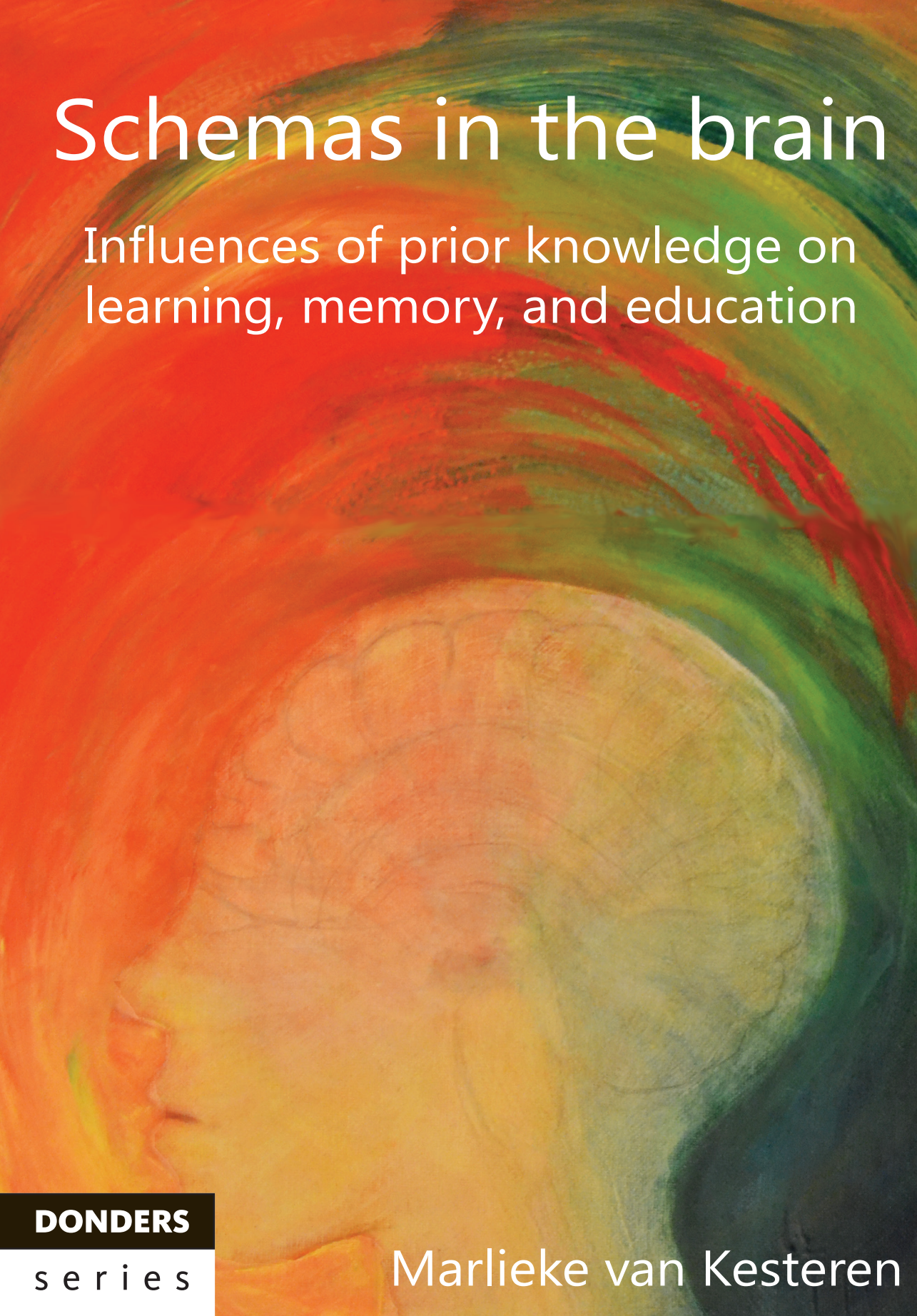
Schemas in the brain

Influences of prior knowledge on learning, memory, and education



DONDERS series

Marlieke van Kesteren

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Schemas in the brain:

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"Memory is like a spiderweb that catches new information. The more it catches, the bigger it grows, and the bigger it grows, the more it catches."

Joshua Foer, Moonwalking with Einstein (2011)

Voor papa en mama

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Introduction

1.1 This thesis

Like every student that is writing the introduction to his or her PhD-thesis, I am (perhaps overly) optimistic that everyone reading it will do so with great enthusiasm. Yet, what exactly you will learn and retain about the contents of this thesis is dependent on many factors, thus differing for each and every reader. One of these factors is your preexisting *schema*: a framework of acquired knowledge implemented within a network of connected neurons in which memory traces of associated information have been stored. This schema can, when activated, alter the manner in which information is processed. For simplicity, I will just assume that at present you are fully awake and truly motivated about reading this thesis. When this is the case, your prior knowledge about the (human) brain, its architecture, and the memory processes that it contains is the chief remaining factor that is of crucial importance for how you will read, comprehend and capture the informative content in this thesis. Similarly, how much of it you will remember after, say, a year's time is largely determined by your schema at this very moment. The preexisting knowledge encapsulated as a schema in your brain thus is a driving factor for online and subsequent offline learning and memory processes that will presumably alter your schema again. These premises, among others, have been investigated by the experiments described in his thesis.

If you are, for example, a fellow cognitive neuroscientist specializing in memory, much of the necessary background information will be known to you. Therefore, you will specifically extract the information that is new, exciting, and important to you and integrate this with your extensive schema about memory systems in the brain. If you are, on the other hand, a family member, a friend, or a layman who is genuinely interested in memory and the brain, most of the information in this thesis will be new, diffuse, and not meaningful to you. This means it will be harder for you to grasp overlapping themes, understand terminologies, and place the content in a broader context. Thus, the preexisting schemas in your brain are an important factor determining how you will remember and comprehend the content of this thesis. Please do not see this as a reason to immediately give up reading it though. In this introduction I will try to equip every reader with a proper, consistent background that can act as an imminent (new) schema and will therefore aid to understand and remember the rest of the content.

In this introduction I will outline the background on behavioral schema literature (chapter 1.2) and memory systems and processes in the brain (chapter 1.3). Then, I will explain the existing literature on the neural processes underlying schema effects on memory (chapter 1.4). After this, I will focus on the dissociation between schema and novelty and their enhancing effects on memory (chapter 1.5), and the possible applications of this research to education

(chapter 1.6). Finally, I will shortly introduce the following chapters reported in this thesis (chapter 1.7).

1.2 History of schema research

Memory is a broad concept that can be defined in different ways. Merriam Webster dictionary defines memory as *the store of things learned and retained from an organism's activity or experience as evidenced by modification of structure or behavior or by recall and recognition*. Next to being this common concept that everyone can adhere to, memory is a notion that is in practice often hard to distinguish from other cognitive features such as perceptual learning, language, consciousness and perception. The *long term memory* system in our brain consists of memory traces and general knowledge structures that are stored for a long period and is theorized to be dissociable from *working memory* resources [1] that can only hold on to new information for a short, limited period of time. Nevertheless, both these forms of memory are intricately connected to each other and with many other cognitive processes in our brain, making it a challenge to investigate it in a *pure* form [2], both in behavior and in the brain.

How knowledge is organized and represented in our brain is a longstanding question that has been addressed extensively throughout history. Additionally, how this organization of your knowledge affects new learning, is of crucial importance for understanding how we learn and remember new information. Reflections on this intriguing question can be traced back to the Greek philosophers Plato and Aristotle, to whom the word *σχήμα* meant *shape* or *form*, and was used in syllogistic reasoning, a deductive reasoning approach that infers conclusions based on particular premises. This rather broad idea of a schema was later slightly differently introduced into education by Jean Piaget in 1926 [3] and into psychology by Frederic Bartlett in 1932 [4]. Bartlett, who is commonly regarded as the founding father of the *schema theory*, described a schema as *a structure that people use to organize current knowledge and provide a framework for future understanding*. Subsequently, this notion became somewhat buried for several decades until cognitive psychology arose in the 1960's and psychologists once again turned towards cognitive and mental processes in the brain. In 1967, Ulric Neisser [5] redefined Bartlett's notion of schemas, leading to a boost in psychological experiments where schemas were widely investigated as related to learning and memory performance [6]. This led to flourishing of the schema theory in psychology that was initiated by Richard Anderson [7] in psychology, but at the same time also found its way in psycholinguistics [8] and artificial intelligence [9-11].

The results that followed from this abundance in schema experiments were

helpful for the progression of (cognitive) psychology [12], education [13] and artificial intelligence [14], commonly showing that information is better retained when congruent with a schema. However, this development also led to many parallel theories, such as frame theory [15] and script theory [16], mainly because the schema theory itself appeared vaguely defined and thus was not always capable to sufficiently explain experimental findings [12,17]. For example, more information was found to be stored by the brain than was initially hypothesized by the schema theory [12] and in some cases information incongruent with a schema was found to be better remembered [17], especially when false memories and guesses were taken into account [18]. Additionally, it was often argued that it makes no sense to learn information that is not truly novel (see 1.3.5 and 1.5), a proposition apparently contradictory to the hypotheses in schema theory [7,17,19]. Consequently, the ideas of the original schema theory faded away in the 1990's and were further investigated as related to scripts and frames in cognitive psychology, mental models in artificial intelligence [10], and situation models [8], discourse [20] and comprehension [21-23] in psycholinguistics. In applied education, schemas were further scrutinized as related to reading strategies and conceptual understanding together with social and cultural perspectives [13], which was expected to more directly lead to applied techniques in classrooms [24] than the previous, more fundamental memory research.

This decay of schema theory in the past decades led to a scattered literature where each theory within each discipline is holding on to its own views on the concept of a schema, its underlying mechanisms, and its effects on behavior. Nevertheless, in all the different subfields of (cognitive) psychology, psycholinguistics, education, and artificial intelligence, substantial progress has been made towards a better understanding of how knowledge is built up in the brain and why it is expressed in that specific way [25,26]. However, consequential to the disintegration of the schema theory over the years, an overlapping unifying account explaining how prior knowledge aids learning of new information, and possibly even influences behavior in a more general way [27], is still lacking. Moreover, no biologically plausible theory about the neural underpinnings of this effect was apparent at the time. By considering neuroscientific views on these purely psychological concepts, cognitive neuroscience research (see 1.4) could turn out to be the key towards uniting these different accounts of schemas and their effects on memory.

1.3 History of the cognitive neuroscience of memory

How is a particular memory stored in the brain? This question fascinates but at the same time puzzles many researchers. Triggered by the ideas of Donald

Hebb [28], it is now widely accepted that memories are represented, at least in part, by the strength of synaptic connections between neurons formed through the now well-established process of long term potentiation (LTP) [29]. LTP is generally thought to be crucial for neuronal survival and the communication between neurons that might reflect the neurobiological basis of memory traces. This *Hebbian* concept stating that *what fires together, wires together* has helped memory researchers progress in their ultimate quest to find and understand the *engram* that represents networks of memories in the brain [30]. However, how memories are associated with other memories to form these networks, how these networks influence new memories, and how memory representations change over time, are questions that are not directly answered by this underlying neural learning principle and thus require further investigation.

1.3.1 The hippocampus

One brain region that is crucial for the formation of new memories is the *hippocampus* [31] (figure 1), a stretched brain structure resembling a sea horse that is hidden away deep in the midst of the human brain and is part of the medial temporal lobe (MTL). The hippocampus is regarded as the most plastic region of the brain [32], because its neurons are found to be extremely sensitive to LTP [33] and because it allows new neurons to be integrated [34]. Moreover, its architecture is optimal for processes that are fundamental to memory formation and retrieval, such as the ability to discriminate stimuli that are similar (by using pattern separation mechanisms), complete stimuli that are incomplete (pattern completion) [35], and associate information [36] in time and space [37,38]. Yet, this does not mean that memories are believed to be stored in the hippocampus proper. Rather, the hippocampus is generally viewed to be the linking node that processes new memories, stores associations to its representations, and retrieves old memories [39]. This way, the hippocampus is thought to be able to most optimally store and retrieve information captured within a network of different associative areas in the *neocortex*.

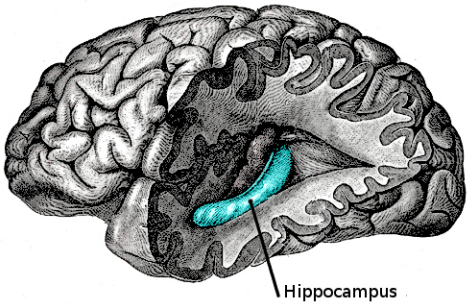


Figure 1: The hippocampus is a brain structure that is crucial for storing new memories and retrieving recent memories. It is a subregion of the medial temporal lobe (MTL, is situated in the middle of the brain in both hemispheres, and has many connections to the rest of the brain. Its appearance as a stretched and curved structure gave rise to its name, which means sea horse. (source: http://en.wikipedia.org/wiki/Hippocampus)

This general notion of hippocampal functioning was formulated after the unfortunate case of Henry Molaison (H.M.), a patient with temporal lobe epilepsy that had both his hippocampi surgically removed to treat his disease, but was subsequently found to be unable to form new memories and recall recently encoded memories [40]. More specifically, H.M. completely lost his capability to store new memories, a deficit known as *anterograde amnesia*. Furthermore, he suffered from temporarily graded *retrograde amnesia*, being unable to retrieve recently learned information, but still retaining more remote memories such as his self-knowledge and childhood memories. After his unlucky surgery, H.M. was examined extensively, experiments that turned out crucial to enlighten the role of the hippocampus in human memory [41]. For one, these investigations gave rise to the *systems consolidation theory* (see 1.3.6 and Figure 4), stating that connections between associative areas in the neocortex that represent different parts of a memory trace are strengthened over time while hippocampal connections are weakened. This way, the memory trace ultimately becomes *hippocampally independent* over time, thus no longer requiring the hippocampus for retrieval [42,43]. Moreover, H.M. was found to still be able to learn motor skills, such as mirror drawing, leading to the hypothesis that only conscious (declarative or explicit, see 1.3.3) memories are dependent on hippocampal processing [44] (see 1.3.3). These findings directed various advances in the field of memory research, positioned the hippocampus as the center of the memory network in the brain [31], and gave rise to theories on multiple memory systems in the brain [2,31] (see 1.3.3).

1.3.2 The medial prefrontal cortex

The *medial prefrontal cortex* (mPFC, figure 2) is a brain region situated in the middle anterior part of the prefrontal cortex that is generally assumed to be involved in executive functioning [45], inhibition [46], cognitive control [47], emotion [48], and meaning [49]. Additionally, it is prominently present in the default mode network (DMN) [50], a network that is reported to become more activate when participants are resting (i.e. not processing external input). Specific to memory, the mPFC is found to be associated with conceptual learning and comprehension [51,52], inference [53], parallel encoding [54], autobiographical memory retrieval [55], and remote memory retrieval [43,56-60], and it shows strong interactions with the hippocampus during these processes [61-64]. In particular, along with the decay in hippocampal dependence, a memory is found to simultaneously become more dependent on the mPFC over time [57,65], suggesting that the mPFC takes over the linking function of the hippocampus as memories become consolidated [56]. Moreover, in rodents, the mPFC is found

to actively replay learning-related neuronal spiking patterns during sleep [66-69] (see also 1.3.6), and it shows task-related interactions with the hippocampus both during learning [62,64] and post-learning sleep [63]. Finally, studies with patients that have lesions to the mPFC report that these patients show an absence of memory enhancement due to semantic congruency [70], self-reference [71], and transitive inference [72] along with confabulation [73] and an increase in errors and false memories during retrieval [74,75], but, interestingly, no general remote memory problems [76]. The mPFC thus seems to be related to a variety of mnemonic mechanisms, specifically related to conceptual learning, integration, inference and meaning [49], but it does not appear to manage our general capability to store and retrieve memories.

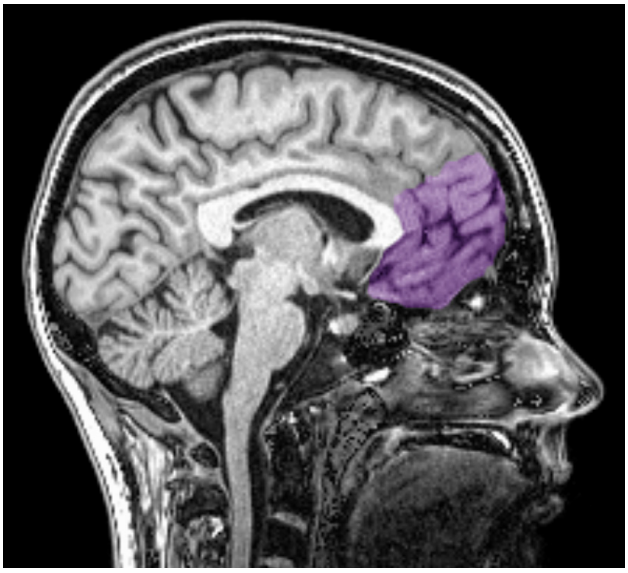


Figure 2: A rough estimate of the medial prefrontal cortex (mPFC) that encompasses the medial part of the prefrontal cortex, and can be subdivided into ventral, dorsal and more lateral subregions (not depicted in this picture). The medial prefrontal cortex regions mentioned and reported in this thesis are comprised of Brodmann Areas (BA) 10, 11 and 32.

1.3.3 Declarative memory

After the finding that H.M., and many amnesic patients with him [77,78], were able to learn tasks that do not require conscious elaboration, Neil Cohen and Larry Squire [79] proposed a memory taxonomy, dividing memory into different types [80] (figure 3a). This taxonomy distinguishes between declarative (or explicit) forms of memory, memories that are conscious and can be articulated (or declared), and non-declarative (or implicit) forms of memory, memories that are unconscious and can thus not be articulated. Since patients with hippocampal damage show particular problems with declarative memory and are spared on their non-declarative memories, it was assumed that the hippocampus is specifically important for formation and retrieval of declarative memories [31],

thus leading to a proposed dissociation between these two memory systems.

With the introduction of neuroimaging methods and the possibility to examine the living brain in addition to patients with lesions, this view of dissociable memory systems in the brain has been both supported and challenged [2,81]. Distinguishing memory systems based on their conscious awareness appears fragile and hard to assess in experimental designs because of its subjective nature. Moreover, memory is not a unitary process and, as stated above, is intricately intertwined with other processes in the brain, such as perception and attention, making it hard to dissociate in practice. Memory consequently rather appears to be a continuous process [82], depending on top-down processes like attention, motivation, emotion, and prior knowledge [83], than a dissociation between two distinct processes per se.

