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Prefrontal – Hippocampal Interaction: An Integrative Review and Model of the Think/No-Think Task with Implications for Psychiatric Conditions

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Abstract

Being able to dynamically control accessibility to memories enables humans to flexibly adapt to their environment. When this control fails we become acutely aware of emotionally painful reminders of past events. Individuals suffering from some psychiatric conditions are plagued by intrusive, uncontrollable thoughts and ruminations of such memories. To gain a better understanding of this pathos, it is first essential to investigate the neural pathways that allow for control over memory accessibility in the non-psychiatric brain. To do so, a review of the neuroimaging Think/No-Think literature is used to provide possible brain regions that contribute to the control over memory accessibility. Using these results combined with literature from comparative anatomy/neurology, a neuroanatomical model is derived that provides more specific neural detail than currently in the literature. This model highlights the importance of PFC – hippocampal interaction and the possible mechanisms by which control over memory accessibility is achieved. By understanding these details, future directions for targeting research on psychiatric conditions will hopefully be achieved.

Keywords: Anatomy; Hippocampus; Memory; Neuroimaging; Prefrontal cortex; Retrieval

Introduction

Memory is the quintessential feature of connecting us to past events. It places us in our current context, reminds us of where we are going, and where we have come from. An important characteristic of humans is that we exhibit the ability to control various aspects of memory, which involves cognitive mechanisms that may flexibly influence our awareness of memory. Our overt attempt to control memory becomes most apparent when we are confronted with thoughts or memories that we wish to avoid thinking about. These memories usually revolve around traumatic events that are emotionally painful. Reliving such affective experiences may be beneficial to a point, as in bereavement [24]. However, lacking control over such memories may allow them to repeatedly become intrusive and ruminative in nature. This is most apparent in some psychiatric conditions, such as post-traumatic stress disorder (PTSD), where retrieval of and rumination over such memories may cause serious distress and impairment. While the connection of memory dysfunction to PTSD is ubiquitous, other psychiatric conditions and their connection to memory dysfunction is somewhat less so, yet easily recognizable. Ruminative thought patterns revolving around memories or thoughts are also present in disorders or classes of disorders such as: anxiety, depression, obsessive compulsive disorder (OCD), acute stress disorder (ASD), among others. One common theme uniting these disorders is a lack of control over thoughts that can be conceived of as internal representations stemming from memory.

One way to increase our understanding of how this lack of control over memory is manifest in psychiatric populations is to first realize how control functions in the normal individual. This empirical question has a long standing interest and history over the last 50 years in psychology and more recently in cognitive neuroscience. Starting with seminal work by Bjork and colleagues with the Directed Forgetting task [27](Bjork, 1971) and Wegner and colleagues with the White Bear Suppression task [47], attempts at understanding our control over memory and its awareness has been an integral part of memory research. More recently and perhaps more appropriately attuned to ecological validity, the Think/No-Think task [1,2,12-15] has been used to investigate our control over memory, during attempts to render memory information less retrievable.

While a number of paradigms have been used to investigate the control over memory retrieval, I focus on the TNT task in the current review for two main reasons: 1) the task requires individuals to associate pairs of stimuli and learn these pairs to a high degree, thus results from this task can be interpreted in the domain of controlling episodic long term memory (LTM) representations. This is of importance because the psychiatric conditions of significance to this review (e.g., PTSD) are characterized by repeated intrusions and lack of control over traumatic negative episodic memories, as well as associating relatively neutral stimuli to these negative memories, in which previously neutral stimuli now becomes threatening or negative in nature. 2) the task also invokes repeated attempts at controlling episodic LTM memory representations. Reducing the accessibility of memory may involve multiple attempts in order to gain control over such information. This has become evident in TNT tasks that evaluate the frequency of attempts which underlie successful reductions of retrieval [1,15,14,19]. These studies indicate that increases in attempts to control memory yield subsequent decreases in behavioral recall of memory information. This may relate to psychiatric conditions (e.g., PTSD), as one of the defining characteristics relates to the frequency of attempting to control thoughts about a traumatic event. Moreover, increases in repeated avoidance of traumatic memories relate to a poorer prognosis in individuals with PTSD [20]. Therefore, it is of utmost interest to understand why such individuals lack control over memory and to

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determine the relative brain circuitry that may contribute to these types of psychiatric conditions.

