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Review

The role of the ventromedial prefrontal cortex in memory consolidation

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ABSTRACT

“System-level memory consolidation theory” posits that the hippocampus initially links the neocortical representations, followed by a shift to a hippocampus-independent neocortical network. With consolidation, an increase in activity in the human subgenual ventromedial prefrontal cortex (vmPFC) has repeatedly been shown. Previously we and others have proposed that this area might link the neocortical representational areas in remote memory, similarly as has been proposed for the rodent anterior cingulate cortex (ACC). Here, we review literature involving the human vmPFC to investigate if the results in other cognitive domains are in line with this proposal. We have taken into account reports on patients with lesions in this area, findings in reward and valuation, fear extinction, and confabulation studies, and integrated these with findings in consolidation studies. We conclude: Firstly, it is unlikely that the rodent ACC is homolog to the human subgenual vmPFC. It is more likely that the rodent infralimbic cortex is, as proposed in the fear extinction literature. Secondly, we propose that the function of the subgenual vmPFC is to *integrate* information which is represented in separate parts of the limbic system (the hippocampus, the amygdala, and the ventral striatum) and that the integrated representation in the subgenual vmPFC might subsequently be used to *suppress* irrelevant representations in the limbic system. With the progression of time, the importance of the integrated representation in the subgenual vmPFC increases, because it may replace some direct connectivity across the limbic areas which decays with time.

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Abbreviations: vmPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex; MTL, medial temporal lobe; mPFC, medial prefrontal cortex; BA, brodmann's area; IL, infralimbic area; PL, prelimbic area; CS, conditioned stimulus; US, unconditioned stimulus; CR, conditioned response.

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1. The human vmPFC becomes more involved with memory consolidation, data and current interpretation

In 1957 William Scoville and Brenda Milner published the now famous case of patient H.M. [1]. Scoville surgically removed large parts of the medial temporal lobe (MTL; including the bilateral hippocampi) in H.M., to relieve him from intractable epilepsy. The surgery was successful in controlling his epilepsy, however, it also elucidated that the hippocampus is essential for the formation of new memory traces. H.M. was severely impaired in learning episodic information and facts (declarative/explicit memory), although the formation of non-declarative (implicit) memory such as procedural memory was not disrupted. Besides encoding deficits, H.M. and other patients with hippocampal lesions showed temporal-graded retrograde amnesia – an impairment in retrieval which decreases in severity with remoteness of the memory [1–3]. Animal studies with controlled lesions of the hippocampus showed the same pattern; memories encoded just before the lesion were impaired, while remote memories were spared [4–6]. These observations showed that gradually over time memories can become independent of the hippocampus, suggesting that other areas, presumably the neocortex, take over the memory representation. The process describing the slow shift from hippocampus dependent to hippocampus independent memory (Fig. 1) is called *system-level consolidation* [3,7]. This is in contrast to the term synaptic consolidation [8] which refers to the initial synaptic stabilization. It is debated however, if this process takes place for all sorts of memory; vivid episodic memories might never become fully independent of the hippocampus [9,10].

In the 70's, Marr proposed that the hippocampus serves as a simple moment-by-moment capturing system, while the neocortex stores information in a structured way [11,12]. Teyler and Discenna later proposed that the way in which the hippocampus stores events, is by indexing those neocortical regions that are collectively active during the occurrence of an event [13,14]. The neocortical representational areas are reciprocally connected to the hippocampus (via the perirhinal cortex and parahippocampal gyrus, and subsequently via the entorhinal cortex), enabling linking of the neocortical representational areas by the hippocampus. McClelland et al. [15] used computational models to illustrate that rapid acquisition of new memories is not possible in the structured neocortex, because this would cause disruption of existing stored information (“catastrophic interference”). Therefore the hippocampus is needed for rapid initial storage, while memories are slowly incorporated into the neocortex for stable long term

storage. The slow reinstatement of memories in the neocortex is proposed to take place by repeated replay of the new information by the hippocampus [16], interleaved with reactivation of existing knowledge already contained within the neocortex. This would eventually result in the strengthening of the connections between the neocortical representational areas [7]. The interleaved reactivation prevents catastrophic interference, and additionally results in a re-representation of information which makes use of shared structure between the new and the existing knowledge [15].

Initially it was proposed that the *direct* connections between the neocortical representational areas are strengthened with consolidation (Fig. 1). Later, however it was suggested that the medial prefrontal cortex (mPFC) might start acting as a *new linking area* in remote memory (Fig. 2a), analogous to the hippocampus in recent memory [17,18]. This idea resulted from a group of studies in rodents that specifically focused on the question of how remote memories become represented in the neocortex after consolidation [17,19–24]. The involvement of the hippocampus consistently decreases with consolidation, while the involvement of the mPFC increases (e.g. Fig. 2b). Lesions to the entire mPFC, and to the anterior cingulate cortex (ACC) in particular, resulted in deterioration of remote memory, while leaving recent memory retrieval intact [20,22,23]. The double dissociation in the role between the hippocampus and the mPFC in recent and remote memory retrieval respectively, led to the proposal that the mPFC might take over (part of) the linking role of the hippocampus in remote memory [18] (Fig. 2a).

