreceptors; (2) a single nucleotide polymorphism (SNP) (valine to methionine) in the *COMT* gene coding the catechol-O-methyl transferase enzyme that metabolizes prefrontal dopamine; (3) a short version of the *5HTTLPR* serotonin transporter gene, which is associated with higher 5-HT levels; and (4) a SNP in the *TPH2* gene coding one phase of 5-HT synthesis. Although we focus on these four polymorphisms, we emphasize that they are a few of many potential genetic variations that may ultimately be found to influence emotional memory, and that links between genetics, brain, and behavior likely involve interactions between multiple polymorphisms and between genetic inheritance and life experience. With that caveat, we will review extant research that sheds light on the role of each of these in specific aspects of memory encoding and consolidation, highlighting important areas for future research (Table 1).

The often-quoted "flashbulb" quality of intense emotional memories refers to their relatively enduring nature – as if they were photographically etched in the brain (Brown & Kulik, 1977). The modulation hypothesis (McGaugh et al., 2002) proposes that the amygdala's role in the formation of everyday emotional memories (as opposed to flashbulb memories) is to modulate activity in other brain regions associated with memory formation, including the hippocampus, caudate nucleus, insula, entorhinal cortex, and prefrontal regions. This model suggests that arousal associated with an emotional event enhances encoding, and interacts with subsequent influences of arousal on consolidation to enhance emotional memory. With regard to emotional enhancement of encoding, growing evidence suggests that the emotional spotlight cast on salient events heightens our perceptual experience of them (Cahill & Anderson, 2009). Such heightened experience may be linked to amygdala enhancement of visual cortex activation for emotional images (Bradley et al., 2003; Padmala & Pessoa, 2008), and may contribute to memory vividness (Cahill & Anderson, 2009). Emotional events also enjoy privileged access to limited attentional resources (Anderson, 2005), and enhanced attention to an event in turn contributes to emotional memory (Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008). Yet subsequent memory is also influenced by amygdala activation associated with post-encoding consolidation processes (for review see Roozendaal et al., 2009). For example, we have shown that neutral pictures of houses were better remembered one week later when they were followed by an emotional rather than a neutral event, provided they followed the event at short intervals. Moreover, individual ratings of a scene's arousal predicted recollection of the house that preceded

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Table 1
Key genes thought to influence specific aspects of emotional and episodic memory.

Memory type	Memory stage	Key brain regions	Gene
Episodic: emotional	Encoding?Consolidation?	Amygdala, hippocampus, PFC	*ADRA2b*
Episodic: emotional?	Encoding?Consolidation?	PFC, amygdala	*COMT*
Non-declarative (Conditioning): emotional	Encoding?Consolidation?	Amygdala, medial PFC	*5HTTLPR*
Episodic: general		Hippocampus, temporal cortex	*APOE*
Episodic: general		Hippocampus, temporal cortex	*5HT2A*
Episodic: general		Hippocampus PFC	*BDNF*
Episodic: general		Hippocampus	*KIBRA*

it (Fig. 1) (Anderson, Wais, & Gabrieli, 2006). To date, the role of specific genetic variations contributing to individual differences in enhanced attention and increased perceptual vividness at the time of an arousing event, effects of arousal on subsequent consolidation processes, and the influence of each of these on emotional memory vividness remains an open question.

We will review convergent evidence supporting a model of genetic influences on emotional memory, the endophenotypic model of emotional memory (EMEM, Fig. 2). Building on the modulation hypothesis, this model proposes that, in humans, increased perceptual vividness at encoding partially predicts emotional memory vividness. We suggest that such perceptual enhancement at the time of encoding combines with the influence of arousal on consolidation, which also enhances memory. The EMEM further proposes roles for candidate genes associated with neurotransmitter activity in specific aspects of emotional perception and memory consolidation: (1) genetic variations influencing emotionally enhanced perception modulate activation in motivational circuitry, including the amygdala, visual cortices, and ventral prefrontal regions associated with stimulus evaluation and prediction (Anderson & Phelps, 2001; Barrett & Bar, 2009; Lim et al., 2009); (2) genetic influences on consolidation influence amygdala modulation of other regions including the hippocampus, caudate nucleus and PFC (McGaugh et al., 2002; Roozendaal et al., 2009). Specifically, we hypothesize that, *5HTTLPR* and *TPH2* (serotonin) contribute to heightened emotional perception by influencing allocation of attentional resources required for perceptual awareness (Anderson, 2005) and/or heightened perceptual vividness (Cahill & Anderson, 2009) at the time of an emotional event. In contrast, *ADRA2b* (norepinephrine) plays a role in arousal-enhanced consolidation processes, influencing amygdala and hippocampus activation immediately following an emotional event (Anderson et al., 2006). We further propose that, *COMT* (dopamine) influences prefrontal regulation of amygdala reactivity to aversive events, which may in turn influence consolidation. However, these hypotheses have yet to be directly tested. Moreover, although there is indirect evidence suggesting a link between each of these polymorphisms and emotional memory, to date only *ADRA2b* has been directly linked to declarative emotional memory, and direct influences of the other polymorphisms on emotional memory remain to be demonstrated.