While significant strides have been made in attempt to understand our control over memory and lessen its retrieval, we still lack a precise neuroanatomical model that details the pathways and mechanisms by which this control is implemented. Therefore, the following brief review examines the neural regions that are putatively involved in controlling the retrieval of memory information, as well as neural regions this control is exerted upon. To do so, I review neuroimaging studies (both ERP and fMRI) using the Think/No-Think task, to elucidate the most commonly identified brain regions that support attempts to control memory. Subsequently, these results are used to base a model that provides at least a beginning structure of the neuroanatomical architecture and mechanisms that contribute to such control. The aim is to introduce such a model that can influence our understanding of how these mechanisms may work, so that subsequent future directions in investigating memory dysfunction in psychiatric conditions can be better targeted.

Think/No-Think (TNT) neuroimaging studies

To understand the relative contribution of TNT neuroimaging studies, a brief introduction of the paradigm and behavioral results are provided. Although the specific methodology may slightly differ from study to study, the general format which is used is presented. The TNT task involves three phases in consecutive order: 1) a training phase, in which individuals learn pairs of stimuli (cue-target) to a prescribed level of accuracy(criterion level). This ensures that the cue-target pairings have been encoded as LTM representations. 2) an experimental phase, in which individuals are presented only the cues of the previous pairings and instructed in one condition to "think" or in another condition to "not think" of the previously associated targets. Attempting to "think" or "not think" of the target when only externally presented with the cue, provides that individuals are manipulating the internal representation of the target stimuli. These cues are then shown a number of times (e.g., 12-16) to allow for multiple opportunities to exert control over memory information. Importantly, a subset of the originally learned pairings' cues are not presented during the experimental phase and serve as a baseline memory condition to which Think (T) and No-Think (NT) trials can be compared. 3) a testing phase, in which individuals perform a cued-recall test for all pairings, using the same cue as presented in the training phase (Figure 1).

Multiple behavioral results indicate that NT items are recalled less than T items and, crucially, less than baseline items that assess normal memory function. Reductions from baseline in recall for NT items suggest that attempts to control retrieval actually reduce the accessibility of these items [1,2,6,7,9,13-15,19,22,30,38,47]. Therefore, reviewing the neuroimaging results may help to understand the putative brain regions involved in the control over memory and the brain regions where such control is directed.

fMRI Studies

Results from fMRI studies are discussed in terms of contrast activity, such that an increase in BOLD activation in one condition is compared in relation to other conditions. In general, findings are placed in the context of greater activation or signal in the condition that requires attempts to reduce retrieval as compared to conditions that enhance retrieval (i.e., NT>T).

The influential first neuroimaging study using word stimuli showed behavioral reductions of NT as compared to both T and baseline trials, important to indicate that individuals actually reduced retrieval (Anderson et al., 2004). fMRI results indicated increased activation (NT>T) in the middle and inferior frontal gyri (MFG, IFG), anterior cingulate cortex (ACC) and parietal cortex, whereas the occipital lobe and hippocampus showed decreased activity. These findings were the first to suggest that reductions in memory are associated with cognitive control processes of the lateral prefrontal cortex (LPFC) interacting to down-regulate the hippocampus. This claim is based on a breadth of literature suggesting that regions of the right LPFC (i.e., rIFG, rMFG) become more active in situations that: require inhibiting or withholding a motor response [3,4], require suppressing or attempting to lessen an emotional response [2,33], or reduce the feelings of social rejection [16].

Following up the Anderson and colleagues study [1,2,30], Depue and colleagues (2007) [14] used the TNT task under fMRI to investigate whether regions of the LPFC were also elicited when control was elicited over emotional and pictorial stimuli. Behavioral reductions of NT as compared to both T and baseline items were found ensuring that participants successfully lessened retrieval during the NT condition. fMRI results showed increased activity (NT>T) in rMFG and rIFG. Decreased activation was seen in visual cortex, the pulvinar nuclei of the thalamus, the hippocampus and amygdala. Moreover, when examining NT vs. baseline trials, these posterior cortical regions again showed reduced activity raising the possibility that these regions are actively being down-regulated. Furthermore, analyzing the data in quartiles (over the experimental phase) and correlating activity between the two PFC and four posterior cortical regions demonstrated specific groupings of regions that were recruited at different stages. Increased activation of the rIFG inversely correlated with decreased activation of visual cortex and thalamus during the first NT attempts. In contrast, increased activation of the rMFG inversely correlated with decreased activation of the hippocampus and amygdala after additional NT attempts. This last grouping also correlated with behavioral success during NT trials such that increased activation of the rMFG and decreased activation of the hippocampus were the only two regions that predicted greater reduction of behavioral recall in a whole brain fMRI analysis [14]. Importantly, these findings replicate the idea that the LPFC interacts with the hippocampus during attempts to lessen retrieval. Furthermore, they introduce a specific interaction between the MFG and hippocampus, evident as the prefrontal region that showed correlations with the hippocampus and greater reduction in behavioral recall. While both these results and the previous results of Anderson and colleagues (2004) [2], suggest that LPFC may communicate with the hippocampus, these findings are corollary and causation cannot be inferred from them.