In agreement with the rodent studies, several neuroimaging studies in healthy humans investigating systems level consolidation, report an increase in activity of the vmPFC with memory consolidation [25–28]. Takashima et al. [27] showed a large set of pictures to subjects and tested recognition memory immediately, one day, one week, and three months later. Activity of the hippocampus decreased with consolidation, while activity of the vmPFC increased (Fig. 2c). This vmPFC activity increase was correlated with the hippocampal decrease. In another study, we observed an increase in vmPFC activity during retrieval of forty face-location association pairs that were intensively trained in the preceding week, compared to retrieval of face-location associations that were learned on the same day of retrieval [26] (Fig. 2d). Two other fMRI studies made use of a sleep deprivation paradigm, one using word pairs [25], the other using emotional picture stimuli [28]. Both studies show a consolidation dependent increase in functional connectivity between the hippocampus and the vmPFC three days after encoding, as well as a general increase in vmPFC activity with consolidation six months later (Fig. 2e and f). This pattern of results suggests a high level of interaction between the vmPFC and the hippocampus in the initial stage of consolidation, which is in line with the idea that a transfer of information between these areas occurs during the process of consolidation. As such, we and others proposed that this could enable the vmPFC to take over, in part, the role of the hippocampus, by linking the neocortical representational areas in remote memory (Fig. 2a). Consequently, the human vmPFC was assumed to be the functional homologue of the rodent mPFC and specifically the ACC, since both areas increase their involvement with consolidation [18,26,27].

Besides being modulated by memory consolidation, studies outside the memory field also report involvement of the human vmPFC. We feel it is important to overlay the finding of the consolidation field with the findings of these other fields. In the following sections, we will review literature reporting the involvement of the equivalent areas of the vmPFC where a consolidation related increase is observed (Fig. 2c–f). Herewith we aim to get more insight into the common mechanistic function of this part of the vmPFC, in order to investigate if the results in other domains of neuroscience are in line with the proposal that the vmPFC (1) is specifically involved

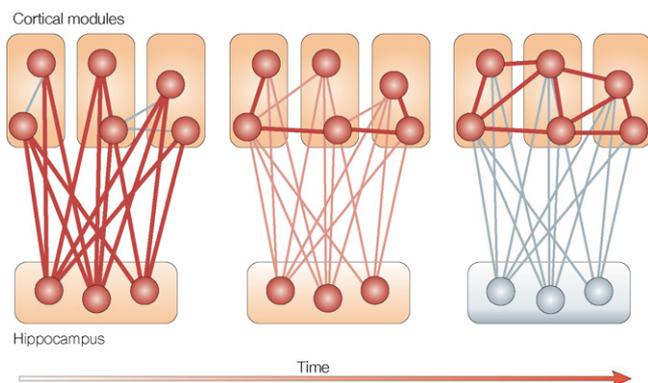


Fig. 1. System-level consolidation. According to the system-level theory of memory consolidation, the neocortical representational areas are initially linked by the hippocampus. With the progression of time, the direct connections between these neocortical areas strengthen, resulting in a consolidated representation which is independent of the hippocampus, reprinted by permission from Macmillan Publishers Ltd [17].

