

Olfaction, Emotion & the Amygdala: arousal-dependent modulation of long-term autobiographical memory and its association with olfaction: beginning to unravel the Proust phenomenon?

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The sense of smell is set apart from other sensory modalities. Odours possess the capacity to trigger immediately strong emotional memories. Moreover, odorous stimuli provide a higher degree of memory retention than other sensory stimuli. Odour perception, even in its most elemental form - olfaction - already involves limbic structures. This early involvement is not paralleled in other sensory modalities. Bearing in mind the considerable connectivity with limbic structures, and the fact that an activation of the amygdala is capable of instantaneously evoking emotions and facilitating the encoding of memories, it is unsurprising that the sense of smell has its characteristic nature.

The aim of this review is to analyse current understanding of higher olfactory information processing as it relates to the ability of odours to spontaneously cue highly vivid, affectively toned, and often

very old autobiographical memories (episodes known anecdotally as Proust phenomena). Particular emphasis is placed on the diversity of functions attributed to the amygdala. Its role in modulating the encoding and retrieval of long-term memory is investigated with reference to lesion, electrophysiological, immediate early gene, and functional imaging studies in both rodents and humans. Additionally, the influence of hormonal modulation and the adrenergic system on emotional memory storage is outlined. I finish by proposing a schematic of some of the critical neural pathways that underlie the odour-associated encoding and retrieval of emotionally toned autobiographical memories.

Key Words: Olfaction; Emotion; Proust phenomenon; Amygdala.

Introduction

“Smell is a potent wizard that transports us across thousands of miles and all the years we have lived... odours, instantaneous and fleeting, cause my heart to dilate joyously or contract with remembered grief.” Helen Keller (blind and deaf educator, 1880-1968)

This quotation articulates a neurophysiological interaction between the systems of olfaction, emotion and memory. Hughlings Jackson (1880), arguably the founder of neurology as a science, termed this kind of forced reminiscence as *“a doubling of consciousness.”* This occurrence is not uncommon during attacks of migraine or

epilepsy, in states of hypnosis or psychosis, and, less radically, in everybody in response to the mnemonic stimulus of certain words, sounds, scenes, and especially smells. Odours are rarely perceived in a purely objective and neutral way, often being loaded with appealing or repugnant feelings. Olfactory pathways involve anatomical structures that are also heavily implicated in emotion and memory. The amygdala is one such structure. The challenge is to propose a model of the neural mechanisms that underlie encoding and retrieval of odour-cued emotionally toned autobiographical memories (see figure one).

Proust Phenomena

The ability of odours to spontaneously cue highly vivid, affectively toned, and often very old autobiographical memories is known as the Proust phenomenon (Chu & Downes, 2000) and is derived from the experiences of Proust himself (1922):

“And soon, mechanically, weary after a dull day with the prospect of a depressing morrow, I raised to my lips a spoonful of tea in which I had soaked a morsel of cake. No sooner had the warm liquid, and the crumbs with it, touched my palate than a shudder ran through my whole body, and I stopped, intent upon the extraordinary changes that were taking place...I was conscious that it was connected with the taste of tea and cake, but that it infinitely transcended those savours, could not, indeed, be of the same nature as theirs.”

Such experiences are not limited to the realm of artistic license. A survey by the National Geographic (Gilbert & Wysocki, 1987) gave readers a set of six odours on scratch-and-sniff cards. From a sample of 26 200 (taken randomly from >1.5 million responses), ~55% of respondents in their 20s reported at least one emotional memory cued by one of the six odours.

Studying odour-cued memories

Many of the approaches used could be described as experiments in odour-cued context-dependent memory rather than autobiographical memory. Context-dependent memory is the effect whereby retrieving information in the same environment in which

it was encoded results in a better memory performance than encoding and retrieving in different contexts (Eich *et al.*, 1985). Schab (1990) used ambient odour as a context, demonstrating that reinstating the same odour at test as that present at study appears to improve memory performance in humans over conditions where the ambient odour is not reinstated at test. By manipulating odours that were appropriate or inappropriate to a situation, Herz (1997) has also shown in humans that distinctive odours result in greater context effects.

These studies indicate that ambient odours present at the time of an event can be encoded in parallel with event details and consequently be used as cues in the retrieval of those event details. The types of memory commonly reported in connection with Proust phenomena are typically especially vivid, emotional and old. Therefore, several critical aspects of these studies do not address the core of Proustian phenomena. Firstly, the age of experiences is limited to time between study and test (typically only a few minutes). Secondly, investigators predetermine the target event, instead of allowing a subject to freely select an autobiographical episode that comes to mind in response to an odour. Lastly, the subject is not always made aware of the presence of the odour during the retrieval phase. Most examples of Proustian recall involve an awareness of the odour.

For empirical substantiation, other paradigms that more closely match the Proustian situation must be applied. In the standard paired-associate learning paradigm, odours and other stimuli are associated with target information. Later, the efficacy of each cue type is compared in a cued recall test. Herz and

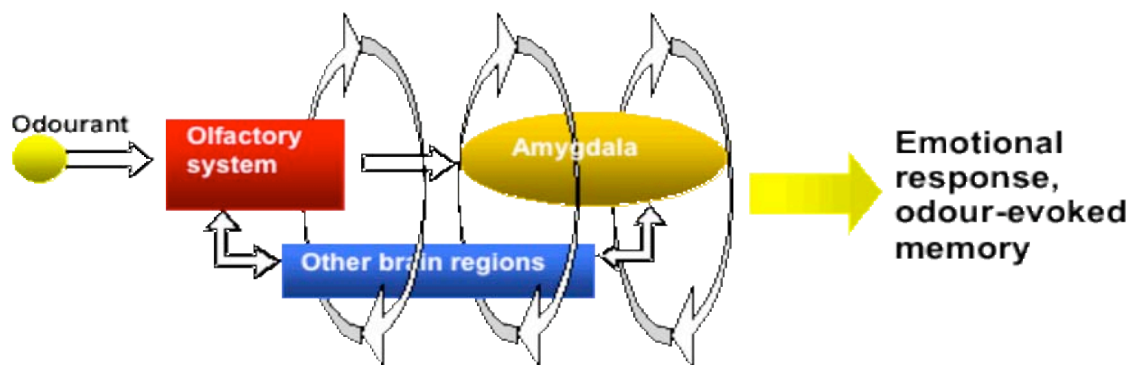


Figure 1 Simplified schematic illustrating neuroanatomical and systems-level interactions during the generation of odour-evoked emotional memories.

Cupchik (1995) asked subjects to associate odours or odour labels with emotional paintings. Later, they were presented with the odours or words and asked to describe the painting with which each had been associated. A higher degree of emotional tone was found in the recollections of paintings cued by odours than those cued by words. Here, subjects are actively using odour as an aid to retrieval of a past experience. However, autobiographical memories are usually formed through a passive encoding process: separate experiential aspects of an incident become associated without any purposeful effort on the part of the subject. Therefore, there are likely to be key differences in the underlying processes recruited during encoding (and the nature of the resulting mnemonic representation) in the above study as compared with naturally acquired autobiographical memories.

Examination of ‘true’ autobiographical memories

Owing to problems of quantitative measurement and application of close experimental controls, only a limited number of studies exist which have directly examined Proustian phenomena.

Laird (1935) wrote about a survey of odours ‘*as revivers of memories and provokers of thoughts in 254 living men and women of eminence.*’ More than four out of five of those surveyed reported olfactory-cued memory experiences that were described as vivid, emotional and old. 76% of women and 46% of men reported that odour-cued memories were amongst their most vivid with only 7% of women and 14% of men describing these memories as hedonically neutral.