A more recent fMRI study using the TNT task examined negative and neutral word pairs [10]. Behavioral differences were reported as close to ceiling, so that interpretation of recall is difficult. Nonetheless, fMRI results for neutral words show increased activation (NT>T) for rMFG, pre- and post-central gyri, and the inferior parietal cortex. Decreased activation was found in the bilateral hippocampus and precuneus. A region of interest (ROI) analysis on the hippocampus comparing both NT and T trials to baseline showed that posterior hippocampal activity was reduced below baseline for NT trials. Examination of negative words yielded increased activity (NT>T) in similar frontal regions (i.e., rMFG, rIFG, pre- and post-central gyri), the ACC and parietal cortex, although it also showed increased activation in the hippocampus, pulvinar, and visual cortex. The authors suggested that one reason that increased activation was seen in posterior cortices for negative and not neutral stimuli is that NT trials lasted half the

duration of most studies (2 vs. 4 sec) and included half the repetitions (6 vs. 12 or 16) of the previous studies by Anderson and Depue and colleagues [1, 2,13-15,30]. These findings further support the putative interaction between the MFG and hippocampus during the control over memory retrieval, although in cases where stimuli are extremely salient, more repetitions may be required to achieve successful control.

Only one study has examined the feasibility of memory control as assessed by the TNT in a psychiatric population. This study conducted by Depue and colleagues (2010) [13] examined whether MFG interaction with the hippocampus was evident in individuals that are characterized as having inhibitory deficits. Thus, individuals with attention deficit hyperactivity disorder (ADHD) were compared to the group of control individuals investigated in a previous study [14]. Behavioral results indicated that individuals with ADHD have similar recall on T and baseline trials, but show no reductions in recall during NT trials, importantly highlighting an inhibitory deficit. fMRI results (NT>T) indicated that when compared to controls, some prefrontal regions exhibit similar activation (i.e., rIFG, BA10), while the rMFG, thought to be crucial in communication with the hippocampus, showed decreased-to-little activation. Supporting this former idea, brain regions outside of the PFC (i.e., hippocampus, amygdala and visual cortex) also showed increased activation as compared to controls. Furthermore, the severity of ADHD symptoms predicted a) less correlated activity between the rMFG and hippocampus, b) increased activity of the hippocampus and c) increased recall during NT trials. Furthermore, increased response time during a Stop-signal task, a task widely used to evaluate control over motor response [3,4], was correlated with a decreased ability to reduce recall, further characterizing these individuals' inhibitory control deficits. In an additional analysis, 5 of the 16 individuals who showed behavioral reductions in recall were compared to the 11 that did not. These 5 individuals showed greater activation (NT>baseline) in the rMFG, whereas reduced activation was exhibited in the hippocampus and amygdala during the fourth quartile, mirroring results of control subjects. These findings, once again, highlight the important interaction between cognitive control of the MFG and its purported modulation of the hippocampus. Taken together, the altered control over memory findings from ADHD individuals support the explanatory power of TNT neuroimaging results identified in psychiatric individuals.

ERP studies

While fMRI evidence is more intuitive because of distinct regional brain activations indicating possible functionality, ERP evidence requires a brief introduction. When discussing ERP evidence, findings are presented in terms of "ERP components or effects," which are distinct waveforms that indicate the spatial and temporal properties of neural processes (i.e., attention, memory). These ERP components have long-standing terminological conventions in relation to retrieval processes. Two main ERP components will be discussed: i) the N2, which is elicited during tasks that require inhibition of a prepotent response (e.g., Stop-Signal, Go-No-Go). This is an early ERP component (~200 msec post-stimlus) localized to midline or right lateralized frontal electrodes that shows greater amplitude for stimuli requiring inhibition than stimuli with no inhibitory requirement. Thus, this component is perhaps indicative of inhibitory processes of cognitive control [43]. ii) the parietal old/new effect, which is elicited during recollection memory. This later ERP component (~400-800 msec post-stimulus) localized to parietal and temporal electrodes shows greater amplitude for stimuli that have been previously memorized than to new stimuli. This component is perhaps indicative of facilitated retrieval of information[37].