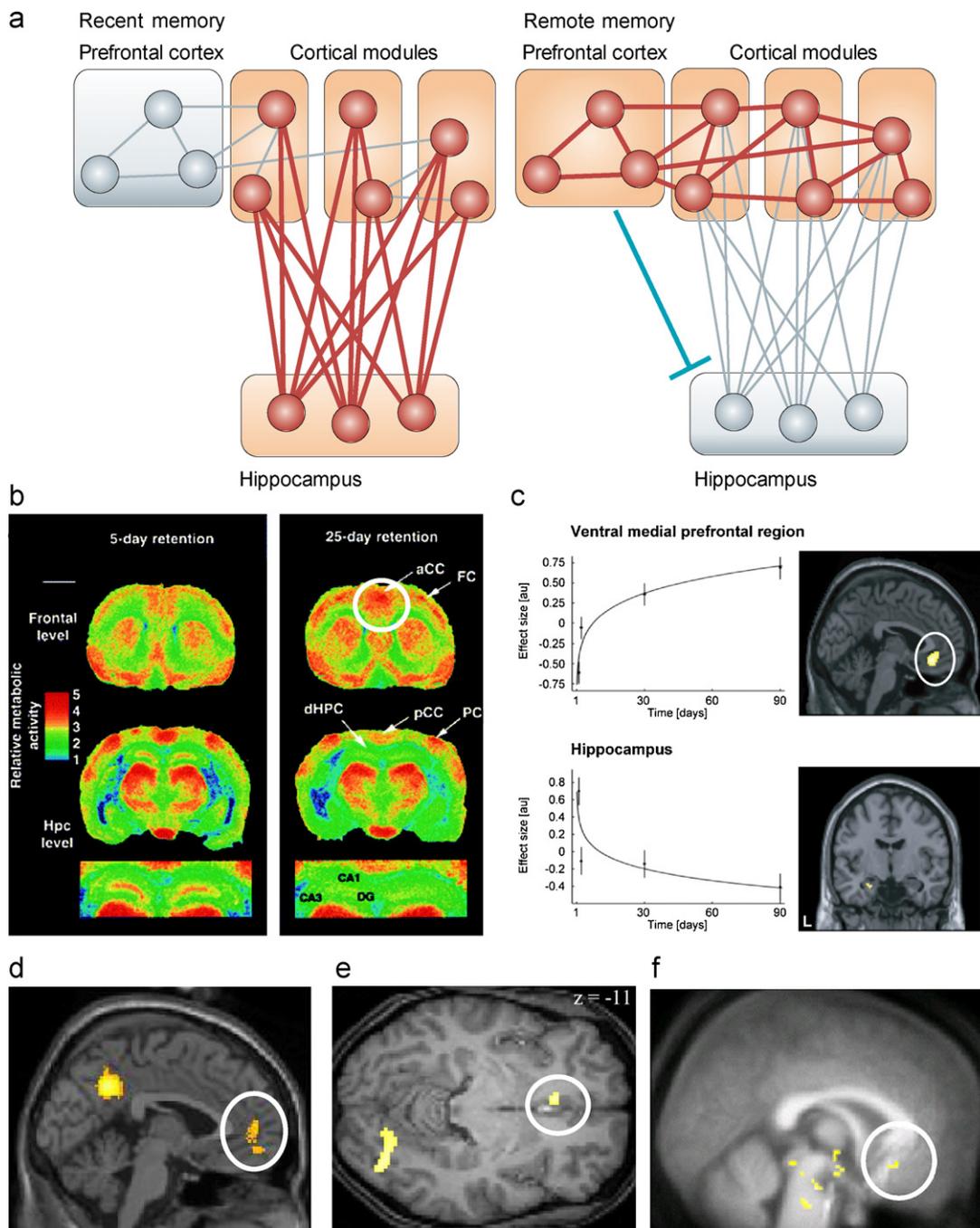


Fig. 2. Ventromedial PFC, model and data. (a) Model proposing that, in remote memory the mPFC takes over, in part, the linking role of the hippocampus, reprinted by permission from Macmillan Publishers Ltd [17]. (b) In rats, the activity in the hippocampus decreases with consolidation, while the activity of the medial prefrontal cortex (anterior cingulate cortex; aCC) increased, adapted by permission from Macmillan Publishers Ltd [19]. (c) Also in humans, the activity of the hippocampus decreases with consolidation, while the activity of the vmPFC increases, modified from [27]. (d) The vmPFC shows more activity during retrieval after one week compared to a few hours of consolidation in a face-location retrieval paradigm, modified from [26]. (e and f) Activity of the vmPFC during remote memory retrieval was higher when normal sleep followed after learning compared to one night of sleep deprivation, (e) modified from [25], (f) reprinted from [28].

in the representation of remote and not recent memory, (2) acts as a linking node for the neocortical modules similar to how the hippocampus acts in recent memory (Fig. 2a). We conclude that the proposed role of the human vmPFC is not in line with the results found in the other cognitive tasks, and therefore we subsequently make a new proposal for the role of the vmPFC. We end this review with suggestions for future research that would test this new proposal and further explore the role of the human vmPFC and rodent homologue areas in memory consolidation in depth.

2. Anatomical structure of human vmPFC and rodent mPFC

The term vmPFC is not defined very precisely in the literature; it is used to refer to any of the brain areas in the ventromedial part of the frontal lobe (Fig. 3a). It covers the medial part of the orbitofrontal cortex, the medial frontal pole and the ventral part of the anterior cingulate. Brodmann [29] assigned unique numbers to the areas of the human brain based on differences in cytoarchitectonic properties (Fig. 3a). However, Brodmann didn't study the vmPFC in much detail, resulting in large areas, and inconsistencies

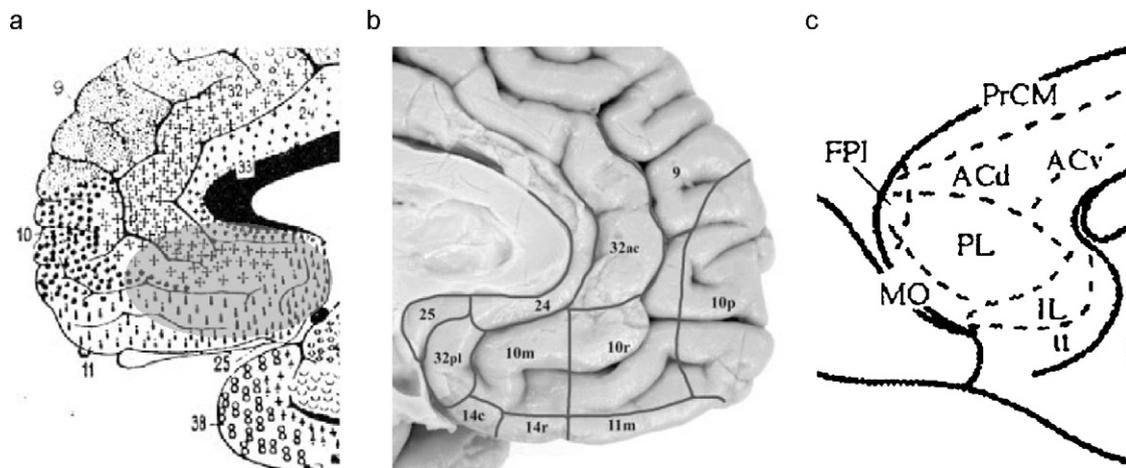


Fig. 3. Anatomical subdivision of medial prefrontal cortex. (a) Medial view of the human vmPFC; areas are marked according to Brodmann's cytoarchitectonic map. Shaded area was found to increase with consolidation: subgenual part, modified from [31]. (b) Further subdivision of the human medial prefrontal cortex based on five histological and immunohistochemical stains, reprinted with permission from [31]. (c) Rodent medial prefrontal cortex. ACd/v = anterior cingulate dorsal/ventral, PL = prelimbic region, IL = infralimbic region, MO = medial orbital, FPI = fronto-polar lateral, PrCM = precentral medial area, modified by permission from Oxford University Press [34].

in numbering across species. Later, it was found that the mPFC was much less homogeneous than Brodmann had specified, and several refinements and further subdivisions were proposed [30–33] (e.g. Fig. 3b). The part of the human vmPFC that was found to increase with consolidation (Fig. 2c–f), and thus the region of interest in our literature search, is roughly the ventral region of the cingulate cortex, thus Brodmann's areas 25, ventral part of 24 and 32, the caudal part of area 10, and the medial part of area 11 (shaded area in Fig. 3a) [25–28]. We will subsequently use the term subgenual vmPFC for this area.

