Review

Neural binding mechanisms in learning and memory

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ABSTRACT

Binding mechanisms are considered as basic cognitive operations, performing different functions in learning and memory. This review will cover two of these binding mechanisms: relational binding of information about stimuli and actions with their spatio-temporal context into a circumscribed cognitive event and representational binding of feature representations common to a number of such events, thereby integrating these representations with existing knowledge and, thus, leading to decontextualized knowledge about the world. I will survey evidence from recent neuropsychological, electrophysiological and neuroimaging studies, including my own work, demonstrating that relational binding operations are performed within the hippocampal system, whereas representational binding is subserved by the surrounding medial-temporal lobe cortex and prefrontal brain areas. I then present examples of conditions that differentially implement both binding mechanisms. Lastly, summarizing the extant literature on binding mechanisms I speculate on whether these binding mechanism operate in a similar way across different cognitive domains or whether they are domain-specific.

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Contents

1. Introduction

Ever since the first report of profound amnesia following medial-temporal lobe (MTL) resection in patient H.M. (Scoville and Milner, 1957), there has been a large amount of research aiming at the functional role of the MTL subregions, especially of the hippocampus, in memory. This research includes all currently available methods, including neuroimaging studies and electro-physiological recordings in humans, single cell recordings in animals and neuropsychological studies of patients with brain injuries or of animals with experimental lesions. Despite that any research method has its own strength and limitations they all converge on the view that the hippocampus implements a variety of computational operations in the service of declarative memory (see Eichenbaum et al., 2007, for review). However, there is an increasing body of evidence challenging the view that hippocampal function is necessarily constrained to long-term memory. Based on the finding that implicit sequence learning caused hippocampal activity even in subjects for whom there was no evidence of awareness of the sequence (Rose et al., 2002; Schendan et al., 2003) it has been proposed that the hippocampus is engaged more generally on tasks requiring association of discontinuous stimuli and their contexts across time (Eichenbaum, 2006a). This so-called relational memory theory assumes that the hippocampus allows the flexible association of information stored in neocortex enabling memory retrieval of relations between elements of an event. Other models of hippocampal function focus on spatial processing, mainly driven by the discovery of "place cells" in a number of species including humans (Ekstrom et al., 2003; O'Keefe

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and Nadel, 1978). It has been proposed that the hippocampus is specialized for processing allocentric (world centered) spatial relationships to aid flexible navigation and provides the spatio-temporal context for episodic memories (Burgess et al., 2002). Moreover, it was demonstrated that even patient H.M., thought to suffer from a pure memory deficit, had severe deficits in language comprehension as indicated by his poor ability to identify the two meanings of visually presented ambiguous sentences (MacKay et al., 1998).

In this review I will briefly summarize the current state of the debate regarding the role of the hippocampus, and MTL in more general, in declarative memory. Although, the highly important contribution of animal research to this debate should be acknowledged, the present review focuses on human data. I then describe a view of MTL function, including its relation to other brain areas, that extends the relational memory theory to domains of cognition outside the domain of declarative memory. Some of the controversies regarding the role of the MTL in declarative memory are then revisited in light of this model and evidence for a domain-general function of the hippocampus will be provided.

2. The medial-temporal lobe and recognition memory

Converging evidence suggests that the MTL plays an essential role in supporting declarative memory (Aggleton and Brown, 2006; Bliss and Collingridge, 1993; Bird and Burgess, 2008; Eichenbaum, 2006a; Manns et al., 2003; Squire et al., 2007). One prominent view assumes that the MTL is involved in the recognition of a previously encountered event. Despite the broad support for this notion, there is an ongoing debate about what computations are performed by different subregions within the MTL. It has been recently suggested that the hippocampus and the surrounding medial-temporal lobe cortex (MTLC) support different aspects of recognition memory. In line with this view recent studies have demonstrated that the hippocampus and the parahippocampal cortex support recollection, i.e. recognition of an item on the basis of the retrieval of specific contextual details of the learning experience, whereas the perirhinal cortex subserves familiarity, i.e. item recognition on the basis of a scalar memory strength but without retrieval of any specific detail about the study episode (Aggleton and Brown, 1999; Eichenbaum et al., 2007). Consistent with this view, patients with severe hypoxic damage to the hippocampus exhibit disproportional deficits in associative recognition (relying on recollection) as compared to item memory (relying on familiarity, e.g. Holdstock et al., 2005; Mayes et al., 2002; Yonelinas et al., 2004). A similar pattern of impaired recollection and preserved familiarity has been observed in a patient with selective hippocampal atrophy caused by meningitis (Aggleton et al., 2005). In the same vein, neuroimaging studies employing tasks like associative recognition or source memory, in which participants were required to recollect specific details of the study event, demonstrated greater hippocampal activity for recollected items than non-recollected items (e.g. Bunge et al., 2004; Cansino et al., 2002; Düzel et al., 2003, but see Stark and Squire, 2001 for different results). Another method capitalizes on the view that recollection is a threshold process whereas familiarity varies in a continuous manner with response confidence (see Yonelinas, 2002). A number of studies have, therefore, used non-linear and linear approximations of confidence ratings (representing recollection and familiarity, respectively) to identify regions where hemodynamic activity increases or decreases with recognition confidence (Daselaar et al., 2006; Montaldi et al., 2006; Yassa and Stark, 2008; Yonelinas et al., 2005). Such parametric analyses showed that the hippocampal activity was related to recollection. In addition some studies found that, as perceived strength of familiarity increased activity in the perirhinal cortex increased (Montaldi et al., 2006; Yonelinas et

al., 2005). In contrast, others reported monotonic decreases in activity with increasing memory strength in the anterior perirhinal cortex and the anterior hippocampus (Daselaar et al., 2006). Yassa and Stark (2008) reported both decreasing and increasing activity as a function of increasing familiarity in the anterior and posterior perirhinal cortex, respectively. The latter finding emphasizes the contradictory results with respect to the role the MTLC plays in recognition memory. Moreover, the vast majority of recognition models argue that familiarity strength may not at all be linearly related to recognition confidence but rather has a normal distribution (Wixted, 2007; Yonelinas, 2002). Nevertheless, based on linearly decreasing activity of the perirhinal cortex and increasing activity in the posterior parahippocampal cortex, it has been proposed that the parahippocampal cortex is associated with familiarity whereas the perirhinal cortex is thought to code stimulus novelty (Daselaar et al., 2006). However, the same result, i.e. decreasing perirhinal activity with increasing memory strength has been taken as a putative familiarity signal (Gonsalves et al., 2005; Yassa and Stark, 2008). Thus, there is a major disagreement in the key operational definitions of familiarity and novelty among these studies. As I will argue below, information on the familiarity or the novelty of a stimulus/event are not encoded in the MTLC but can rather be derived from the operations carried out in the MTLC.