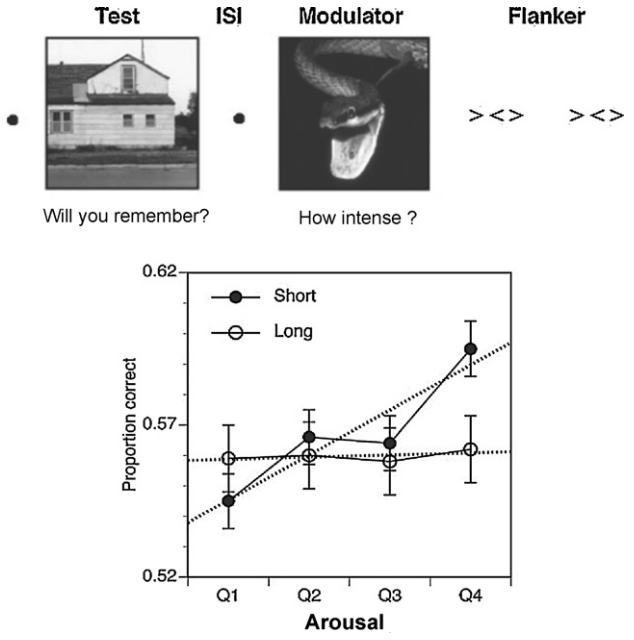

Fig. 1. Anderson et al. (2006) found neutral pictures were better remembered one week later when they preceded arousing images. (A) Schematic illustration of trial structure. Participants viewed photographs of neutral faces and houses and were asked to indicate whether they thought the event was memorable. Either 4 or 9 s after test events, modulator events depicted neutral (e.g., household items), positive arousing (e.g., erotica) or negative arousing (e.g., mutilations). Observers indicated their emotional arousal by rating the intensity of emotional response to the modulator event, after which they performed a distractor flanker task to allow arousal to return to baseline. (B) Relation between modulator arousal and recognition memory for test events. Test events are sorted into quartiles (Q1 = low arousal quartile, Q4 = high arousal quartile). Short indicates intervals of 4 s, long intervals of 9 s. Dotted line represents best linear fit.

1.1. Noradrenergic influences on emotional memory

As William James pointed out, 'An experience may be so exciting emotionally as almost to leave a scar on the cerebral tissues' (James, 1884). A large body of literature suggests that norepinephrine (NE) activity enhances this initial excitement. Emotional arousal releases NE from the locus ceruleus of the brainstem, activating NE receptors in the amygdala, which in turn enhances consolidation of emotional memory (McGaugh et al., 2002; Roozendaal et al., 2009). The modulation hypothesis (McGaugh et al., 2002) proposes that NE activity implicated in arousal-enhanced consolidation interacts with arousal levels at encoding to enhance emotional memory.

The EMEM model suggests that enhanced selective attention to emotionally salient events at the time they are experienced, as well as arousal-enhanced memory consolidation processes, may influence the vividness and accuracy of memory. With regard to the enhanced selective attention, the role of NE on an attentional advantage for emotional events was demonstrated in a recent attentional blink (AB) study (De Martino, Strange, & Dolan, 2008). This study compared the effects of propanolol (a beta blocker that impairs β-adrenergic transmission in the brain) and reboxetine (a selective NE reuptake inhibitor that increases the amount of available NE). In a standard AB paradigm, two target words are embedded in a stream of rapidly presented distracters. The blink effect occurs when the second target (T2) is presented within 500 ms of the first target (T1). During this brief time window, awareness of T2 is impaired due to attentional limitations gating perception. The blink effect can be reduced if T2 words are emotionally arousing, suggesting privileged access to awareness for emotional words (Anderson, 2005), an effect that depends upon an intact amygdala (Anderson & Phelps, 2001). De Martino and colleagues found that although the propanolol group showed impaired target detection, or a larger blink, for all stimuli, the reboxetine

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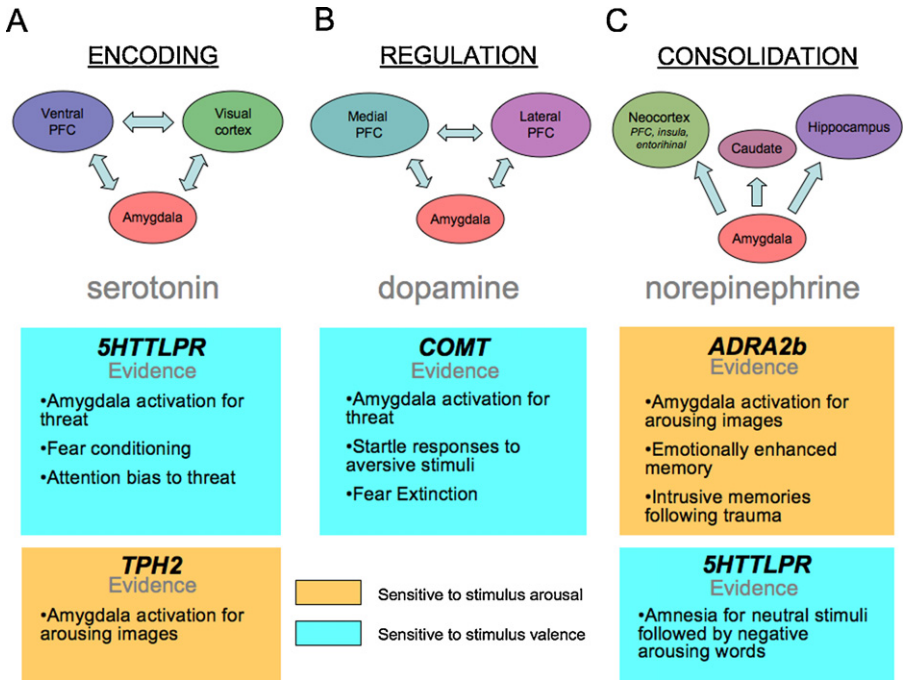