Contemporary studies employ more scientific and empirical approaches, for example the single-cue comparison method. Data is collected on memories that are retrieved in response to odours and are directly compared with those retrieved in response to stimuli from other sensory modalities. Rubin *et al.*, (1984) found that odour-cued memories were thought of and spoken of with less frequency than those cued by other stimuli. Contrary to Proustian expectations, no differences were found between different cue types, and

analysis of the pleasantness of memories yielded mixed and inconclusive results.

Herz and Cupchik (1992) aimed to formulate a characterization of odour-evoked memories rather than compare the efficacy of different cue types. Their results characterize odour-evoked memories as highly emotional, vivid, specific, rare, and relatively old but leave unanswered the question as to whether odour-evoked memories are, for example, *more* emotional. Herz and Schooler (2002) have now answered this question. The emotional and evocative qualities of autobiographical memories cued by odours and visual cues were compared using a new repeated measures paradigm. Results demonstrated that memories evoked in the context of odours were significantly more emotional than those recalled in the context of the same cue presented visually and by the verbal label for the cue. This is the first unambiguous demonstration that naturalistic memories evoked by odours are more emotional than those evoked by other cues.

Aggleton and Waskett (1999) provided an excellent demonstration of the potency of olfactory cues. Their experiment focused on a display at a Viking museum (York) in which unusual odours were used to enhance the impact of the display. They asked whether representing these Viking odours to individuals who had visited the museum a number of years ago would allow them to remember more about the display than those presented with non-Viking odours or a no-odour control group. Mean memory performance for those receiving the Viking odour was numerically higher than for those receiving the non-Viking odour and the no-odour control group. However, due to the expected large variation in performance, the difference failed to reach statistical significance.

This type of study design is getting closer to a fully ecologically valid approach to Proustian phenomena. Naturally occurring experiences are used and the association between experience and ambient odour is passively formed. Several clear-cut results strongly support the proposition that odours *are* effective reminders of autobiographical experience.

The apparent emotional, vivid and deep-rooted nature of odour-evoked memories can be explained by two hypotheses. (1) The ‘differential cue affordance value’ hypothesis

suggests that different sensory modalities vary in terms of cue affordance value (or the efficiency with which they access autobiographical event details). Olfactory cues are assumed to have a higher cue affordance than other cue types. (2) The ‘differential encoding bias’ hypothesis proposes that cues do not differ in terms of their efficacy in *retrieving* event details, but in terms of the *types of event* with which they become associated and consolidated in memory. Olfactory details may become associated only, or preferentially, with more complex (emotional, personal, and unusual) autobiographical episodes. Consequently, the presentation of an olfactory cue will bias retrieval towards more complex episodes.

The encoding specificity principle (Tulving & Thomson, 1973) proposes that consolidated memory traces include not only target information, but also salient contextual features in the immediate environment in which the episode was experienced. Later presentation of such contextual features (which include odours) can therefore act as retrieval cues for related details that comprise the original episode. If this alone were the case, then all cue types would function in the same manner and with equal effectiveness. However, assuming the superior ability of olfactory cues to evoke emotional autobiographical memories, encoding specificity alone does not provide a satisfactory explanation. Here lies the challenge.

Olfaction is mediated by a number of anatomical structures that are also heavily implicated in emotion and memory. The olfactory bulb, for example, projects to structures including the amygdala, hippocampus, and thalamus. These structures have been shown to be involved in memory function and the modulation of emotions. Proustian effects may also be linked to the ability of odours to elicit affective reactions. Hinton and Healey (1993) compared reactions to stimuli presented in visual, lexical, and olfactory modalities. Odours elicited by far the most affective reactions.

Some (Herz, 1997; Aggleton & Waskett, 1999) have ascribed the efficacy of odours in memory retrieval, at least partially, to the acknowledged connection between emotional arousal and the information associated with such affective reactions. This link is expected

to be mediated by the action of the amygdala (Cahill *et al.*, 1995, 1996).

Now equipped with a behavioural background to odour-cued emotional memory, we move on to analyse the subject from a neurobiological perspective.

The amygdala and olfactory processing

The amygdala refers to a highly differentiated region near the temporal pole of the mammalian cerebral hemisphere. Burdach discovered and named the amygdala nucleus in the early nineteenth century (Burdach, 1819-1822). Subsequent microscopic examination began to reveal a progressively complex structural differentiation. The extent of the amygdala’s outer border, and the number and classification of its subdivisions, remains controversial today. Swanson and Petrovich (1998) suggest that the amygdala is neither a structural nor a functional unit. One part is a specialized ventromedial expanse of the striatum, a second part is caudal olfactory cortex (nucleus of the lateral olfactory tract, cortical nucleus, and postpiriform and piriform-amygdalar areas) and a third part is a ventromedial extension of the claustrum.

Cell groups within the amygdala are derived from different regions: their connectivity and the distribution of neurotransmitters within each grouping form the basis of differentiation. Consequently, different groups can be distinguished functionally into four obvious systems – accessory olfactory, main olfactory, autonomic and frontotemporal cortical.

The amygdala receives highly processed sensory data and is in a position to integrate this data both within and across modalities. The only sensory modality with *direct* access to the amygdala is smell (see figure two). All other modalities connect with the amygdala via a series of sensory association cortices. The amygdala can also influence autonomic, hormonal and motor function via its subcortical connections.

Amygdala involvement in non-pheromonal forms of olfactory related behaviour

Lesion studies involving rodents: Combined electrolytic lesions of the posterior lateral olfactory tract and anterior amygdala in rats showed no effect on the retention or learning of new olfactory discrimination tasks (Slotnik, 1985). Bilateral amygdala lesions showed no effect on learning of multiple odour discriminations (Eichenbaum *et al.*, 1986). Failure of amygdala lesions to result in impaired performance seems surprising given

tests used to date must lack the requisite specificity to pick up amygdala-dependent aspects of olfactory function.

Electrophysiological studies: In one study 229 neurons were recorded in the lateral and basolateral nuclei of rats during olfactory discrimination learning (Schoenbaum *et al.*, 1999). Of these, 60 were found to show selective responses depending on whether a particular olfactory cue was paired with a pleasant or an unpleasant outcome. Selectivity often occurred early in learning and many units could be reversed, indicating that the amygdala neurons encoded the motivational significance of the cues.