In an alternative view the same brain regions have been implicated in memory encoding rather than retrieval (e.g. Davachi et al., 2003; Ranganath et al., 2004). It was shown that encoding activity in the rhinal cortex was positively correlated with subsequent confidence in an item recognition task, whereas higher activity in the hippocampus and posterior parahippocampal cortex during encoding was linked to better source memory (Ranganath et al., 2004). Consistent with these reports, Stark and Okado (2003) observed that the activity in these regions during encoding predicted subsequent recognition performance. In addition, during recognition, MTL activity for the novel foil stimuli correlated with subsequent memory for these stimuli. That is, during recognition, these stimuli were incidentally encoded. This encoding-related activity was shown to obscure recognition-related activity. Taken together these results are suggestive of a more general role of MTL substructures in memory.

3. The binding view of MTL function

To overcome the explanatory limitations of models explicating MTL function in terms of novelty, familiarity, recollection or in terms of spatial mapping (Burgess et al., 2002; Ekstrom et al., 2003) recent models propose that the perirhinal and the parahippocampal cortex support the encoding and retrieval of item-specific and contextual information, respectively whereas the hippocampus stores representations of item–context associations (Davachi, 2006; Diana et al., 2007). This view is based on increased hippocampal activity in tasks emphasizing relational memory such as memorizing paired associates (Eldridge et al., 2005; Kirwan and Stark, 2004), source memory tasks (Davachi et al., 2003; Ranganath et al., 2004) and tasks requiring the spatial location of a previously presented item to be remembered (Staresina and Davachi, 2008; Uncapher et al., 2006). Conversely, in many of those studies activity in the perirhinal cortex correlates with item rather than relational memory performance (Eldridge et al., 2005; Kirwan and Stark, 2004; Uncapher et al., 2006). Although both models are similar to each other with respect to the relational binding operations subserved by the hippocampus, they differ in some important aspects. While the model proposed by Davachi (2006) is tied to encoding operations, Diana et al. (2007) view the binding operations in the hippocampus in support of recollection.

Extending the notion of binding outlined above, I propose that the hippocampus mediates the *relational binding* of disparate

cortical representations of items, actions, etc. and their spatio-temporal context that compose a unique experience. Such bindings can be described in terms of relational operations (e.g. identity, greater than or earlier than) that link together and organize the individual elements of this experience (Eichenbaum, 2006a; Engelkamp et al., 1998). For example, two persons meeting each other at a restaurant provide relational information about their identity with respect to the spatio-temporal context. The main properties of relational bindings, as described in the following, have considerable generality and potential utility in a large number of cognitive domains. Consequently, as the most import difference to the above-mentioned models of hippocampal functioning the present account proposes relational binding across several domains of cognition. Thus I suggest that the hippocampus is involved in a large variety of cognitive domains in addition to recognition memory including language and working memory whenever relational properties of the stimuli have to be processed. This is because relational bindings are highly flexible in that they allow for the rearrangement of the elements of individual experiences to deal with novel situations. Imagine a colleague, you usually meet at work or at a conference and you happened to meet him at a restaurant. You can easily master this new situation because there is no rigid relation between your colleague and the work/conference environment. This flexibility or productivity of relational bindings is achieved by their second property: compositionality. This means that the elements of a relation retain their identity in any binding, i.e. the representation of an element remains the same irrespective of the actual binding demands, so the representation of "your colleague" is the same regardless of the meeting situation. Thirdly, relational binding is a mandatory and automatic process in the sense that it is carried out whenever arbitrary information that has no pre-existing relationship has to be bound into a unique experience. Crucially the hippocampal circuitry possesses anatomical and computational characteristics to support all the properties of relational bindings described above (see Eichenbaum, 2006a, for a detailed discussion). This is also in line with a recently proposed biologically plausible neuro-computa-tional model suggesting that sparse neural coding within the hippocampus leads to two related phenomena (Norman and O'Reilly, 2003; O'Reilly and Norman, 2002). Firstly, sparse coding will reduce the probability that the same neurons within the hippocampus are activated by two different inputs, thereby leading to distinct (pattern-separated) representations and secondly, sparse coding will foster convergence of arbitrary item context bindings into a coherent representation of that event (Fig. 1A).

In contrast, as proposed by O'Reilly and Norman (2002) the MTLC assigns similar representations to similar input using overlapping representations to code for the shared structure of events. By this representations become sharper over repeated exposures. That is, the first encounter of an event weakly activates a large number of MTLC units, whereas repeated and thus familiar events strongly activate a smaller number of units (Fig. 1B). By this the MTLC is capable to mediate *representational bindings*, i.e. bindings linking common information shared by several events. That is the MTLC extracts the general regularities inherent in the recent experiences. These regularities mainly comprise frequency of co-occurrence but may also include transition probabilities or temporal contingencies (e.g. red and green in a traffic light). The representation of these regularities constitutes decontextualized knowledge (cf. Craik, 2006; Eichenbaum, 2006a), that is independent of the particular experience or context in which this information was initially encoded. The concept of *representational binding* can be contrasted with the notion of a perceptual representation system (PRS) that mediates the improvement in processing a stimulus as a results of its prior observation (Schacter, 1990). In contrast to *representational binding* the PRS does not represent elaborative information about the actual stimulus that can be linked to pre-existing knowledge. Instead, it provides a scalar signal of the perceptual similarity of two stimuli, that can be utilized in category learning, but is insufficient to establish a decontextualized representation of the regularities among these stimuli (Casale and Ashby, 2008).