Two ERP studies by Bergstrom and colleagues using the TNT task with word stimuli dissociated early and late components of the ERP signal [6,7]. The first study showed behavioral reductions in NT items compared to T, but not compared to baseline. ERP results were analyzed on the basis of T and NT, as well as learned vs. not learned stimuli. Parietal old/new effects were greater for Think-learned than the other three conditions, perhaps indicative of increased retrieval processes of these items. These latter results suggest that NT items regardless of learning may undergo control processes that are aimed at reducing retrieval.

The second study included an "aided" condition during NT trials in which individuals were instructed to think of a diversionary memory to distract themselves [6]. Behavioral results indicated that both standard NT and aided NT items were reduced below baseline. Although, an independent probe condition (IP) used during recall testing to assess memory items (NT, T) with an alternative cue (cue-independent), indicated only a behavioral reduction in NT items from both T and baseline in the standard NT condition. ERP results showed an increased N2 effect in both NT (standard, aided) as compared to T conditions, although was larger for the standard NT items. Furthermore, the N2 showed a correlation between the magnitude of this effect and individual differences in NT item IP recall only in the standard NT condition. This finding suggests that the N2 may be associated with successful cue-independent reductions of NT items. Additional frontal effects (~300-500) elicited only by the standard NT items showed the greatest increase in signal for NT-forgotten trials as compared to, intermediate levels for NT-remembered trials and the least increase in T-remembered trials. Parietal old/new effects were decreased in the standard NT but not in the aided NT condition. These results indicate that standard NT trials elicit increased N2 and later frontal effect that is subsequently followed by reductions in parietal old/new effects, perhaps further indicative of a frontal control mechanism aimed at retrieval processes.

To assess the similarity of ERP components that may be involved during the control of memory and motor information, one study examined both the TNT task and a Stop-signal task [25]. Although behavioral results showed no effect of NT items in terms of reduction below baseline, NT items did show similar ERP effects to other studies [6,7], in that a decreased parietal old/new effect was seen for NT as compared to T items. An increased N2 effect was also present in NT>T trials and also in NT-forgotten vs. NT-remembered trials. Furthermore, correlations were found for the N2 component from the TNT and Stop-signal tasks, indicating a positive relationship between the control over memory and motor information. These results support previous findings of an increased N2 followed by a decreased parietal old/new effect for NT items, perhaps again indicating frontal control mechanism aimed at retrieval processes.

An interesting ERP study examined how anticipatory cues affect the ERP components associated with the TNT task using face-word pairs [19]. Red (NT) and green (T) crosses were presented as anticipatory cues 1 sec prior to the T and NT trials to assess anticipatory control. This study also included a separate repetition manipulation that assessed recall for NT and T trials at 5 and 10 attempts. Behavioral results showed no reduction in recall for NT items compared to baseline at 5 repetitions, but reduced recall after 10 repetitions. ERP results indicated an early and late effect that changed over the course of repetition. As repetition increased, reduced signal in the early slow-

wave frontal component and later parietal old/new effect was seen in NT trials, perhaps indicative of increased control manifest in early NT repetitions. The frontal component, furthermore suggests, control in response to the anticipatory NT cue, which consequently results in reduced retrieval as indicated by the later reduced parietal component. Supporting this view, the two ERP effects were highly correlated, such that magnitude of the early effect predicted the magnitude of the later. These results indicate an increased early slow-wave frontal component (which may be functionally related to the N2) elicited by anticipatory cues, subsequently followed by a reduced parietal component (perhaps functionally relate to parietal old/new effects) elicited during NT trials.