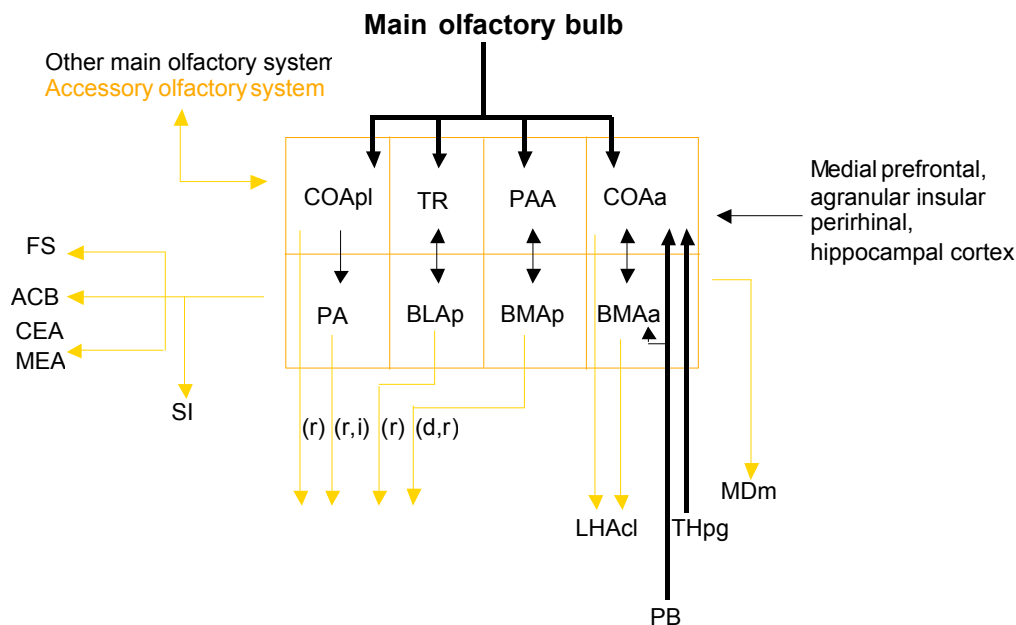


Figure 2 Major neural inputs and outputs of the main olfactory system as they relate to the rat amygdala (adapted from Swanson and Petrovich, 1998). Abbreviations: ACB, nucleus accumbens; BLAp, basolateral nucleus amygdala, posterior part; BMAa,p, basomedial nucleus amygdala, anterior, posterior parts; CEA, central nucleus amygdala; COAa,pl, cortical nucleus amygdala, anterior part, posterior part, lateral zone; d, medial hypothalamic defensive behavior system; FS, fundus of the striatum; i, medial hypothalamic ingestive behaviour system; LHAcl, lateral hypothalamic area, caudolateral part; MDm, mediodorsal nucleus thalamus, medial part; MEA, medial nucleus amygdala; PA, posterior nucleus amygdala; PAA, piriform-amygdala area; r, medial hypothalamic reproductive behavior system; SI, substantia innominata; THpg, thalamus, perigeniculate region (includes medial geniculate complex, posterior limiting nucleus, and parvicellular subparafascicular nucleus); TR, postpiriform transition area.

the extensive connections of the olfactory system illustrated previously and the finding that approximately 40% of rat amygdala neurons respond to olfactory stimuli (Cain & Bindra, 1972). The lack of obvious deficits appears to be caused, in part, by the existence of parallel olfactory inputs to other regions that are able to counterbalance the destruction of amygdala olfactory routes. The olfactory

Immediate Early Gene (IEG) studies: *c-fos* imaging data supplements evidence for involvement of the basolateral amygdala (BLA) as olfactory learning progresses (Hess *et al.*, 1997). Different stages of olfactory discrimination learning by rats were compared. Initial exploration (no specific odours) led to raised medial (medial, anterior, and posterior cortical nuclei) and, to a lesser extent, raised

basolateral activation. In contrast, central nucleus levels stayed low. Following initiation of cued olfactory discrimination training there was high basolateral but relatively low medial activation. In over-trained rats, the differences in these amygdala regions were reduced. Balance of amygdala activation shifts in a dynamic manner that depends on the demands of the task and upon the stages of learning.

Lesion studies involving primates: The contribution of the primate amygdala, and in particular the human amygdala, to olfactory processing remains poorly understood. Group studies have shown that comprehensive, unilateral temporal lobectomies can confuse olfactory identification (Rausch & Serafetinides, 1975) and the recall of odours (Rausch *et al.*, 1977). However, these experiments provide limited direct evidence for the specific involvement of the amygdala. As a rule, studies recording the effects of surgery to remove just the amygdala or parts of the amygdala have described no disruption to the sense of smell (Scoville *et al.*, 1953; Narabayashi, 1977), though these studies lack proper test details. A more systematic study has investigated odour discrimination in three groups of unilateral temporal lobe resection cases where the site of surgery was classed as either (1) primarily neocortical, (2) amygdalohippocampectomy, or (3) anterior temporal lobe with impingement on the amygdala or hippocampus (Jones-Gotman *et al.*, 1997). All three groups were impaired, although no clear correlations could be drawn between the presence of an impairment and amygdala damage.

Human electrophysiological studies: These have confirmed the responsiveness of amygdala neurons to odours (Andy & Jurko, 1975) and shown that amygdala activity can lead to olfactory auras (Andy *et al.*, 1975). A small body of single-case clinical studies also implicates the amygdala in aspects of olfactory processing. One case involves a woman who had received an extensive, bilateral amygdalotomy that had involved the entorhinal cortex in one hemisphere (Andy *et al.*, 1975). Although her *detection* of odours was largely unchanged, her *identification* of odours was impaired. Similarities are seen in patient H.M., in whom the amygdala, entorhinal cortex, and hippocampus were removed bilaterally (Corkin *et al.*, 1997). Odour discrimination, identification, and

matching are severely impaired, although H.M. can detect weak odours and appreciate odour intensity (Eichenbaum *et al.*, 1983). In both instances, it is possible that the combination of amygdala and entorhinal pathology is critical for identification. These and related case studies suggest that the involvement of the human amygdala in olfaction is often not made apparent by lesion studies. Presumably, this reflects the presence of multiple olfactory projection routes (i.e. parallel routes to orbitofrontal, thalamic, and other temporal regions), just as is seen in rodents. To further investigate involvement of the human amygdala in olfaction, the use of functional imaging studies and the development of more selective tests is necessary.

Functional imaging studies: Zald and Pardo (1997) reported that exposure to a highly aversive odourant produces a strong increase in cerebral blood flow as measured by positron emission tomography (PET) in both amygdalae as well as in the left orbitofrontal cortex (see figure three).

Interestingly, activity within the left amygdala was associated significantly with subjective ratings of aversiveness, suggesting that amygdala activity is related to the perceived hedonic value of the stimulus. Tests conducted with pleasant smells (fruits, spices, and florals) only produced a non-significant increase in blood flow in the right anterior amygdala/periamygdaloid area. This study suggests that amygdala activation occurs when olfaction engages strong negative emotional reactions.

Aversive odours can affect amygdala activation via associative processes, as has been shown by Schneider *et al.*, (1999) in a functional magnetic resonance imaging (fMRI) study. The presentation of a neutral face that had previously been paired with an aversive odour led to a decrease in amygdala activity in a group of 12 normal subjects, whereas increased amygdala activation was found in a group of 12 subjects suffering from social phobia.

Activation of the amygdala by aversive smells and their associations may suggest other ways in which smells can influence memory. Aggleton's real world study (Aggleton & Saunders, 2000) examined the long-term retention of specific smells by people who had previously visited a Viking museum. People

who had visited the museum many years previously almost always recalled that there had been smells. However, only those that were independently rated as being most aversive were remembered consistently. It was also found that the same cues acted as contextual cues to help subjects to recall details of the museum, despite having not visited it for many years (Aggleton & Waskett, 1999).

al., 1995). A substantial body of evidence suggests, however, that lasting explicit/declarative memory for emotionally arousing information is stored in other brain regions and that the activation of the amygdala modulates the storage of memory in those brain regions (e.g. Cahill & McGaugh 1998; Weinberger, 1995).