However, there are limitations to the ability of the MTLC to abstract the regularities inherent in the recent experiences. As the
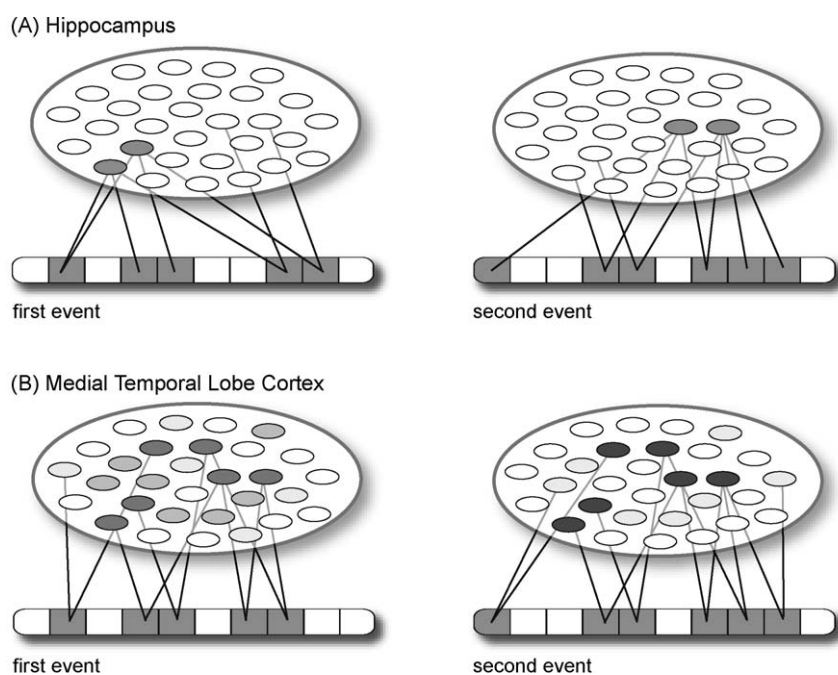
Fig. 1. Schematic representation of the neural coding elicited by two distinct but similar events. Small ellipses represent neurons in the hippocampus (A) or the perirhinal cortex (B). Gray ellipses denote active neurons. (A) In the hippocampus the two largely overlapping events will yield completely separated, relationally bound representations. (B) In the medial-temporal lobe cortex similar input yields similar, overlapping representations to code for the shared structure of events.

MTLC receives the majority of its inputs from unimodal and polymodal association areas (Suzuki and Amaral, 2004), *representational bindings* within the MTLC are necessarily based on superficial perceptual features. Within this framework I assume that the perirhinal cortex and the parahippocampal cortex independently encode different aspects of a particular event. While the perirhinal cortex encodes featural information about objects, the parahippocampal cortex represents the respective context of that event (see Diana et al., 2007; Eichenbaum, 2006b, for a similar view). This binding view is supported by recent studies demonstrating an impairment of patients with anterior MTL lesions, including the perirhinal cortex, in perceptual discrimination of complex objects with a large number of overlapping features (Barense et al., 2007). More importantly, this impairment was largest for objects with pre-existing semantic representations, e.g. beasts as compared to novel objects such as bar codes. This is consistent with the present view, that representational bindings supported by the perirhinal cortex link the actual experience to stored representations of previous encounters of a similar event. In other words, the perirhinal cortex binds the actual appearance of a particular object to the mental representation of previous experiences with that same object. In a similar vein, the parahippocampal cortex mediates representational bindings of contextual features. For instance, Bar and Aminoff (2003) have demonstrated that the parahippocampal cortex is more active for objects that are strongly associated with a specific context (e.g. roulette wheel) than for objects that are very weakly associated with many possible contexts (e.g. cherry). These examples underscore the important role of both cortices for representational binding by demonstrating that readdressing object and/or contextual features of object occurrence during the repeated processing of a particular event require the integrity/activity of perirhinal and parahippocampal cortex, respectively.

Although the MTLC has powerful binding abilities, it is tied to perceptual regularities and, consequently, is hardly capable to create abstract representations that are essential for goal-directed behavior (Miller, 2000). However, the prefrontal cortex (PFC) seems ideally suited for the abstraction of such behavior-guiding representations. The PFC has direct anatomical connections with many brain regions, including sensory and motor areas, the parietal association areas and temporal regions (Barbas, 2000; Uylings et al., 2003). It also has reciprocal connections via the uncinate fasciculus with the MTLC and the hippocampus (e.g. Lavenex and Amaral, 2000; Suzuki and Amaral, 1994). PFC neurons exhibit synchronous activity for learned stimulus–response associations and the associated reward (Miller, 2000). Moreover, activity of PFC neurons does reflect abstraction such as perceptual categories and general rules (Muhammad et al., 2006; Wallis et al., 2001). In addition PFC activity, that is elicited by a transient event, can be sustained for many seconds, allowing the PFC neurons to form representational bindings between events separated in time (Asaad et al., 1998; Fuster, 2001). Recent neuroimaging studies also indicated that activity in the lateral PFC increased when several items can be bound into larger representational units (chunks, Bor et al., 2003; Prabhakaran et al., 2000). Based on this large body of evidence I assume that the PFC (in addition to many other functions) mediates the representational binding between the current event and existing knowledge representations in the brain/mind. This shares some aspects with the notion of depth of processing (Craik and Lockhart, 1972; Craik and Tulving, 1975) in which deep processing can be seen as some form of representational binding, namely the integration of the actual event with existing knowledge. On the one hand, deep and elaborate processing fosters the understanding of new events through binding the actual event to existing knowledge. On the other hand, representational binding gradually modifies this existing knowl-

edge by abstracting the general information, and thus, contribute to the formation of semantic knowledge (Craik, 2006). These abstract representations of general regularities can be seen as rules that specify the most appropriate response under given environmental demands. Rule-guided behavior is mediated by different subregions of the PFC in different ways (for review, see Bunge et al., 2005). For instance an anterior–posterior gradient of PFC involvement as a function of decreasing rule complexity has been proposed (Christoff and Keramatian, 2007). Drawing on these findings it is conceivable, that representational bindings in different cognitive domains recruit different PFC subregions depending on the prevailing rule complexity. Thus, binding within the language domain might depend on another PFC subregion than working memory. Consistent with this view it has recently been proposed that the inferior PFC mediates representational bindings within the language domain (Hagoort, 2005), whereas the strategic organization, or 'chunking,' of information in working memory involves the dorsolateral PFC (Cowan, 2001; Rypma and D'Esposito, 2003).

Due to the reciprocal connections the PFC exerts top-down influence on the MTLC and the hippocampus (see Simons and Spiers, 2003, for a detailed review of PFC–MTL interactions). Recently it could be demonstrated that the PFC inhibits hippocampal activity in mice (Bontempi et al., 1999; Frankland et al., 2004). From a functional point of view this inhibition seems reasonable, as representational bindings enable the fast and efficient processing of information, whereas relational bindings, because compositional by nature, are more effortful. Hence, the PFC might prevent relational binding supported by hippocampal activity when representational bindings were easily formed. That means that the PFC and the MTL do interact to flexibly form bindings in accord with the current goal. This interaction is, thus, adopted to the actual task demands as, for instance, in the case of deep/elaborate or shallow processing (Craik and Lockhart, 1972; Craik, 2006).