Öngür and Price have defined two networks within the human orbital and medial prefrontal cortex; the orbital network consisting mainly of areas 12 and 13 and the medial network consisting mainly of areas 9, 10, 11, 24, 25, and 32, with the areas 13 and 14 connecting the two networks [31,34]. The medial network, which includes most of vmPFC that is of interest here, has anatomical connections with olfactory and gustatory inputs, limbic areas (the amygdala, subiculum and CA1 of the hippocampus), entorhinal, perirhinal and temporal polar cortices, the striatum (especially the nucleus accumbens and the medial part of the caudate nucleus), the various nuclei in the thalamus, the hypothalamus and the brainstem [34]. The ventral part of the cingulate cortex is considered to be part of the limbic system [35–37].

Due to the enormous expansion of the PFC in humans, it is difficult to indicate homologous areas across different species. In the rodent, the mPFC consists of the ACC most dorsally, the prelimbic area (PL) underneath, followed by the infralimbic area (IL) most ventrally (Fig. 3c). The connectivity pattern is different for the distinct areas. For instance, the IL projects to the shell of the nucleus accumbens, while the PL projects to the core of the nucleus accumbens and the medial part of the caudate nucleus [34]. Also the PL projects primarily to the basal amygdala, while the IL preferentially targets areas containing GABAergic neurons in the lateral subdivision of the central nucleus of the amygdala and the intercalated cell masses, an area situated in between the basolateral amygdala and the central nucleus [37,38]. In the rodent consolidation studies mentioned above, lesions were performed mainly to the ACC, but sometimes the lesion extended to the whole mPFC [20,22,23]. The IL, PL and ACC have all shown an increase in activity when memories become remote, however, importantly, only lesions of the ACC (and not to the adjacent PL) have shown to disrupt remote and not recent memory [20].

Summarizing, both the human vmPFC and the rodent mPFC consist of different subareas as reflected in different cytoarchitectonic properties, connectivity patterns, and (in rodents) the effect of a lesion on remote memory. Therefore it is likely that the different subregions have distinct functions, which should be taken into account in exploring the role of the human vmPFC in memory consolidation.

3. The role of the vmPFC in other fields of neuroscience

3.1. General description of patients with vmPFC lesions

What happens if the vmPFC is damaged? Patients with lesions to the vmPFC (including the medial orbitofrontal cortex) can show a range of deficits, including personality changes, changes in emotional and behavioral regulation and control, increased risk taking, anterograde amnesia, and confabulation, in spite of otherwise preserved intellect [39–47]. These symptoms may occur independently from each other, indicating that different areas within the vmPFC may fulfill distinct roles. A limitation of lesion studies in human patients is that the extent of the lesion cannot be controlled. However, by studying overlap in the area of the lesion and behaviors over many patients, it is possible to infer the function of more confined brain regions.

Numerous descriptions of patients suffering from bilateral lesions in the vmPFC have been made, starting in 1848 with the report of the most famous case of Phineas Gage [44]. Gage was a railroad construction foreman, and the lesion occurred during a work accident when a large iron rod penetrated his frontal cortex. Before the accident he was described as the most efficient and capable foreman of the railroad track construction team. After the accident, his personality was completely changed. He showed impulsive, socially inappropriate behavior, while retaining all of his intellectual facilities, leading him to dramatic decline in his social and working life. This same pattern was reported after Gage in many other patients with vmPFC lesions [39,41,48,49]. Importantly, a specific deficit in remote memory retrieval is not reported in these patients.

Several behavioral paradigms have been developed to study the neural mechanisms underlying the deficits in emotional and behavioral regulation and control in patients with vmPFC lesions. Bechara et al. have developed a gambling task (Iowa gambling task) in which participants have to try to gain play-money by selecting cards from

four different decks [39]. Choosing cards from two of the four decks results in a high initial gain of money, followed by an even higher unpredictable loss. Drawing from the other two decks, results in a small immediate gain followed by an even smaller unpredictable loss. The first two decks are, thus, the disadvantageous decks, which healthy subjects learn to avoid when playing this game. Patients with lesions to the vmPFC, however, continue to select more cards from the disadvantageous decks. Patients are sensitive to reward and punishment in this task, but they are insensitive for future consequences in general, and guide their behavior solely by immediate outcomes [41].

VmPFC lesioned patients also seem to suffer from a form of disinhibition. This is, for instance, reflected while playing the Cambridge gambling task. This task showed that these patients are sensitive to the odds of winning to the same degree as the healthy controls; however, the patients were overall less conservative in the amount of money they bet, resulting in a worse end result in the game [50]. Furthermore, it is proposed that the vmPFC is also involved in the extinction of drug seeking [51,52]. Cocaine drug cravers showed a deactivation in these region when they were cued with cocaine related objects [53]. In summary, a loss of vmPFC function appears to impair proper use of past outcomes to predict future probabilities, and an accurate valuation of the options, leading to risky decisions.

3.2. The vmPFC in neuroimaging studies of valuation

In neuroimaging studies, areas in the subgenual vmPFC have been shown to increase in activity during value computation. The vmPFC is proposed to encode the value of goals [54], reflect the value of goods ranging from food to monetary prizes [55] and to be involved in the selection of a devaluated compared to a non-devaluated action [56]. The activity of the vmPFC also tracks the amount with which an immediate reward is devaluated if it is delayed [57] and increases in activity with gains and decreases in activity with loss [58]. A recent study shows that the vmPFC (ventral part of BA24/BA10) additionally reflects complex social decisions like the subjective value of a voluntary charity donation [59]. Although the vmPFC is often simultaneously involved with the ventral striatum, both areas can be sensitive to different aspects of a task. For instance, only the vmPFC (ventral BA24/caudal BA10), and not the striatum, shows correlation with both the expected value and the reward magnitude in a conjunction analysis [60]. Hare and colleagues show that the vmPFC (BA 11/25, 24/32) might be more involved in the representation of the goal value, while the ventral striatum reflects the prediction error [61]. Summarizing, the subgenual vmPFC appears to be involved in the valuation of accumulated information, derived from past experiences, benefiting future decision making.