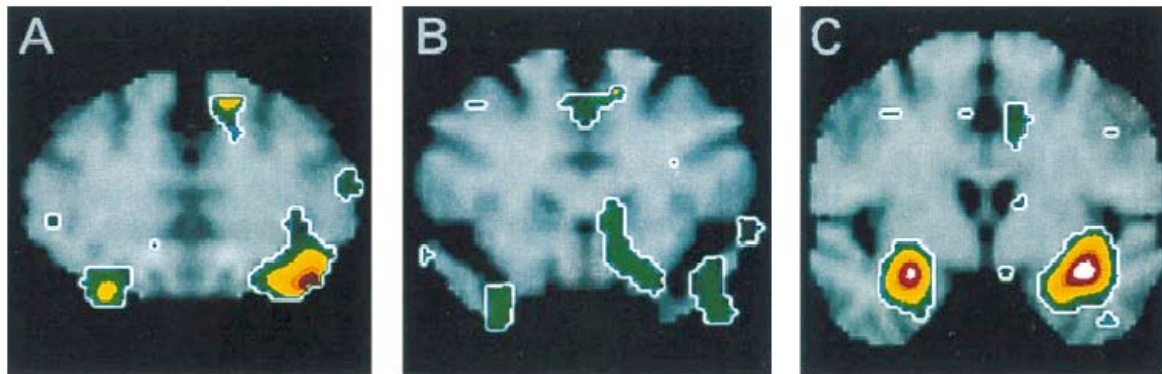
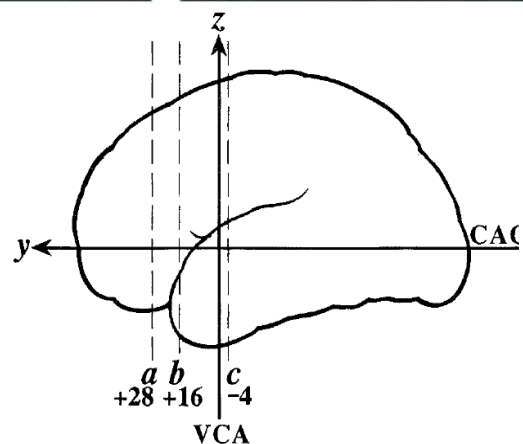


Figure 3 (above and right) Cerebral activation during aversive olfaction. Changes in regional cerebral blood flow (rCBF) are rendered in colour with white indicating the greatest magnitude (Z score > 5) of activation. The relative positions of coronal sections (A, B, and C) through the frontal (a and b) and temporal (c) lobes are shown schematically to the right of this text. Maximal areas of rCBF change are displayed superimposed on a standard T-1-weighted magnetic resonance image. The rCBF maxima map to the amygdala bilaterally and the left posterior lateral orbitofrontal cortex. The right side of this figure shows the left side of the brain. Abbreviations: VCA, vertical line through anterior commissure; CACP, intercommissural line (reproduced with kind permission from Zald & Pardo, 1997, © 1997 by PNAS).



Intriguingly, this suggests that the amygdala enhances learning when a subject is emotionally aroused, and that arousing smells might also be effective contextual cues through a similar process.

This pathway is a strong candidate for having a role in the neural underpinnings of Proustian phenomena. An in depth look at arousal-dependent memory modulation by the amygdala follows.

The amygdala and modulation of memory storage: animal studies

There is now general agreement that the amygdala is involved in the learning of emotionally arousing information (Cahill *et*

Hormonal modulation of memory storage

Gerard (1961) proposed “...*epinephrine...is released in vivid emotional experiences, such that an intense adventure should be highly memorable.*” He was the first to advance this hypothesis. Gold and van Buskirk (1975) found that systematic post-training injections of adrenaline administered to rats enhances long-term retention of inhibitory avoidance. These findings have been confirmed by experiments using *many different types of learning tasks*, all in support of the hypothesis that endogenously released adrenaline modulates memory storage (e.g. Liang, 2000; Williams, 2000). As with adrenaline, post-training administration of moderate doses of

glucocorticoids also induce dose- and time-dependent modulation of memory storage (Roosendaal & McGaugh, 1996a). These findings strongly suggest that glucocorticoids released by strongly emotionally arousing experiences enhance the consolidation of the memory for those experiences (Roosendaal,

clenbuterol into the amygdala produces dose-dependent enhancement of memory storage (Hatfield & McGaugh, 1999). This strongly supports the hypothesis that the amygdala plays a critical role in memory consolidation. In the periphery, β -adrenoceptors are located on vagal afferents that project to the nucleus of

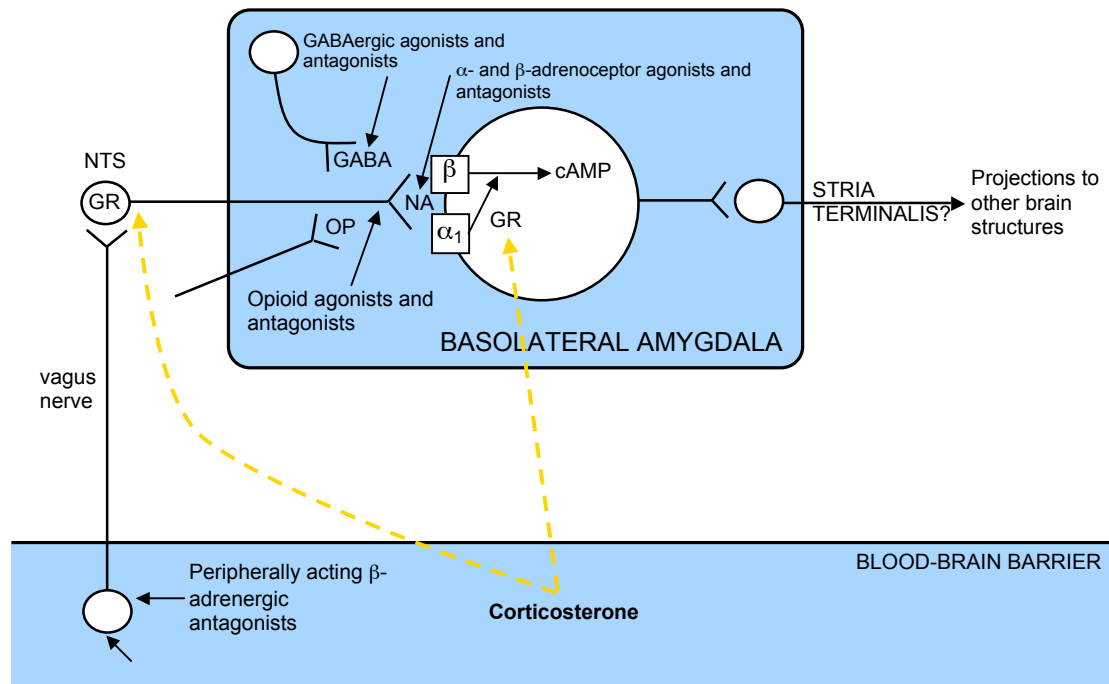


Figure 4 Schematic summarizing the interactions of neuromodulatory influences in the basolateral amygdala on memory storage. Abbreviations: α_1 = α_1 -adrenoceptor; β_1 = β_1 -adrenoceptor; cAMP = cyclic 3'5' adenosine monophosphate; GR = glucocorticoid receptor; NA = noradrenaline; NTS = nucleus of the solitary tract; OP = opioids (adapted from McGaugh *et al.*, 2000).

2000).

Amygdala mediation of neuromodulatory influences on memory storage

Noradrenaline (NA) release in the brain may regulate memory consolidation (Kety, 1972). Gold and van Buskirk's finding (1978) that adrenaline and footshock induce the release of NA in the forebrain of rats has provided evidence consistent with Gerard and Kety's suggestions. Contemporary studies now indicate that NA release within the amygdala is critically important in enabling neuromodulatory influences on memory storage. Post-training intra-amygdala infusions of β -adrenoceptor antagonist propranolol block adrenaline effects on memory storage (Liang *et al.*, 1986) and post-training infusions of NA or the β -adrenoceptor agonist

the solitary tract (NTS) (Schreurs *et al.*, 1986). Projections from the nucleus of the solitary tract are known to release NA within the amygdala (Ricardo & Koh, 1978). Adrenaline does not readily pass through the blood brain barrier. It seems likely that adrenaline effects memory storage by activation of peripheral β -adrenoceptors on vagal afferents. In support of this theory, inactivation of the NTS with lidocaine blocks adrenaline effects on memory storage (Williams & McGaugh, 1993).

Recent findings also indicate that the amygdala is involved in mediating glucocorticoid influences on memory storage (Roosendaal, 2000). Lesions of the stria terminalis or of the amygdala block the memory enhancing effects of post-training systematic injections of synthetic glucocorticoid dexamethasone (Roosendaal & McGaugh, 1996a,b). These glucocorticoid

effects involve noradrenergic activation of the amygdala.