Memories might thus better be classified based on their processing modes [81], governed partly by these top-down processes, rather than their subjective awareness (figure 3b). This contrasting view on memory processing classifies memories based on their flexibility, associability, and processing speed, and not by whether they are subjectively conscious or not. It thus does not categorize declarative memory as such, but distinguishes between two established different subtypes of declarative memory, which are detailed below.

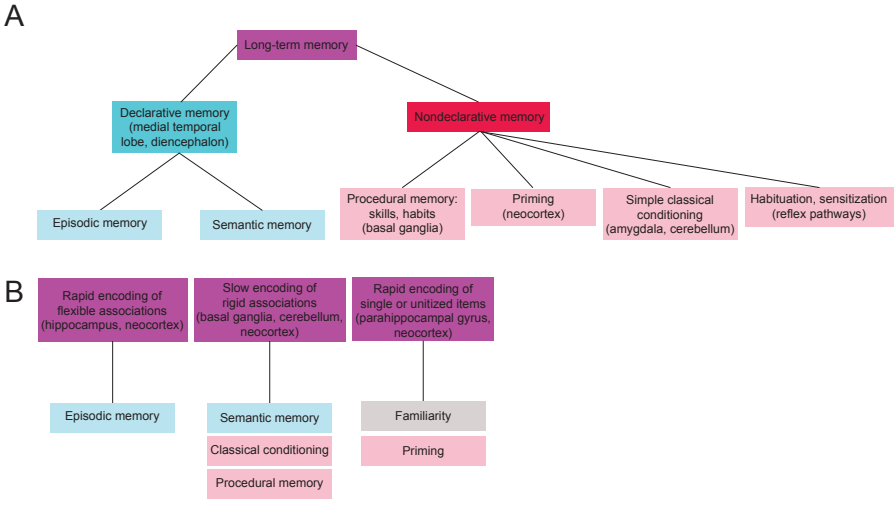


Figure 3: Memory taxonomies based on a distinction in consciousness (i.e. declarative versus non-declarative memories) (A) and processing modes (B). In the former, memories are distinguished based on subjective behavioral and patient data along with the brain regions associated. In the latter, they are distinguished based on how memories are believed to be processed by the brain and what network of regions is related to these processes, irrespective of (subjective) differences in consciousness. Figures based on [80,81].

1.3.4 Episodic and semantic memory

Declarative memory can, as depicted in Squire's taxonomy (figure 3a), once more be divided into two different sorts of memories, one for events (*episodic memory*) and one for facts (*semantic memory*). The distinction between these two types of memory was first described by Endel Tulving in 1972 [84]. Episodic memory is generally defined as a memory of an experience that can be vividly recollected and is very specific and detailed, both in time and space [85]. Semantic memory, on the other hand, is defined as a memory that is more factual and concept-based in nature and that is not related to any contextual details, thus representing more general knowledge and understanding about the world [86]. This distinction is supported by studies reporting patients with specific episodic [40,87] or specific semantic [77,88] amnesia, and by neuroimaging studies reporting different brain structures involved in either episodic or semantic memory formation and retrieval [86,89-91]. Recently, the hippocampus has been suggested to specifically be involved in episodic memory, allowing a processing mode characterized by rapid encoding of flexible associations [81]. Additionally, the hippocampus does not always appear necessary to recall semantic memories [38,92] (see also 1.3.6), which are thought to be more slowly integrated into a long-lasting, rigid association within the neocortex [81]. The declarative memory system is thus subdivided into episodic and semantic memories which are additionally found to, at least in part, rely on differential processing modes in the brain.

1.3.5 Memory encoding

When new declarative information enters the brain, it is presumed to be *encoded* by processes in the MTL and preserved in different associative parts in the brain that represent parts of this memory trace [93]. This encoding process is short-lasting and is suggested to be closely associated with perceptual learning [94] and working memory [95], serving as a gateway to store a memory into the neocortical association areas (see 1.3.6.). Neural processes in the brain during memory encoding are generally assessed by obtaining memory scores on a subsequent retrieval test, and identifying encoded stimuli according to whether they are subsequently remembered or forgotten (known as the *subsequent memory effect* [93]). This procedure effectively allows detection of brain regions that are active during successful memory encoding, focusing in particular on the MTL.

Then how does the MTL determine what part of the continuous information stream entering our brain will be encoded and integrated into long-term memory? In general, it is believed that the MTL serves as a *novelty detector*, predicting and

detecting interesting novel information that needs to be stored [19,96,97]. Already familiar information is thereby hypothesized to be less well encoded, as there is no apparent reason to store information that is already available. This novelty encoding theory [19] is more recently suggested to be grounded in *predictive coding theory* [26], that assumes that the brain is continuously predicting future input. Based on this notion, the amount of deviation from the prediction, the so-called *prediction error*, has recently been hypothesized to be the driving factor for encoding of novel information [27,97,98]. These constructed predictions are, however, intrinsic and thus inevitably based on preexisting schemas.

Memory encoding is thus, next to well-known top-down influences such as attention, motivation, and emotion [93], found to be influenced by schemas, affecting encoding processes in two, seemingly opposite ways. On the one hand, a schema appears to facilitate encoding by relating new information with knowledge networks in the brain, while on the other hand, a schema can also lead to a prediction error when information is novel, thus not predicted by that particular schema. Either way, the schema is the driving factor that determines how memory is stored in the brain, a process I will elaborate on in chapters 1.5 and 8. Encoding is however just the first process that acts to retain memories. After encoding, a memory is further processed so it can be assimilated and *consolidated* into memory networks in the brain leading it to be retained for a longer period of time.

1.3.6 Memory consolidation

The consolidation of memory traces is a process that is generally thought to occur during post-learning offline periods when the brain is not consciously encoding or retrieving a certain memory [99]. Consolidation was first characterized in 1900 by Georg Müller and Alfons Pilzecker, who showed that newly learned memories can be disrupted by new information after learning [100]. This consolidation process was previously suggested to follow the time-dependent Ribot's law of regression, leading more remote memories to be better stabilized, and is additionally suggested to arise through strengthening of initially weak memory traces. This time-dependent pattern, with more remote memories less vulnerable to disruption than more recent memories, was later established in amnesic patients such as H.M. [40]. Consolidation is thus historically defined as a time-dependent process that is ongoing after learning of novel memories, can be disrupted by interference, and acts as a slow integrative process that fixates memory traces so they will most optimally be preserved for the remainder of our lifetime [99].

During sleep, the brain is found to replay learning-related spiking patterns

[101]. This replay is suggested to be the mechanism driving consolidation by actively reactivating memories in the MTL and related neocortical areas in order to integrate them into neocortical knowledge networks [102]. These replay patterns have been observed in several regions in the brain [103], among which the hippocampus [101,104] and the mPFC [67-69]. Even though there is still little evidence for a functional role of these replay patterns [but see 105], sleep in general has been consistently found to increase performance on motor learning and declarative learning tasks [106,107]. Moreover, sleep is suggested to be important to obtain insight into problems that are difficult to solve [108], presumably by integrating and assimilating new memories in preexisting schemas [109-112]. Next to sleep, also periods of awake rest are thought to show processes related to memory consolidation [113-115], suggesting an expansion of the period in which consolidation can occur to any period where the brain is focused internally rather than externally [116,117].

What happens to memory traces throughout this consolidation process is described by two, partly complementary and partly opposing, theories. The *standard systems consolidation theory* (see 1.3.1) states that memories are consolidated in the long run through strengthening connections within the neocortex, rendering them independent from the hippocampus that initially binds all memory traces [42,43]. Throughout this process, the memory itself is suggested to remain unchanged. Recently, this theory has been extended to concomitantly entail an increase in mPFC involvement, suggesting the linking function of the hippocampus transfers to the mPFC during consolidation [56,57,118,119] (figure 4). The *multiple trace or transformation theory* generally agrees with this systems consolidation theory, but states that whether a memory becomes hippocampally independent through consolidation is dependent on the nature of the memory. Consequently, this theory hypothesizes that only semantic memories (see 1.3.4.) become hippocampally independent through consolidation while episodic memories remain hippocampally dependent during their entire lifespan and will never be fully consolidated into the neocortex [38,92].

Memories are thus assumed to *semanticize* over time [111,120,121], so they become generalized and lose contextual details, presumably changing their representation. However, some memories might not semanticize, often due to secondary influences on the memory trace related to emotion, stress, or saliency and novelty [97]. These particular memories will then remain hippocampally dependent, as suggested by the transformation theory [92]. Note that one particular memory can, according to this theory, wind up having both an episodic, hippocampally dependent trace, and a semantic one, that is merged with similar episodes over consolidation, possibly by using a regularity detection process [110]. A memory of a certain occasion can thus in principle exist in different

states at different time points during the consolidation process, an assumption that is not supported by the systems consolidation theory. Although not mutually exclusive in general terms, these two theories lead to inherently different hypotheses and contradictions that have dominated debates in consolidation research in the past few decades [122].

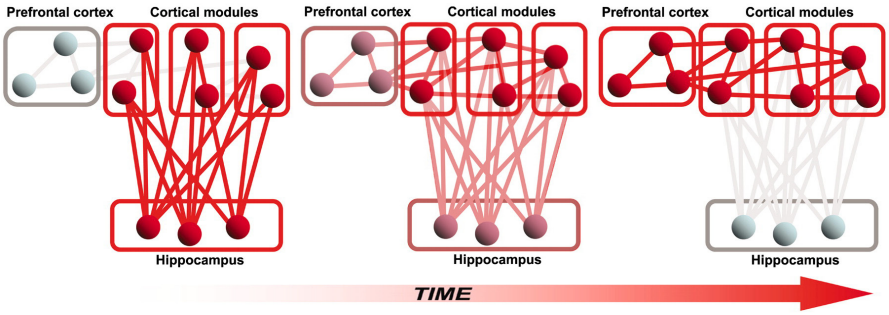


Figure 4: The (adapted) systems consolidation theory that assumes temporally graded hippocampal involvement during consolidation and retrieval of newly learned memory traces. During and right after learning (panel 1), the hippocampus is thought to bind different parts of a memory trace in the cortical modules. During consolidation (panel 2), these traces degrade, while traces within the nodes in the cortical modules and between the medial prefrontal cortex and the cortical nodes become stronger. During retrieval of remote memories (panel 3) that are fully consolidated, the memory trace will be hippocampally independent, but dependent on mPFC and connections within the cortical modules. This adapted model thus assumes a transfer from hippocampus to mPFC involvement in time. Additionally, it allows for introducing the role of a schema (in this figure the connections within the cortical modules in panels 2 and 3 within which a new memory can be assimilated) in this process, allowing it to be facilitated. Figure adapted from [56], with permission.

1.3.7 Memory retrieval

Memories are stored for a reason. Next to a role for these memories in affecting new learning [112], as argued above, they will obviously also have to maintain the possibility to be retrieved at some point in the future. Memory retrieval is a process that is assumed to be equivalent and complementary to memory encoding processes in terms of brain regions that are activated [123,124], and is often, though not exclusively (e.g. when fully consolidated, see 1.3.6), found to be dependent on the MTL [125]. Retrieval can differ in nature, ranging from vague familiarity with a cued stimulus to full recollection of an entire episode, processes that are suggested to be functionally distinct and rely on different regions within the MTL [126], although this is debated [2,82,127]. Which brain regions are activated when successfully retrieving a memory is thus dependent on many factors, such as the remoteness of the memory trace, the nature and strength of the memory, and the cue that is given.

In empirical research, retrieval is often considered an end-station of the processes a memory has undergone before being retrieved. Therefore, along with the fact that the timing of consolidation processes during offline processes such as rest and sleep is very hard to determine, retrieval processes are often measured at different time points after encoding [57] to examine consolidation processes that occurred in the meantime [128]. Nevertheless, retrieval is not merely regarded as a passive process only representing a blueprint for processes that occurred previously. Next to the earlier mentioned distinction in familiarity and recollection [126], and the significant role of consolidation [128], retrieval processes are additionally thought to involve re-encoding [128,129] and reconsolidation processes [111]. These processes are argued to allow a stored memory trace to become labile for a certain period of time so it can be modified according to novel information. Despite these interesting premises and their consequences for memory representations in the brain, these putative processes are beyond the scope of this thesis, which will focus on encoding, consolidation, and retrieval processes specifically.

1.4 Schema effects on mnemonic processing

As previously stated, a schema, represented as associative networks of prior knowledge in the brain, has been found to show pronounced effects on memory performance in behavioral experiments [12]. When relating this notion to brain functioning, the question arises which of the mnemonic processes described above are specifically affected by schemas. This question has only recently been addressed in empirical neuroscientific research when Richard Morris and his colleagues investigated it in rodents, using an event arena where rats learned to associate certain locations in the environment with specific flavors [130]. They found that when the rats were equipped with a specific flavor-location spatial map, new flavor-location associations could be learned in one trial. Moreover, these specific associations were found to readily become hippocampally independent after a 48-hour period, while non-schema related associations were still found to be hippocampally dependent after the same consolidation period [131]. These results suggested that schemas facilitate the consolidation process specifically, since no hippocampal independence was yet observed after a 3-hour interval [112]. In a follow-up experiment, they found that during encoding of flavor-place associations, not only the hippocampus was significantly activated, but that also the mPFC (prelimbic area in rats) showed enhanced activation specifically for schema-related information [54]. These findings additionally suggest that schemas already affect memory formation during encoding, and that both the hippocampus and the mPFC are involved in this process, allowing for

parallel encoding for schema-related learning. Schema effects on rodent memory thus appear to be governed by both online encoding and offline consolidation mechanisms and require an intricate interplay between the hippocampus and the mPFC.

In humans, little research has been performed investigating the effect of schemas on mnemonic processing. Some studies in psycholinguistics and decision making have shown schema effects in mPFC, hippocampus and other regions [51,52,132] on memory encoding processes, but results have mainly been discussed in a language setting [21,22]. The above-mentioned recent spatial memory experiments in rodents, however, show that schema can be investigated with a more memory-oriented focus. This approach allows us to, for the first time, examine the mnemonic processes underlying the assimilation of new information into networks of prior knowledge in humans, and focus on processes in and interactions between MTL and mPFC [112]. Chapter 2-6 of this thesis will extend above-mentioned literature by applying a memory-oriented approach towards schema effects in humans, both during retrieval before and after consolidation (chapters 2 and 3) and during encoding (chapters 4, 5 and 6).

1.5 Schema and novelty

As outlined above, the suggested behavioral enhancement of schema-related memories has been debated [12,17]. Behaviorally, it seems that only particular features of a schema-consistent memory are strengthened, enhancing recall and showing less interference on particular memory tests, yet leading to weakened memory and more false alarms on other tasks. On the other hand, schema-inconsistent information is in some cases found to lead to enhanced memory compared to schema-consistent information, particularly when it comes to differences in specific details [18,133]. Moreover, as hypothesized by the novelty encoding theory, schema-inconsistent memories are specifically attended to, and are shown to be related to enhanced MTL processing during encoding [19,97], while schema-consistent mnemonic processing is suggested to involve mPFC processing.

Clearly, these seemingly contradicting results that show memory enhancement for both schema-consistent and schema inconsistent memories, demonstrate that the question whether schema enhances memory in general is not a very straightforward one. Additionally, when considering all the different forms of memory and the wide range of memory tests that can be used in empirical memory research, the big picture becomes even vaguer. Rather, it seems that at both sides of the spectrum, from very schema-consistent to very schema-inconsistent memories, memory traces profit in different ways from their consistency with a

particular schema, each leading to their own benefits and pitfalls. These opposite, perhaps even competing, effects on novel, schema-inconsistent memories in MTL, and their relation to processing of schema-consistent memories in mPFC reflect another question that is yet unanswered [112], but will be elaborated on in chapter 7 of this thesis.

1.6 Schemas in education

Fundamentally, investigating schema effects on mnemonic processing is useful as it accounts for some of the inherent problems with encoding and consolidation paradigms, such as forgetting, interference, and variability across subjects. Moreover, considering that new memories are always related to preexisting knowledge, and thus they cannot be considered to be written on a *tabula rasa,* gives a broader, more ecologically valid view of mnemonic processing. Next to this fundamental power, schema research can also influence education by investigating how knowledge is organized in the brain, why it is organized in this way, and how this information can be used to improve student learning and to organize and set-up well-structured curricula. With this knowledge, teachers and students can additionally be taught how their brain stores information and how they can best connect newly learned information to their already existing schemas. Thus, schema research is of critical importance for the nascent discipline of educational neuroscience [134,135], that is trying to improve education by utilizing insights from cognitive neurosciences [136]. Bridging the gap between these disciplines is crucial to ultimately develop a *new science of learning* [137], encompassing psychology, machine learning, education and neuroscience.

Schema theory has focused upon education already from the early years onwards [3], and has been elaborated on in several educational theories led by Lev Vygotsky [138], Jean Piaget [3] and David Kolb [139]. While many of these theories all agree that prior knowledge is crucial for successful learning, they differ on how this would be represented in the brain and how it should be used in practice. In general though, it is vital within educational theory to distinguish between the process of learning itself and its effects on the long-term storage and recollection of information learned, much like the encoding and retrieval concepts outlined above. Additionally, next to cramming of facts and lists, and hopefully as a result of these endeavors, education ultimately aims to improve *conceptual learning* [140], and *comprehension* of subject matter [141] for a longer period of time. These skills are then ultimately expected to lead to *learning transfer* of the acquired knowledge [142], so that it can be used in more general problem solving. Students are thus expected to build their knowledge schemas as efficient as possible with the tools that are available, while teachers

are expected to organize their subject matter accordingly, eventually leading to students' ability to use this information in situations similar to the concepts learned in the classroom.

Even though there are still multiple gaps to fill and various bridges to cross [134,136], educational neuroscience is a promising new scientific discipline integrating education and cognitive neuroscience. To understand what drives our learning and memory capabilities and how these inherent biological principles can be translated adequately to educational practice, more research is necessary to bring education and cognitive neuroscience closer together. Schema theory can play a central role in this integration, as it deals with the essence of knowledge structures and their effects on subsequent learning. Along with advances in other disciplines, this is hoped to lead to an overlapping scientific discipline that will incorporate overlapping features between the disciplines at hand [137]. Chapter 8 of this thesis will examine the possibilities of applying schema research to (medical) education.