Fig. 2. Endophenotypic model of emotional memory (EMEM). (A) Key brain regions implicated in enhanced encoding of arousing visual stimuli include the amygdala, regions of ventromedial PFC implicated in stimulus evaluation and prediction, regions of ventrolateral PFC implicated in selective attention, and visual cortex. Based on evidence for the influence of these alleles on amygdala activation and perceptual processing, the EMEM proposes that serotonergic processes modulated by *5HTTLPR* and *TPH2* influence brain systems implicated in enhanced encoding of emotional stimuli. (B) Brain regions important for regulation of amygdala activity include dorsal and ventral medial PFC as well as lateral PFC. The EMEM proposes that *COMT* allele influence on prefrontal dopamine levels influences prefrontal regulation of amygdala reactivity to aversive events, which may in turn modulate consolidation processes. (C) Brain regions modulated by amygdala activity in consolidation of emotional memories according to the modulation model. The EMEM predicts that noradrenergic processes modulated by *ADRA2b* in the amygdala may play a role in arousal-enhanced consolidation processes. *5HTTLPR* may also influence memory consolidation by modulating post-encoding amnesia.

group showed enhanced target detection, or a reduced blink, for arousing trials only. These results suggest that increased levels of NE are selectively associated with privileged access to awareness for emotionally salient stimuli. We speculate that such an attentional advantage may contribute to enhanced encoding of emotional events.

Several pharmacological studies have found an influence of NE on emotional memory in humans. Blocking β-adrenergic processes with propanolol prior to encoding has been found to impair recall for arousing but not for neutral items (Cahill, Prins, Weber, & McGaugh, 1994; Strange, Hurlemann, & Dolan, 2003). However, it should be noted that studies using the more selective reboxetine have found a more complex pattern of NE influence on human emotional memory, either finding no effect of reboxetine on recall of negative arousing events (Papps, Shajahan, Ebmeier, & O'Carroll, 2002), or finding an effect of valence, with improved recall of positive relative to negative stimuli (Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006; Harmer, Shelley, Cowen, & Goodwin, 2004).

Proponents of a consolidation account, which suggests that NE influences consolidation rather than encoding processes (de Quervain et al., 2007), emphasize findings that participants given propanolol do not rate stimuli as less emotional than a placebo group when they rate images a few seconds after first viewing them (Cahill et al., 1994). A consolidation account is consistent with animal evidence that post-encoding noradrenergic activity in the amygdala modulates emotional memory consolidation processes in the hippocampus and other regions (Ferry, Roozendaal, & McGaugh, 1999; Hatfield & McGaugh, 1999; LaLumiere, Buen, & McGaugh, 2003), and that it influences downstream glucocorticoid processes implicated in memory consolidation. Human studies have also found that injection of epinephrine after viewing pictures enhances memory for pictures one week later (Cahill & Alkire, 2003). However, it should be noted that memory for an item can be inhibited as well as enhanced by subsequent arousal, and that this retrograde amnesia is also linked to NE processes in the amgydala (McGaugh et al., 2002; Strange et al., 2003). Such conflicting findings have been explained in terms of a u-shaped curve, in which lower doses improve and higher doses impair subsequent memory (Introini-Collison & McGaugh, 1986). Other contributing factors in humans may include when memory is measured (recall measured minutes after encoding may not capitalize on important consolidation effects) as well as the type of encoding task used.

What is the role of genetic influences on NE-modulated emotional perceptual and mnemonic processes? A deletion variant of the *ADRA2b* gene, which influences activity in pre-synaptic adereno-receptors, is thought to be indirectly linked to increased NE availability in the amygdala (Cousijn et al., 2010). More specifically, it impairs receptor regulation by G protein-coupled receptor kinases (GRKs) in inhibitory noradrenergic α_{2B} receptors, and leads to a loss of receptor desensitization (Small, Brown, Forbes, & Liggett, 2001). Behavioral and imaging data suggest an association of this functional deletion with increased NE availability, although a causal link between the deletion variant and increased NE has not been directly demonstrated (Cousijn et al., 2010; de Quervain et al., 2007; Rasch et al., 2009). Just as amygdala activity influences allocation of somatic and attentional resources, activity of α_{2B} receptors is associated with both basic somatic and higher cognitive processes: At the somatic level these receptors play a role in vasoconstriction (Fava et al., 2009; Zhang et al., 2005), and the deletion variant has been found to be linked to increased diastolic blood pressure (Fava et al., 2009); at the level of higher cognition, the deletion variant may influence memory encoding and consolidation processes that enhance emotional memory (de Quervain et al., 2007). The finding that a gene regulating α_{2B} activity linked to vascular regulation also influences emotional memory is consistent with

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Proust's view of emotional memory as akin to involuntary bodily processes – although links between noradrenergic influences on vasoconstriction and emotional memory are strongly qualified by findings that central, but not peripheral, noradrenergic antagonists impair emotional memory enhancement (van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998).