Noradrenergic activation in the amygdala is also critical for other neuromodulatory influences on memory storage. Post-training systemic injections of opioid peptides and opiates generally impair memory storage and opiate antagonists enhance memory storage (Izquierdo & Diaz, 1983; McGaugh, 1989; McGaugh *et al.*, 1993). GABAergic antagonists and agonists administered post-training enhance and impair retention, respectively (Brioni & McGaugh, 1988; Brioni *et al.*, 1989). Lesions of the amygdala or stria terminalis block opioid peptidergic and GABAergic influences on memory storage (McGaugh *et al.*, 1986). Also, and perhaps most importantly, intra-amygdala infusions of the β -adrenoceptor antagonist propranolol block opioid peptidergic and GABAergic control of memory storage (McGaugh *et al.*, 1988). These neuromodulatory interactions within the amygdala are summarized schematically in figure four.

Studies that have not involved inhibitory avoidance training have yielded similar results to those summarized above. Hence, there is evidence that amygdala influences on memory storage are not restricted to the learning of aversive information.

Modulation of long-term memory (LTM) in humans: adrenergic activation and the amygdala

I begin here with the assumption that the brain must possess a means to 'weight' or moderate the actual information storage mechanisms in approximate proportion to the importance of the information being stored (Gold & McGaugh, 1975). Without modulatory mechanisms, the brain would be unable to distinguish the important from the trivial in LTM. There appear to be, at minimum, two interacting neurobiological components mediating the modulatory actions of emotional arousal on memory: the adrenergic system and the amygdala (especially BLA). An interaction between endogenous stress hormones activated by emotional experiences and the amygdala appears critical. According to animal studies, we can hypothesize that sufficiently emotionally arousing (i.e. sympathetic nervous

system-activating) learning situations should engage amygdala participation in memory formation, independently of whether the particular emotions involved are positive or negative. Hence, an emotionally toned olfactory stimulus is 'predisposed' to preferential consolidation by the amygdala and therefore improved storage.

Although there is strong evidence in humans for amygdala participation in LTM storage for emotionally arousing events, evidence for its participation in memory retrieval, or for its production of emotion, *per se*, is currently less clear.

Emotionally influenced LTM: the role of the adrenergic system

Propranolol (a synthetic β -adrenergic receptor blocking agent) attenuates the enhanced LTM associated with emotionally arousing information without affecting memory for more emotionally neutral information (Cahill *et al.*, 1994). Hence, activation of the adrenergic system in humans is required for the enhancing effect of arousal (either emotionally or physically induced) on memory. The action of propranolol is mediated centrally (van Stegeren *et al.*, 1998). Adrenergic stimulation can act in a retrograde manner to enhance memory in humans (Soetens *et al.*, 1995).

Emotionally influenced LTM: the role of the amygdala

Scoville and Millner examined memory in ten patients, including some with relatively selective amygdala damage and concluded "*removal of the amygdala bilaterally does not appear to cause memory impairment*" (Scoville & Millner, 1957). However, their tests involved short-term memory, and/or memory for non-emotionally arousing material. These findings fit well with the 'memory modulation' view of amygdala function, which predicts that amygdala activity should not be critical for STM, or for LTM of non-emotionally arousing events or material. A rare patient with damage confined almost exclusively to her amygdala reported deficits

in memory for emotional material (Babinsky *et al.*, 1993). Enhanced LTM associated with an emotionally arousing story is impaired in patients with selective (Cahill *et al.*, 1995) or nearly selective (Adolphs *et al.*, 1997) amygdala damage. Amnesic patients with undamaged amygdalae show reasonably intact enrichment of memory for emotional data despite their overall impaired memory performance (Hamann *et al.*, 1997). The emotional reactions of patients with amygdala damage to emotionally provocative stimuli are not significantly different from those of controls even though LTM for emotional material is impaired (Cahill *et al.*, 1996). Electrodermal responses to emotionally stressful events are intact in humans with amygdala damage (Adolphs *et al.*, 1997). On the basis of these and PET studies described, Cahill *et al.*, (1996) propose that amygdala activity in humans “*may be more important for the translation of an emotional reaction into heightened recall than it is for the generation of an emotional reaction per se.*”

Brain imaging studies: In one study, subjects received two PET scans: one while viewing a series of relatively emotionally arousing films, another while viewing a series of relatively emotionally neutral films (Cahill *et al.*, 1996). Memory for the films was tested in a surprise free recall test three weeks later. Activity in the right amygdala correlated very highly ($r=0.93$) with the number of emotional films recalled three weeks later, but not with recall of the neutral films (see figure five).

observed either pleasant or unpleasant arousing images. Memory for the images one month later correlated very highly with amygdala activity while viewing either the pleasant or unpleasant images. Amygdala activity whilst viewing emotionally neutral images (including images of novel, but not emotionally arousing objects) did not correlate with recall. The arousing dimension of the pictures was essential to amygdala engagement in memory, as indicated in another recent fMRI study (LaBar *et al.*, 1998).

Although activity of both the left and right amygdala correlated with recall of arousing material, the degree appeared greater on the right for negative slides (Hamann *et al.*, 1999). Cahill *et al.* (1996), who used emotionally negative material and found a unilateral effect, also suggest that differences in left versus right amygdala participation in memory for emotionally arousing events may relate to their pleasant/unpleasant nature. Left amygdala activation appears to be produced consistently by any of a variety of aversive stimuli used in human brain imaging studies (Cahill & McGaugh, 1998; Zald & Pardo, 1997, 2000 for olfactory examples). No compelling explanation exists at present for such asymmetries in amygdala function.

Canli and colleagues (1999) reported that amygdala activity in response to emotionally negative pictures correlated with long-term (2-14 months) retention of pictures. In an individual fMRI study conducted in

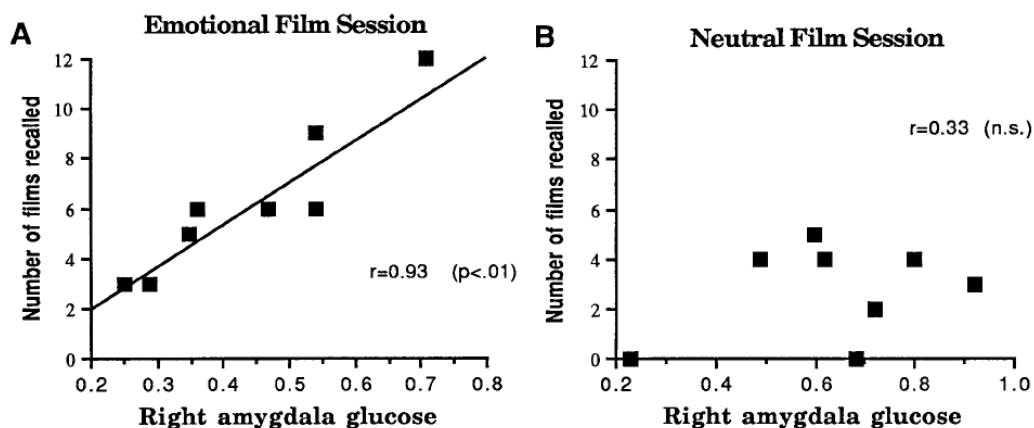


Figure 5 (A) Amygdala activity while watching a series of emotionally arousing films correlated very highly with long-term (three-week) recall of the films. (B) Amygdala activity in the same subjects while viewing a series of relatively emotionally neutral films did not correlate significantly with recall (reproduced with kind permission from Cahill *et al.*, 1996, © 1996 by PNAS).