3.3. Involvement of the vmPFC in fear extinction

Neuroimaging experiments have shown that the human vmPFC is involved in retaining the extinguished memory of conditioned fear [62–65]. In studies examining fear extinction, subjects are first conditioned to a fear response: A neutral stimulus such as a light (conditioned stimulus; CS) is paired with an aversive event such as a shock (unconditioned stimulus; US) leading to a fear response to the neutral stimulus (conditioned response; CR). In the extinction phase, the CS is presented alone, without the US, which leads to a diminishing of the fear response. Extinguishing is, however, not the erasing of the original fear memory, but the formation of a new memory that coexists with, but opposes, the initial conditioned fear memory. This idea is based on observations that the CR can return after extinction in some situations, for example when returning to the context where the initial fear

conditioning took place, or spontaneously after the passage of time [66].

Fear conditioning depends on the amygdala, and initial extinction learning is independent of the vmPFC [40]. However, on the day following initial extinction learning, activity in the vmPFC correlates with the relative extinction success and with amygdala activity [65]. Milad and colleagues showed that the thickness of the vmPFC (BA25), as measured by MRI, is correlated with how well humans retain their extinction memory one day after having been conditioned and subsequently extinguished [63]. Another neuroimaging study by the same lab, specifically examined the effect of context during extinction learning [64]. They found positive correlations between vmPFC (BA32) and hippocampal activation during extinction recall on the day after initial extinction. Note that the areas of the human vmPFC reported in fear extinction experiments largely overlap with the subgenual vmPFC which increases in activity with consolidation.

Fear extinction has been extensively studied in rodents [38,67,68]. This has the advantage that the function of the separate brain areas can be examined in more detail with invasive techniques. These studies show that fear conditioning itself is dependent on the amygdala. Initial extinction learning can occur without the mPFC, however *retention* of extinction to the next day does depend on the integrity of the mPFC [69]. An important conclusion by the rodent studies is that the different subregions of the mPFC have distinct roles in fear extinction [38,70]. The IL specifically (Fig. 3c) is critical for fear extinction by suppressing the output of the amygdala [67,69–71]. In the fear-extinction literature it is proposed that the rodent IL is the functional homologue of the human subgenual vmPFC [38,64,65,67].

In the domain of fear extinction, the vmPFC (IL in rodents) is proposed to integrate competing pieces of information (memories), and subsequently inhibit those parts that are inappropriate in the current situation [38,68,71]. After fear conditioning, several partly opposing memories are present, dispersed over different parts of the limbic system (hippocampus and amygdala). First a fear memory is created, linking the CS to the US resulting in a conditioned fear response. Subsequently, another memory is created during extinction learning, in which the same CS is linked to no-US resulting in the extinction of the CR. Either the original CS-US memory is suppressed, resulting in no CR, or in the case of spontaneous recovery, the CS-no-US memory is suppressed resulting in recovering of the CR. Which memory is perceived as inappropriate depends on yet other information in the limbic system, namely information about the specific context represented by the hippocampus [64,66,72–74]. This hippocampal context information influences the expression of fear extinction through mediation of the vmPFC (or IL) [64,66,74]. Inactivation of the hippocampus has similar effects on extinction recall as inactivation of the vmPFC, suggesting that these two structures work together to mediate behavioral responses to conditioned stimuli [74]. Also in humans, the vmPFC and hippocampus are activated in concert, and functionally connected during recall of fear extinction [64].

3.4. Damage to the vmPFC can lead to confabulation

Another disorder that is associated with damage to the vmPFC, including the subgenual vmPFC, is confabulation [43,46,75]. Confabulating patients produce spontaneous narrative reports of events that never happened, often during autobiographical memory recollection. Although confabulators frequently show memory impairments, confabulation is widely believed to result from impairments in selective executive or memory control processes, responsible for the verification of recollected information [46,75–77]. The content of confabulations mostly relate to the recent past, the present and the future, while remote semantic

memory commonly is not mixed up [75]. Some studies report that patients occasionally confabulate about remote autobiographical memory, and in some studies confabulations extended to remote semantic memory [9,42,78]. Furthermore, confabulators fail to distinguish between current and previous events [79].

Confabulations can often be traced back to elements of actual events in the patient's past [75]. It is proposed that the deficit underlying confabulations in patients with vmPFC lesions is the inability to suppress currently irrelevant memory traces [75,79,80]. In line with this, patients with vmPFC lesions often show increased false alarm rates in memory test, while having normal hit rates [42,79,81]. These findings suggest that the patients are able to retrieve memory but fail to monitor or select the retrieved information for task appropriate response. Gilboa and Moscovitch propose that the vmPFC is involved in rapid and preconscious monitoring of retrieved memories, and lesions in this area result in failure to filter out erroneous memories [42,43]. This interpretation is somewhat different from the above suppression interpretation by Schnider and colleagues [79]. Both interpretations, however, agree that the vmPFC is not involved in memory storage, but in monitoring retrieved memory.

3.5. Conclusions for proposed function of the vmPFC in remote memory representation

Recapitulating, it was found that the activity of the subgenual part of the human vmPFC (shaded area in Fig. 3a), increases with consolidation, just as the rodent mPFC does (Fig. 2). A lesion of the rodent ACC impairs specifically remote, and not recent memory, while a lesion of the hippocampus impairs recent and not remote memory [20,22,23]. Therefore we and others proposed earlier that this part of the human vmPFC is homologous to the rodent ACC and involved in the representation of specifically remote memory, by linking the neocortical representational areas (Section 1, and Fig. 2a). However, after reviewing the above literature on the human vmPFC, the subgenual part in particular, we come to the conclusion that the proposal about the linking function of the human vmPFC is not supported by the data from these other fields of research.