In a seminal study by de Quervain et al. (2007), genetic samples were collected from 435 Swiss participants, who viewed neutral and emotionally arousing images (positive and negative) and rated them for intensity and valence. Following the encoding task they were asked to freely recall the images they had seen. As would be expected, all participants showed greater recall for arousing images; however, carriers of the deletion variant showed significantly greater emotional enhancement of memory than non-carriers. Memory was enhanced for both positive and negative images, suggesting *ADRA2b* facilitates memory processes related to arousal rather than valence. Following up on this research, an outstanding question about *ADRA2b* concerns whether the deletion variant enhances the vividness of emotional memory via noradrenergic enhancement of encoding or post-encoding consolidation. Because deletion carriers did not rate the emotional pictures as more arousing during encoding, the authors speculated that the primary influence was on consolidation processes. However, it is possible that participant ratings made seconds after viewing may not be sensitive to arousal-related enhancement of perception or selective attention occurring at a scale of milliseconds. Moreover, perceptual enhancement or increased selective attention to arousing images for deletion carriers might not result in the conscious experience of increased arousal captured by the rating scale.

Given the role of *ADRA2b* in enhanced emotional memory, the authors predicted that deletion variant carriers might be more susceptible to PTSD. They collected genetic samples from 202 refugees from the Rwandan civil war and examined the relationship between *ADRA2b* and PTSD symptoms (de Quervain et al., 2007). Regardless of the presence of PTSD, carriers of the deletion variant were more likely to experience intrusive traumatic memories. Yet they were not more likely to show other PTSD symptoms, such as hyperarousal or avoidance, suggesting the deletion variant has a selective effect on emotional memory. Finally, to examine the relationship between *ADRA2b* and amygdala activation, the same group collected fMRI data from 57 Swiss participants who again viewed emotionally arousing and neutral pictures and performed a free recall task 10 min after the scan (Rasch et al., 2009). Here there were no significant behavioral differences related to genotype, conceivably because of the considerably smaller *N*. Carriers of the deletion variant showed greater amygdala activation for arousing stimuli than non-carriers, indicating greater amygdala reactivity to emotional events. There were, however, no genotype-related differences in amygdala activation associated with subsequent memory for emotional stimuli. Although one cannot interpret null fMRI results, an interaction between genotype, arousal, and memory in the amygdala would provide important support for the authors' consolidation account of the influence of *ADRA2b* on emotional memory.

A recent study by Cousijn et al. (2010) provides convergent physiological support for the proposal that deletion variant carriers do *not* experience greater arousal at encoding than non-carriers. In order to measure the interaction of *ADRA2b* variant with the influence of transient environmental stress on amygdala activation, the authors showed participants violent movies (with a neutral movie control condition) and, following the stressor, showed participants blocks of dynamic fearful and happy faces. They then measured amygdala activation in response to the stressor movies as well as in response to the blocks of faces. In addition to subjective ratings of negative affect, they measured salivary cortisol, heart rate, and α-amylase. While there was no difference between deletion variant carriers and non-carriers in amygdala activation following the stressors, the groups did differ in amygdala activation to the face blocks: Deletion carriers showed increased amygdala response to emotional faces (both happy and fearful, again suggesting an arousal effect) following both stress and no stress conditions. In contrast, non-carriers showed amygdala responses to faces only in the non-stress condition. The authors suggest that whereas non-carriers may have reached a ceiling for amygdala reactivity under stress, carriers possess enough range to increase amygdala activation even when baseline levels are high. We suggest that increased activation following faces may reflect differences in sustained activation related to consolidation processes following stressor events. Finally, despite differences in amygdala responses to faces, there was no difference found between carriers and non-carriers using more "objective" peripheral physiological measures in response to the stressful movies. Again, this suggests that, under higher stress conditions, greater amygdala activation may be associated more with consolidation than enhanced perception of the event. For future research, more sensitive measures separating enhanced attention/perception of emotional stimuli and feelings of arousal at encoding are required.

An important caveat is that research on amygdala noradrenergic influence on emotional memory has focused on β-adrenergic processes. The *ADRA2b* deletion variant affects activity of α adrenoreceptors. The role of α adrenergic activity is more indirect, modulating the influence of β adrenoreceptors on memory (Ferry et al., 1999). Parallels between findings that *ADRA2b* variation is linked to amygdala responsiveness to emotional images (Rasch et al., 2009) and that arousal-enhanced amygdala responses at encoding are modulated by administration of the β adrenergic antagonist propanolol (Strange & Dolan, 2004; van Stegeren et al., 2005) are consistent with a putative indirect influence of *ADRA2b* on β adrenoreceptors. Finally, to date there is no direct evidence suggesting an influence of *ADRA2b* on enhanced encoding vs. consolidation processes. To directly test the hypothesis that the deletion variant facilitates enhancement of consolidation processes, future research can investigate the role of the *ADRA2b* on both emotionally enhanced attention/perception during emotional events and post-encoding arousal.

1.2. Dopaminergic influences on emotionally enhanced perception and memory

Pharmacological studies also indicate a role for dopamine in emotional memory formation. In non-human animals, inhibition of both D1 and D2 dopamine receptors in the amygdala has been found to inhibit fear conditioning, and evidence suggests that dopamine influences both consolidation and expression of conditioned fear (Greba, Gifkins, & Kokkinidis, 2001; Guarraci, Frohardt, & Kapp, 1999; Guarraci, Frohardt, Young, & Kapp, 1999). In humans, administration of dopamine antagonist amisulpride (which blocks D2/D3 receptors) impaired the memory advantage for emotional stimuli (Gibbs, Naudts, Spencer, & David, 2007). It did not impair the attentional advantage for emotional stimuli measured by an emotional AB task, suggesting a potential role for dopamine in arousal-related consolidation rather than encoding.