Hamann and colleagues (1999) used PET to study cerebral blood flow while subjects

collaboration with the above, it was found that increasing the degree of emotional arousal

induced by emotional pictures increases the degree to which amygdala activity is correlated with long-term recall of pictures (Canli *et al.*, 2000).

In conclusion, evidence from several human brain imaging studies, including both PET and fMRI, converges with both neuropsychological data and findings from animal research to support the view that the amygdala is involved preferentially with long-term storage of explicit memory for emotionally arousing events.

encoding/consolidating but not retrieval processes. Two fMRI studies of amygdala involvement in aversive classical conditioning reported that the amygdala was active in response to a conditioned stimulus during learning of a conditioned association, but not once the association was learned (Büchel *et al.*, 1998; LaBar *et al.*, 1998). A PET investigation reported amygdala activation while subjects initially viewed emotional pictures, but not when retrieval of the pictures was tested later (Taylor *et al.*, 1998). Similarly

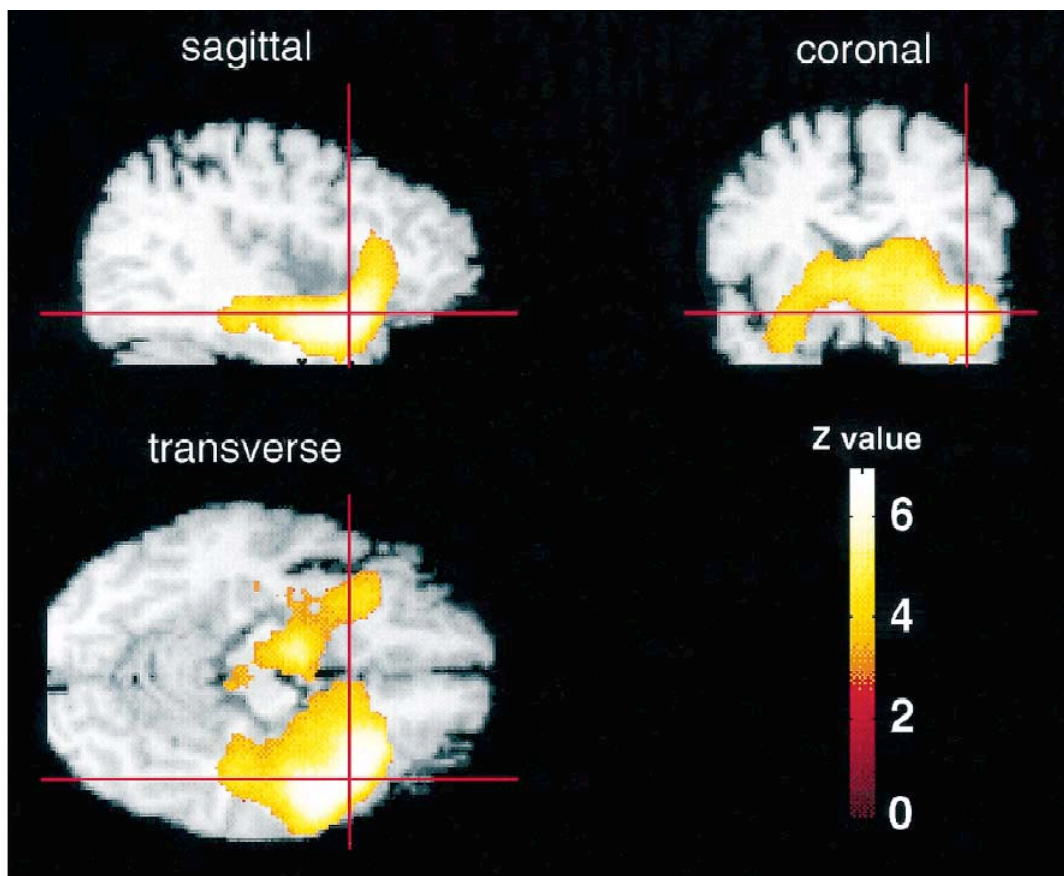


Figure 6 Functional anatomy of temporal activations during affect-laden autobiographical memory, as indicated by PET-measured changes in rCBF. This figure details the functional anatomy of temporal activations associated with autobiographical memory and their relationship to underlying anatomy. N.B. Activations are predominantly on the right (left image corresponds to subject's left) and include temporomedial, temporolateral, and insular cortices. Red-cross hair indicates local maximum within area of activation (reproduced with kind permission from Fink *et al.*, 1996, © 1996 by the Society for Neuroscience).

Does the amygdala participate in acquisition, retrieval or both?

The imaging studies discussed above clearly implicate the amygdala in encoding/consolidating processes, but do not address its role in the retrieval process. Some studies report evidence consistent with amygdala participation in

viewing, and presumably forming memories of, emotionally arousing films has been reported to activate the amygdala (assessed with PET), although retrieval of previously experienced events did not (Reiman *et al.*, 1997).

Other reports *do* indicate activation of amygdala during retrieval of emotional events. For example, Fink *et al.*, (1996) reported unilateral amygdala (and temporal lobe)

activation in subjects retrieving emotionally laden autobiographical memories (see figure six). Others report amygdala activation in people with post traumatic stress disorder (PTSD) when they recall the distressful event that caused their disorder (Rauch *et al.*, 1996). There are many confounding variables in this type of imaging study. In the study by Fink and coworkers (1996), the relative rCBF differences were monitored in subjects reading either sentences containing affect-laden autobiographical information or sentences containing semantically similar episodic but non-autobiographical information. Material presented during the autobiographical phase was (1) familiar to the subjects for many years, (2) affectively more significant, and (3) more personal. Any or all of these factors could be (partly) responsible the activations described. When considering evidence of amygdala participation in retrieval, it is essential to distinguish between retrieval *with or without concomitant emotional arousal*. According the 'memory modulation' hypothesis, the amygdala should influence memory storage processes whenever a situation is sufficiently emotionally arousing - independent of whether the emotion is produced by an external or an internal event (such as a memory that induces an emotional response, Cahill & McGaugh, 1998). Indeed, Fink *et al.*, (1996) reported that their subjects probably experienced substantial emotional arousal during retrieval. Similarly, retrieval of traumatic events in PTSD patients is generally very emotionally stressful. Thus amygdala activation during retrieval occurring with a concomitant emotional response may in fact reflect amygdala participation in memory storage, rather than retrieval, processes. To clarify this issue, future studies need to be designed to determine whether concomitant emotional arousal is critical to amygdala activation at the time of retrieval. Recent imaging studies provide clues as to

potential brain regions with which the amygdala interacts to effect memory. Activation of the cholinergic basal forebrain (the 'substantia innominata') correlated significantly with recall of emotional but not neutral films (Cahill *et al.*, 1996). Animal research incriminates the hippocampal region as a likely site of modulation by the amygdala (Packard & Teather, 1998). Data suggesting concurrent amygdala and hippocampal region activation during emotionally arousing events (Cahill *et al.*, 1996; Hamann *et al.*, 1999) are consistent with, while definitely do not prove, the idea that the amygdala affects memory via influences on the hippocampal region. Currently available imaging data, combined with neuropsychological investigations in single cases with selective retrograde amnesia, suggest right hemispheric temporal regions as being key for autobiographical memory ephory (the process by which retrieval cues interact with stored information so that an image or a representation of the information in question appears). Surrounding right hemispheric 'satellite' regions such as the amygdala, hippocampus-parahippocampus, posterior cingulate, and insular and prefrontal cortex support these regions. Such satellite regions might be responsible for contributing additional information, such as the emotional-affective components of a memory.