Firstly, lesions to the human vmPFC do not result in a clear impairment of remote memory while sparing recent memory, as is shown in rodents after ACC lesions. Instead, lesions of the human vmPFC result in much more extended deficits, i.e. in the regulation of emotional behavior, deficits in valuation leading to risky decision making, and confabulation. If the vmPFC has a role in remote memory specifically, it would be expected that confabulating patients would mostly make errors or false reports about remote memory. This is, however, not what is observed. Additionally, neuroimaging studies show that the subgenual vmPFC is involved in the valuation of accumulated information, derived from past, but not specifically remote experiences.

Secondly, the literature on fear conditioning, which is thoroughly investigated in both rodents and humans, proposes that the functional homologue of the subgenual vmPFC is the rodent IL and not the rodent ACC [38,64,65,67]. Furthermore, it is proposed that the dorsal part of the human ACC is the homologue of the rodent PL [38]. The rodent ACC is located even more dorsally than the PL (Fig. 3c). Therefore it is likely that the human homologue would also be located in the dorsal ACC, or even in the dorsolateral prefrontal cortex [82]. Based on the enormous expansion of the prefrontal cortex in humans compared to rodents, the homologue of the rodent ACC might be distributed over a much larger area of the dorsal prefrontal cortex in humans. Thus, even though both the human subgenual vmPFC and the rodent ACC increase their involvement with memory consolidation, and are both located in the medial PFC, the function of the rodent ACC in remote mem-

ory representation cannot be extrapolated to the human subgenual vmPFC.

4. New proposal for the role of the subgenual vmPFC

What could then be the function of the subgenual vmPFC, which explains the involvement of this area in memory consolidation, and is also compatible with the findings reported in other fields of neuroscience? A striking commonality in the reviewed literature is that the subgenual vmPFC specifically plays a role in tasks involving *limbic structures*, e.g. the amygdala, the ventral striatum and the hippocampus. This is not surprising since, as mentioned in Section 2, the subgenual vmPFC contains the ventral region of the cingulate cortex which is part of the limbic system. Additionally, the whole vmPFC is intensively interconnected with the structures in the limbic system [35–37]. We propose that the subgenual vmPFC most likely *integrates* information which is represented in these separate areas of the limbic system. Based on this integrated information, the subgenual vmPFC appears to subsequently *control* (mostly in an *inhibitory* way) these limbic areas, preventing them from responding inappropriately (Fig. 4). Finally, we propose that the integrated representation which is present in the subgenual vmPFC becomes *increasingly important over time*, because it might replace some of the direct connectivity amongst the limbic areas.

4.1. The subgenual vmPFC integrates activity in the limbic system, and subsequently suppresses inappropriate limbic activity

Our proposal that the human subgenual vmPFC is important for integration, and subsequent inhibition of activity in the areas of the limbic system, is in line with the fear extinction literature, where the subgenual vmPFC (and rodent IL) is proposed to *integrate* the original amygdala dependent CS-US memory and the competing CS-no-US memory, depending on the specific context represented by the hippocampus. Subsequently, the subgenual vmPFC *inhibits* the activity of the limbic areas which is inappropriate in the current situation [38,68,71].

Our new proposal is also supported by the results in the valuation literature, firstly, because the vmPFC seems to *integrate* information from the limbic system to achieve valuation. In several studies, the vmPFC unites separate representations of value in the ventral striatum, resulting in vmPFC activation in conjunction analyses. For instance, the vmPFC appears to integrate gains and losses [58], as well as expected value and reward magnitude [60]. Additionally, the vmPFC might integrate value information in the striatum with the appropriate memories stored in the hippocam-

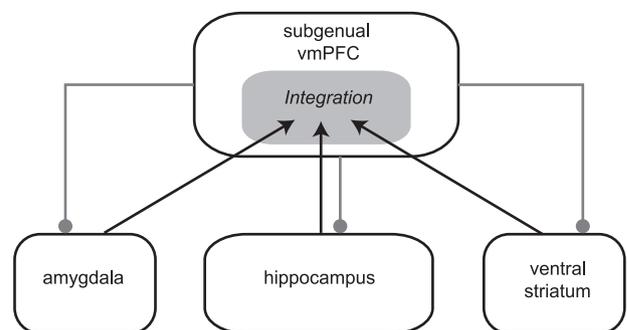


Fig. 4. Role of the subgenual vmPFC. The subgenual vmPFC receives input from the separate areas of the limbic system, the amygdala, the hippocampus and the ventral striatum. The information is integrated and weighted and it is subsequently stored how the information in the different areas relates to each other. The integrated representation is used to suppress irrelevant information in the limbic structures. See text for more explanation.

pus, since a loss of the vmPFC impairs especially the proper use of past reward outcomes to predict future probabilities. Secondly, the subgenual vmPFC (rodent IL) is also proposed to *suppress* the activity of the ventral striatum through excitation of the inhibitory network via the shell of the nucleus accumbens [34,38]. Rodent studies investigating the extinction of (ventral striatum dependent) drug seeking behavior, indicate that the IL is involved in the suppression of this behavior [83,84]. As mentioned, damage to the vmPFC can lead to increased risk taking in humans, which may also be due to an impaired inhibition of the ventral striatum signaling reward expectancy. The vmPFC might compute the probability of gain, as accumulated over past episodes, and subsequently suppress the ventral striatum when the accumulated prediction of gain is low.

Furthermore, confabulation, which can occur with extended damage in the vmPFC, might be the result of impaired integration and suppression of limbic activation. However, due to the lack of a good animal model of confabulation, and the uncontrolled extent of the lesions in human patients, this interpretation is more speculative than in the valuation and fear extinction fields. The subgenual vmPFC may weight or “value” different memories retrieved from the hippocampus, possibly based on the integrated activity present across the limbic structures. This would be related to the interpretation of Moscovitch and Gilboa and colleagues, who have described the function of the vmPFC as determining a quick intuitive “feeling of rightness” [42,43]. The subgenual vmPFC might subsequently use this new valued representation of the memories to *suppress* inappropriate activity in the hippocampus, i.e. inappropriate hippocampus dependent memories.