A uniquely human valene (val) to methionine (met) substitution (val158met) in the gene regulating Catechol-*O*-methyltransferase (COMT), an enzyme involved in degradation of dopamine in the prefrontal cortex (PFC) as well as degradation of NE, has been linked to both emotionally enhanced perception and memory among numerous other characteristics. Individuals with two copies of the met allele (met/met) have 25–75% less COMT enzyme activity, resulting in higher levels of extracellular dopamine (DA) in the PFC, than those with two copies of the val allele (val/val) (Chen, Lipska, et al., 2004). In contrast, the ancestral val variant is associated with

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lower levels of prefrontal DA, but more DA uptake in the midbrain (Akil et al., 2003; Meyer-Lindenberg et al., 2005). Met/met carriers generally perform better than val/val carriers in tasks requiring working memory (Egan et al., 2001; Raz, Dahle, Rodrigue, Kennedy, & Land, 2009; Weinberger et al., 2001), a behavioral advantage that is reflected in lower levels of prefrontal activation during working memory tasks (Bertolino et al., 2006; Dennis et al., 2010); however, the met/met genotype has also been associated with behavioral rigidity (Drabant et al., 2006), anticipatory worry (Enoch, Schuckit, Johnson, & Goldman, 2003), and obsessive compulsive disorder (Karayiorgou et al., 1999).

It has been established that DA modulates amygdala reactivity to emotional stimuli in humans (Hariri et al., 2002; Tessitore et al., 2002), and the met allele is associated with increased amygdala-mediated processing of emotional – and particularly threatening – stimuli. Carriers of the *COMT* met/met variant show greater amygdala activation in response to arousing negative, but not equally arousing positive, scenes (Smolka et al., 2005), and the degree of amygdala activation has been found to be correlated with the number of met alleles (Heinz & Smolka, 2006). The met allele is also associated with increased startle responses to aversive stimuli and behavioral inhibition (Montag et al., 2008). Overall the selectivity of these responses to aversive stimuli suggests the effects of the allele are valence or threat specific. Research also suggests that *COMT* val158met interacts in an additive fashion with other polymorphisms to enhance perception of threatening stimuli (Smolka et al., 2007). In particular, because COMT is also implicated in NE degradation, *COMT* influences on enhanced emotional processing may also involve NE systems.

COMT-related differences in amygdala activation to threat have *not* been associated with differences in subjective arousal ratings when stimuli are first viewed (Smolka et al., 2005). Moreover, blocking dopamine receptors does not influence performance on an emotional AB task (Gibbs et al., 2007), again suggesting a putative influence on emotional memory would work by enhancing consolidation processes. Nonetheless, carriers of the met/met variant have been found to show enhancement of a relatively early (between 200 and 300 ms) event related potential [ERP] component associated with enhanced perceptual processing, known as the early posterior negativity (EPN), as well as a response bias to arousing stimuli (Herrmann et al., 2009). The relatively short latency of this difference suggests that the *COMT* met allele may nonetheless enhance the perceptual experience of an emotional event.

Mechanisms by which *COMT* influences attentional and perceptual processes are not yet fully understood. Dopamine storage in the amgydala is positively correlated with BOLD response (Kienast et al., 2008), and animal research suggests dopamine influences amygdala function by reducing inhibitory input from the PFC and enhancing excitatory input from sensory cortices (Rosenkranz & Grace, 2002). It has been suggested that the met allele is associated with greater *COMT* expression, and therefore higher dopamine levels in the amygdala (Herrmann et al., 2009). Yet although *COMT* is expressed in the human amygdala, it is expressed less there than in many other brain regions (Hong, Shu-Leong, Tao, & Lap-Ping, 1998), and met/met has been primarily associated with higher tonic levels of *prefrontal* dopamine (Bilder, Volavka, Lachman, & Grace, 2004). Consistent with a *COMT* influence on prefrontally mediated-processes, the met allele has been associated with reduced capacity to flexibly update and shift attention, resulting in an inability to disengage attention from stimuli associated with threat (Bishop, Cohen, Fossella, Casey, & Farah, 2006; Herrmann et al., 2009). It has also been associated with reduced capacity for extinction following fear conditioning (Lonsdorf et al., 2009). Thus, the influence of *COMT* genotype on enhanced amygdala processing of threat may result from differences in prefrontally mediated regulatory processes.

Whereas links between *COMT* and enhanced amygdala response to threat have been solidly established, there is less evidence linking the *COMT* val158met polymorphism with emotionally enhanced memory. Initially the met/met variant was associated with greater executive function/working memory rather than emotionally enhanced memory (e.g., Egan et al., 2001). However, a recent study found an interaction between *COMT* and *ADRA2b* in modulating memory for both arousing and neutral images (Gibbs, Naudts, Azevedo, & David, 2010). In this study, participants viewed neutral and negative arousing images and were given a recognition memory test one week later. Participants who were homozygous for the val allele (val/val) who were not carriers of the deletion variant showed relatively poorer memory for all items compared to all other participants, suggesting that for val/val carriers, possessing the deletion variant may mitigate memory impairments associated with *COMT* genotype. While this data is suggestive, more research on the influence of *COMT* genotype on emotional memory as well as other types of memory, using larger sample sizes and more refined measures, is required.