1.7 Set-up of this thesis

The research described in this thesis replicates and elaborates on earlier findings regarding the schema effect on memory while it advances beyond the classic behavioral and animal studies by using functional Magnetic Resonance Imaging (fMRI) to look into online and offline mnemonic processes in the human brain. The memory experiments described in this thesis are based on item recognition, cued recall, and associative memory paradigms, and brain activity and connectivity is measured during different mnemonic processes such as encoding, reactivation during awake rest (or early consolidation), and retrieval. Moreover, results are related to more common behavioral measures that relate to long term educational learning. Therefore, the research reported here extends existing schema and memory literature by building on previous behavioral, animal and computational findings and applying it to human cognitive neuroscience, educational theories, and general memory theories of encoding, consolidation, and retrieval.

Chapter 2 and 3 elaborate on consolidation and retrieval effects on the schema effect on memory. Chapter 2 reports the brain mechanisms during retrieval after learning and consolidation of congruent and incongruent associations, while chapter 3 extends this finding with additional behavioral data showing how the schema effect on memory evolves through consolidation. These findings illustrate that consolidation influences the schema effect on memory and that schema can be used to further investigate these mechanisms to help resolve remaining controversies in the field of memory consolidation.

Chapter 4, 5 and 6 refine schema effects on memory encoding. Chapter 4 shows that new information consistent with a preexisting schema leads to enhanced communication between the hippocampus and the mPFC, chapter 5 explains the specific activity profiles of this effect and their relation to educational learning and chapter 6 extends these findings by examining schema effects in three congruency levels that are subjectively identified. These studies demonstrate that schema already affects memory formation during encoding, a process that might continue during subsequent consolidation, as reported in chapters 2 and 3.

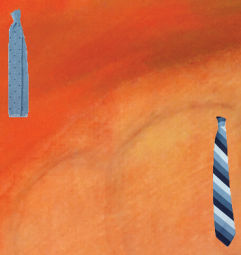
Chapter 7 and 8 provide a more theoretical elaboration on the previous chapters. Chapter 7 addresses the apparent contradiction between memory enhancement due to schema and novelty (schema-inconsistent memories), and aims to reconcile these seemingly opposite processes into one unifying framework. This framework partly accounts for opposite findings in behavioral schema research, patient studies, and computational mechanisms underlying memory systems in the brain, and additionally provides hypotheses for future experiments on schema, novelty, and memory. Finally, chapter 8 applies the outcomes of current schema research to (medical) education, where accurate schema construction and active and meaningful conceptual learning are of great importance.

Finally, chapter 9 discusses findings described in the previous chapters, linking the results to theories mentioned in this introduction and elaborating on the use of schemas in memory research. Moreover, it will provide a general conclusion of the work reported in this thesis, and hypotheses and applications for future research.

Part II:
Schema effects on consolidation and retrieval

Chapter 2

Retrieval of associative information congruent with prior knowledge is related to increased medial prefrontal activity and connectivity



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Abstract

We remember information that is congruent instead of incongruent with prior knowledge better, but the underlying neural mechanisms related to this enhancement are still relatively unknown. Recently, this memory enhancement due to a prior schema has been suggested to be based on rapid neocortical assimilation of new information, related to optimized encoding and consolidation processes. The medial prefrontal cortex (mPFC) is thought to be important in mediating this process, but its role in retrieval of schema-consistent information is still unclear. In this study, we regarded multisensory congruency with prior knowledge as a schema and used this factor to probe retrieval of consolidated memories either consistent or inconsistent with prior knowledge. We conducted a visuo-tactile learning paradigm in which participants studied visual motifs randomly associated with word-fabric combinations that were either congruent or incongruent with common knowledge. The next day, participants were scanned using functional Magnetic Resonance Imaging (fMRI) while their memory was tested. Congruent associations were remembered better than incongruent ones. This behavioral finding was parallelized by stronger retrieval-related activity in and connectivity between medial prefrontal and left somatosensory cortex. Moreover, we found a positive across-subject correlation between the connectivity enhancement and the behavioral congruency effect. These results show that successful retrieval of congruent compared to incongruent visuo-tactile associations is related to enhanced processing in an mPFC-somatosensory network, and support the hypothesis that new information that fits a pre-existing schema is more rapidly assimilated in neocortical networks, a process that may be mediated, at least in part, by the mPFC.

Introduction

New information that is consistent with prior knowledge is remembered better. Why this enhancement arises, and how it is expressed in the brain, however, is still relatively unknown. Prior knowledge is suggested to lead to easier assimilation within an interrelated set of neocortical representations, or schema, when this new information finds multiple links within such a schema [112]. Neural processes related to optimized encoding [143] and consolidation [112,131] have been suggested to play an important role in this enhancement. However, how prior knowledge affects processes related to memory retrieval has not yet been investigated.

Next to the hippocampus, an important brain region that is indicated to be involved in the retrieval of consolidated memories is the medial prefrontal cortex (mPFC) [56,57,67]. Moreover, the interaction between the hippocampus and the mPFC is believed to be important already in early stages of memory formation, as discovered in rodents [64], as well as humans [143]. Specifically, hippocampal-mPFC coupling is found to decrease during encoding of new information that fits prior knowledge [143], suggesting that next to hippocampal involvement, the mPFC may play an important role already during initial processing of schema-related information. Based on these insights, the pointer function of the hippocampus, binding distributed memory representations [39,102], has been suggested to gradually shift to the mPFC [56,57], a process that is potentially facilitated by a pre-existing schema [143]. Consequently, retrieval of a stimulus consistent with prior schema is expected to lead to improved memory performance [6,132], related to enhanced mPFC activity and connectivity with specific brain areas, representing elements of the learned information [124].

In this study, we investigated the effect of pre-existing schema on retrieval-related brain activity by manipulating semantic congruency of multisensory stimuli [144,145]. We chose for this setup, because multisensory stimuli that fit with prior knowledge can be regarded as schema-congruent, and remembering multisensory information is easier if it represents a feature combination congruent with prior experience [145,146]. This semantic congruency can be regarded as information that can readily be assimilated into pre-existing mental schemata. If this hypothesis holds, semantic congruency of multisensory stimuli will act as a schema and lead to enhanced memory performance along with enhanced activity in and connectivity between the mPFC and specific sensory cortices at retrieval [147]. Concomitant with this mPFC enhancement, hippocampal involvement at retrieval is expected to decrease.

Material and Methods

Participants

Twenty-six native Dutch female right-handed students participated in this study. All were healthy and had normal or corrected-to-normal vision. They were paid to participate and were told that they could earn extra money for better performance. Three participants were excluded after data acquisition, one because of excessive movement during scanning, and two because of poor item memory performance (total item recognition hits < 30), which left 23 participants for analyses. This sample covered an age range of 18-30 years, with a mean age of 22.65 years. They self-reported to have slept on average 7.67 hours in between both examination days (ranging from 6 – 9 hours). We decided to recruit women only, because they generally have more interest in and knowledge about fashion-like stimuli, and they are shown to have more tactile spatial acuity in their fingertips than men [148]. Ethical approval was obtained from the institutional review board (CMO Region Arnhem-Nijmegen, The Netherlands), and all participants gave written informed consent.

Stimuli

Participants learned a series of triplets of simultaneously presented stimuli that, when associated with each other, formed an object likely to be present in real life. These associations consisted of 1) motifs (200), visually presented as a 2-dimensional, pictorial square without tactile information; 2) visually presented object words (20) describing objects primarily composed of fabrics; and 3) fabric samples (20) that could be linked to the object words. Motifs (400 in total, including lures) were obtained from the internet, and were equalized in size (256 x 256 pixels, 28.35 pixels/cm, indexed color mode) and auto contrasted using Adobe Photoshop CS3, version 10.0.1 (Adobe, San Jose, CA, USA). Fabric samples were cut into squares of five by five cm, and object-fabric combinations were categorized as being either semantically congruent (for example a leather jacket) or semantically incongruent (for example a lace umbrella). The (in) congruency of these combinations was verified in an independent behavioral pilot, where participants (n = 12) were asked to rate the congruency of word-fabric combinations from 1-6. Combinations rated on average 2.5 or lower were considered incongruent, and combinations rated on average 3.5 or higher were considered congruent. Combinations in between these ratings were altered to either fit a congruent or incongruent representation.

Design and general procedure

Participants were tested using a within-subjects 2x3 factorial design with

congruency (congruent items versus incongruent items) and memory (associatively remembered items versus associatively forgotten items versus completely forgotten items) as within-subject factors (see figure 1). They were invited to come to the center on two consecutive days with on average 19.83 hours between the two visits (ranging from 18.5 – 21 hours). On day one, participants were instructed to memorize simultaneously presented triplets of visual motifs, visual object words, and tactile fabric samples by imagining how the combination of these features would look like. They were told that their memory would be tested in the MR-scanner on the next day, but they received no information about the specifics of this memory test. Using Presentation 10.2 (Neurobehavioral systems, Albany, CA, USA), the motif and the word were visually presented on a computer screen for six seconds, the word situated above the motif. Concurrently, participants were instructed in a practice session to tactilely explore a fabric for the complete 6 seconds, and imagine how the combination of motif, word, and fabric would look. The fabric was presented by the experimenter underneath a heightened plateau on which the computer screen was placed, and was not visible to the participant. After presentation of each stimulus combination, participants were asked to indicate whether they thought the triplet characterizing the imagined object was either pretty or ugly (see figure 1).

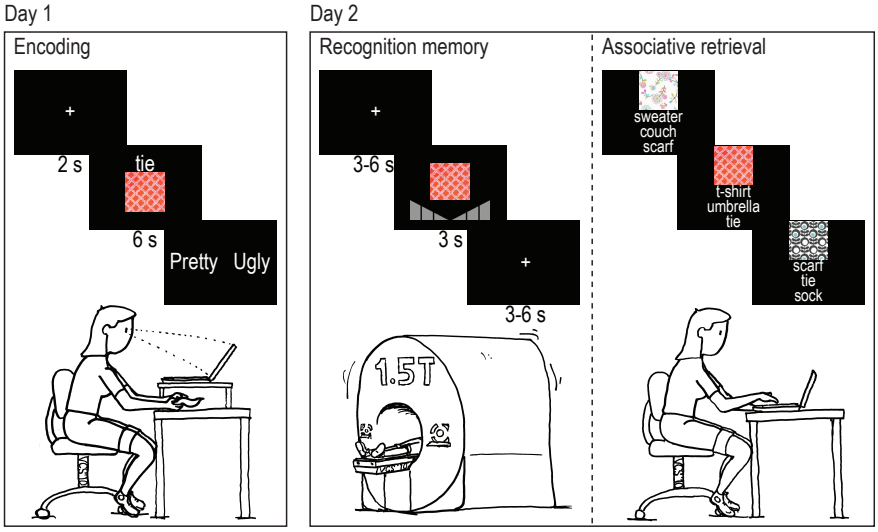


Figure 1: Experimental design. On day 1, participants learned associations of visual motifs and congruent or incongruent object-fabric combinations, where the object was presented together with the motif as a written word on the computer screen, and the fabric simultaneously as a tactile stimulus underneath the computer screen. On day 2, participants were tested in the MR scanner by means of a visual item recognition test (motifs) and subsequently with an associative memory test outside the MR scanner in which the motifs served as cues and the associated word was asked for in a three-choice test.

In total, participants memorized 200 sequentially presented combinations, 100 congruent and 100 incongruent, divided into three sessions of consecutively 80, 80, and 40 trials. The 20 object words and 20 fabric samples were combined into 80 possible combinations, with each object word linked to two congruent and two incongruent fabrics. For the last session of 40 presentations only one congruent and one incongruent object-fabric combination was used instead of two. Within each session, object-fabric associations were randomly divided, but equal for each participant, whilst motifs were randomly shuffled for each participant. Thus, every participant learned the same object-fabric combinations, but for each participant these were differently associated with the motifs.

On the second day, participants were scanned while they performed an item recognition memory test (with confidence rating) for the motifs presented the day before. Participants lay supine in the scanner, wore headphones (Commander XG, Magnetic Resonance Technology, Northridge, CA, USA), and responded using left and right button boxes, which were fastened with tape to the upper legs so they would not move. They viewed the screen through a mirror positioned on top of the head coil. They were instructed to respond within the three seconds presentation time, try to move as little as possible, and keep their fingers as still as possible to avoid involvement of somatosensory stimulation during button presses. Participants received a practice session before starting the experiment. Stimuli were presented in the center of the screen for three seconds, and were followed by a fixation cross, presented for three to six seconds. Furthermore, 10 fixation cross baseline trials of 10 seconds duration were included. These baseline trials were distributed so that within every 40 trials, a baseline trial was presented. After the item recognition memory test, which lasted 51 minutes and 20 seconds, a structural scan of 9 minutes and 38 seconds was made. Finally, a localizer for the somatosensory cortex (6 cycles of a simple blocked design; 15 seconds on, 15 seconds off) was performed where participants received somatosensory stimulation on all fingers of both hands by simultaneously moving two cotton swabs across their fingers. This localizer scan lasted 3 minutes and 15 seconds in total, and was performed to be used as an ROI for further analyses, since the somatosensory cortex has been suggested to be the primary location of somatosensory memories [149,150]. After the scan session, participants were taken to another room to perform an associative retrieval task additionally.

Memory tests and analyses

Item recognition memory was tested in the MR-scanner using a confidence level approach (6 levels) in which participants were instructed to indicate whether a perceived stimulus (200 old and 200 new) was old or new. Six answer options were provided: sure old, nearly sure old, not sure old, not sure new, nearly sure

new and sure new. Answers were given both with left and right ring finger, middle finger, and index finger, with the old/new side counterbalanced across participants. The order of the motifs was pseudorandom; no more than four consecutive old or new stimuli were presented. Participants could only answer once and were given feedback on which button they pressed. Answers that were given too late (i.e. after the three seconds presentation time), or were indicated as not sure, were not included in the analyses.

Subsequent to the item recognition memory test, participants performed a self-paced, three-alternative forced-choice associative memory task outside the scanner, in which they were instructed to indicate which object word was associated with a certain motif on the previous day. All 200 memorized motifs were randomly and sequentially presented on a computer screen as cues, together with three words of which one word was the correct answer, and the two other words were randomly sampled from the other 19 words. After participants finished this test, they filled out a study-specific questionnaire.

Behavioral measures of item recognition scores were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) by calculating the percentage of hits and false alarms (both sure old and nearly sure old confidence levels) for both conditions (congruent and incongruent). Next, these values were z-transformed and subtracted from each other to calculate d-prime for both conditions. Subsequently, Student t-tests were performed to determine differences from chance level (0; one-sample t-test) and differences between the congruent and incongruent conditions (paired sample t-test). Associative memory was analyzed using only the items that were correctly recognized during item recognition. Of these items, percentage correct was calculated for both conditions, and again one-sample (with chance level 1/3) and paired sample Student t-tests were performed to determine congruency differences. Also, in both memory tests, reaction time differences between both conditions were assessed using the same statistical tests. Alpha was set at .05 throughout.

MRI scanning parameters

Participants were scanned using a 1.5 Tesla Siemens Magnetom Avanto system equipped with an 8 channel phased array head coil (MRI Devices). For BOLD fMRI images, we used a T2* weighted gradient echo EPI sequence with the following parameters: TR: 2.48 s, TE: 35 ms, 34 slices, ascending slice order, 3.5 mm slice thickness, .35 mm slice gap, matrix size: 64*64, FOV: 212*212 mm, flip angle: 90°, voxel size: 3.3x3.3x3.5. Slices were angulated in an oblique axial manner to reach whole brain coverage. To ensure reaching a steady state condition, the first five scans were discarded. Additionally, T1 weighted anatomical scans at 1 mm isotropic resolution were acquired with TR of 2250 ms, TI of 850 ms, flip angle of

15° and FOV of 256 x 256 x 176 mm.

fMRI data pre-processing and analyses

Raw fMRI data were preprocessed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). First, motion correction was performed by using iterative rigid body realignment to minimize the residual sum of squares between the first and all further functional scans. Then, ascending slice timing correction was performed such that all slices were corrected to the time of acquisition of the reference slice (i.e. the middle slice, 17). Subsequently, rigid body co-registration to corresponding individual T1 images was performed using mutual information optimization. Hereafter, data were spatially normalized into a common space, defined by the Montreal Neurological Institute (MNI) 152 T1 image (voxel size = 2x2x2), and smoothed by convolving the data with an 8 mm FWHM 3D kernel. The first five scans were excluded, which left 1242 scans for analysis.

After preprocessing, statistical parametric maps were generated by modeling the evoked blood oxygen level dependent (BOLD) response for each memory bin (associative hits: item hit + association remembered; associative misses: item hit + association forgotten; forgotten: item forgotten) as a boxcar function of three seconds convolved with a hemodynamic response function (HRF). Furthermore, individual movement regressors were added to each first-level model. Subsequently, a random-effects 2x3 factorial design was constructed in which congruency (congruent and incongruent) could be tested against memory (item hit + association remembered; item hit + association forgotten; item forgotten). Whole brain activity for main and interaction effects was considered significant at $p < .05$ corrected at cluster-level, after creating a $p < .001$ uncorrected map or small volume corrected (SVC) at $p < .05$ based on a $p < .001$ uncorrected map, with independently determined regions of interests: bilateral hippocampi taken

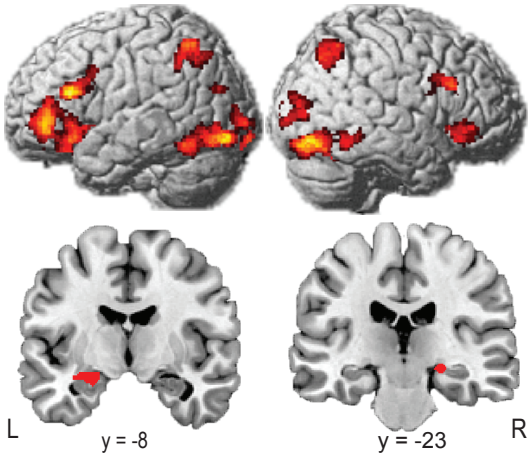


Figure 2: Main effect of associative memory. GLM analyses revealed a set of brain regions comprised of dorsal and ventral visual areas, inferior parietal sulci, dorsolateral and ventrolateral prefrontal cortices (cluster-level corrected; p < 0.05), and bilateral hippocampi (p < 0.05 SVC corrected; peaks [-32,-10,-12] and [22,-22,-10]).

from the AAL-template [151], and the somatosensory localizer (left side).