Although it is already proposed in the confabulation literature that confabulation might be caused by the inability to suppress currently irrelevant memory traces [75,79,80], we now add the notion that specifically memories dependent on the limbic system, and thus the *hippocampus* in particular might be insufficiently suppressed. This claim is in line with the observations that the erroneous content in confabulations mostly relates to hippocampus dependent memory, namely events from the recent past and present, besides producing plans for the future that are incompatible with the current state of the patients [75,80,85,86]. Some studies report that patients occasionally confabulate about remote autobiographical memory, but this memory can also still be supported by the hippocampus [9,77]. Confabulations can also extend to remote semantic memory [9,42,78]. At first glance, this might seem in contradiction to our hypothesis, since semantic memory is thought not to rely on the hippocampus. However, the confabulating patients were instructed to retrieve a series of historical facts or semantic narratives (fairy tales or bible stories). The act of retrieving in itself also creates new hippocampal (episodic) memory about the event of retrieving. It is reported that the patients incorporated details from one story into another [42,87]. This could be due to a failure in suppression of the just newly encoded events. If this is the case, it is expected that confabulation increases over the course of the experiment, and that mainly details are incorporated from previously retrieved stories. Unfortunately, it is not conclusive from the description of the studies above, whether this pattern was present in the data or not [42]. It has indeed been shown that preceding retrieval (in the form of a 5-min intensive discussion) can subsequently induce confabulations [88]. An explanation for confabulations extending the semantic domain in the study by Kopelman and colleagues [78], might be that the patients in this study had more extensive lesions than the vmPFC.

Specific experiments are needed to explicitly test whether the subgenual vmPFC suppresses activated hippocampal memory traces and if so, how this happens. The subgenual vmPFC is directly and indirectly connected to the hippocampus, making it very suited

for exerting control over memory retrieved by the hippocampus. The vmPFC receives direct connections from the hippocampus [89–91], and projects back to the hippocampus via the nucleus reuniens of the thalamus and to the entorhinal and perirhinal cortex [35–37,92]. The suppression of irrelevant memories could either be realized by directly inhibiting them in the hippocampus, or the vmPFC might act as a filter, only passing through the relevant hippocampal events. This filter might work by facilitating and/or inhibiting specific flows of output from the hippocampus. Concordantly, the mPFC (IL and PL) in cats has been shown to facilitate communication from entorhinal to perirhinal cortex after consolidation [93].

In summary, we propose that the role of the human subgenual vmPFC is (1) to integrate representations which are present in the separate areas of the limbic system (e.g. the hippocampus, the amygdala and the ventral striatum) and based on this integrated representation, (2) to subsequently suppress the activity of those limbic areas that would otherwise respond inappropriately. This proposal is in line with results in the literature of fear extinction, risky decision making and valuation. Moreover, our proposal adds to the current confabulation literature that confabulations in patients with vmPFC damage might be caused by the lack of inhibition of specifically *hippocampus* dependent memory. Finally, direct measurements of activity in the involved brain regions in animal studies also support our hypothesis, e.g. extracellular recordings of single-unit activity in anesthetized rats show that excitatory and inhibitory inputs from the hippocampus and amygdala converge and interact in the IL [94].

4.2. The subgenual vmPFC takes over connectivity within the limbic system with the progression of time

An important remaining question is how the reported increased involvement of the vmPFC with memory consolidation is in line with our new proposal. In other domains of neuroscience, the involvement of the subgenual vmPFC or IL also increases with time. For instance, in the fear extinction domain, it is reported that initial extinction depends on the amygdala and hippocampus alone, while after 24 h the extinction memory additionally becomes dependent on the subgenual vmPFC (or rodent IL) for retention of the extinction memory [65,69]. In a trace conditioning study, in which cats learned to associate a visual stimulus with a food reward, the involvement of the IL increased across the 9 days of learning, facilitating hippocampus to neocortical communication [93] (note that the cat and rat IL are very similar [95]). Interestingly, sleep following emotional memory learning, increases subgenual vmPFC activity and functional connectivity between the hippocampus and the subgenual vmPFC specifically for emotional memories compared to those that were neutral [96]. Additionally, there is evidence that stimulation of hippocampal cells induces monosynaptic AMPA-receptor dependent activation of IL neurons, indicating that the hippocampal-prefrontal network can participate in the formation and consolidation of memories [97]. In summary, both the activity in the subgenual vmPFC (or IL) and the connectivity between the hippocampus and the subgenual vmPFC, seem to increase with memory consolidation.

We propose that the importance of the integrated representation in the subgenual vmPFC might increase with the progression of time, because it may replace some direct connectivity across the limbic areas, which decays with time. This is supported by the study of Narayanan and colleagues [98] which investigated the network activities in the amygdalo-hippocampal system of mice at different stages of fear memory consolidation and retention. They show enhanced theta phase synchronization between the hippocampus and amygdala during the retrieval of fear memory

24 h post-training, but retrieval of remotely conditioned fear (30 days post-training) failed to induce an increase in synchronization despite there still being memory retention.