Taken together, I propose that the hippocampus is involved in the relational binding of the elements of individual experiences through sparse representations while the perirhinal and parahippocampal cortex bind representational information about items and context, respectively, with similar previous occurrences (Fig. 2). While these binding processes are tied to superficial

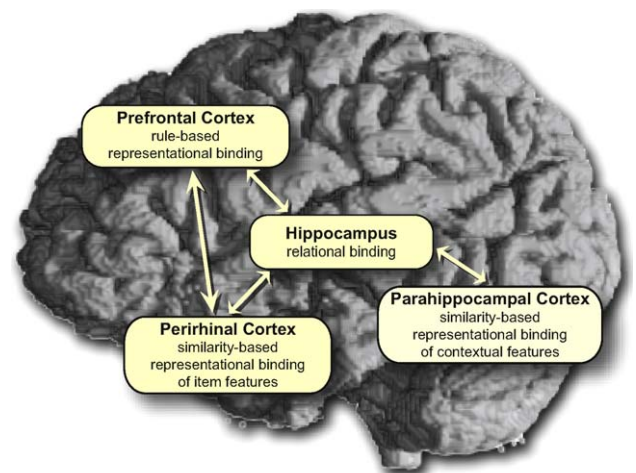**Fig. 2.** Summary of the binding mechanisms mediated by medial-temporal lobe structures (MTL) and the prefrontal cortex. The hippocampus is involved in the relational binding of the elements of individual experiences. The surrounding MTL cortex and the PFC extract the common information across multiple experiences forming representational bindings based on perceptual features (MTL) or abstract rules (PFC).

perceptual features the PFC performs representational binding at a more general rule level. Thus, while the MTLC mainly binds the representation of the actual item/context to the representation of a previous occurrence of that same item/context, the PFC mediates the binding of the actual event to the abstract or prototypical representation of invariant and non-accidental features of that event. Even though this view builds on previous models of MTL organization, it differs in some important aspects. In contrast to the majority of other recent models (e.g. the BIC model, Diana et al., 2007; Eichenbaum et al., 2007) related to mnemonic processes, it proposes different types of binding in hippocampal, medial-temporal lobe cortical structures and the prefrontal cortex for domain-general processing. In addition, the model proposed by Eichenbaum (Cohen and Eichenbaum, 1993; Eichenbaum, 2000) is similar to the present model with respect to relational binding operations within the hippocampus, but it does not make specific predictions for the perirhinal and parahippocampal cortices. Within this model hippocampal codings that are broader in the features represented encode the spatial and non-spatial regularities of events shared across different episodes.

The assumptions outlined above lead to several predictions that are discussed in the following sections. Most importantly the binding view implicates hippocampal involvement in tasks requiring the flexible relational binding of items, actions and their spatio-temporal context that compose a unique experience irrespective of other task demands. In the following, the binding view is scrutinized in episodic memory, working memory and the domain of language learning.

4. The binding view on episodic memory

In a typical episodic memory task, the item presented during the recognition test must be identified as what was presented during learning. Thus, at the time of learning, an association must be made between a to-be-remembered item and its context, and later this association must be retrieved. Indeed, the use of this kind of association can be considered an example of forming relational bindings and retaining them across time that is fundamental to declarative memory. In line with a recently proposed biologically plausible neuro-computational model I suggest that sparse neural coding within the hippocampus leads to distinct (pattern-separated) representations of arbitrary item context bindings irrespective of their contextual similarity (Norman and O'Reilly, 2003; O'Reilly and Norman, 2002). Thus, the hippocampus is able to reconstruct the entire studied pattern, i.e. the item bound to its context (pattern completion, O'Reilly and Rudy, 2001), thereby enabling the retrieval of contextual information. Thus, relational binding of an item to its study context will lead to recognition based on recollection. In contrast, the MTLC assigns similar representations to similar input using overlapping representations to code for the shared structure of events. That is, the first presentation of an item during encoding weakly activates a large number of MTLC units, whereas repeated and thus familiar stimuli strongly activate a smaller number of units. At test, the presentation of a studied test probe initiates a set of processes that may be described as a comparison between the short-lived representation of the actual stimulus and the sharpened representation in the MTLC. As a result, a scalar familiarity signal is provided that tracks the global similarity between the test probe and the studied items (Hintzman, 2001). Consequently, the binding view on episodic memory implicates that recollection, familiarity and novelty emerge as a consequence of relational and/or representational binding. That is, recollection can be conceptualized as the retrieval of a great number of item and contextual features bound into a coherent episodic memory representation. The close connection between relational binding

and recollection was corroborated by animal studies and neuroimaging studies (extensively reviewed by Diana et al., 2007; Eichenbaum et al., 2007). A great number of studies showed increasing hippocampal activity for successful recollection of encoding context as compared to failed source recollection (Cansino et al., 2002; Dobbins et al., 2003; Kahn et al., 2004; Weis et al., 2004). In one experiment participants studied a word list while alternating between a pleasant/unpleasant decision and a concrete/abstract decision (Dobbins et al., 2003). At test, they were required to discriminate between two simultaneously presented test words by selecting the member of the pair previously associated with a particular encoding task. Successful source retrieval was associated with increased activity in the left hippocampus. Together these studies demonstrated that an increase of activity of the hippocampus is essential for the process of binding an item to contextual information during retrieval.