Summary of neuroimaging studies

This neuroimaging review, although brief, has indicated two major reoccurring findings. The first is evident from fMRI experiments clearly showing increased activation of regions of LPFC (most prominently rMFG), associated with decreased activation of the hippocampus during NT trials in both whole brain and ROI analyses [2,10,13,14]. Correlations between these two regions, as well as correlations of each of these regions independently [2,14] and their combined correlation [13] predict behavioral reductions in recall. Second, multiple ERP results from the TNT task indicate increased N2 effects, suggesting increased prefrontal control. Perhaps indicative of this control, reduced parietal old/new effects are found, suggesting a decrease in retrieval processes [6,7,19,25].

Taking the fMRI and ERP results together, the best indication of the processes occurring during attempts to control memory highlights MFG interaction or communication with the hippocampus to reduce the retrieval process. This is evident in all fMRI studies, which show increased activation, specifically of the MFG, as well as decreased activation of the hippocampus. Although not as spatially precise, ERP studies corroborate the fMRI findings with temporal specificity, which indicates that this process may involve early frontal control (N2) over retrieval processes (parietal old/new). Moreover, these findings are supported by one study examining individuals with ADHD that show a lack of activity in the MFG, the control area putatively thought to be important for communication with the hippocampus. Perhaps indicative of this lack of control, posterior cortical regions that support memory representation were also found to show increased activity and subsequently no behavioral reduction in NT trials. Importantly, these results indicate the possible utility of using models derived from TNT results to assess aberrations in the control over memory retrieval. Therefore, the culmination of these results indicate that perhaps the most fruitful endeavor, concerning control over memory retrieval, is uncovering a better understanding of the interaction of the MFG and hippocampus.