The localizer scans were processed using the same procedures as the experimental scans, but without slice time correction. Hemodynamic responses were modeled using a statistical parametric map in which blocks of 15 seconds on/off were modeled as boxcar functions convolved with a hemodynamic response function, and individual movement regressors were again added to each first-level model. To assess a random effects analysis of somatosensory stimulation, a one-sample t-test was performed. Because activity appeared very strong, we used a threshold of $p < .00005$ uncorrected for this analysis. To determine whether activation was close to the region in the somatosensory cortex dedicated to the fingers, we furthermore used coordinates from a previous study revealing these regions for the separate fingers [152], surrounded by a 6 mm sphere, as ROI ($p < .001$ uncorrected; $p < .05$ SVC).

Psychophysiological interactions were calculated to assess functional connectivity between regions. They were executed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm) in combination with in-house software, written in Matlab 7.5 (The Mathworks, Inc., Natick, MA, USA). Psychophysiological interaction analyses probe differences in coactivation of a certain seed region (physiological factor) with the rest of the brain modulated by an external factor (psychological factor). Here, we examined coactivation differences that were significantly larger for congruent than for incongruent items and vice versa. Only voxels that were significantly active in an effect of interest analyses were used for this analysis. The single-subject GLM-model constructed for previous analyses was extended with two regressors: the general deconvolved signal from the seed region, and the deconvolved signal from the seed region for the contrast congruent hits versus incongruent hits. For each subject, this second physiological activity was used as input for the second-level random effects analysis. The seeds in mPFC and somatosensory cortex, present in the congruency x subsequent associative memory interaction, were defined by taking the peak voxel surrounded by a 5mm sphere. Connectivity was again considered significant at $p < .001$ uncorrected at voxel-level and $p < .05$ corrected at cluster-level or at $p < .001$ uncorrected at voxel-level and small volume corrected (SVC) at $p < .05$ with the somatosensory localizer.

To determine correlations between PPI strength and behavior across participants, PPI measures were extracted from SPM and analyzed using SPSS. A two-tailed Pearson correlation test between PPI measures and congruency benefit of associatively remembered items (congruent / incongruent), was performed. Alpha was again set a .05.

Results

Memory performance

Memory performance measures showed a semantic congruency effect on associative memory ($t(22) = 4.09$, $p < .001$), with both measures different from chance level (congruent items: $t(22) = 8.16$, $p < .001$ (mean = .51; SD = .11), incongruent items: $t(22) = 5.30$, $p < .001$ (mean = .43; SD = .09)). Also item recognition memory for the visually presented motifs showed a congruency effect ($t(22) = 2.13$, $p < .05$), and were different from chance (congruent items: $t(22) = 9.97$, $p < .001$ (mean = .80; SD = .38), incongruent items: $t(22) = 9.32$; $p < .001$ (mean = .71; SD = .36). Reaction times during both item recognition and associative memory were not different in either of these bins ($t(22) = .52$, p = n.s.; $t(22) = 1.67$, p = n.s.).

Neuroimaging results: Differential activity

When analyzing fMRI data related to successful recognition memory differing in terms of correct associative retrieval (associative hits versus associative misses) we revealed a set of brain regions encompassing bilateral hippocampus (peaks [-32,-10,-12] and [22,-22,-10]; SVC corrected; figure 2), areas in the dorsal and ventral visual streams, inferior parietal sulci, dorsolateral and ventrolateral prefrontal cortices and basal ganglia (cluster-level corrected; figure 2). When performing a congruency x associative memory ANOVA, testing activity differences for congruent > incongruent and associatively remembered > associatively forgotten, an interaction in the medial prefrontal cortex (mPFC), extending from anterior cingulate cortex (ACC, BA 32) into BA 10 was found. This interaction was based on larger differential responses for congruent as opposed to incongruent trials (peak = [-6,34,12]; cluster-level corrected; figure 3). Another cluster of interacting voxels was found within the left hemispheric region activated by the somatosensory localizer scan (peak [-50, -20, 32]; cluster-level corrected; figure 3). This cluster was located within a sphere with 6 mm radius surrounding an area in the somatosensory cortex previously found to be related to sensory sensation in the thumb [-52, -19, 42][152]. No significant effects were observed for the opposite contrast.

Neuroimaging results: Differential connectivity

To assess connectivity differences, we performed psychophysiological interaction (PPI) analyses on the mPFC cluster found in the congruency x subsequent associative memory interaction for congruent versus incongruent associative hits. This seed region revealed significant coactivation with the left somatosensory cortex (peak [-56,-16, 48]; SVC corrected; figure 3), which was

stronger for congruent associative hits than incongruent associative hits. Again, this cluster was within a sphere with 6 mm radius surrounding the areas in the somatosensory cortex related to sensory sensation in the thumb [152]. No significant effects were observed for the opposite contrast.

Brain-behavior relation

We next tested whether across participants this congruency effect on mPFC connectivity predicted the behavioral benefit in terms of memory performance. Here, we found that the PPI between the mPFC and the left somatosensory cortex for the congruent versus the incongruent associatively remembered items predicted the congruency benefit of associatively remembered items (congruent / incongruent) ($r(22) = .531$; $p < .01$; figure 3).

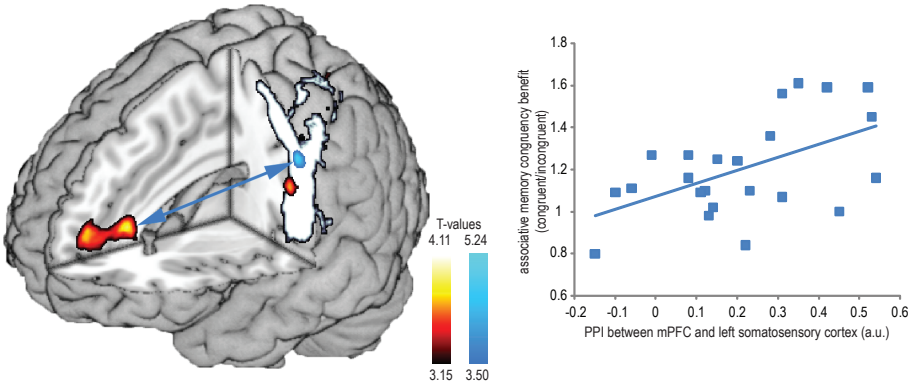


Figure 3: Congruency x associative subsequent memory interaction and PPI results from mPFC. The congruency x associative subsequent memory interaction showed activity (red/yellow) in mPFC ($p < .01$ cluster-level corrected), and in the left somatosensory cortex ($p < .05$ cluster-level corrected) (overlayed on the localizer scan in white/grey). A psychophysiological analysis with mPFC as seed region showed a significant coactivation (blue arrow) with the left somatosensory cortex, which was stronger for congruent hits than for incongruent hits (blue). Finally, a correlation between mPFC-somatosensory coupling and behavioral congruency benefit was found. The more connectivity present during item recognition of associatively remembered items, the higher the congruency benefit for subsequent associative retrieval ($r(23) = .531$; $p < .01$).

Discussion

The current results show that mPFC-activity and connectivity with a specific representational cortical area is enhanced when multisensory learned information is retrieved that is congruent with a general, pre-existing mental schema. Additionally, this increase in functional connectivity was found to be positively correlated to the behavioral benefit associated with this pre-existing knowledge across participants. These results are in line with a model in which the mPFC is involved in readily assimilating new information into pre-existing

schemata during memory formation and consolidation [112,143].

Behaviorally, our results show enhanced memory for semantically congruent compared to incongruent multisensory associations. This memory enhancing effect of semantic congruency has previously been identified [146], but its underlying neural mechanisms were largely unknown. This effect has previously been suggested to be related to working memory mechanisms [8], or intertwined encoding and consolidation processes during and immediately after learning [143]. The present data show congruency effects in the mPFC during retrieval processes. Therefore, next to working memory, encoding, and post-learning consolidation, distinct retrieval processes may be related to this behavioral advantage. Our results can thus be explained by adopting a framework where modulation of both learning and post-learning processes leads to long-term modulation of memory traces, with semantic congruency allowing new information to be faster and better embedded into an existing associative mnemonic network [112,131,143].

The congruency effect that we found at the behavioral level was expressed in within-subject activity and connectivity differences in mPFC and left somatosensory cortex, and was additionally related to connectivity differences between these regions across participants. These results confirm that the mPFC plays a key role in retrieving consolidated memories [56,57,67]. Additionally, since semantic congruency reflects the degree to which the newly learned information fits to pre-existing knowledge (i.e. schema) [145], and given the assumption that such congruent information is more rapidly assimilated than information that does not fit a prior schema [131,143], our data further support the view that such a fast track in memory consolidation might also be present in humans.

Additionally, our results partly support the hypothesis that the pointer function of the hippocampus, binding distributed memory representations [39,102], shifts to the mPFC [56,57]. This functional balance is suggested to be facilitated by prior knowledge [143]. However, this hypothesis predicts a reduction in hippocampal contribution to memory retrieval of congruent stimuli along with an increase in mPFC contribution, which we did not find. One explanation for this null finding related to hippocampal processing and connectivity may be that we scanned memory retrieval processes after only one day/night cycle (on average 20 hours later). Although systems consolidation mechanisms have been indicated to be more rapid than previously assumed [57,109], and facilitated by prior knowledge [131,143], these mechanisms are still very likely to abide in an early phase as observed here. Therefore, retrieving the memory trace still requires hippocampal mediation for both congruent and incongruent associations. Further research will be needed to reveal whether hippocampal

activity will decrease in time [57,129], or whether the hippocampus remains activated while such associative memories are retrieved [38], irrespective of the occurrence of a (partial) shift of its pointer function to the mPFC.

Similar to the hippocampus, the function of the mPFC in consolidation is broadly investigated whilst many questions remain. Next to its putative role in systems consolidation and retrieval [55-57,67], the mPFC has been indicated as a region involved in a diversity of functions, among which many with a mnemonic nature. The prefrontal cortex in general is believed to be involved in updating, maintenance and manipulation of memory traces [45,125], and the mPFC in particular is thought to be related to feeling of knowing [153], conceptual knowledge integration [51], perceptual matching [154], comprehension [22,52], remote associative memory [59,67], and is shown to actively replay learning-related neuronal spiking patterns during sleep [66,67]. Furthermore, mPFC lesions lead to specific retrieval impairments for remote, presumably consolidated memories [68,74], and an absence of semantic congruency memory enhancement [70]. Finally, its connectivity to several other brain regions deems it very well suited to retrieve distributed memory traces [83]. This accumulating line of evidence clearly shows the critical importance of the (m)PFC in all stages of mnemonic brain functioning.

In contrast with its mnemonic function, more dorsal parts of the mPFC have also been suggested to be involved in rather general control mechanisms such as error monitoring and effort related to task difficulty [47]. However, since enhanced memory performance in our study is positively related to larger mPFC activity, it is unlikely that the mPFC activity observed during remote memory retrieval in this and previous studies [57,59] is related to such general control function of the mPFC. In sum, our findings extend current literature on the mnemonic function of the mPFC by showing its congruency-dependent involvement in remote memory retrieval, and support the view that the mPFC offers a fast track into consolidated memories if newly stored information fits pre-existing schemata [56,143].

The presence of prior knowledge is widely known to enhance memory of new information that fits this knowledge [6], but hitherto one could only speculate on the actualization of this memory enhancement. Our data elucidate some of the underlying neural mechanisms of this process. How a prior associative schema enhances memory formation, however, remains to be determined. A plausible hypothesis is that two different learning systems (focused/fast learning versus interleaved/slow learning) are present in the brain, as proposed by McClelland and colleagues [25]. We suggest, based on this theory and our data, that when new information is inconsistent with prior knowledge, more interleaved learning is necessary in order to assimilate this information in pre-existing

memory networks. In turn, consistent information needs less interleaved learning to be adequately integrated, speeding up assimilation and concurrent mPFC involvement. In this view, the presence of prior knowledge can modulate the processing speed of consistent incoming information due to less necessity to interleave it with inconsistent prior memory networks.

Learning of multisensory perceived stimuli, as applied here, is a relatively underinvestigated area of learning and memory [144]. Here, by modulating congruency, multisensory learning proved a very efficient tool to investigate mnemonic mechanisms at retrieval, but might accordingly also be employed to investigate encoding and consolidation mechanisms. In particular, since associative sensory features of a learned stimulus are found to reactivate sensory areas at retrieval [147], even when only one sensory modality is cued [123,155], these reactivations can reliably probe binding of modality-specific distributed brain regions while retrieving relevant information, either hippocampally [129,132] or neocortically mediated (as reported here). Furthermore, the assimilation of multisensory perceived stimuli into one coherent whole [156,157], can be more thoroughly investigated when considering long-term consequences of these assimilative mechanisms [144], and the mediating effect of (semantic) congruency [145,146]. Finally, since training can modify congruency judgments [158], sometimes even modulated by other modalities [159], these findings can be very helpful when designing educational programs where multisensory learning is an integral part of the curriculum [160] (e.g. in medical education [161]).

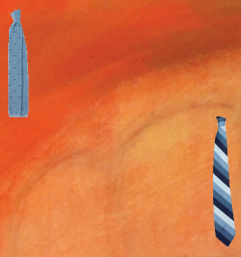
These results provide support for the view that the mPFC is crucially involved in retrieval of consolidated associative memories, and the role of prior knowledge in these mechanisms. By modulating prior knowledge, this paradigm shows that we can gain more insight into how new information is assimilated in pre-existing knowledge networks. This insight is of crucial importance to advance mnemonic research to memory formation, consolidation, and retrieval. Furthermore, the memory enhancing effect related to the facilitatory nature of prior knowledge is of great importance to educational strategies. By understanding more about the mechanisms underlying this facilitation, educational programs can be better structured, leading to more efficient learning in classroom settings [162].

Acknowledgements

The authors wish to thank Vincent Schoots for graphical assistance.

Chapter 3

Consolidation differentially modulates schema effects on memory for items and associations



Marlieke T.R. van Kesteren, Mark Rijpkema, Dirk J. Ruiter, and Guillén Fernández

In press at PLoS One

Abstract

Newly learned information that is congruent with a preexisting schema is often better remembered than information that is incongruent. This schema effect on memory has previously been associated to more efficient encoding and consolidation mechanisms. However, this effect is not always consistently supported in the literature, with differential schema effects reported for different types of memory, different retrieval cues, and the possibility of time-dependent effects related to consolidation processes. To examine these effects more directly, we tested participants on two different types of memory (item recognition and associative memory) for newly encoded visuo-tactile associations at different study-test intervals, thus probing memory retrieval accuracy for schema-congruent and schema-incongruent items and associations at different time points (t=0, t=20, and t=48 hours) after encoding. Results show that the schema effect on visual item recognition only arises after consolidation, while the schema effect on associative memory is already apparent immediately after encoding, persisting, but getting smaller over time. These findings give further insight into different factors influencing the schema effect on memory, and can inform future schema experiments by illustrating the value of considering effects of memory type and consolidation on schema-modulated retrieval.

Introduction

Information that is congruent with prior knowledge (or a schema) is often found to be better remembered than incongruent information [4,6]. This congruency effect or schema effect on memory is suggested to be dependent on mnemonic mechanisms [112,163], such as differentially efficient encoding [54,143] and consolidation processes [31,43,131]. However, the relative contribution of these processes to schema-dependent memory enhancement is largely unknown. Moreover, reports of enhancing schema effects on memory are not always consistent in the literature, as not all types of memory appear to be enhanced by a pre-existing schema [12,17], suggesting that the way a memory is cued can influence the schema effect as well. Thus, the relative contribution of encoding and consolidation processes on the schema effect and their enhancing effects on different memory measures still remains to be established.

The schema effect on memory has been a fairly consistent finding for decades, showing that information that fits with a pre-existing schema is better remembered [6,164], and more efficiently processed [54,143]. However, opposing observations where schema-inconsistent memories are shown to be enhanced are also occasionally reported [12]. These paradoxical effects are generally related to detailed recognition [133], interference effects [11], false memories and confidence [18,165], and category learning [17,133], and are largely consistent with the novelty encoding principle stating that information that is novel is preferentially encoded [19]. Partly as a result of these seemingly contradictory results, the schema theory was rendered more labile over the past decades [12]. As learning of congruent information does not always consistently lead to better memory performance than incongruently learned information, it was suggested that the schema effect might be dependent on various additional factors, such as how a memory is cued and after which delay it is measured [17,163]. These additional factors might account for the paradoxical effects of a schema on memory performance that are mentioned above.

During memory encoding, a new memory trace is processed such that it can be most efficiently stored [93]. Encoding is suggested to be dependent on many factors, such as depth of processing [166] and semantic elaboration [167], processes that are found to be enhanced when an encoded stimulus is congruent with prior knowledge [132]. However, also novelty is suggested to drive (presumably different [163]) encoding processes [19], leading stimuli incongruent with prior knowledge to be better encoded as well. After encoding, a memory is thought to be integrated into existing knowledge structures through consolidation mechanisms [43,44,168], which are proposed to process memory traces off-line in order to most efficiently assimilate them into preexisting

schemas [109,110]. This consolidation process is found to be facilitated specifically for information that was related to a pre-existing schema [131,164], and might additionally be related to tagging of a schema-related memory during and right after encoding [169]. The ease and nature of retrieval of a certain memory is thus suggested to depend not only on how a memory trace is encoded but also on how it is consolidated and integrated into the preexisting schema [112,170]. Consolidation of a memory after encoding is moreover found to favor strengthening of salient and important memories, such as memories that are emotional [171], rewarding [172], or semantically related [173], thus suggesting that consolidation, next to encoding, can have profound effects on long-term storage of a memory trace [110].

In this experiment, we therefore examined how the congruency effect on memory progresses over time by examining memory performance before or after consolidation on retrieval of congruent versus incongruent item and associative memories. Participants were randomly divided in three different groups (delay t=0 hours, t=20 hours (as described in [164]), or t=48 hours after encoding), and were tested using a between-subjects 3x2 factorial design with study-test interval (delay) and congruency as factors. They completed a paradigm in which they learned visuo-tactile associations that were either congruent or incongruent with prior knowledge (see [164] and figure 1), and performed memory tests either after 0 hours (group 1), after 20 hours (group 2) or after 48 hours (group 3). They were first tested on item recognition and subsequently on associative memory. Analyses were conducted on both these memory measures and compared for all three groups. We expected the schema effect to be apparent for both item recognition and associative memory scores, but hypothesized that differences could arise over time, through consolidation.