This notion has gained further support from neuropsychological studies in amnesic patients (Holdstock et al., 2002; Mayes et al., 2004). For instance, Helmstaedter et al. (1997) investigated patients suffering from temporal lobe epilepsy with circumscribed temporomesial lesions (hippocampal sclerosis). These patients were severely impaired in memorizing triplets of unrelated and loosely related words but had almost normal memory performance for highly associated words, i.e. words from well defined and limited categories learned together. In a similar vein it was demonstrated that amnesic patients could well discriminate between old and new scenes but were unable to distinguish between intact old scenes and manipulated old scenes (e.g. by left–right shifting of particular elements within the scene) (Ryan et al., 2000), indicating a deficit in relational binding rather than recollection. Further support for the notion that relational binding leads to recollection is provided by a wealth of findings from electrophysiological studies, using event-related potentials (ERPs) to delineated the functional characteristics of recognition memory for paired associates. For example, Donaldson and Rugg (1998) observed the late parietal ERP old/new effect, indicative for recollective processes, to be larger for correctly classified same than rearranged pairs of words. This suggest that the successful binding of words into an arbitrary pair in a recognition memory test supports recollective processes. Indeed much of the conditions eliciting the late parietal ERP old/new effect reflecting recollection can be conceptualized as requiring binding. When subjects are asked to recollect the presentation modality (Wilding et al., 1995), speaker's voice (Wilding and Rugg, 1996) or temporal source (Trott et al., 1997) of studied words, the judgment requires binding between the words and these specific attributes. In all cases, the late parietal ERP old/new effect has been shown to depend upon arbitrary relational bindings of these attributes. Recording directly from neurons in humans, Viskontas et al. (2006) found that cells in the hippocampus respond to novel stimuli with an increase in firing (excitation). On the second presentation of a stimulus, there is an additional recruitment of neurons in the hippocampus showing inhibitory (decrease from baseline firing) responses. This is consistent with the present proposal in that the hippocampus mediates relational processes by means of sparse coding.

One assumption that is directly derived from the binding view described above is that context information is representationally bound by the parahippocampal cortex. Accordingly, the model predicts that the parahippocampal cortex is involved in recognition memory whenever contextual information can be utilized in the service of memory retrieval. Thus, contrary to other theories, that use verbally stated dichotomies (e.g. familiarity vs recollection) the present model's predictions cut across these boundaries. Consistent with the present proposal, parahippocampal activity was not only observed during memory for spatial information (Suzuki et al., 2005) or for correct as compared to incorrect source

judgments (Cansino et al., 2002; Dobbins et al., 2003; Kahn et al., 2004, but see Weis et al., 2004) but also by the observation of changing spatial arrangements (Pihlajamki et al., 2004) and by the observation of scenes with rich contextual associations compared with scenes with less associations (Bar et al., 2008). Further neuroimaging studies demonstrated increased activity of the parahippocampal cortex in binding contextual information (Düzel et al., 2003; Preston et al., 2004). In the study by Preston et al. (2004) face-house pairings, each presented four times, had to be learned. Recognition judgments on repeatedly learned face-house pairs, thereby forming bound representations lead to increased activity in the parahippocampal cortex. Together with other findings demonstrating increased parahippocampal activity (Daselaar et al., 2006; Bar and Aminoff, 2003) this points toward enriched context associations in the parahippocampal cortex.

This nicely corresponds with intracranial recordings in patients with temporal lobe epilepsy (Viskontas et al., 2006). This study reported a dramatic decrease in the number of parahippocampal neurons each exhibiting an enhanced responding to the stimuli. These results suggest that, consistent with the present proposal, the parahippocampal region mediates representational bindings of contextual information by means of sharpened representations (O'Reilly and Norman, 2002).

Another expectation derived from the model is that the perirhinal cortex mediates recognition by providing a scalar familiarity signal computed from the representational binding between the test probe and the studied item. Crucially, more efficient binding is mediated by a larger overlap in activated perirhinal neurons (i.e. a sharpening of the representation of the item) and, as a consequence, by a smaller number of activated neurons. Thus, a decrease in BOLD activity in the perirhinal cortex should be predicted (Norman and O'Reilly, 2003). Supporting evidence for this prediction is provided by several neuroimaging studies demonstrating that activation in the perirhinal cortex is significantly decreased when studied images, words or faces are recognized based on familiarity (e.g. Eldridge et al., 2005; Rugg et al., 2003). Most studies employed confidence ratings bearing on a linear relationship between recognition confidence and familiarity. Most studies consistently report decreasing perirhinal activity with increasing familiarity ratings (e.g. Daselaar et al., 2006). Other studies, however, demonstrated the inverse relationship between confidence ratings and activity in the perirhinal cortex (Montaldi et al., 2006; Yonelinas et al., 2005). As in these studies activity in perirhinal cortex was largest for recollection responses relative to correct rejections of new items, this might indicated a very efficient encoding of new items rather than a familiarity response to old items (see Stark and Okado, 2003, for a similar argument). In a similar vein studies using the Remember/Know Procedure or source memory judgments reported decreased perirhinal activity for recognized old as compared to new or forgotten items (Cansino et al., 2002; Gonsalves et al., 2005; Weis et al., 2004).

In addition, recent evidence suggests that the perirhinal cortex is also involved in familiarity-based recognition of associations if the paired features are "unitized", i.e. forming representations that "fuse" conjunctions of features within an item into a unified whole (Jäger et al., 2006; Quamme et al., 2007; Yonelinas et al., 1999). As an example unitization can be manipulated by encoding pre-experimentally known compound words (e.g. land scape, traffic jam) in contrast to arbitrarily paired words (e.g. surgeon arrow Giovanello et al., 2006) or by study procedures that either encouraged or did not encourage encoding the pairs holistically (Quamme et al., 2007). A problem that arises with this view is the difficulty to exactly define which features can be unitized under which conditions and which cannot (see Ecker et al., 2007, for a detailed discussion). As an illustrative example of this problematic issue, different results have been observed with respect to item-color bindings, despite using a highly similar experimental protocol (Diana et al., 2008; Staresina and Davachi, 2008). In both studies participants were required to form a mental image of the referent of a word and a simultaneously presented color under either a plausibility task or a valence task. While Staresina and Davachi (2008) observed activity in the perirhinal cortex for unitized word/color combinations in both tasks, Diana et al. (2008) reported familiarity-based recognition only under valence task instructions. Moreover, a number of ERP studies demonstrated familiarity-based recognition for associated items that are related with respect to their common pre-experimentally existing meaning but were hardly unitizeable into a single representation (Greve et al., 2007; Opitz and Cornell, 2006; Rhodes and Donaldson, 2007). For instance Opitz and Cornell (2006) demonstrated familiarity-based recognition for words that were encoded in triplets with pre-experimentally existing semantic coherence (e.g. desert, camel, oasis) but not for words encoded in triplets that required their sorting according to the natural size of the denoted objects. Consistent with the binding view on MTL function, familiarity seems to support associative recognition judgments when the items form an easy to access bound representation. Such representations arise when items occur frequently together in the environment, e.g. hen and egg (see Carson and Burton, 2001, for a similar argument). Within this view unitization can be regarded as a special case of representational bindings. Although the available empirical evidence does not allow to provide a definitive prediction, the present model would propose that representational bindings based on perceptual similarity (as for instance in the studies by Jäger et al., 2006; Yonelinas et al., 1999) would engender perirhinal involvement in familiarity, bindings grounded on more abstract representations (e.g. Opitz and Cornell, 2006) might require the contribution of the PFC.