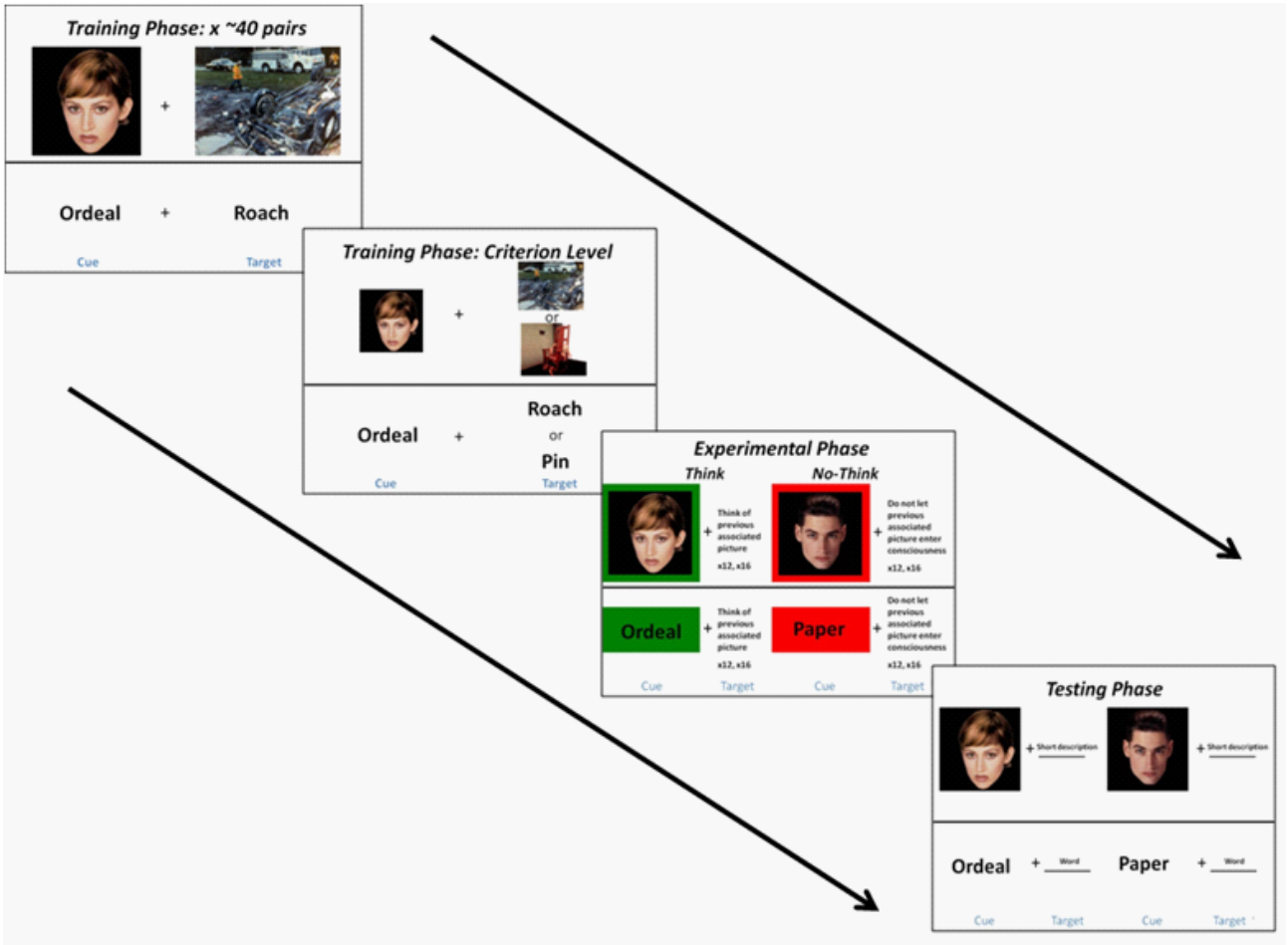

Figure 1: Depiction of the TNT task. The tops of panels show examples of picture stimuli, while the bottoms show examples of word stimuli.

A neuroanatomical functional model

A model of the interaction of MFG and the hippocampus to control memory accessibility is rather incomplete unless it can be detailed with more anatomical and functional specificity. Therefore, I attempt to illustrate this model using literature from comparative anatomy to include more fine grained neural aspects. The goal is to provide a testable model that can guide future research examining the control over memory accessibility, as well as how dysfunction is manifest within such neural pathways.

Taken from the neuroimaging results, one mechanism appears to be critical during attempts to control memory retrieval, the MFG-hippocampus interaction. Therefore, it is important to first illustrate the specific anatomical connections of the MFG and hippocampus. While the specific anatomical substrates have been somewhat overlooked in cognitive neuroscience, comparative anatomy/neurology has strongly supported a reciprocal connection of the MFG and hippocampus [18,26]. The literature has primarily focused on three pathways connecting disparate parts of PFC and subregions of the hippocampal complex: the hippocampal-prefrontal, the lateral and the medial.

All three pathways have been shown to contain reciprocal connections of the PFC and hippocampus in animals and humans. The hippocampal-prefrontal pathway primarily connects the medial prefrontal cortex to the hippocampal complex through regions of the basal ganglia and thalamus and is involved with output of the hippocampus to regions involved in dopaminergic transmission (e.g., nucleus accumbens) [23,41,42]. The lateral pathway directly connects MFG areas BA9/46 (dorsal/mid) to the anterior hippocampal complex [18] and to the perforant path (all subfields of the hippocampus), considered the main route in which multimodal cortical pathways reach the hippocampus for subsequent encoding [45]. While undoubtedly important for memory processes, these pathways either do not involve the MFG, or are more involved with hippocampal input and encoding and as such will not be focused on.

However, the medial pathway connects the MFG, areas BA9/46 (dorsal/mid) to the presubiculum via the cingulum bundle [18,26]. This pathway courses medially and posteriorly from areas BA9/46 through the cingulum bundle, innervating the presubiculum and retrosplenial cortex/posterior parahippocampal gyrus, thus connecting more posterior regions of the hippocampal complex (Figure 2). Retrograde tracers injected in various areas of the PFC indicate that the MFG (BA9/46) projects to the posterior hippocampal complex, whereas frontal-polar (BA10), posterior dorsolateral PFC (DLPFC; BA8) and ventrolateral PFC (VLPFC; BA44/45/47) do not. These findings suggest a specific fiber bundle directly linking the MFG with regions of the posterior hippocampal complex [5,26]. Of note, these posterior regions of the hippocampal complex (i.e, retrosplenial cortex, presubiculum) send dense projections back to the MFG (BA9/46), suggesting these areas from a reciprocal neural network [5,26]. To demonstrate the function of this network, ablations to posterior regions of the hippocampal complex result in self-paced working memory (WM) deficits, while ablations to the anterior hippocampal complex (i.e., entorhinal cortex) yield no such deficit, therefore, suggesting that posterior areas are involved in output or retrieval processes of the hippocampus important for WM operations [26].Therefore, the medial pathway connecting the MFG and hippocampus may be of critical interest in the control over memory accessibility.