1.3. Serotonergic influences on emotionally enhanced perception and memory

Serotonin has also been linked to emotionally enhanced memory. Research in non-human animals implicates serotonergic systems in fear conditioning (for review see Buhot, Martin, & Segu, 2000). In humans, administration of citalopram, a serotonin reuptake inhibitor, abolished potentiated startle following negative images and increased episodic memory for positive relative to negative stimuli (Harmer et al., 2004). Conversely, acute tryptophan depletion (tryptophan is a 5HT precurser) has been found to impair delayed memory recall for positive and neutral, but not negative, words (Klaassen, Riedel, Deutz, & Van Praag, 2002) (for review see Merens, Willem Van der Does, & Spinhoven, 2007). These results suggest that serotonergic influences on emotional memory are sensitive to valence.

Two polymorphisms influencing serotonergic processes have been linked to enhanced perceptual processing of emotionally arousing images and to temperamental anxiety: a short version of the *5HTTLPR* serotonin transporter gene, which is associated with higher serotonin levels, and a SNP in the *TPH2* gene coding the first phase of serotonin synthesis from tryptophan.

1.3.1. 5HTTLPR

The short version of the *5HTTLPR* gene is associated with higher levels of neuroticism and harm avoidance (Lesch et al., 1996; Munafo, Clark, & Flint, 2005) and attentional bias to negative stimuli (Canli, Ferri, & Duman, 2009). Carrying the short allele interacts with life stress to influence vulnerability to clinical anxiety and depression (Canli et al., 2006; Fox et al., 2005), and is associated with panic disorder (Maron, Hettema, & Shlik, 2010) and altered patterns of emotion regulation (Canli & Lesch, 2007). It has been robustly linked to enhanced amygdala activation in response to negative facial emotion (Dannlowski et al., 2009; Hariri & Weinberger, 2003) and other threatening stimuli (Munafo, Brown, & Hariri, 2008). However, the *tonic model* (Canli et al., 2005, 2006) challenges this interpretation, pointing to evidence that heightened amygdala reactivity in short allele carriers reflect decreased activation to neutral stimuli rather than increased activation to negative stimuli, possibly reflecting greater tonic amygdala activation in short allele carriers. There is also evidence that the short *5HTTPLPR* allele is associated with altered patterns of amygdala–prefrontal connectivity, mediating prefrontal regulation of amygdala activity (Heinz et al., 2005; Pezawas et al., 2005). Importantly, short allele carriers show greater conditioned startle potentiation than non-carriers, suggesting a role for *5HTTLPR* in

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emotional learning, whereas *COMT* variation has not been found to predict the acquisition of fear conditioned responses (Lonsdorf et al., 2009).

1.3.2. TPH2

A more recently discovered polymorphism in the *TPH2* gene has found to have similar effects on amygdala responses to emotional stimuli (Canli, Congdon, Todd Constable, & Lesch, 2008). An additive effect has been found for *TPH2* and *5HTTLPR* for the same early posterior negative ERP component (EPN) that is modulated by *COMT* genotype. Like the *COMT* met allele, the T variant of *TPH2* and the short variant of *5HTTLPR* predict a larger EPN for arousing images (Herrmann et al., 2007). At a latency of ~240 ms, the timing of this occipital ERP component is consistent with a time-course required for altered perceptual processing following meaning extraction from a complex visual scene. Although it has been plausibly suggested that this EPN effect is due to amygdala modulation of visual processing, to the best of our knowledge there is no direct evidence to support that hypothesis. Although all three polymorphisms influence perceptual processing at ~240 ms, suggesting a similar role in enhancement of emotional processing, the *COMT* met allele and the short *5HTTLPR* allele have often been associated with biased response to negative stimuli. In contrast, carrying the T variant of *TPH2* is associated with heightened amygdala response to both positive and negative stimuli. Thus, whereas all three polymorphisms may enhance perceptual processing, amygdala sensitivity to valence vs. arousal may depend on the neuromodulator system mediating the response.

Despite evidence linking these serotonergic polymorphisms to enhanced emotional perception, which may in turn be linked to emotional memory, there is, to our knowledge, no direct evidence of an effect on emotionally enhanced memory. Importantly, only *5HTTLPR* has been associated with fear learning, suggesting an influence of serotonin on emotional memory – at least for non-declarative forms of memory. However, Strange, Kroes, Roiser, Tan, and Dolan (2008) found that, whereas carriers of the short allele did *not* show enhanced memory for negative words in a free recall task given shortly after encoding, they *did* show a larger effect of retrograde amnesia for neutral words directly preceding emotional words. This suggests that the allele influences arousal effects on post-perceptual memory processes in a manner that resembles dose effects of higher levels of NE. Future studies can test *5HTTLPR* influence on recall following longer intervals (e.g., 24 h to one week), as well as investigating the influence of *5HTTLPR* on consolidation and reconsolidation processes (Dudai & Eisenberg, 2004; Nader, Schafe, & Le Doux, 2000; Schiller et al., 2010) implicated in specific aspects of emotional memory.

In summary, evidence to date supports a model wherein amygdala sensitivity to salient stimuli may vary according to genetic variations influencing the contributions of specific neuromodulatory systems. Based on this evidence, we hypothesize that serotonergic processes linked to amygdala discrimination of valence or arousal, depending on the gene, contribute to heightened emotional perception. In contrast, noradrenergic processes mediated by *ADRA2b* may play a role in arousal-enhanced post-encoding processes mediated by amygdala influence on hippocampal activity. Finally, we propose that differences in prefrontal dopamine mediated by the *COMT* gene may modulate prefrontally-driven regulatory processes that in turn influence amygdala activity linked to enhanced modulation of hippocampal consolidation (Fig. 1). However, evidence suggesting the role of each of these polymorphisms in each stage of emotional memory mixed and these hypotheses will need to be directly tested.