5. The binding view on working memory

The traditional view on hippocampal function implies that working memory involves different psychological processes and, hence, neural substrates as compared to long-term memory. This dichotomous view of memory is grounded on neuropsychological evidence that lesions to the hippocampal system lead to severe impairments in long-term declarative memory, whereas short-term memory is preserved. This is unquestionable the case for some sort of material, but this does not imply that the hippocampal system is necessarily constrained to long-term declarative memory. Rather, the proposed binding view incorporates accumulating evidence suggesting that working memory and long-term memory, despite apparent differences, share some underlying neural mechanisms. Thus, within the binding view the hippocampus is critical when relational binding of associative information is involved. This extends previous notions on the relationship between working memory and episodic memory. In a recent modification of their working memory model Baddeley (2000) proposed an episodic buffer that holds episodes in working memory whereby information is integrated across space and potentially extended across time. In the present binding view of working memory this would be equivalent to relational binding operations mediated by the hippocampus. This view is supported by the growing body of evidence that documents specific impairments in retaining associative information over short intervals, even when controlled for working memory load (Olson et al., 2006a; Piekema et al., 2007). For example it was demonstrated that for patients with bilateral hippocampal lesions working memory for objects or locations was at normal levels, but memory for conjunctions of both features was severely impaired (Olson et al., 2006b). In further support of this notion, several studies specifically examined neural responses to relational

stimuli held in working memory (Doeller et al., 2005, 2006; Hannula and Ranganath, 2008; Holdstock et al., 2000). Using a n-back task Kumaran and Maguire (2006) investigated the role various medial-temporal lobe substructures play in working memory for sequences consisting of the consecutive presentation of four objects (i.e. a quartet). Crucially, during the immediately following second presentation of the quartet the sequential order of objects either remain intact, was rearranged or was entirely different from that during the first presentation. In line with the present proposal rearranged sequences elicited greater hippocampal activity than new sequences indicating a hippocampal involvement in relational binding operations. In contrast, perirhinal activity decreased for repeated as compared to new sequences. In a similar vein Doeller et al. (2005) compared task performance and neural activity in two conditions that required subjects to memorize four sequential object–position conjunctions, and to indicate subsequently whether or not a probe stimulus was identical to one of the four object–position conjunctions. Crucially, the two conditions differed with respect to their binding requirements manipulated across experimental blocks. In a relational binding condition objects and positions were variable within experimental blocks, i.e. object–position relations were trial-unique, requiring relational processing for every object–position relation within a block. In the representational binding condition, the positions were invariant within a block. That is, different objects were presented at the same four positions in each trial of an experimental block, thereby enabling the extraction of spatial regularities and the binding of the actual stimulus configuration to the representation of the invariant positions. Thus, the presented objects can be bound to the same positions within a block, and increased task performance across trials within a block should result from facilitated object–position bindings. In fact, behavioral data showed that subjects benefit from the learned spatial regularities in the representational binding condition as indicated by increasing Pr values relative to the relational condition during the time-course of experimental blocks. Using this working memory performance as a regressor for the fMRI analysis dissociable neural correlates for both conditions were observed (see Fig. 3). The hippocampus showed continuously enduring activity in the condition requiring the relational binding of variable objects to variable positions. This activity abated, when the relational binding requirements decreased during the time-course of each block as it was the case in the representational condition. Here the probability for specific object–position conjunctions was substantially increased causing reduced relational binding requirements. As the four objects can be bound to the same four positions within a block, learning presumably results from facilitated representational binding. It is important to note that a particular object–position conjunction is presented only once in each block. Thus, the decrease of hippocampal activity in the representational condition cannot be attributed to a differential amount of novelty in both conditions.

Also in line with the proposed binding view the lateral PFC exhibited increased activity with increasing involvement of representational bindings (cf. Fig. 4). As the learning progress continues, the lateral PFC supports the extraction of invariant spatial features, leading to a representation of task-relevant knowledge. Supporting evidence for this notion is provided by recent studies (Bor et al., 2003; Prabhakaran et al., 2000), demonstrating increased activity in lateral prefrontal activity, when information is stored in a bound, rather than in a separated representation. Given the representations of the extracted regularities, object–position conjunctions of the current trial could be reorganized to be encoded more efficiently. The lateral PFC has been posited to subserve such reorganization operations during memory encoding (Fletcher and Henson, 2001; Simons and Spiers, 2003).

Doeller et al. (2006) further explored whether the representational bindings are built on the surface structure of a regular input pattern based on the superficial similarity between learning instances or on abstract rules. Capitalizing on the successful transfer of knowledge about regularities to new instances as a main index of rule-based learning (Mathews et al., 1989), an increase of activity in the dorsolateral PFC associated with knowledge transfer was observed. This activity might indicate the establishment of rule-like representations that might be flexibly adapted to the task requirements at hand, thereby bringing about higher levels of generalization (Rougier et al., 2005).

6. The binding view on language learning

The binding view on language proposes that relational and/or representational bindings are inherent to both language comprehension and memory. One related view also proposes close relations between language, memory, and the hippocampal system. Within this so-called "distributed-memory" framework (e.g. Carpenter and Grossberg, 1993; McClelland et al., 1995) verbal memory results from forming and strengthening connections between nodes, representing semantic, phonological, etc. aspects of normal language comprehension. The comprehension of everyday words and phrases, thus, involves already established connections between these nodes that have been formed during childhood and strengthened throughout a lifetime of use. In contrast, sentences communicating never previously encountered ideas require the formation of new connections within the language cortex, that normally involves input from binding nodes located within the hippocampal system (MacKay et al., 1998). In support of this view it has been shown that patient H.M. exhibits severe deficits in semantic-level binding processes e.g. in comprehending sentences with ambiguous meaning, although his construction of sentences was generally correct (Skotko et al., 2005). The present view proposes that binding operations may operate not only in semantic bindings but also in other subdomains (e.g. phonological or syntactic) within the domain of language. In the following I will focus on the syntactic (structural) level, as this has been the subject of most neuroimaging and ERP studies on language learning. The binding view suggests, that with respect to a grammatical system, words have to be bound to their specific syntactic categories (e.g. noun) and thereby their possible positions (e.g. subject vs object position) within a sentence. In the sentence "My colleague meets me at the restaurant" the word "colleague" has to be bound to the functional role of the subject, i.e. the agent of the sentence. It has been argued independently that this form of binding, which operates on perceptual characteristics of each word in a sentence, can be assumed as a specific form of relational processing (Gomez and Gerken, 2000) and should, therefore, be dependent on the hippocampus. Supporting evidence is provided by a number of recent studies demonstrating hippocampal activity elicited by artificial grammar strings that had to be judged with respect to their grammaticality (Forkstam et al., 2006; Lieberman et al., 2004; Strange et al., 2001). Crucially, in all studies this activity supports the relational processing of superficial substring features.