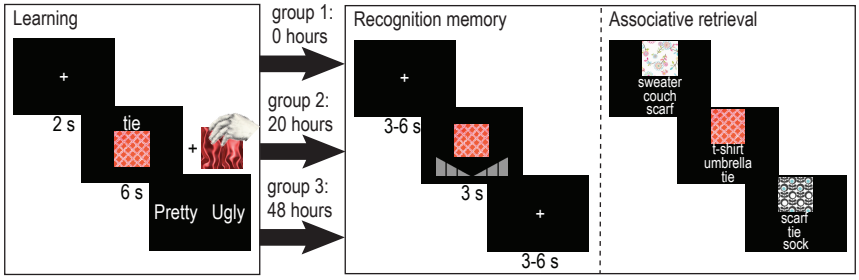


Figure 1: Experimental design. On day 1, participants learned associations of visual motifs and congruent or incongruent object-fabric combinations, where the object was presented together with the motif as a written word on the computer screen, and the fabric simultaneously as a tactile stimulus underneath the computer screen. Participants were tested after different time intervals (group 1: t = 0 hours, group 2: t = 20 hours, group 3: t = 48 hours) by means of a visual item recognition test (motifs) and an associative memory test in which the motifs served as cues and the associated word was asked for in a three-choice test.

Results

Item recognition memory scores (d-prime, figure 2A) showed a delay x congruency interaction ($F(2,66) = 5.04$, $p < .01$), with item memory significantly better for congruent items in group 2 ($t(22) = 2.12$, $p<.05$), and group 3 ($t(22) = 2.55$, $p< .05$), but not in group 1 ($t(22) = 1.55$, p = n.s.). No main effect of congruency was found ($F(2,66) = 2.53$, p=n.s.). All measures were significantly different from chance (group 1 congruent: $t(22) = 9.42$, $p<.001$, group 1 incongruent: $t(22) = 10.92$, $p<.001$, group 2 congruent: $t(22) = 9.97$, $p <.001$, group 2 incongruent: $t(22) = 9.32$, $p<.001$, and group 3 congruent: $t(22) = 10.32$, $p<.001$, group 3 incongruent: $t(22) = 8.85$, $p<.001$). Reaction times did not show any differences for either group (group 1: $t(22) = .44$, p =n.s., group 2: $t(22) = .52$, p =n.s., group 3: $t(22) = .12$, p=n.s.), or between-groups (congruent: $F(1,66) = .31$, p=n.s., incongruent: $F(1,66) = .36$, p=n.s., also not in any post-hoc analyses). These results show a delay x congruency interaction for item recognition memory scores based on a schema effect that arises only after a delay that allows consolidation processes to take place (figure 2A).

Associative memory scores (figure 2B) showed a main effect of congruency ($F(1,66) = 17.59$, $p < .001$) without a delay x congruency interaction ($F(2,66) = 2.44$, p=n.s.). Also all these measures were significantly different from chance (group 1 congruent: $t(22) = 6.58$, $p<.001$, group 1 incongruent: $t(22) = 6.18$, $p<.001$, group 2 congruent: $t(22) = 8.16$, $p<.001$, group 2 incongruent: $t(22) = 5.30$, $p<.001$, and group 3 congruent: $t(22) = 6.39$, $p<.001$, group 3 incongruent: $t(22) = 6.16$, $p<.001$). Associative memory scores thus show a main effect of congruency and no interaction with delay (figure 2B).

Assessing the strength of the congruency effect (congruent – incongruent) over time (delay) (figure 2C and 2D) showed a significant positive increasing relationship for item recognition ($t(2) = 2.75$, $p<.01$, congruent > incongruent, figure 2C), which was significant for group 2 > group 1 ($t(44) = 2.57$, $p< .05$) and group 3 > group 1 ($t(44) = 2.82$, $p<.01$), but not for group 3 > group 2 ($t(44) = -.07$, p=n.s.). For associative memory (figure 2D), this analysis did not reveal a significant delay x congruency effect interaction ($t(2) = -1.38$, p=n.s.). Thus, a delay x congruency effect interaction was only found for item recognition, where the congruency effect was found to become larger over time.

Discussion

The results reported here show that encoding and consolidation differentially affect the schema effect on memory for different memory types. By testing the schema effect for both item recognition and associative memory at different

delays after learning, we show that the schema effect for item recognition increases with consolidation, while not yet being apparent immediately after encoding. On the other hand, for associative memory the schema effect is found to be present already immediately after encoding, and, although the difference grows smaller, shows persistence over consolidation. These results show that the schema effect on memory depends on delay and type of memory test.

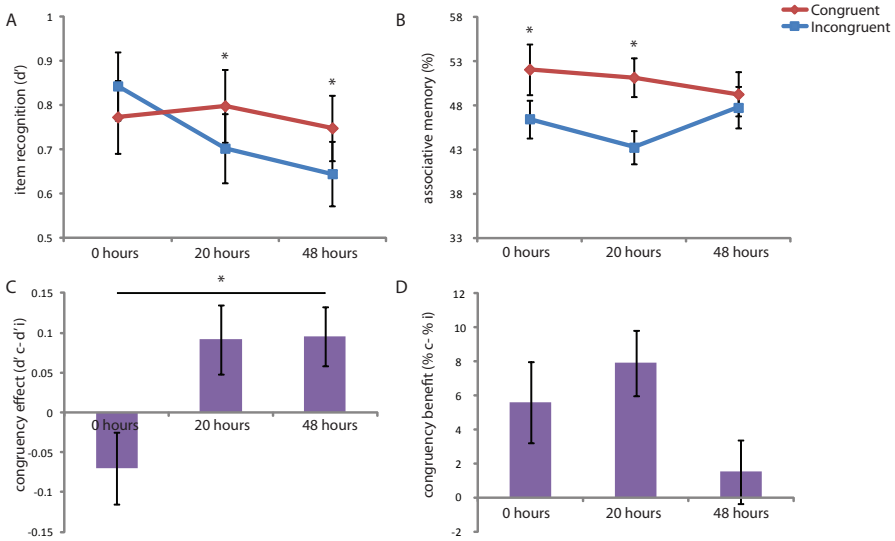


Figure 2: Behavioral results. Item recognition scores (d') for schema-congruent memories were enhanced only after consolidation (A), while schema-congruent associative memory scores (% correct) were enhanced already immediately after encoding and this effect persisted during time (B). Panels C and D show the congruency effect for both these memory measures over time, where the congruency effect on memory is found to increase for item recognition (C), but not for associative memory (D).

These results are generally consistent with the schema theory [4], while the finding that the schema effect only arises after consolidation for item recognition additionally partly accounts for findings that are inconsistent with it [17]. Schema theory has gained a challenging character over the past decades [12] because of paradoxical findings that showed enhanced memory for either information congruent or incongruent with a pre-existing schema. Schema effects were therefore suggested to be dependent on several factors [17,163], of which two were specifically tested here. We believe our findings along with previous inconsistencies in the literature can partly be explained by (schema) consolidation theories [111,112,163], stating that schema-congruent memories are preferentially consolidated in an accelerated manner, and its effects on memory performance over time for both item recognition and associative memory measures. Therefore, we propose that future research on schema-dependent memory should take these modulatory factors into account.

Schema effects have thus been suggested to be highly dependent on the specific task at hand. For example, while we report schema effects on item recognition, this enhancing effect is not always consistently found. When item recognition is tested in a two-alternative-forced-choice (2AFC) task where participants are instructed to choose between the target and a highly similar lure items that are incongruent with a pre-existing schema are found to be better remembered [17,133]. Moreover, these results are generally reported when tested immediately after learning without consolidation. While our results show no significant effect of schema on item recognition immediately after learning (figure 2), they do show an interaction with performance over a delay, when allowing consolidation processes to take place. This suggests that enhancing effects of incongruent memories right after encoding could inverse after consolidation has taken place, favoring schema-consistent memories in the long run only [110,173]. Additionally, the incongruency of a memory trace might lead to novelty and saliency processes that possibly preferentially enhance short-term storage of the memory [19,163]. Therefore, schema-inconsistent memory enhancements e.g. in the 2AFC task would benefit from future research where retrieval tests are performed both before and after consolidation, to more specifically determine whether this effect is specifically related to encoding mechanisms and to better understand its relation to consolidation mechanisms. Other factors determining schema-congruent and schema-incongruent memory enhancements, such as the type of task, type of cue, and confidence could profit in the same way when future research will more clearly distinguishes between encoding and consolidation effects.

In sum, these findings give more insight into two different factors that modulate schema effects on memory: memory type and consolidation. Results show that the schema effect on item recognition performance is mostly influenced by consolidation processes occurring after learning, while the schema effect on associative memory is already present immediately after encoding and persists after consolidation. These results thus demonstrate that schema effects on memory performance can be more complex than previously thought since they are affected both by the type of cue during retrieval and the degree of consolidation that passed before retrieval. Further research will need to examine the specifics of this phenomenon, both behaviorally and neurally.

Material and Methods

Participants

This experiment is an extension of a previously published experiment [164], which is taken along in the analysis reported here (group 2). Stimuli, design,

and procedures are exactly the same as reported in this previous study. Seventy-six native Dutch female right-handed students participated in this study. All were healthy and had normal or corrected-to-normal vision. They were paid to participate and were told that they could earn extra money for better performance. Participants were randomly assigned to either group (with delay t=0 hours (group 1), delay t=20 hours (group 2) or t=48 hours (group 3) between encoding and retrieval), with 26 participants in group 1 and 25 participants in group 2 and 3. Seven participants (3 in group 1 and 2 in group 2 and 3) were excluded after data acquisition, because of poor item memory performance (total item recognition hits < 30), which left 69 (23 per group) participants for analyses. This sample covered an age range of 18-33 years, with a mean age of 22.14 years. There were no age differences between the different groups (group 1: 22.48, group 2: 22.65, group 3: 21.30, F = 1.106, p=n.s.). Participants in group 2 self-reported to have slept on average 7.67 (range 6 – 9) hours in the night after learning and participants in group 3 self-reported to have slept on average 7.22 hours (range 2.5 – 10) in the night after learning and on average 7.46 hours (range 5.5 – 10) in the night before testing. Hours of sleep was not significantly different between these groups for the first night (t = 1.26, p = n.s.). We decided to recruit women only, because they generally have more interest in and knowledge about fashion-like stimuli, and they are shown to have more tactile spatial acuity in their fingertips than men [148]. Ethical approval was obtained from the institutional review board (CMO Region Arnhem-Nijmegen, The Netherlands), and all participants gave written informed consent.

Stimuli

Participants learned a series of triplets of simultaneously presented stimuli that, when associated with each other, formed an object likely to be present in real life [see also 164]. These associations consisted of 1) motifs (200), visually presented as a 2-dimensional, pictorial square without tactile information; 2) visually presented object words (20) describing objects primarily composed of fabrics; and 3) fabric samples (20) that could be linked to the object words. Motifs (400 in total, including lures) were obtained from the internet, and were equalized in size (256 x 256 pixels, 28.35 pixels/cm, indexed color mode) and auto contrasted using Adobe Photoshop CS3, version 10.0.1 (Adobe, San Jose, CA, USA). Fabric samples were cut into squares of five by five cm, and object-fabric combinations were categorized as being either semantically congruent (for example a leather jacket) or semantically incongruent (for example a lace umbrella). The (in) congruency of these combinations was verified in an independent behavioral pilot, where participants (n = 12) were asked to rate the congruency of word-fabric combinations from 1-6. Combinations rated on average 2.5 or lower were

considered incongruent, and combinations rated on average 3.5 or higher were considered congruent. Combinations in between these ratings were altered to either fit a congruent or incongruent representation.

Design and general procedure

Participants were all tested using the same procedure, with the only dependent variable the delay between encoding and retrieval (0 hours for group 1, 20 hours for group 2 and 48 hours for group 3). They were tested using two (one for item recognition and one for associative memory) within-subjects 2x2 factorial designs with congruency (congruent items versus incongruent items) and memory (associatively remembered items versus associatively forgotten but item remembered items and item remembered versus completely forgotten items) as within-subject factors [see figure 1 and 164], and were subsequently tested in a between-subjects design with different study-test delay (group 1 versus group 2 versus group 3). They were invited to come to the center on one (group 1) or two days (group 2 and 3) with 48 hours between the two visits. On day one, participants were instructed to memorize simultaneously presented triplets of visual motifs, visual object words, and tactile fabric samples by imagining how the combination of these features would look like. They were told that their memory would be tested either directly after (group 1) on the next day (group 2 and 3), but they received no information about the specifics of this memory test. Using Presentation 10.2 (Neurobehavioral systems, Albany, CA, USA), the motif and the word were visually presented on a computer screen for six seconds, the word situated above the motif. Concurrently, participants were instructed in a practice session to tactilely explore a fabric for the complete 6 seconds, and imagine how the combination of motif, word, and fabric would look. The fabric was presented by the experimenter underneath a heightened plateau on which the computer screen was placed, and was not visible to the participant. After presentation of each stimulus combination, participants were asked to indicate whether they thought the triplet characterizing the imagined object was either pretty or ugly (see figure 1). After encoding, participants in group 1 was tested while participants in group 2 and 3 went home and returned to the center respectively 20 or 48 hours later.

In total, participants memorized 200 sequentially presented combinations, 100 congruent and 100 incongruent, divided into three sessions of consecutively 80, 80, and 40 trials. Because the object words and fabric samples had to be divided equally for each session and each condition, the 20 object words and 20 fabric samples were combined into 80 possible combinations (40 congruent and 40 incongruent), so each object word and each fabric sample was linked to two congruent and two incongruent fabrics. Within each session, these 80 object-

fabric associations were randomly divided, but equal for each participant, whilst motifs were randomly shuffled for each participant and thus unique for each combination. For the last session of 40 presentations only one congruent and one incongruent object-fabric combination was used instead of two. Thus, every participant learned the same object-fabric combinations, but for each participant these were differently associated with the motifs.

During retrieval, participants performed an item recognition memory test (with confidence rating) for the motifs presented the day before. They were instructed to respond within the three seconds presentation time. Participants received a practice session before starting the experiment. Stimuli were presented in the center of the screen for three seconds, and were followed by a fixation cross, presented for three to six seconds. Furthermore, 10 fixation cross baseline trials of 10 seconds duration were included. These baseline trials were distributed so that within every 40 trials, a baseline trial was presented. The item recognition memory test lasted in total 51 minutes and 20 seconds. After, participants performed an associative retrieval task additionally.

Memory tests and analyses

Item recognition memory was tested using a confidence level approach (6 levels) in which participants were instructed to indicate whether a perceived stimulus (200 old and 200 new) was old or new. Six answer options were provided: sure old, nearly sure old, not sure old, not sure new, nearly sure new and sure new. The order of the motifs was pseudorandom; no more than four consecutive old or new stimuli were presented. Participants could only answer once and were given feedback on which button they pressed. Answers that were given too late (i.e. after the three seconds presentation time), or were indicated as not sure, were not included in the analyses.

Subsequent to the item recognition memory test, participants performed a self-paced, three-alternative forced-choice associative memory task, in which they were instructed to indicate which object word was associated with a certain motif on the previous day. All 200 memorized motifs were randomly and sequentially presented on a computer screen as cues, together with three words of which one word was the correct answer, and the two other words were randomly sampled from the other 19 words. After participants finished this test, they filled out a study-specific questionnaire.

Behavioral measures of item recognition scores were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) by calculating the percentage of hits and false alarms (both sure old and nearly sure old confidence levels) for both conditions (congruent and incongruent). Next, these values were z-transformed and subtracted from each other to calculate d-prime for both conditions.

Subsequently, a repeated measures ANOVA with the factors time (group 1, group 2, and group 3) and congruency (congruent versus incongruent) were performed to test interactions and main effects between these factors. Group effects on single measures were conducted using a one-way ANOVA. For post-hoc analyses, Student t-tests were performed to determine differences from chance level (0; one-sample t-test) and differences between the congruent and incongruent conditions within both groups (paired-samples t-test), and differences between groups (independent-samples t-test). Associative memory was analyzed using only the items that were correctly recognized during item recognition. Of these items, percentage correct was calculated for both conditions, and again tested using a one-sample (with chance level 1/3) and again tested using a repeated measures ANOVA and subsequent paired samples and independent samples Student t-tests, as described above. Congruency effects were calculated per group and per memory type by subtracting individual incongruent memory scores from congruent memory scores (so congruent – incongruent) and were subsequently tested using a linear regression analysis. Also reaction time differences between both congruency conditions were assessed using the same statistical tests. Alpha was set at .05 throughout.

Part III:
Schema effects on encoding

Chapter 4

Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and post-encoding rest in humans

Marlieke T.R. van Kesteren, Guillén Fernández, David G. Norris, and Erno J. Hermans

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Abstract

The hippocampus is thought to promote gradual incorporation of novel information into long-term memory by binding, reactivating, and strengthening distributed cortical-cortical connections. Recent studies implicate a key role in this process for hippocampally driven crosstalk with the (ventro)medial prefrontal cortex (vmPFC), which is proposed to become a central node in such representational networks over time. The existence of a relevant prior associative network, or schema, may moreover facilitate this process. Thus, hippocampal-vmPFC crosstalk may support integration of new memories, particularly in the absence of a relevant prior schema. To address this issue, we used functional Magnetic Resonance Imaging (fMRI) and prior schema manipulation to track hippocampal-vmPFC connectivity during encoding and post-encoding rest. We manipulated prior schema knowledge by exposing 30 participants to the first part of a movie which was temporally scrambled for 15 participants. The next day, participants underwent fMRI while encoding the movie's final 15 minutes in original order, and subsequently, while resting. Schema knowledge and item recognition performance show that prior schema was successfully and selectively manipulated. Intersubject synchronization (ISS) and interregional partial correlation analyses furthermore show that stronger prior schema was associated with more vmPFC ISS and less hippocampal-vmPFC interregional connectivity during encoding. Notably, this connectivity pattern persisted during post-encoding rest. These findings suggest that additional crosstalk between hippocampus and vmPFC is required to compensate for difficulty integrating novel information during encoding and provide tentative support for the notion that functionally relevant hippocampal-neocortical crosstalk persists during off-line periods after learning.