To understand the influence of the medial pathway and its putative

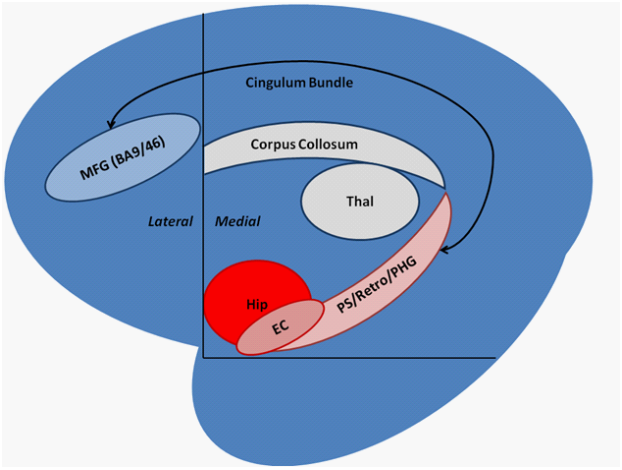

Figure 2: The medial pathway connecting MFG (BA9/46) to the posterior hippocampal complex (Thal = thalamus, Hip = hippocampus, EC = entorhinal cortex, PS = presubiculum, Retro = retrosplenial cortex, PHG = parahippocampal gyrus).

functionality in the control over memory accessibility, it is necessary to illustrate how retrieval of episodic LTMs occurs. Retrieval of a specific memory episode involves the activation of the neural representation of an internal or external cue, which fires in a feed-forward manner to the hippocampus, causing a sparse representation indexed, through original encoding, within the hippocampus to pattern complete [35]. Pattern completion then reactivates all the specific component representations of the memory episode through feed-back activation from the hippocampus to sensory regions that were activated during encoding of the original event. As more attention is focused on the emerging component representations of the features of the original memory event, the specific representations which were first engaged in perception are reactivated to some degree. Attentional resources (e.g., prefrontal and parietal regions) then continue the firing of these representations as a composite memory, which enables the maintenance of the memory and allows it to be accessible for other WM processes [21].

Taking the idea of pattern completion and the reactivation of memories into account, controlling the retrieval of memory may involve PFC down-regulation of these processes, so that subsequent maintenance for WM is reduced or does not occur. Reverting back to the fMRI results illustrates the biological plausibility of this mechanism transpiring and associates it to the medial pathway. Increased MFG activation is apparent across all fMRI TNT studies, possibly indicating PFC control [2,10,13,14], as this increase in activation is correlated with decreased hippocampal activation across and within individuals [2,13,14]. ROI analyses indicate decreased activation specifically in posterior hippocampal regions, the regions under influence of the medial pathway [10]. Moreover, across all fMRI TNT studies widespread deactivation was found in posterior cortices (i.e., ventral visual pathway, visual cortex) [2,10,14]. This is of great importance, because it suggests that these regions are less active, possibly as a result of decreased processing of the hippocampus and subsequent reductions of pattern completion and reactivation.

One question that remains is how down-regulation of the hippocampal complex is achieved. That is, how does MFG signal posterior hippocampal regions to reduce output?. Because the cell populations in the posterior projection zones of the medial pathway are

largely unspecified the question remains unclear. Perhaps providing some indication, regions of the presubiculum, as well as the entorhinal cortex contain dense GABAergic cells that enable feed-forward inhibition of input to the hippocampus [11,17,34,39,44]. Speculatively, regions of the posterior presubiculum, i.e., retrosplenial cortex and posterior hippocampal gyrus may also contain inhibitory inter-neurons that function as a gating mechanism to reduce the output of the hippocampus. This may be so, because flexible retrieval for WM may be necessary when determining relevant vs. irrelevant information. In any case, more research is needed to elucidate the specific cellular/physiological mechanisms by which the medial pathway functions.

In sum, using the previous anatomical details and functional account, a model of control over memory involves alterations of the retrieval process. This perhaps occurs via the medial pathway, reflected as increased cognitive control or activation of MFG to down-regulate the output of the hippocampus, which would likely involve reductions in (i) pattern completion and reactivation, (ii) subsequent activity in posterior cortex, and (iii) information to be accessed or maintained by WM, all of which are likely to affect the retrieval of memory information at any given moment.