Interestingly, these neuroimaging studies also report the involvement of the left inferior PFC in the rule-based classification of artificial grammar strings. This supports the binding view insofar, as the left inferior frontal region is engaged in the processing of structural aspects of language representations and might provide a neural substrate for the structural integration of particular sentences into the knowledge about the grammar system. This integration of information into higher level representations
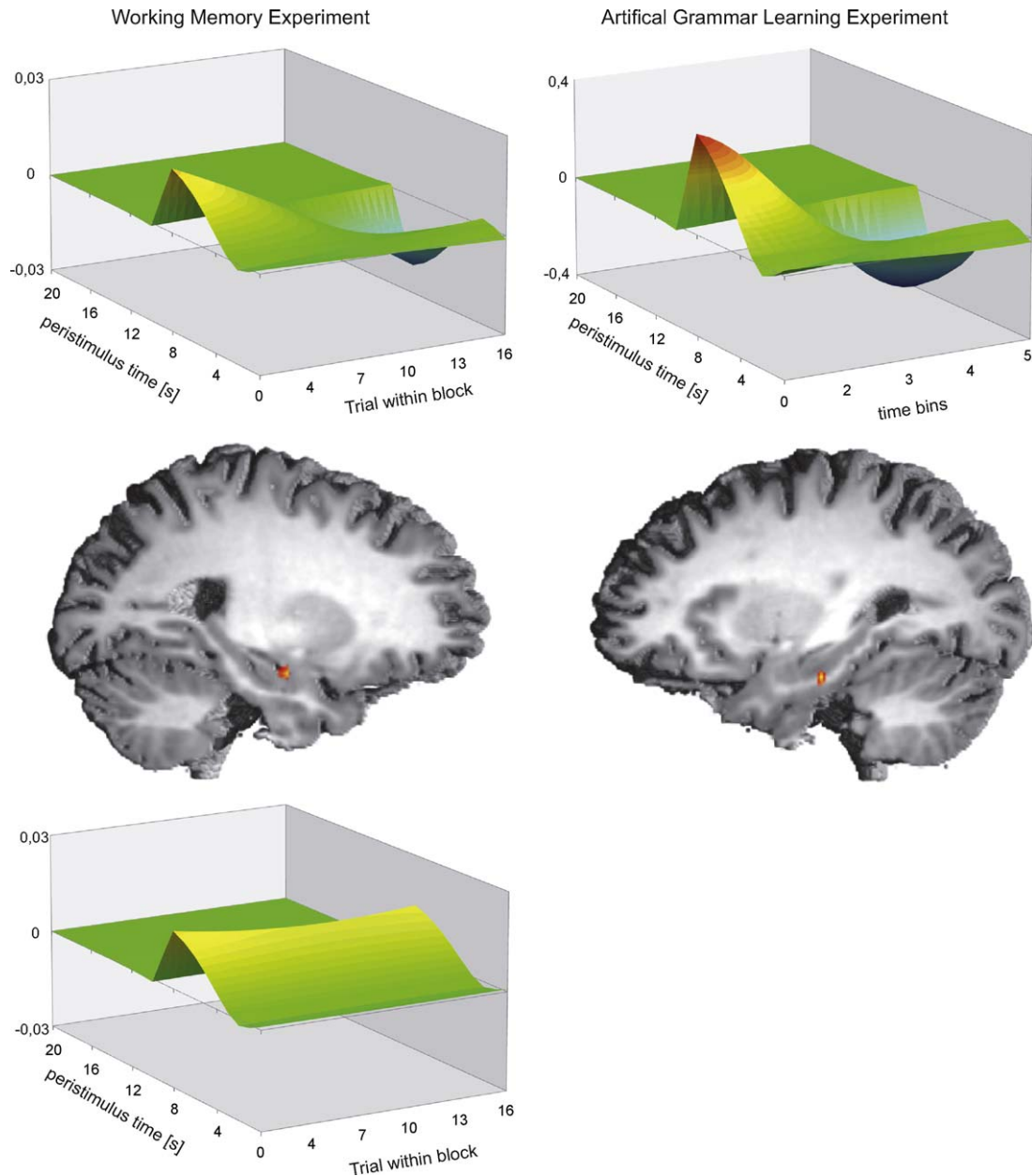
Fig. 3. Activity profile of the hippocampus in a Sternberg-like working memory task (left) and an artificial language learning task (right). Note the remarkable similarity of decreasing hippocampal activity whit decreasing relational binding demands (upper panel) as compared to a task requiring enduring relational binding (bottom panel, for details see text). Data taken from Doeller et al. (2005) and Opitz and Friederici (2003).

shares many aspects with the unification processes proposed by Hagoort (2005), supposed to bind lexically retrieved information into a representation of entire sentences.

Furthermore, the binding view also predicts, that the representational bindings supported by the left inferior PFC render relational bindings mediated by the hippocampus unnecessary. This implies, that in the course of learning hippocampal activity should decrease whereas the activity in the PFC should increase. This was tested in a recent experiment, using fMRI to examine in detail this interaction by assessing learning-related changes in hemodynamic activity during artificial language acquisition (Opitz and Friederici, 2003). During scanning, participants learned an artificial language whose miniature grammar meets the universal principles of a natural language. Increased proficiency in using the artificial language was associated with decreased left hippocampal activity (Fig. 3). Supporting the binding view, an increased

recruitment of the left inferior frontal gyrus was also observed (Fig. 4). Within the binding framework, the hippocampal activity can be interpreted to reflect the resources needed to process learned relationships between words and their possible syntactic roles. Repeated occurrence of a particular relationship facilitates the binding of a word to its syntactic category and thereby its role in the sentence. Therefore, a hippocampal involvement is observed which apparently governs the initial state of learning the artificial grammar and which is no longer used once the grammatical rules of the artificial language have been acquired.