Introduction

The formation of long term memory traces involves a gradual integration of newly acquired information into neocortical associative networks [39,174]. The hippocampus is thought to promote this process by binding, reactivating, and strengthening connections between distributed neocortical representations, thus gradually reducing hippocampal dependence of the memory trace [43,102,175]. Recent findings, however, show a concomitant increase in dependence on the (ventral) medial prefrontal cortex [57,69,176,177] that may develop rapidly depending on contextual factors [131]. These findings suggest that the binding role of the hippocampus may be transferred to the vmPFC [56,57,67] and implicate hippocampal-neocortical interactions in early stages of long term memory formation [see 112].

Several lines of animal and human research indeed suggest that coupling between these regions occurs at different stages of long term memory formation. During encoding, neurons in medial PFC have been shown to exhibit unit activity that is phase locked to hippocampal theta oscillations [62]. Moreover, functional connectivity between these regions as measured using functional MRI in humans has been shown to predict subsequent memory [178]. There is furthermore evidence of post-encoding reactivation of memory traces within similar circuits. For instance, task-related neuronal spiking patterns are spontaneously "replayed" during post-learning off-line periods such as awake resting [113,179] and sleep [69,101,104]. Such replay patterns have been found in the hippocampus and neocortical regions [103], including the (v)mPFC [67,69]. Evidence for a functional relevance of such reactivation processes is moreover accumulating [105,180,181]. The hippocampus and the vmPFC may thus form a neural circuit for reactivation of memory traces that is crucial for the integration of novel information into neocortical networks.

The existence of a relevant prior associative network, or schema, contributes to learning speed and improves subsequent memory performance for schema-related information [6,8,10]. This suggests that a prior schema facilitates incorporation of schema-related information into neocortical networks, and therefore, increases speed of hippocampal independence [112,130]. In rats, such an effect has indeed been reported [131]. Moreover, if long-term memory formation involves connectivity between the hippocampus and the vmPFC, then it can be hypothesized that when novel encountered information is consistent with prior schema, the hippocampus and vmPFC need less interaction to be able to integrate this information. In contrast, when novel information is inconsistent with prior schema, compensatory mechanisms will be necessary to integrate the information. In line with with this notion, vmPFC activity during encoding

has indeed been shown to be dependent on prior schema [22,52]. However, no studies to date have directly investigated such effects of prior schema on hippocampal-vmPFC connectivity during encoding or thereafter.

We therefore investigated schema-dependent hippocampal-vmPFC connectivity during encoding and post-encoding rest in humans using functional Magnetic Resonance Imaging (fMRI). One day prior to scanning, we manipulated schema knowledge by exposing participants to the first 80 minutes of a movie either in the correct (consistent schema group, n=15) or in a temporally scrambled order (inconsistent schema group, n=15; see fig. 1). Procedures on the following day were identical for both groups: first, participants were tested for schema knowledge (i.e., understanding of the storyline of the movie) and item recognition memory for still frames from the movie to control for item memory. Participants then underwent fMRI while watching the last 15 minutes of the movie in correct order and during an equally long period of post-encoding rest. In between and after these two scans, participants completed an item recognition memory test for still frames and a multiple-choice questionnaire assessing schema knowledge. Importantly, these tests only probed knowledge of the last part of movie. We adopted this "natural viewing" paradigm, because it does not dictate the pace of stimulus encoding [182] thus allowing for assessment of spontaneously coinciding fluctuations in both conditions. For fMRI analysis, two recent model-free analysis methods were applied. First, we calculated interregional partial correlations [see 183] between the hippocampus and vmPFC during encoding and post-encoding rest. As additional control for the specificity of between-group differences in hippocampal-vmPFC connectivity, we applied the same analysis to connectivity of the hippocampus with regions comprising the ventral visual stream. Second, we assessed intersubject synchronization [cf. 184] during exposure to the movie using newly developed group-level cluster-based randomization tests to investigate schema modulation of stimulus-driven activity.

This design allowed us to test several predictions. First, we expected that our prior schema manipulation would lead to impaired memory performance in the inconsistent schema group, but that this impairment would be specific to schema-related questions and not affect item recognition memory of still frames. Second, we predicted that hippocampal-vmPFC connectivity would be stronger in the inconsistent schema group, and negatively related to prior schema knowledge within this group, because participants in this group would need to compensate for their inconsistent prior schema. Third, we expected these effects to persist during post-encoding rest. Finally, we conjectured that prior schema might also affect stimulus-driven activity and therefore intersubject synchronization during movie viewing in our main regions of interest (ROIs).

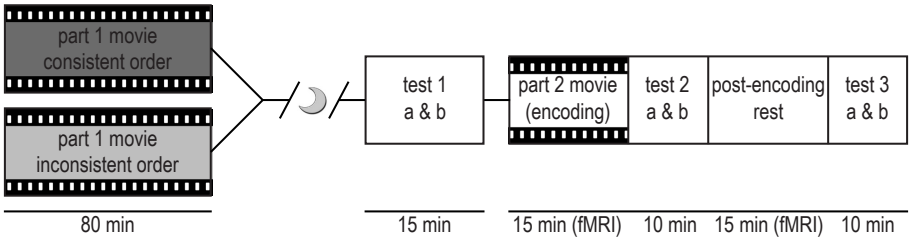

Fig. 1. Experimental design. One day prior to scanning the consistent schema group viewed the first 80 min of a movie in correct order while the inconsistent schema group viewed a temporally scrambled version. The next day, both groups performed an item recognition memory test (1a) and a test with open schema-related questions (1b). Then, they viewed the final 15 min of the movie inside the MRI scanner. Interleaved by a 15 min resting state scan, participants then completed two similar sets of tests: item recognition memory tests (2a and 3a) and multiple choice tests on the content of the movie (2b and 3b).

Results

Memory performance

As expected, memory performance on open schema-related questions about the first part of the movie (see fig. 1, test 1b) revealed a group difference ($t(28) = 3.32$; $p = .002$, higher for the consistent schema group; see fig. 2), demonstrating successful prior schema manipulation. In contrast, item recognition memory scores (hits minus false alarms) did not differ significantly ($t(28) = .73$, n.s.) between groups, indicating that there is no evidence that the group difference in prior schema strength can be explained by a difference in item processing.

Next, we investigated whether this difference in prior schema affected encoding of novel information that was equal for both groups. Specifically, we tested whether our prior schema manipulation would translate into a performance difference between groups in multiple choice tests (2b and 3b; see fig. 1 for design) probing content of the final 15 minutes of the movie seen inside the MRI scanner. In a repeated measures ANOVA on the number of correctly answered questions (see table S1) with TIME (multiple choice tests completed right after encoding [2b] versus after a subsequent 15 minute rest period [3b]) as within subject factor and GROUP (consistent versus inconsistent schema) as between subject factor, we found no main effect of GROUP ($F(1, 28) < 1$) or interaction of GROUP by TIME ($F(1, 28) < 1$). Moreover, similar tests on the two item recognition memory tests performed in the MRI scanner (2a and 3a, see fig. 1 for design) yielded similar null-results: no significant main effect ($F(2,28) < 1$) or interaction involving TIME ($F(2,28) = 3.15$, $p =$ n.s.) was found. Thus, despite the fact that one group had a significantly poorer prior schema, the two groups were able to memorize information about the last part of the movie to an equal degree.

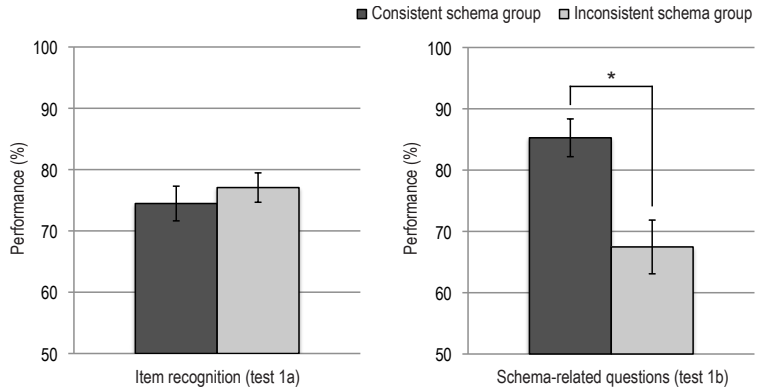

*Fig. 2. Mean memory performance (and SEM) on tests regarding the first 80 min of the movie for the two experimental groups. For the item recognition memory test (1a), percentages represent percentage hits minus percentage false alarms. For schema-related open questions (test 1b), percentages of correct responses are shown. The item recognition memory test did not show a group difference, while the open schema questions test did, indicating a successful and specific manipulation of schema knowledge. SEM, standard error of the mean; *, p < .01.*

Neuroimaging results: interregional partial correlations

For the fMRI data, we first calculated interregional partial correlations [183]. We performed anatomical parcellation of the fMRI data based on a previously described template [i.e., the automatic anatomical labeling template, AAL; 151]. Subsequently, we extracted averaged regional time courses for each region, and used these to calculate a partial correlation matrix containing pairwise correlation coefficients between regions after partialling out any variance explained by time courses of any of the other regions (see Experimental Procedures for more details). This procedure was repeated for every participant and condition (encoding and post-encoding rest). Based on our a priori ROIs, we restricted our subsequent group analyses to partial correlations between the hippocampus and eight areas comprising ventral and medial parts of the prefrontal cortex (see fig. 3a), treating these subregions as repeated measures. Thus, partial correlation coefficients were entered (after Fisher-z transformation) into a mixed factorial ANOVA with TIME (encoding versus post-encoding rest) and SUBREGION (eight different vmPFC subregions) as within subjects factors, and GROUP (consistent versus inconsistent schema) as between subjects factor. As hypothesized, this ANOVA revealed a main effect of GROUP ($F(1,28) = 13.97$, $p = .001$), with stronger overall interregional partial correlations between hippocampus and vmPFC for the inconsistent schema group (see fig. 3a). Moreover, we found stronger overall interregional partial correlations during encoding than during post-encoding rest (main effect of TIME: $F(1,28) = 6.75$, $p = .015$). These effects of prior schema, however, did not differ between the encoding and post-encoding rest conditions:

we found no significant interaction between GROUP and TIME, and moreover, GROUP main effects remained significant when testing the encoding ($F(1,28) = 5.48$, $p = .027$) and post-encoding rest condition ($F(1,28) = 7.27$, $p = .012$) separately. In further agreement, the strength of prior schema (i.e., performance on test 1b prior to scanning) for the inconsistent schema group was negatively correlated with hippocampal connectivity to the vmPFC during encoding ($r(13) = -.64$, $p = .011$), whereas no such effect was found in the consistent schema group ($r(13) = .23$, n.s.; see fig. 4). Thus, participants that saw the scrambled movie but were able to reconstruct the storyline had connectivity patterns comparable to the participants that did see the movie in the correct order. Finally, we found a main effect of SUBREGION ($F(1,28) = 3.67$, $p = .009$), indicating that overall, connectivity strength with the hippocampus differed between subregions of the vmPFC. However, because no significant interactions of SUBREGION with any of the other factors were found, we did not perform any further tests specific to subregions. In sum, our hypothesis of schema dependent connectivity between hippocampus and vmPFC during encoding was confirmed: participants that had an inconsistent prior schema needed more, likely compensatory, connectivity between hippocampus and vmPFC to reach a same level of performance. Moreover, this effect persisted during post-encoding rest.

To further test whether these effects were specific to hippocampal connectivity with the vmPFC, we applied the same analysis to another set of regions, namely a set of eight regions in the extrastriate / inferotemporal cortex that comprise the ventral stream, which is regarded to be importantly involved in perceptual identification of objects [185]. First, we averaged the partial correlation coefficients (after Fisher-z transformation) over the eight subregions for both connectivity to vmPFC and the ventral stream, and entered these into a repeated measured ANOVA with PATHWAY (vmPFC versus ventral stream) and TIME (encoding versus post-encoding rest) as within subject factors, and GROUP (consistent versus inconsistent schema) as between subjects factor. This ANOVA yielded a significant main effect of PATHWAY ($F(1,28) = 124.42$, $P < .001$, higher for the ventral stream), and a PATHWAY * GROUP ($F(1,28) = 6.29$, $p = .018$) interaction, but importantly, no GROUP main effect or main effect or interaction involving TIME (see fig. 3b). Further testing revealed that the PATHWAY * GROUP interaction was indeed carried by a GROUP effect for the vmPFC (described above): no GROUP effect was present for ventral stream ($F(1,28) = 1.00$, $p = .33$). Thus, prior schema had no effect on connectivity between the hippocampus and the ventral visual stream.

Neuroimaging results: ISS

The second model-free analysis method that we applied was an extension of an earlier described voxel-wise intersubject synchronization (ISS) method [184].

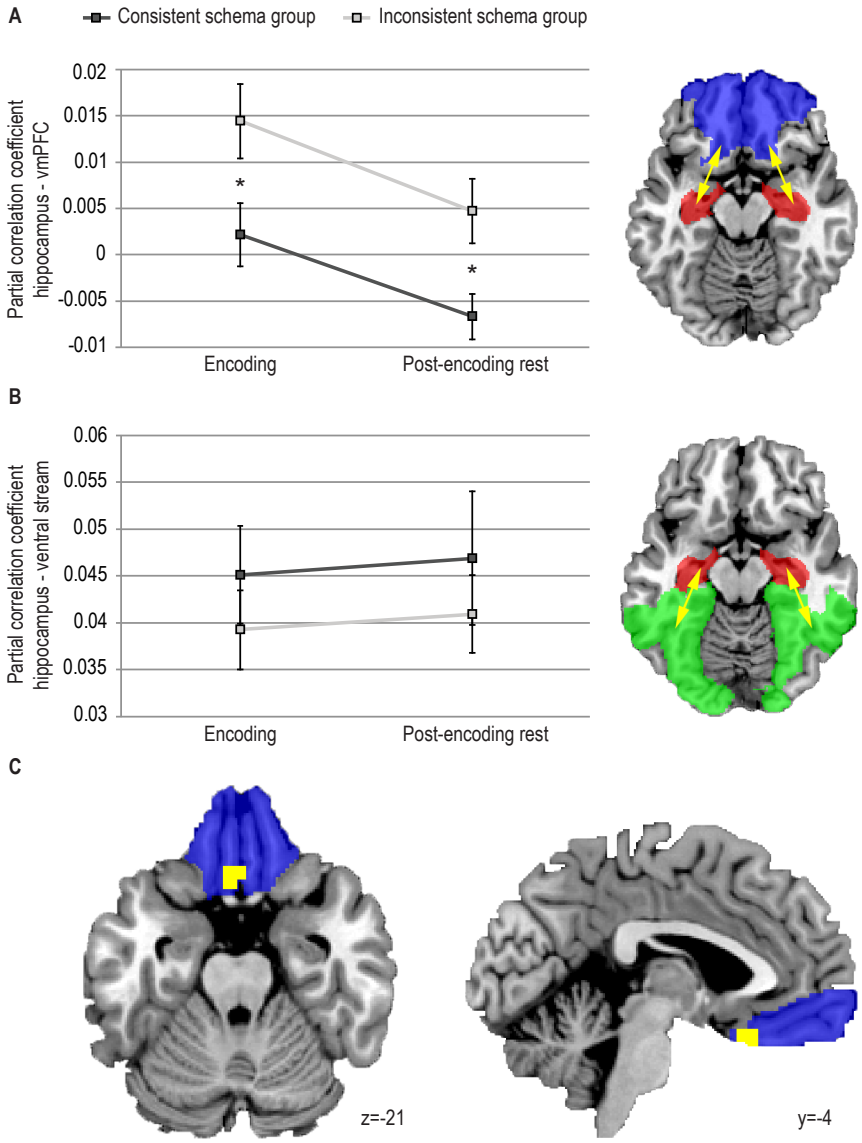

*Fig. 3. Interregional partial correlations and intersubject synchronization analyses. Means (and SEM) of interregional partial correlations of the hippocampus with the vmPFC (A) and with ventral visual stream regions (B) for both experimental groups during encoding and post-encoding rest. Connectivity between the hippocampus and vmPFC was stronger for the inconsistent schema group both during encoding and during post-encoding rest. In contrast, this effect was not found for hippocampal connectivity with ventral visual stream regions. Main ROIs are depicted in red (hippocampus), blue (vmPFC), and green (visual stream). (C) ISS difference between groups (in yellow), with stronger ISS in the consistent schema group in the vmPFC (blue; statistical parametric map thresholded at $p < .001$, uncorrected, for visualization purposes; peak voxel coordinates in MNI152 space [-4,24,-21], corrected pcluster = 0.05). SEM, standard error of the mean; vmPFC, ventromedial prefrontal cortex; ISS; intersubject synchronization; MNI, Montreal Neurological Institute; *, $p < .05$.*

In this method, BOLD signal time courses are correlated across participants in a voxel-wise fashion to obtain an estimate of regional synchronization of brain activity. This method is particularly applicable to data acquired during natural viewing of real-world stimuli such as movies, in which BOLD activity cannot be modeled, but can be assumed to exhibit meaningful temporal coherence across participants. Notably, such synchronization of the BOLD signal across participants does not necessarily reflect an increase in neural activity, but rather indicates that activity is more tightly coupled to sensory input. Our method (see experimental procedures for details) allowed us to quantify and test main effects of ISS in both conditions and to make a statistical comparison between the two movie conditions, both using cluster-based randomization tests. Results of the ISS main effect analysis revealed significant ISS in large parts of the brain, among which the entire occipital lobe extending ventrally into inferior temporal cortex and medial temporal lobe, and parts of the frontal lobe (both $p < .001$, whole brain corrected at cluster-level) for both groups. When comparing groups, a significant cluster in vmPFC with peak voxel coordinates [-4, 24, -21] was found to exhibit stronger ISS in the consistent schema group ($p = .05$, corrected at cluster-level for a reduced search region; see fig. 3c). No effects were found for the opposite contrast, and in the hippocampus and the ventral stream for either contrast. In sum, differential ISS was found only in the vmPFC, with a consistent schema resulting in stronger synchronization when encoding novel information related to this schema.