Modulatory circuits in olfactory perception

Savic (2002) suggests that perception of odour compounds is mediated by a set of core regions (see figure seven). Depending on the task associated with odour perception, core regions are associated together with other circuits in a parallel and hierarchical manner. Interestingly, some of the structures involved here correspond with those involved in

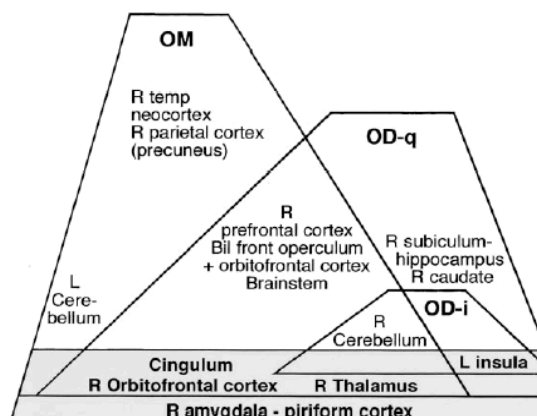


Figure 7 A hierarchical and parallel system for odour processing based on data from tests of different cognitive load. Regions shared by several olfactory tasks and the regions specific to a particular task are depicted, with each pyramid indicating a separate task. The higher up the pyramid, the more complex the task. The grey zone indicates the olfactory core regions, activated by passive smelling of odours. Abbreviations: OM, odour-recognition memory task; OD-I, discrimination of odour intensity task; OD-q, discrimination of odour quality task; Bil, bilateral; L, left; R, right (reproduced with kind permission from Savic 2002).

autobiographical memory ephory.

Discussion

In this section I propose a unification between various neural mechanisms, outlining some of the processes that may be involved in encoding and retrieval of emotionally toned odour-evoked memories. Figures eight and nine aim to bring together a portion of the large and diverse body of evidence related to olfaction, emotion, and the amygdala.

So why do odours act so effectively as cues for certain emotionally toned, vivid, and old autobiographical memories? At encoding, the subject is emotionally aroused due to the context, resulting in systemic release of adrenaline and corticosterone. Noradrenergic activation of the BLA results in the situation/memory being labelled as a priority for LTM storage. Hence, the episode is preferentially encoded in brain areas via the stria terminalis. However, this arrangement alone does not suffice as an explanatory concept as to why odours are better than other sensory modalities at evoking those memories that are particularly emotionally toned.

Here, I think that it must be related to the direct input of olfactory stimuli into the amygdala. There is a connection from the main olfactory bulb to the post piriform area to the BLA. Do olfactory stimuli (present at the time of arousal) therefore have the opportunity to become better associated with these emotional memories than stimuli from other sensory modalities (which must first travel through a series of cortical association areas before eventually reaching the amygdala)? The end result of this encoding process is the formation of a memory trace with very strong olfactory associations. This is in agreement with the 'differential encoding bias' hypothesis whereby cues do not differ in terms of their efficacy in retrieving event details, but in terms of the types of event with which they become associated and consolidated in memory.

At retrieval, the presence of the same odour as that present at encoding cues the recall of the original episode. As this memory is so emotionally toned, sympathetic activation occurs and there is concomitant retrieval of memory and emotion. Recall is centred on

right hemispheric temporal cortical areas, with satellite regions contributing additional dimensions to the retrieval experience. The right amygdala is a common component in both olfactory perception pathways and emotionally toned autobiographical memory retrieval.

Future research direction

To test the idea described above, there is a need to design experimental paradigms that investigate whether odourant information does indeed become more strongly associated with emotionally toned memories that are modulated by the BLA.

It would be interesting to see whether a person with bilateral amygdala damage were able to appreciate the emotional aspect of odours chosen to evoke emotional responses. This would indicate whether the amygdala is necessary for the generation of emotion for olfactory stimuli. In addition, the subject of laterality of amygdala function in relation to emotion and memory is evidently an important area for future research.

Pragmatically, techniques currently used to investigate amygdala function are not capable of sufficient anatomical resolution or specificity to distinguish between subregions. Improvements in spatial and temporal resolution are required.

Experiments examining the covariance of amygdala activity with additional brain regions in the context of emotionally arousing versus emotionally neutral situations should aid identification of a network of structures through which the amygdala modulates memory.

Clinical applications

Several clinical disorders involve olfactory impairments and/or pathology in structures associated with higher level olfactory processing. For instance, the olfactory system shares a common neural substrate with many of the cognitive and emotion processes that are abnormal in schizophrenia. Schizophrenic patients exhibit abnormalities in certain