In line with the binding view on artificial language learning it has been suggested previously that artificial grammar systems might be learned by evaluating pattern-based relations in word sequences and generalizing beyond specific word order, that is, rule abstraction (Brooks and Vokey, 1991). A representational binding mechanism that considers the similarity to exemplars
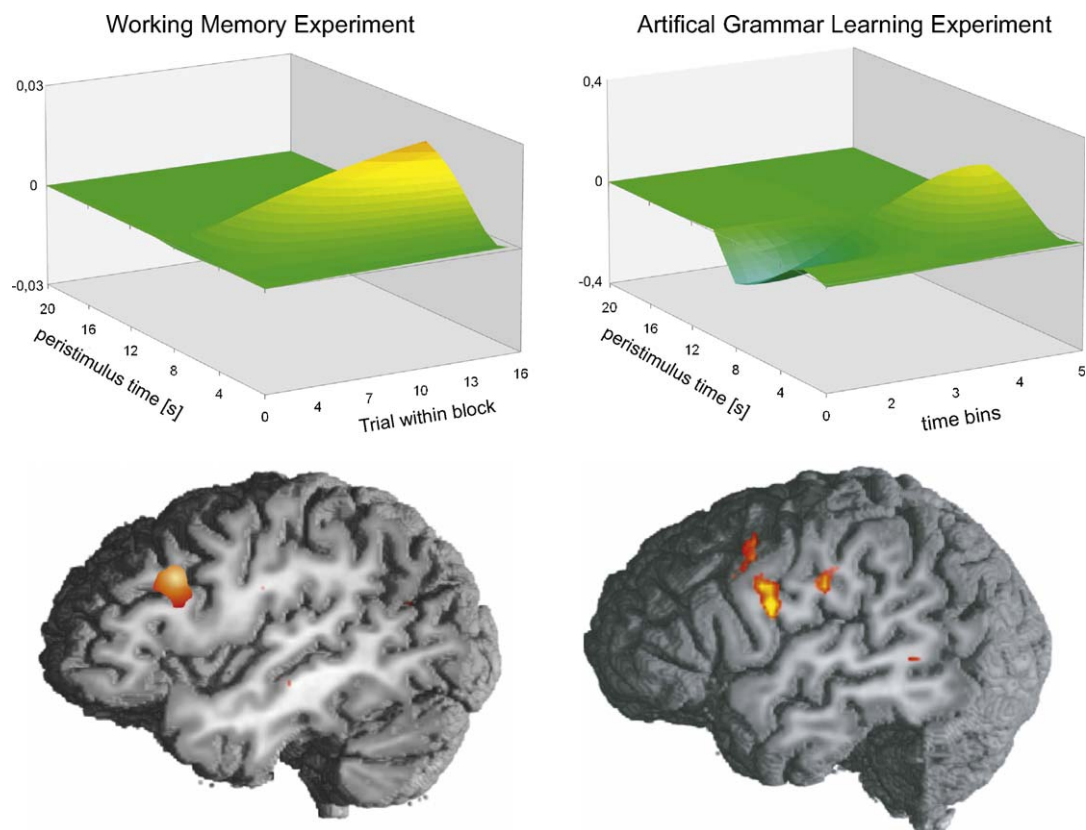
Fig. 4. Activity profile of the PFC elicited in the two tasks mentioned in Fig. 3. Although different subregions within the PFC were recruited in the two tasks, the increased activity as a function of representational binding demands is akin across both tasks. Data taken from Doeller et al. (2006) and Opitz and Friederici (2003).

presented earlier might well explain the acquisition of a grammar system, that possess only local organizational principles, with regularities limited to neighboring units. Such grammars are a set of continuation relations among symbols that allow the specification of symbol sequences (Chomsky, 1965), i.e. they can be fully specified by transition probabilities between elements in a sequence. Thus, the relational binding of two adjacent words determine the grammaticality of such a grammar system. In contrast, so-called phrase structure grammars (PSGs) determine how words are combined into phrases and sentences. In addition to concatenating items into a linear stream of words a PSG can embed sequences within other sequences, thus creating complex hierarchical structures and long-distance dependencies, a universal property shared by all natural languages. Consistent with Chomsky understanding a sentence containing hierarchical structures must involve the representational binding of this particular sentence to the abstract rule representation of the underlying grammar system. Only the acquisition of such a PSG lead to activity in the left inferior PFC, whereas learning of linear word sequences did activate the MTL and the premotor cortex (Musso et al., 2003; Opitz and Friederici, 2004; Tettamanti et al., 2002). A recent study directly contrasting local, i.e. relational dependencies and hierarchical, i.e. representational dependencies corroborated these results (Opitz and Friederici, 2007). This study demonstrated that the processing of local dependencies involves the left ventral premotor cortex, whereas the left inferior PFC plays a key role in the efficient processing of long-distance dependencies. These findings were confirmed by a recent intriguing study investigating the role of the left inferior PFC in learning natural languages, independently of the linguistic family to which the language belongs (such as Italian and Japanese, Musso et al., 2003). This brain region became more active over the course of time as participants became adept with theses rules. Crucially, comparable

presentations of pseudo-linguistic rules (i.e. rules that are not based on the principles of PSG) using the same vocabulary did not activate the IFG. A second, equally important finding of this study indicated that only high proficiency participants did engender this brain region when processing hierarchical structures. For low proficient subjects, along with their poorer performance, mainly for hierarchical structures, increased activity was observed in the ventral premotor cortex only. This supports the view that the left inferior PFC mediates the rule-based representational binding, i.e. it comes into play when successful computations of hierarchical dependencies are necessary for successful language processing.

7. Conclusions

The evidence summarized in this selective review, along with many findings not covered (e.g. the extensive literature on animal data or neuropsychological findings) provided significant insights into the functional organization of the MTL and partly of the PFC. The pattern of activity in the hippocampus observed in a wide range of tasks is indicative for a role in relational binding of items and their spatio-temporal context into a unique experience across domains of cognition. At the same time there is a growing body of literature suggesting that cortical areas within the MTL and various structures in the PFC support representational bindings linking the general regularities inherent in the recent experiences. The few available results indicated that the precise role of these structures in representational bindings might be based on global similarity or underlying rules depending on the organizational structure of the material to be learned. However, understanding how activity in these regions supports representational bindings and, even more important, specifying the interaction between MTL and PFC structures in service of goal-directed behavior in greater detail remains an important issue for future research.

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