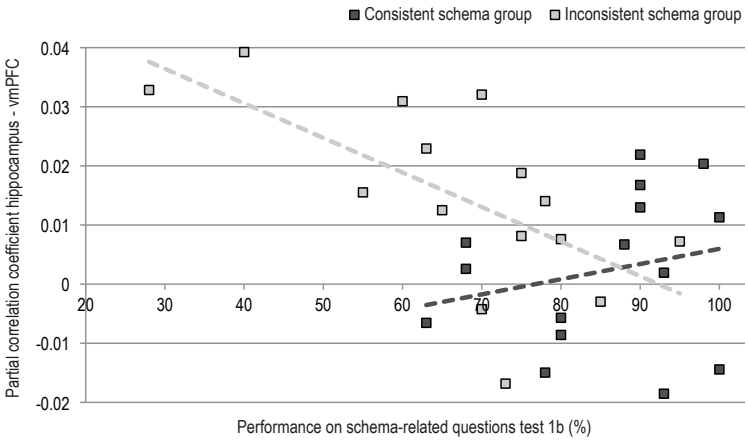

Fig. 4. Interregional partial correlations between hippocampus and vmPFC as a function of prior schema knowledge during encoding. Data from the inconsistent and consistent schema groups are shown separately. These measures revealed a significant negative correlation within the inconsistent schema group ($r(13) = -.607$, $p < 0.05$) but not within the consistent schema group ($r(13) = .234$, n.s.), indicating that those participants that were able to reconstruct the storyline had connectivity patterns comparable to participants that saw the first part of the movie in correct order. vmPFC, ventromedial prefrontal cortex.

Discussion

Using a novel approach involving a manipulation of prior schema knowledge and a model-free functional MRI design, this study shows that connectivity between the hippocampus and the vmPFC is enhanced when novel information is encoded that does not fit a consistent prior associative schema. We found this effect both as a between-group effect and within the group that did not have a consistent prior schema, where those participants that had least schema knowledge had the strongest connectivity. Interestingly, the pattern of differential connectivity between groups persisted during a post-learning rest period. Moreover, decreased ISS in the vmPFC was found for the inconsistent schema group during encoding. Manipulation of prior schema thus leads to modulations in and between memory-related brain structures, both while acquiring novel information and during an off-line period immediately thereafter.

Memory performance measures clearly indicate that prior schema knowledge was selectively manipulated in the inconsistent schema group. This group had lower scores on the schema test prior to scanning, but did not show any impairment in item recognition memory. On the second day, performance on neither content related questions nor item recognition memory tests differed between groups. These final tests only probed the newly encoded final part of the movie, which was identical for both groups. We therefore interpret differences in brain activity observed during movie encoding and post-encoding rest as related to compensation of an inconsistent prior associative schema.

The present study adds to a body of evidence associating the vmPFC with integration and comprehension of knowledge. For instance, previous studies have shown that schema manipulation affects vmPFC activity during processing of a storyline [52]. In line with this, several studies have related narrative comprehension to (more dorsal) medial PFC activity [21,186]. Also, vmPFC activity has recently been linked to representation of conceptual knowledge [51]. Here, we show that ISS in the vmPFC was larger in the group that had a more consistent prior schema. It is important to note that enhanced ISS does not necessarily imply an increase in activity. Rather, it points towards a more direct coupling between activity in this region and sensory input, in this case, the movie that was presented synchronously across subjects. Because elaborative processes in prefrontal regions would likely yield activity that is not directly coupled to the input and therefore does not synchronize across subjects [184], our finding of enhanced ISS related to larger prior schema suggests that prior schema facilitates processing in this region.

Our findings furthermore show that a lack of prior schema leads to enhanced partial connectivity of this region with the hippocampus during learning. A

large body of behavioral literature has demonstrated that information that is not consistent with prior associative knowledge is less easily comprehended, integrated, and remembered [6,8,10]. Our finding may thus reflect increased allocation of neural resources to integrative mnemonic processes. In agreement, a previous study showed enhanced hippocampal-neocortical connectivity during successful memory encoding [178]. An interesting parameter, however, is the directionality of such interactions [see 63]: if such interactions indeed promote integration into cortical-cortical networks, one would expect directional dominance towards the neocortex. Because of limited temporal resolution, human studies using functional MRI cannot provide a definite answer to this question. However, rodent studies have shown that activity of mPFC neurons is phase locked to hippocampal theta oscillations during learning [62,187,188], and that mPFC activity is delayed by approximately 50 ms with respect to these oscillations [62]. Thus, it appears that hippocampal activity may drive information transfer to the neocortex already during learning. These observations, however, cannot exclude the possibility that such processes are themselves triggered by a cortically cued retrieval process. Hippocampal-neocortical interactions during encoding may therefore be best understood as a reciprocal process in which retrieval and integration processes are intricately intertwined.

Additionally, we found schema-dependent differences in hippocampal-vmPFC connectivity to persist during a post-encoding resting period, suggesting that a lack of prior schema resulted in increased spontaneous reprocessing of newly encoded information. Spontaneous reoccurrence of prior task-related brain activity has been observed previously in a number of domains. For instance, learning experiences have been shown to modulate brain activity in a subsequent unrelated cognitive task [189]. Moreover, numerous studies have shown that functionally relevant brain networks remain active even in the absence of an explicit task [190-192], and are thought to subserve offline reprocessing of prior experiences [189,193-196]. The present findings therefore suggest that persistence of hippocampal-neocortical connectivity patterns may be functionally relevant [50,115] and relate to spontaneous reactivation of newly formed memory traces. Consistent with such notions, rodent studies have repeatedly demonstrated replay of learning-related hippocampal neuronal spiking patterns during subsequent off-line periods. Such replay phenomena have been found to occur during sleep [69,101,103,104], but also during post-encoding waking states [113,179]. Notably, similar effects have been reported in the mPFC [67,69], suggesting that concerted reactivation occurs in hippocampal and mPFC circuits. A recent study has moreover shown that PFC cell firing during sleep follows hippocampal cell firing with a delay of approximately 100 ms and is driven by hippocampal sharp wave-ripple bursts during slow wave sleep [SWS;

63]. Thus, spontaneous post-learning hippocampal-neocortical interactions, at least during SWS, may also exhibit directional dominance towards the neocortex. In humans, comparable reactivation of hippocampal memory-related activity has been observed during SWS using functional MRI [181]. Additionally, intracranial recordings during sleep and waking states shortly after learning have shown functionally relevant ripples in the medial temporal lobe [180]. The apparent directionality of hippocampal-neocortical reactivations is in accordance with models of systems consolidation. These assume reverse temporal gradients over the course of consolidation for involvement of the hippocampus (less over time) and the mPFC [more over time; 57,176,177]. Furthermore, it has been postulated that the vmPFC becomes a central node in newly established cortical-cortical networks [43,56,57,67,176,177]. Finally, the existence of a prior schema has also been shown to accelerate such systems consolidation processes in rats [131]. Thus, although such processes cannot be observed directly, our finding of prior schema-dependent hippocampal-neocortical connectivity during post-encoding rest is consistent with the view that hippocampally driven reactivations of distributed memory representations during off-line periods facilitate gradual incorporation of information into neocortical associative networks.

An alternative account of our findings could be that connectivity differences are driven by differences in attention or arousal. However, such an explanation would not seem very plausible. First, attention differences would likely yield memory performance differences after viewing the last part of the movie (particularly for the schema-related tests), while we found differences neither in item recognition nor in schema-related knowledge. Second, a difference in attention and arousal would likely lead to differences in perceptual processing and thus altered connectivity between the hippocampus and perceptual areas. To rule this out, we repeated the interregional partial correlation analysis for hippocampal connectivity to regions comprising the ventral visual stream, which carry visual information to the hippocampus [185,197] and are affected by attention [198,199]. This analysis yielded no connectivity differences between groups. A comparison between the two hippocampal connectivity pathways moreover confirmed that the prior schema effect was significantly larger for the hippocampal-vmPFC pathway. We furthermore examined ISS effects in the ventral stream, which revealed strong ISS for both groups, but no group differences. Third, an attentional account would not readily explain our finding that partial connectivity differences persist during post-encoding rest without attentional requirements. Finally, it should be noted that our measure of partial connectivity assesses the amount of unique variance shared by two regions by partialing out any variance explained by signal fluctuations in other regions [as defined in the AAL template, see 151,183], and is thus a highly specific connectivity measure.

In sum, there is no compelling reason to assume that the observed differences in hippocampal-vmPFC connectivity merely reflect unspecific differences in arousal or attention between the two groups.

The findings of this study raise a number of important issues that should be addressed in future research. First, an important limitation of the present experimental design is that it did not allow us to directly observe whether increased hippocampal-vmPFC connectivity indeed led to integration of information into neocortical long-term memory networks. Future studies using a similar schema manipulation should therefore test behaviorally whether enhanced hippocampal-neocortical connectivity will lead to stronger consolidation strength over a longer time interval. Moreover, it should be shown in humans that retrieval of information encoded in the presence of a relevant prior schema would exhibit less hippocampal dependence [131] but stronger vmPFC recruitment in combination with cortical-cortical connectivity [129]. Second, it will be highly informative to track the time-course of post-learning hippocampal-vmPFC connectivity. For instance, it should be investigated whether this connectivity decreases over time and whether it is reinstated during sleep [124]. Finally, investigation of schema building periods over longer periods of time may provide crucial information regarding schema acquisition itself, and may yield important applications in educational strategies.

In conclusion, the present study demonstrates enhanced hippocampal-vmPFC connectivity during and shortly after successful encoding of novel information when no consistent prior associative schema is present. These findings converge with a growing body of evidence suggesting that the incorporation of novel information into neocortical long-term memory networks is facilitated by hippocampal-neocortical crosstalk that extends from encoding into early stages of consolidation.

Experimental Procedures

Participants

Thirty native Dutch right-handed healthy students (12 men, age 18-31 (mean 22.17), randomly divided into both groups) participated in this study. All had normal or corrected-to-normal vision, no hearing problems, no current depression [score below 11 on the Beck Depression Inventory, BDI; 200], and no history of neurological or psychiatric disease. All stated that they had not seen the movie used in this study before. They were paid for participation and were notified that they could earn extra money for better performance. Possible confounding factors (age, gender, hours of sleep, time of day, and English language skills [tested by means of the Oxford placement test: 201]) did not differ

significantly over groups. One participant had to be excluded for falling asleep during the rest period. Therefore, the final groups consisted of 15 individuals each. Ethical approval was obtained from the institutional review board (CMO Region Arnhem-Nijmegen, The Netherlands) and all participants gave written informed consent. More specific information regarding the design and movie used can be found in SI Materials and Methods.

Memory tests

Before MRI scanning, participants were tested on their memory about the first part of the movie. These tests consisted of an item recognition test where participants had to indicate whether a certain scene had been present in the first part of the movie or not (test 1a), and open questions where schema-related knowledge was tested (test 1b). Memory of (exclusively) the final part of the movie was tested inside the scanner using similar item recognition memory tests and multiple choice questions probing schema-related knowledge. These tests were performed directly after the movie (test 2), and after a 15 minute resting state fMRI scan (test 3), in counterbalanced order across participants. More specific information regarding the memory tests used and the statistical analyses can be found in SI Materials and Methods.

fMRI data pre-processing

Raw fMRI data were preprocessed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). First, motion correction was performed by using iterative rigid body realignment to minimize the residual sum of squares between the first and all further functional scans, and subsequent rigid body co-registration to corresponding individual T1 images using mutual information optimization. Subsequently, data were spatially normalized into a common space, defined by the Montreal Neurological Institute (MNI) 152 T1 image (voxel size = 3.5x3.5x3.5), and smoothed by convolving the data with an 8 mm FWHM 3D kernel (used only for the ISS analysis). The first 11 scans were excluded, which left 409 scans per condition (movie and rest) for analysis.

Interregional partial correlation analysis

Interregional partial correlation analysis was performed using in-house software written in Matlab (The Mathworks, Inc., Natick, MA, USA) in accordance with the method previously described by Salvador et al. [183]. This procedure determines unique interregional connectivity by partialling out the contributions of interregional pairwise correlations on the regional time courses of a set of control regions. It effectively circumvents some of the concerns with the validity and interpretation of interregional correlations observed in BOLD fMRI data, for

example the possibility that pairwise interregional correlations may be driven by third regions. Additionally, head movements or undersampling (and aliasing) of physiological pulsations have been argued to inflate interregional correlations [see 202,203]. However, such effects are unlikely to be regionally specific, and are therefore strongly attenuated when controlling for a large number of control regions [183]. Specific implementation of this method is explained in SI Materials and Methods.

ISS analysis

The second model-free fMRI data analysis method we used was a group-level extension of a voxel-wise ISS analysis method [cf. 184]. This novel procedure uses cross-correlations of time courses across participants to estimate (group differences in) regional synchronization across participants. Instead of using one brain as a model for activity patterns in another brain in a pairwise fashion [see 184], we calculated, for each voxel and for each participant, the correlations between this participant and the mean of other participants. Because of dependencies within these measures, these correlations were subjected to cluster-based randomization tests [see 204,205] to test the null hypotheses that A) time series data of a random set of participants can be sign permuted without affecting group-level ISS and B) participants can be randomly assigned to groups without affecting differential ISS between groups. Reduced search regions were used for statistical tests in regions of interest (hippocampus, vmPFC, and the ventral stream). Specific implementation of this method is explained in SI Materials and Methods.

Supplementary information

Materials and Methods

Design and general procedure

Participants were tested in a mixed factorial design with prior schema manipulation as between subjects factor (see figure 1). One day prior to fMRI scanning, participants watched the first part of the movie (80 minutes) either in normal (consistent schema group) or temporally scrambled (inconsistent schema group) order. They were instructed to pay attention because they would get detailed questions about the movie on the next day. Procedures on the second day were equal for both groups and lasted approximately 1.5 hours. Participants were first tested on their memory for the first part of the movie by means of an item recognition memory test (1a; see figure 1) and a test with open questions about the schematic content of the movie (1b). They were then placed in the MRI-scanner and were instructed to watch the second part of the movie (15 minutes, in normal order) and again pay attention because they would get questions about this part as well. Subsequently, while still in the scanner, they were asked to complete an item recognition memory test (2a) and a multiple choice test on the content of the movie (2b). After this, fMRI scanning resumed with a resting period of the same length as the final part of the movie. During this rest period participants were instructed to lie still, close their eyes, think of nothing in particular, and try not to fall asleep. Finally, participants completed another item recognition (3a) and multiple choice memory test (3b). Functional scans were obtained only during watching of the movie and the rest period.

We controlled for two potential confounds that could influence performance. First, to control for consolidation time, participants were always tested in the MRI scanner 21 to 26 hours (average 23.4 hours; no significant group difference) after viewing the first part of the movie. Second, to verify that participants could optimally perceive the sound of the movie against a background of scanner noise, we employed a quieter EPI sequence (for details see fMRI scanning parameters section), and supplied the participants with earplugs and headphones (Commander XG, Magnetic Resonance Technology, Northridge, CA, USA). Before starting the movie, we performed a sound test to verify whether participants could easily discriminate movie-related sounds from the scanner noise. After the experiment, participants were once more asked whether they had had difficulty hearing the movie (on a scale from 1 to 5), and they reported little difficulty (1.9). This score did not differ between groups, and subsequent memory performance was not significantly related to these ratings.

Movie and schema manipulation

To manipulate schema knowledge while not altering perceptual input, we temporally scrambled the first part of a movie using Windows Movie Maker version 5.1 (Microsoft Corporation, Redmont, WA, USA) using scenes of minimally 20 seconds and maximally 144 seconds of length. The movie that was used was named Go (Banner Entertainment, Columbia Pictures and Saratoga Entertainment, 1999). This movie was chosen because it contains three different story lines that merge together in the last 15 minutes (shown during scanning). When properly understood, the first part therefore provides a "schema" that facilitates integration of the last 15 minutes into a coherent story. We chose temporal scrambling of the first part of the movie as a method of manipulating schema knowledge over simply not showing it to avoid group differences in familiarity of the scenes and actors in the movie. No subtitles were shown in any of the movies.

Memory tests and analyses

Before MRI scanning, memory for the first part of the movie (shown either in scrambled or correct order) was tested using an item recognition memory test and open questions. The first item recognition memory test (test 1a) consisted of 60 still frames. Of these, 30 were extracted from the movie that was shown, and 30 were taken from other movies similar in setting, actors, or type of scenery. The stimuli were all equal in size. Contrast and luminance was equalized using Adobe Photoshop 7.0 (Adobe, San Jose, CA, USA). Pictures were presented for 500 ms using Presentation 10.2 (Neurobehavioral systems, Albany, CA, USA). Participants were instructed to indicate whether the still frame was taken from the movie they saw the day before (yes or no). Performance on this test was expressed as the percentage of hits minus the percentage of false alarms. The 20 open questions (test 1b) were constructed to reflect comprehension of the storyline of the movie. Names of characters and objects were explicitly named and not explained and the questions did not contain any clues related to events in the second part of the movie. Participants were instructed to write the answers to the questions on a paper answer sheet and to recall as much as they could remember. Answers to these questions were scored, blind for condition, as either correct or incorrect, and performance was expressed as a percentage of correct answers.

Memory of the final part of the movie, shown in the correct order for all participants during scanning, was tested inside the scanner using item recognition memory tests and multiple choice questions probing content-related knowledge. The order of the tests was counterbalanced across subjects, and they were performed directly after the movie (2a and 2b), and after a 15

minute resting state fMRI scan (3a and 3b). The item recognition memory tests (tests 2a and 3a) had the same setup as described above, but contained only 40 still frames. Half of these were extracted from the final part of the movie, and the other half were again taken from other movies. Since these questions had to be answered in the MR-scanner, multiple choice questionnaires (test 2b and 3b) were used to test schematic memory of the movie. These multiple choice questionnaires consisted of 35 questions each. The questions were created in accordance with the constraints described in a previous study testing memory of movies [206]. All questions targeted distinct events and all questions together covered the whole content of the second part of the movie. With 70 questions in total, this means that approximately every 13 seconds of the movie was covered by a question. Additionally, we applied constraints particularly related to this study: questions could not be answered based only on the first part of the movie, but could be answered based only on the second part of the movie. Each multiple choice question was displayed together with a still frame of the movie and three answer options using Presentation 10.2. Participants were instructed to indicate the answer (a, b, or c). Questions were divided over the two tests (2b and 3b) in such a way that each test covered events from the entire duration of the second part of the movie. Performance on the multiple choice tests was expressed as the percentage of correct answers.

All performance data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The memory tests on the first part of the movie (test 1a and 1b) were analyzed using independent samples t-tests with GROUP (consistent versus inconsistent schema) as between-subjects factor. Statistical analyses on the tests on the final part of the movie (2a, 2b, 3a, and 3b) were performed using repeated-measures ANOVAs with GROUP (consistent versus inconsistent schema) as between-subjects factor and TIME (after movie versus after rest) as within-subject factor. Alpha was set at .05 throughout.