2. Other polymorphisms associated with episodic memory

Contrasting effortful retrieval processes with embodied and involuntary aspects of memory, Proust pointed out, "It is the same with our past. It is a waste of effort for us to try to summon it; all the exertions of our intelligence are useless. The past is hidden outside the realm of our intelligence and beyond its reach, in some material object (in the sensation that this material object would give us) which we do not suspect" (Proust, 1913: 2002). We suggest that the genetic polymorphisms influencing amygdala activation, reviewed above, may contribute to the effortless sensory quality of emotional memory via a system that is at least partly independent of more effortful fronto-hippocampally mediated processes. This proposal is supported by evidence that variations in the *ADRA2b* gene fail to predict memory for neutral items (de Quervain et al., 2007), just as adrenergic agonists enhance access to awareness selectively for emotional but not neutral events (De Martino et al., 2008). Yet counter to Proust's introspective observations of the nature of memory, there is also evidence that encoding of remembered emotional events is not entirely effortless. Memory for arousing events has been associated with activity in frontal regions that mediate explicit semantic elaboration at encoding (Dolcos, LaBar, & Cabeza, 2004), although differences in the degree of memory rehearsal have been found insufficient to account for differences in emotional memory (Guy & Cahill, 1999). Moreover, convergent evidence suggests that amygdala-centered systems implicated in emotionally enhanced memory are at least partly independent of frontally mediated voluntary memory. For example, activity in frontal–hippocampal networks, associated with controlled encoding processes, predicts memory for less arousing events (Kensinger & Corkin, 2004). These networks are functionally distinct from amygdala–hippocampal networks which are active during encoding of highly arousing events (Kensinger & Corkin, 2004). Thus, the fate of neutral and even low arousal emotional memories may be influenced more by prefrontally mediated semantic associations on hippocampal activity. Finally, developmental evidence indicates that, whereas numerous aspects of explicit memory and executive function decline with age, emotional memory remains relatively preserved (Denburg, Buchanan, Tranel, & Adolphs, 2003), again suggesting partial independence of emotional memory systems.

Based on laboratory evidence of partial independence of emotional memory systems, we have focused on polymorphisms associated with effects of arousal on emotional memory. However, there is growing evidence that, at the level of brain systems, emotion and cognition cannot be fully disembedded (Lewis, 2005; Pessoa, 2008). In keeping with this view, probes of naturalistic autobiographical memory (Levine, 2004; Levine et al., 2002) suggest that in daily life other aspects of memory, primarily mediated by fronto-hippocampal and temporal networks, may work in tandem with amygdala systems to contribute to memory vividness. Thus, whereas all of the polymorphisms reviewed above are associated with altered amygdala activation, and may contribute to aspects of emotional memory, some of these and other genes also modulate hippocampal and prefrontal regions, with associated effects on episodic memory. Additional genes, which we will briefly review, include a (Val to Met) SNP in the *BDNF* gene (Val66Met), a (His to Try) SNP in the *HTR2A* gene (His452Try), the $\varepsilon 4$ variant of the *APOE* gene, and a (T to C) SNP in the *KIBRA* gene.

The *BDNF* gene is involved in hippocampal synaptic plasticity and long-term potentiation (Huang, Kirkwood, Pizzorusso, Porciatti, Morales, & Bear, 1999; Lu, 2003). At the molecular level, the Val66Met polymorphism is associated with reduced secretion of brain-derived neurotrophic factor (BDNF), a protein promoting neuron survival and growth, in the hippocampus (Chen, Patel, et al., 2004; Egan et al., 2003). Carriers of this variant show reduced episodic memory performance (Egan et al., 2003; Goldberg et al.,

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2008; Hariri et al., 2003) [although see (Harris et al., 2006; Strauss et al., 2004) for inconsistent findings]. Carriers also show altered structure and function in brain regions associated with episodic memory formation and retrieval. They have reduced neuronal integrity in the hippocampus (Egan et al., 2003), as well as smaller hippocampal volume (Bueller et al., 2006; Pezawas et al., 2004; Szeszko et al., 2005), abnormal hippocampal activation (Hariri et al., 2003), and smaller prefrontal cortex volumes (Pezawas et al., 2004).

A (His to Try) SNP in the *HTR2A* gene (His452Try) is related to reduced function of the serotonin 2A receptor. Carriers of this variant also show reduced episodic memory performance (de Quervain et al., 2003; Reynolds, Jansson, Gatz, & Pedersen, 2006; Sigmund, Vogler, Huynh, de Quervain, & Papassotiropoulos, 2008; Wagner, Schuhmacher, Schwab, Zobel, & Maier, 2008), and reduced brain volume in the temporal lobes and hippocampus (Filippini et al., 2006). More recently additional episodic memory-related variants have been identified within *HTR2A* gene (Sigmund et al., 2008).