Implications for psychiatric conditions

Although the current paper indicates a possible neuroanatomical pathway and functional mechanism that contributes to the control over memory retrieval, it is important to attempt to illustrate how this model may help us to better understand dysfunction in psychiatric conditions. The clearest and most direct example can be taken from the Depue and colleagues study (2010) [13] examining individuals with ADHD. When comparing these individuals to a control sample, reduced activity specifically in the rMFG and increased activity in the hippocampus and visual regions were observed. Furthermore, negative correlations between increased activity in the rMFG and decreased activity in the hippocampus, normally present in control samples, were absent. Incorporating these findings with the proposed model suggests that these individuals may lack PFC control, indicated by reduced recruitment of rMFG, over posterior cortical and non-neocortical regions (i.e., the hippocampus). Of course this is not novel in and of itself, as long-standing theoretical notions concerning these individuals implicate lack of behavioral control. This lack of control in ADHD has been most clearly evidenced in numerous studies that indicate reduced control over motor response, as well as reduced activation of regions of the right LPFC thought to underlie such response (i.e., rIFG) [36,40]. That being said, results from these individuals using the TNT task and proposed model help to understand lack of control in other psychological domains outside motor. This is important, because we gain insight into the emergence of what appears to be a "general" lack of control manifest in these individuals. Through the modeling of control over these individual domains (i.e., memory, motor) a greater specificity of dysfunctional brain circuitry can be achieved.

While relatively direct conclusions can be made from the study examining individuals with ADHD [13], no other studies examining individuals with psychiatric conditions using the TNT with neuroimaging have been published. Therefore, relating current findings and the present model to other psychiatric conditions is speculative. Nonetheless, psychiatric conditions that are signified by lack of control over memory and thought may benefit from understanding the specific neural pathways involved in controlling memory retrieval. PTSD is the clearest example in which individuals suffer reoccurring flashbacks and anxiety about specific LTM memory episodes. Anxiety, depression and OCD all have hallmarks of uncontrollable ruminative thought patterns. While PTSD is clearly about a "specific" memory representation, ruminative thoughts indicated in other conditions, must surely also stem from some LTM memory representation (e.g., leaving the oven on, I am worthless, people are going to laugh at me). Thus, understanding whether a lack of control over these memory representations is inherent to these conditions is highly of interest.

Of course other factors may exist, such as aberrant encoding of specific emotional events, which may create a hyper-accessible memory representation that functional control mechanisms simply cannot contend with. Providing such neuroanatomical models may help to decipher such differences. In the former case, the recruitment of putative control mechanisms over memory retrieval (i.e., MFG) should be relatively reduced in these individuals, as was indicated in individuals with ADHD. Whereas, in the latter case the control mechanisms maybe recruited in a relatively similar manner, although may have no effect on down-regulating brain regions they are targeting (i.e., the hippocampus). Understanding these dissociations is but one manner in which a model conceived from the normal functioning brain may be applied to understand the dysfunctional brain in psychiatric conditions.

Conclusion

In sum, the current review of neuroimaging TNT literature has indicated a specific interaction of the MFG and hippocampus to control the accessibility of memory information. Modeling the neuroanatomical circuitry of this interaction has provided specificity of the medial pathway reciprocally connecting the MFG and posterior regions of the hippocampal complex, involved in the output or retrieval processes of LTM. Control processes of the MFG may involve a mechanism to down-regulate the hippocampus, such that pattern completion and reactivation of LTMs are less likely to occur. If pattern completion and reactivation of such memories is reduced, accessibility of these memories for subsequent processes of WM maintenance may be lessened.

Relating the neuroimaging findings from the TNT task and proposed model may help to understand how lack of control over memory accessibility in some psychiatric conditions is manifest. Results from individuals with ADHD have demonstrated the utility of this endeavor. However, future research is required to understand the specific deficits in other psychiatric conditions which may display more selective control over memory impairments. Understanding whether these control mechanisms are dysfunctional, or whether specific memories become hyper-salient, such that functional control mechanisms have reduced effect, is imperative.

Moreover, understanding control over memory retrieval enables us to further understand higher-order cognitive processes of the PFC and their control over lower-order brain circuitry. Control processes over memory, emotion and complex motor response may function to adjust the flow of information from one brain region to another. This ability enables humans to be flexible in their environment and capitalize on adaptive advantages for on-going goal-related behavior. Only by understanding the specific neuroanatomical substrates of how this control is achieved in the normal brain, can we more fully understand dysfunction in the pathological brain.

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