Thus, the emotional value of memories might be first represented by direct connectivity between the hippocampus and amygdala (and possibly also the ventral striatum). Subsequently, over time the subgenual vmPFC (or rodent IL) starts capturing the integrated limbic representation, while the direct hippocampal to amygdala (and ventral striatum) connections weaken. Importantly, the integrated representation within the subgenual vmPFC does not seem to be independent of the limbic structures, rather it seems that the subgenual vmPFC somehow represents how the representations in the limbic structures relate to each other. Therefore, besides an increase in subgenual vmPFC activity, also the interactions between the vmPFC and the limbic system should increase over time. Numerous studies indeed report an increase in hippocampus to subgenual vmPFC interactions with time (for review see [99]). In the first few days after learning, the subgenual vmPFC and the hippocampus show a sleep dependent increased interaction [25,28]. In offline periods after learning, also crosstalk between the hippocampus and subgenual vmPFC has been shown [100]. Additionally, coordinated activity between hippocampal ripples and spindles recorded in the mPFC has been shown during slow wave sleep in rats [101].

Our proposal that the subgenual vmPFC integrates the representations that are spread out across limbic system (hippocampus, amygdala and ventral striatum), leads to the prediction that the subgenual vmPFC is specifically involved in memories containing a reward, or fear component, i.e. emotional memories. In many of the laboratory studies that reported an increase of subgenual vmPFC activity with consolidation, the task had some emotional or reward component, or contained feedback which likely results in an emotional response [25–28]. Also, the mere motivation of the subjects to perform well on the expected memory test may result in limbic activation. Another possible explanation for the increase in vmPFC activity with time is related to the fact that memory decays over time. The subgenual vmPFC could play an important role in rapid and preconscious monitoring of retrieved remote memories: a theory that was proposed in the confabulation literature [42,43]. Additionally, the decay of remote memory could make reactivation of the target memory trace more difficult, resulting in a more extensive search process to access and retrieve the appropriate, task relevant remote memory. This extensive search could concurrently activate additional related, but irrelevant hippocampal traces, whose activity subsequently needs to be suppressed by the vmPFC. Thus, the activity of the vmPFC might be correlated with the amount of potential co-activation of related but irrelevant memory traces, and is therefore expected to be high in (decayed) remote memory, but also in memory (recent and remote) with high interference by related events.

In summary, we propose that the integrated representation in the subgenual vmPFC becomes increasingly important with memory consolidation, by replacing the direct connectivity amongst the limbic structures. Our new proposal has several important differences from what was proposed before (Section 1, Fig. 2a): First, although the importance of the subgenual vmPFC representation increases over time, the subgenual vmPFC is both involved in recent and remote memory. Second, the subgenual vmPFC is specifically important for memories that contain information which is spread out over different areas of limbic system, thus memories containing reward, or fear information (emotional memories). Third, the subgenual vmPFC does *not* start linking the neocortical representational areas with memory consolidation, but instead links the areas of limbic system. Finally, the subgenual vmPFC is not homologous to the rodent ACC, but to rodent IL.

5. Implications and recommendations for future research

There are several testable predictions that come forth from our proposal. The activity of the subgenual vmPFC should increase more during the consolidation of emotional memories, or memories with a reward component, than for neutral, unrewarded memories. Damage confined to the IL (or subgenual vmPFC) should impair hippocampus dependent memory retrieval, especially when there are related irrelevant memories present that can interfere with the target memory. The connectivity amongst the limbic structures should decrease with consolidation, together with an increase in the functional interactions between the subgenual vmPFC and the limbic structures. In future studies, it is highly important to discriminate between the different substructures of the mPFC in both humans and animals. As we and others have pointed out, the mPFC consists of several functionally distinct areas. It would be interesting to investigate the differences between the activity of the IL, the PL and the ACC during consolidation in rodents. Prefrontal trace reactivation was shown during sleep [102–104]. According to our theory, they should interact strongly with the structures in the limbic system, while the ACC might functionally interact to the neocortical representational areas. Replay of activity in the IL should be synchronized with replay in the amygdala, and the ventral striatum, as has been shown with replay in IL and the hippocampus [104]. The role of the IL and the PL is proposed to be opposite; the IL is suppressive, while the PL has an increasing effect [38,70]. It is plausible that the IL interacts with hippocampal networks representing context memories that have to be suppressed, while PL is indexing the memories that have to be supported. It would be interesting to compare reactivation of IL, PL and ACC neurons and how that affects the consolidation of the memory trace. Based on the previous speculation, neurons in the PL might be reactivated most, as they index those hippocampal memories that have to be maintained. On top of that, the time between learning and replay might be different for the specific brain areas. Hippocampal replay might first lead to synaptic modifications in IL and PL. Subsequently those areas might also engage in replay leading to synaptic modifications in the ACC, which may code representation of the remote memories.

Although the extent of lesions is uncontrollable in humans, and the precision of non-invasive neuroimaging studies is more limited compared to animal studies, important efforts can be and are being made to study the function of localized mPFC areas in a meaningful way. An example is to perform similar tasks in animals and humans, and converge findings over species. Another example is to make use of functional connectivity analyses in neuroimaging studies during the execution of specific memory paradigms. Since the anatomical connections to other areas profoundly differ between the distinct subareas of the mPFC, this could elucidate their specific functional role.

The rat ACC does seem to be crucial specifically for remote and not recent memory retrieval [20,22,23]. It is interesting to further examine the function of this brain area in remote memory, and to investigate if this area indeed links the neocortical representational areas in remote memory, similarly as the hippocampus in recent memory [17,18]. This could be examined by focusing on changes in functional interactions between the rodent ACC and the neocortical representational areas with consolidation. It is conceivable that the rodent ACC specifically represents the integrated part of remote memory that deals with value, fear and reward, by interacting with the IL and PL.

In this article, we have reviewed the role of subgenual vmPFC in relation to memory consolidation. After converging findings on the role of vmPFC in memory consolidation with results from decision making, fear-conditioning, and confabulation, we propose that the subgenual vmPFC functions as an integrator and suppressor of

activity in the limbic areas. Future studies are needed to empirically test this working hypothesis.

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