The *APOE* gene, which is responsible for lipoprotein metabolism (Mahley, 1988), has also been associated with episodic memory. Carriers of the ε4 allele of the APOE gene again show reduced performance on episodic memory tasks (De Blasi et al., 2009; Deary et al., 2002; Nilsson et al., 2006; Wikgren et al., 2010), although there have been conflicting results for APOE (Bennett et al., 2005; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Savitz, Solms, & Ramesar, 2006). This allele is also associated with differences in structure and function consistent with poorer episodic memory, including reduced hippocampal volume (Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Plassman et al., 1997) and reduced medial temporal lobe function during mnemonic tasks (Borghesani et al., 2008; Kukolja, Thiel, Eggermann, Zerres, & Fink, 2010). Moreover, carrying the ε4 allele increases an individual's risk fourfold for developing late-onset Alzheimer disease (Bondi et al., 1999; Corder et al., 1993), in which episodic memory loss is a defining feature. Some research suggests that the effects of ε4 on cognitive performance are primarily due to a greater prevalence of preclinical Alzheimer's disease participants in ε4 groups. Indeed, studies have shown that the effects of ε4 on episodic memory are greatly reduced or diminished when Alzheimer's disease is accounted for (Bennett et al., 2005; Bondi et al., 1999; although see (Deary et al., 2002). Additional studies in healthy subjects are needed to determine the nature of the relationship between APOE, cognition and disease.

Finally, the *KIBRA* gene has recently been associated with episodic memory performance in a replicated genome-wide association study (Papassotiropoulos et al., 2006). Specifically, carriers of a (T to C) SNP in this gene show enhanced episodic memory performance in comparison to non-carriers (Papassotiropoulos et al., 2006). Although this association has been replicated in subsequent studies, conflicting results have also been found (e.g., Need et al., 2008). *KIBRA* is most highly expressed in sub regions of the hippocampus and temporal lobes (Johannsen, Duning, Pavenstadt, Kremerskothen, & Boeckers, 2008; Papassotiropoulos et al., 2006). Non-carriers of the T-allele show increased activity in the hippocampus and other regions during episodic memory when behavioral performance is matched to that of T-allele carriers (Papassotiropoulos et al., 2006), suggesting that non-carriers require increased hippocampal processing to achieve the same level of performance as T-allele carriers. Recent research suggests that *KIBRA* may interact with other genes to modulate episodic memory performance (Hintsch et al., 2002). The interactive effects of multiple genetic variants may account for some inconsistent findings and will need to be explored further in relation to episodic memory (de Quervain & Papassotiropoulos, 2006).

Whereas the studies reviewed above established links between specific genotypes and episodic memory in general, the goal of future research is to delineate more carefully the influence of these genotypes on stages of memory formation and retrieval as well as different sub-processes that influence episodic memory (e.g., vividness, emotion, etc.). Although some effort has been made to investigate, more specifically, some of these factors (e.g., Bates et al., 2009; Chen, Lipska, et al., 2004; Chen, Patel, et al., 2004; de Quervain et al., 2003; Egan et al., 2003; Hariri et al., 2003; Preuschhof et al., 2010; Sigmund et al., 2008; Wagner et al., 2008), this research has focused on laboratory material to probe episodic memory. Employing more naturalistic autobiographical stimuli, with a greater reliance on memory vividness, may provide a more sensitive and ecologically valid measure of episodic memory, which is relevant given the small effect sizes that plague genetic studies of cognition.

3. Conclusions

Proust conjectured that vivid, emotionally laden memories are more closely linked to automatic bodily processes than the higher-order meaning-making systems that drive voluntary memory. That is, emotional memories reconstitute the personal past through the vehicle of the body and its sensory engagement with the world beyond voluntary control (Thompson, 2007). The genetic polymorphisms reviewed in this paper, which influence activity of neurotransmitters linked to emotional memory, are all associated with individual differences in amygdala responses to salient events. We suggest that the amygdala's role in formation of emotional memories contributes to a relatively involuntary type of memory that, as Proust suggested, is embodied, tangible, and sensorily vivid. This view of amygdala-mediated memory is distinguished from other aspects of memory driven more by prefrontal influences on hippocampal activity.

Anatomical support for the Proustian view can be found in evidence that the amygdala has been found to be anatomically linked to all but eight cortical structures (Young, Scannell, Burns, & Blakemore, 1994), and is thus neuroanatomically optimally located to integrate information from the body and the world. In addition to its influence on hippocampal memory consolidation (Roozendaal et al., 2009) it may influence perceptual processing via structural and functional links with multiple levels of the ventral visual stream (Amaral, Behniea, & Kelly, 2003; Anderson & Phelps, 2001; Lim et al., 2009). Via connections to the brainstem, the amygdala can also evoke basic action repertoires (such as freezing and startle responses and facial actions linked to emotional expression) and trigger changes in heart rate, blood pressure, galvanic skin response, corticosteroid release, pupil dilation, and respiration (Davis & Whalen, 2001). Thus, connections from the amygdala to hypothalamus and brainstem facilitate activation of the body's automatic response systems, connections from the amygdala to sensory systems facilitate enhanced sensory processing, and connections to the hippocampus and PFC provide an architecture that can support the embodied sensuality of emotional memory. These emotional effects promote richness of episodic memory that is associated with multisensory recollective processes. In turn, it is likely that polymorphisms influencing more effortful aspects of episodic memory combine with those primarily implicated in emotional memory in both an additive and interactive fashion, further contributing to individual differences in episodic memory recall.

New findings on genetic influences on emotional encoding and memory open the possibility of understanding genetic foundations of an evolutionarily conserved emotional memory system – one that may emerge earlier in development and resist decline in old age. Such a genetically endowed motivated memory system ensures that memory retention is modulated by memory importance (Cahill & McGaugh, 1998). Yet such a system is always modulated – and modulates – newer, PFC influences on mnemonic

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processes. An important area of future research will involve mapping developmental trajectories of these genetic influences. This includes various aspects of motivated encoding, consolidation, reconsolidation, and retrieval, and the brain networks that mediate them, across the lifespan.

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