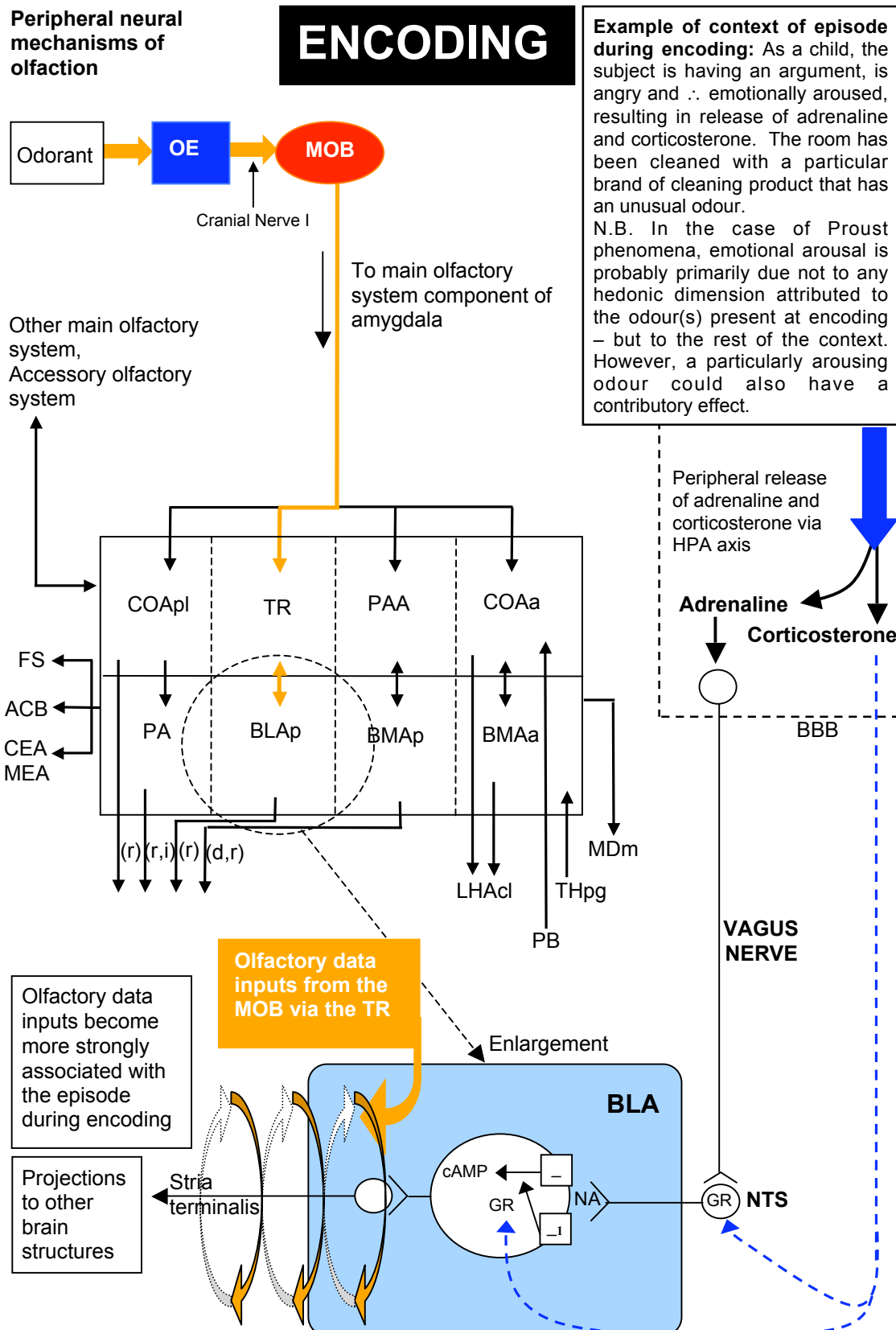


Figure 8 Novel schematic illustrating some key components of the encoding process employed during the generation of Proustian memories. See discussion for details. Abbreviations: α_1 , α_1 -adrenoceptor; ACB, nucleus accumbens; β , β -adrenoceptor; BBB, blood brain barrier; BLAp, basolateral nucleus of amygdala- posterior part; BMAa,p, basomedial nucleus of amygdala- anterior, posterior parts; CEA, central nucleus of amygdala; COAa,pl, cortical nucleus of amygdala- anterior, posterior lateral parts; d, medial hypothalamic defensive system; FS, fundus of striatum; GR, glucocorticoid receptor; LHAcl, lateral hypothalamic area – caudolateral part; MDm, mediodorsal nucleus thalamus; MOB, main olfactory bulb; MEA, medial nucleus of amygdala; NA, noradrenaline; NTS, nucleus of the solitary tract; OE, olfactory epithelium; PA, posterior nucleus amygdala; PAA, piriform-amygdala area; PB, parabrachial nucleus; r, medial hypothalamic reproductive behaviour system; THpg, thalamus perigeniculate region; TR, postpiriform transition area.

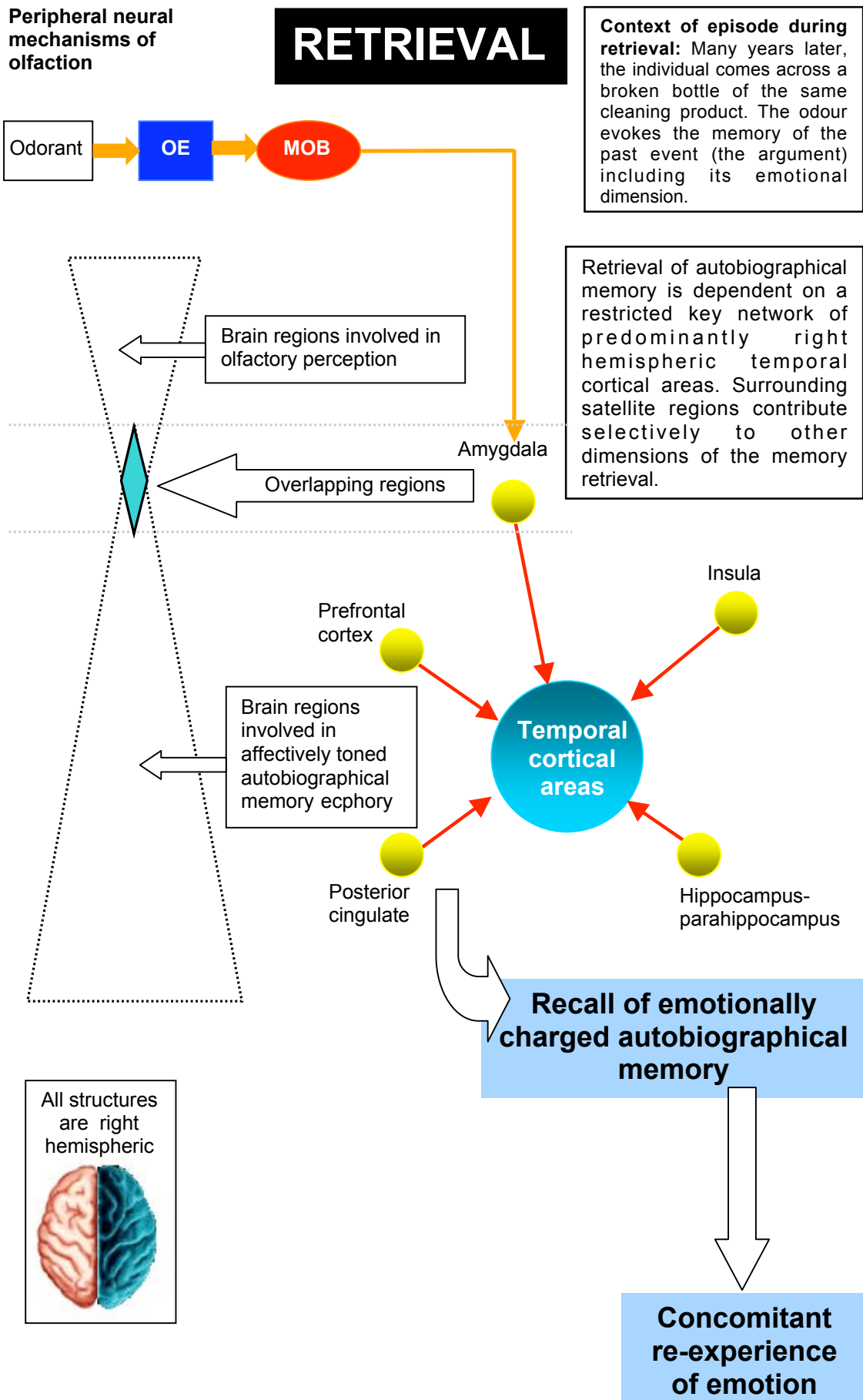


Figure 9 Schematic illustrating some key components of the retrieval process employed during the recall of Proustian memories. See discussion for further details.

components of the olfactory evoked potential (Turetsky *et al.*, 2003). Additionally, abnormal olfactory identification has been found in individuals with obsessive compulsive disorder (Goldberg *et al.*, 1991). Continued research and improved understanding of the neural underpinnings of higher level olfactory processing will improve understanding of these disorders.

One potential clinical effect of the proposed amygdala/adrenergic system memory-modulating mechanism is worth considering. The formation of excessively intrusive memories characteristic of PTSD may occur as a result of over-activation of this typically adaptive mechanism. If so, appropriate treatment with β -blocking drugs immediately after a person has experienced an emotional trauma should reduce/prevent the development of PTSD. Results from one small-scale clinical trial (Pitman *et al.*, 2002) support the clinical possibility that a course of propranolol begun shortly after an acute traumatic experience is effective in reducing PTSD symptoms 1 month later. Definitive conclusions, however, must await adequately powered studies with larger samples.

Conclusion

Odours are capable of evoking very emotional memories because of the way that such memories are encoded originally. Due to a spatial and temporal coincidence in the BLA, olfactory information has the capacity to become more strongly associated with emotional episodes. Consequently, only odour stimuli have the capacity to retrieve them.

Returning to Proust, some important points need to be clarified. When an odour evokes a Proustian (emotionally charged) memory this involves recollection with concomitant re-experience of the emotional side of the memory. It is not the case that the odour itself is evoking an emotion; instead it evokes a memory with a strong emotional component. Similarly, at encoding, enhanced LTM storage most probably occurs principally as a result of emotional arousal unrelated to any hedonic dimensions attributable to the odour present at the time. However, the presence of an odour that is itself emotionally arousing would evidently contribute.

Chemical sense was originally used to move away from 'bad' (predators) and towards 'good' (food). In evolutionary terms, limbic structures grew out of the olfactory system. Consequently, the emotional dichotomy between bad (death, danger, failure) and good (survival, love, reproduction) echoes the chemosensory one. Perhaps emotion began merely as an abstracted façade of primitive olfactory instructions. This would explain why odour has such a potent emotional cascade.

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Acknowledgements

I thank G Arbuthnott, K Campbell, N McLeod, and E Wood for comments and Chlo_.

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