MRI scanning parameters

Participants were scanned using a 1.5 Tesla Siemens Magnetom Avanto system equipped with an 8 channel phased array head coil (MRI Devices). For BOLD fMRI images, we used a T2* weighted gradient echo EPI sequence with the following parameters: TR: 2.31 s, TE: 35 ms, 34 slices, ascending slice order, 3.5 mm slice thickness, .35 mm slice gap, matrix size: 64*64, FOV: 212*212 mm, flip angle: 90°, voxel size: 3.3x3.3x3.85. Slices were angulated in an oblique axial manner to reach whole brain coverage. To reduce the gradient acoustic noise, we used a relatively low readout bandwidth of 1396 Hz/pixel, which halves the amplitude of the readout gradient [207], in combination with a GRAPPA parallel acceleration factor of 2 [208]. To ensure reaching a steady state condition and

to let participants become accustomed to the scanner noise, the first 11 scans were discarded. Additionally, T1 weighted anatomical scans at 1 mm isotropic resolution were acquired using an MP-RAGE sequence with TR of 2250 ms, TI of 850 ms, flip angle of 15º and FOV of 256 x 256 x 176 mm. Acquisition time was again reduced by using GRAPPA with acceleration factor 2 and 24 reference lines.

Interregional partial correlations analysis

We implemented interregional partial correlation analyses as follows. First, functional images were parcellated anatomically based on the Automatic Anatomical Labeling (AAL) template [183] which consists of 116 regions. We merged right and left hippocampi into a single area reflecting the bilateral hippocampus to prevent the known strong interhemispheric correlation of both hippocampi [see 209] from reducing partial correlations with other regions. Time courses of the remaining 115 regions were calculated by averaging the signal over constituent voxels. Then, a 115 by 115 partial correlation matrix was calculated, which contained, in each of the off-diagonal cells, pairwise interregional correlation coefficients after partialling out any variance explained by time courses of any of the other regions. Such partial correlation matrices were calculated for each participant and each condition (natural viewing of the movie and rest). Subsequently, we defined the vmPFC as a set of eight (four bilateral) regions within the AAL (orbital part of the middle frontal gyrus, orbital part of the superior frontal gyrus, medial orbital part of the superior frontal gyrus, and gyrus rectus, see figure 3a) located around the area previously found to increase its involvement in memory retrieval as a function of remoteness of memory [57].

In order to allow valid inferences on group differences, we applied a Fisher's z transformation to all individual partial correlation coefficients. Resulting values were then analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) by applying a repeated measures ANOVA with TIME (encoding versus post-encoding rest) and AREA (eight different regions) as within-subjects factors, and GROUP (consistent versus inconsistent schema) as between-subjects factor. Moreover, we investigated whether performance measures of prior schema strength was predictive of interregional partial correlations by using bivariate Pearson's correlations. Finally, to investigate to what extent any group differences in connectivity between hippocampus and vmPFC would be specific, we compared connectivity of the hippocampus with the vmPFC to connectivity with a control pathway. For this purpose, we selected an equal number of regions within the extrastriate / inferotemporal ventral visual processing stream (bilateral lingual gyrus, inferior temporal gyrus, fusiform gyrus, and parahippocampal gyrus, see figure 3b), shown to be involved in object identification [185]. This aspect of perceptual processing is likely independent of schema knowledge, and therefore

unaffected by our prior schema manipulation. Partial correlation coefficients were averaged over the eight subregions for both pathways and then entered into a repeated measures ANOVA with TIME (encoding versus post-encoding rest) and PATHWAY (vmPFC and ventral visual) as within-subjects factors, and GROUP (consistent versus inconsistent schema) as between-subjects factor. Alpha was set at .05 throughout.

Intersubject synchronization analysis

Calculations were implemented in Matlab 7.5 (The Mathworks, Inc., Natick, MA, USA) using custom scripts combined with cluster-based nonparametric randomization tests as applied in the Matlab toolbox FieldTrip (fieldtrip.fcdonders.nl; Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands), a Matlab toolbox for analysis of biological data. First, low frequency confounds (.01 Hz cut-off discrete cosine transform high pass filter) and movement-correlated (six parameter rigid body transformation-derived translations and rotations) signals were removed from all subjects' functional scan series. Second, data were masked using a MNI152 space grey matter tissue probability map (see International Consortium for Brain Mapping: http://www.loni.ucla.edu/ICBM) with a probability threshold of .45, allowing for extraction of the non-selective component [see 184], i.e., the mean BOLD signal time course over all grey matter voxels of a single participant. Fourth, the non-selective component was low-pass filtered (moving average of three timepoints) in order to remove supra-BOLD frequencies, and this signal was again regressed out of each voxel's time course, resulting in filtered 3D time series data for each participant, thus removing the contribution of global signal fluctuations to voxel-wise time-series.

ISS main effects were tested as follows: for each voxel, each subject's time series was correlated with the mean of all other subjects' time series in the same voxel, and this correlation was expressed in a t-statistic, resulting in one ISS map for each participant. Subsequently, a one-sample t-test was run across these subject-specific ISS maps. To accommodate dependencies within these t-statistics, non-parametric randomization tests were applied to validly test the null hypothesis of zero ISS across the group. Specifically, this procedure tests the null hypothesis (H0) that the time series data of a random set of subjects can be sign permuted without affecting ISS t-statistic across the group. This sign permutation procedure destroys any synchronization of time series across subjects without affecting either the autocorrelational structure of the signal or dependencies between the subject-specific ISS maps, and can therefore be used to estimate a null distribution. To achieve an accurate approximation of this null distribution, 1000 randomizations (limited by computational resources) were performed, and the null distribution was pooled across voxels. This null distribution was used to

threshold the t-maps at a P < .001, uncorrected. Subsequently, weights (i.e., the sum of all t-values) were calculated for each cluster of adjacent voxels. The same procedure was applied to all 1000 randomization-derived t-maps, thus resulting in a null-distribution of cluster weights. Clusters within the non-randomized ISS t-map exceeding a threshold based on the 5% largest clusters within all randomizations were considered significant. This method implements an alpha = .05, one sided, test for cluster significance corrected for multiple comparisons [205] at the whole-brain level.

Group differences in ISS were tested using a similar method, now testing H0 that assignments of participants to groups could be permuted without changing the difference in ISS between groups. For each voxel, each participant's time course was correlated with the mean of all time courses of other participants within the same group (consistent versus inconsistent schema). These correlations were expressed in a t-statistic, resulting in one ISS map for each participant. Group differences across these maps were tested using voxel-wise independent t-tests. Voxel and cluster level null distributions were obtained by randomizing group assignments and repeating these calculations (1000 random permutations). The voxel level null distribution was used to threshold the group-level t-map at P < .001, uncorrected. Cluster-level alpha for this group comparison was set at .05, corrected for our three a priori reduced search regions (i.e., voxels in aforementioned bilateral hippocampus, vmPFC, or extrastriate/ inferotemporal ventral stream regions of interest; see figure 3a and 3b) by restricting all calculations (including randomizations) to voxels comprising the search regions.

	Test 2	
Groups	a: Item recognition memory	b: Content-related memory
Consistent schema	0.79 (0.12)	0.72 (0.11)
Inconsistent schema	0.82 (0.13)	0.69 (0.10)

	Test 3	
	a: Item recognition memory	b: Content-related memory
	0.81 (0.10)	0.70 (0.11)
	0.77 (0.13)	0.68 (0.11)

Table S1: Memory performance on tests regarding the final 15 min of the movie for the two experimental groups. For item recognition memory tests (2a and 3a), values represent means (and SD) of proportions hits minus proportions false alarms. For content-related multiple choice tests (2b and 3b), mean proportions of correct responses (and SD) are shown. SD, standard deviation.

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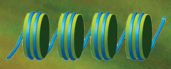
Chapter 5

Building on prior knowledge: Schema-dependent neural processes relate to academic performance



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Under review

Abstract

The acquisition and retention of conceptual knowledge is more effective in well-structured curricula that provide an optimal conceptual framework for learning new material. However, the neural mechanisms by which pre-existing conceptual schemas facilitate learning are not yet well understood despite their fundamental importance. A pre-existing schema has been previously shown to enhance memory by influencing the balance between activity within the medial temporal lobe (MTL) and the medial prefrontal cortex (mPFC) during mnemonic processes such as encoding, consolidation, and retrieval. To further investigate interactions between these regions during conceptual encoding in a real-world university setting, we probed brain activity and connectivity using functional Magnetic Resonance Imaging (fMRI) during educationally relevant conceptual encoding carefully embedded within two course programs. Early second-year undergraduate biology and education students were scanned while encoding new facts that were either related or unrelated to the pre-existing conceptual knowledge they had acquired during their first year of study. Subsequently, they were tested on their knowledge of these facts 24 hours later. Memory scores were better for course-related information, and this enhancement was associated with larger medial-prefrontal, but smaller medial-temporal subsequent memory effects (SME). These activity differences went along with decreased functional interactions between these regions. Furthermore, schema-related medial-prefrontal SMEs measured during this experiment were found to be predictive of second-year course performance. These results, obtained in a real-world university setting, reveal brain mechanisms underlying acquisition of new knowledge that can be integrated into pre-existing conceptual schemas and may indicate how relevant this process is for study success.

Introduction

How knowledge-acquisition guides successful remembrance is of fundamental importance for education. The fact that prior conceptual knowledge – an activated schema – can facilitate new knowledge-acquisition has been widely investigated behaviorally [4,162]. Additionally, recent research in both rodents [54,131] and humans [143,164] has provided essential insight into the underlying neuronal processes of schema-enhanced memory consolidation [131,164], and encoding [54,143]. However, to substantiate how a pre-existing schema facilitates successful encoding of new information in humans, specifically in situations relevant for long-term educational learning, mechanistic evidence is required. Such an account is of critical importance for the nascent discipline of educational neuroscience [134,135], to develop a new science of learning [137].

A pre-existing schema is suggested to facilitate memory consolidation by enabling relevant new information to be more rapidly assimilated [112,131] into this activated schema [112,163]. The acquisition of knowledge is mediated by an interplay between the medial temporal lobe (MTL), with the hippocampus at its core, the medial prefrontal cortex (mPFC), and posterior brain areas representing elements of to-be-learned information [43,102]. Newly learned information represented in these posterior brain areas is initially bound by the MTL [31]. With consolidation, this hippocampal dependence of a memory trace is thought to shift to neocortex, including specifically the mPFC [56,57], a process that is now known to accelerate with a relevant schema [131,164]. Next to consolidation, both parallel processing and inter-regional hippocampal-mPFC interactions are found to show functional effects already during encoding [62,64], depending on a pre-existing schema [54,143]. This suggests that MTL-mPFC interactions are important already during initial stages of knowledge-acquisition, possibly leading to long-term performance benefits.

Here, we sought to clarify schema-related conceptual encoding processes using an educationally relevant fMRI-paradigm (figure 1) by probing memory formation for course material that was carefully integrated into a university curriculum. We predicted that new discipline-related information would be better remembered after a 24-hour interval, related to more mPFC-involvement [54,164], whereas nondiscipline-related encoding, being more novel [163], would show more MTL-involvement along with greater interactions between the MTL and mPFC [143]. Last, we wondered whether the facilitated shift to mPFC-processing of task-related new information might be related to subsequent course performance. Such results would further support the view that schema-related knowledge processing shifts the MTL-mPFC balance during encoding in a way that is relevant for effective knowledge acquisition and thus academic

success.

Materials & Methods

Participants

Thirty-nine native Dutch female right-handed undergraduate students participated in this experiment. Twenty were education (pedagogy, developmental psychology, and education) students, and nineteen were biology students, all at the Radboud University Nijmegen. All students were in their second year, thus going through the same curriculum when tested. None of the students had studied anything related to the other discipline before (i.e. education for the biology students or biology for the education students), except for studying biology at high-school. All participants were healthy and had normal or corrected-to-normal vision. They were paid to participate and were told that they could earn extra money for better performance. Eight participants were excluded after data acquisition because they did not have enough confident trials (< 10) for analysis, which left thirty-one participants for analysis. This sample covered an age range of 18-21 years, with a mean age of 19.16 years. They self-reported to have slept on average 7.9 hours in between both examination days (ranging from 6 – 10 hours). No group differences were found for age, sleep, first-year grades, and intelligence (as measured by four different intelligence-tests: Wordlist and

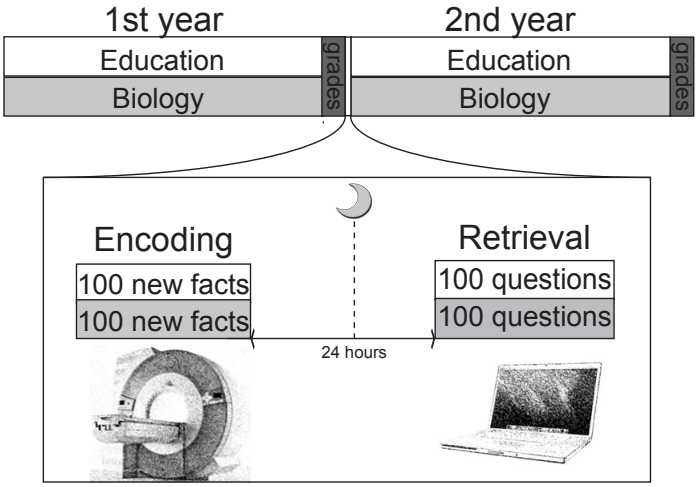

Figure 1: Study design, embedded in educational curricula (education and biology). The experiment was performed after one study-year (on average around the time the second year started), and participants' grades were obtained for study-year 1 and study-year 2. During the experiment, participants started on day one with a pre-test where they answered forty questions (twenty for each discipline). They then learned 200 factual sentences (100 for each discipline) in the MR-scanner. The next day (24h later), they returned for the test, where they answered 200 questions, one for each fact they learned the day before.

Matrices from the Groninger Intelligentie Test (GIT-2) [209] to test for verbal comprehension and logical reasoning, and Symbol search and Digit Span from the Wechsler Adult Intelligence Scale (WAIS; official Dutch translation) [210] to test for processing speed and working memory performance). Ethical approval was obtained from the institutional review board (CMO Region Arnhem-Nijmegen, The Netherlands), and all participants gave written informed consent.

Stimuli

Participants learned sentences containing factual information that was either related to their discipline (congruent) or not (incongruent). In total, 240 sentences were constructed (120 for biology, 120 for education), of which forty (twenty per discipline) were used to test pre-test performance before learning. The sentences were constructed by two student-assistants, one was finishing his study biology biology, and the other just finished studying education, both at the Radboud University Nijmegen. All sentences were constructed so they contained at least one term or concept that was learned in the first year of study, and one new term or concept (for example: Glutamate is an excitatory neurotransmitter, in which students knew the term excitatory neurotransmitter, but not the word glutamate). Participants thus learned new information either fitting to the knowledge obtained in their first year of study or hardly fitting any prior knowledge (e.g. for education students both excitatory neurotransmitter and glutamate are new concepts). For each fact, a multiple-choice question with three options was constructed, in which the wrong options were intermixed with information from other facts to reduce effects of familiarity (for the example above: What is a neurotransmitter? 1. glutamate. 2. colchicine. 3. alpha-actine; where the remaining two answers are taken from the facts Colchicine blocks the growth of microtubuli and Alpha-actines are often found in muscles).

The sentences and the experimental setup were piloted in an independent sample of biology and education students (n = 10). The sentences and questions that were indicated to be already known, and sentences that turned out to be too easy (as determined by memory performance and confidence measures) were discarded or adjusted. Subsequently, the sentences were carefully counterbalanced for number of words, number of syllables, and lemma-frequencies (as tested using the CELEX database [211]). Numbers and abbreviations were avoided unless directly related to the prior knowledge. None of the sentences were longer than ten words or sixty syllables so reading times would not be extensive and the facts could easily be read within the six-second presentation time.

Design and general procedure

In this experiment, we used a 2x2 design of schema (congruent versus incongruent) x memory (confident correct versus incorrect items) as within-subject factors (see figure 1). Participants were invited to come to the imaging center on two consecutive days with 24 hours between the two visits.

Pre-test

On day one, participants completed initially a self-paced pre-test on a computer using Presentation 10.2 (Neurobehavioral systems, Albany, CA, USA), in which they answered forty questions (twenty of either discipline) of which they did not learn the corresponding sentences before, to assess pre-test knowledge. These forty questions were randomly drawn from the entire sample of 240 questions and were presented in pseudo random order (i.e. no more than three consecutive facts of the same field of study). The questions were presented for twenty seconds maximally, and participants could only answer after five seconds of presentation to make sure they would not answer without reading the question and answers, using three different buttons (1, 2, or 3). After answering the question, participants were asked to indicate how certain they were of the answer given (1: Sure, 2: Somewhat sure, 3: Guess), within five seconds. They were furthermore instructed that they would have to answer the same sort of questions on the day after about the sentences they were going to learn in the MR-scanner. In total, this pre-test lasted on average around ten minutes.

Encoding

After the pre-test, participants were taken into the MRI-scanner. Participants lay supine in the scanner, and responded with their right hand using a button box. They viewed the screen through a mirror positioned on top of the head coil. Lights in the MRI scanner-room were switched off during the task to allow better contrast for reading the sentences. After instruction on the task, preparatory, and weighting scans (necessary for weighting optimal echo times for different brain regions, see MRI scanning parameters), they were scanned while encoding the 200 remaining sentences, presented in pseudo random order (applying the same rules as during the pre-test) using Presentation 10.2 in the middle of the screen for six seconds. During presentation, participants were instructed to encode the sentence, and indicate after the six seconds presentation time whether (1) they already knew the fact, (2) thought they would remember it the next day, or (3) did not think they would remember it the next day, within three seconds. After responding, the trials were interleaved with a fixation cross presented for two to four seconds. After the encoding session, which lasted for forty minutes, a structural MRI scan was acquired. Then, the participants went home and were asked to keep track of how many hours they slept that night.

Retrieval

On day two (24 hours later), participants were tested on their knowledge of the facts by answering 200 three-choice questions, each related to a sentence they encoded the day before. This test was presented in exactly the same way as the pre-test. After they finished the questions, participants were asked to fill out questionnaires, consisting of intelligence tests and a study-related self-report questionnaire. This part of the experiment lasted on average around one hour.

Memory tests and analyses

Behavioral measures were analyzed using PASW Statistics Data Editor 18.0.0 (Polar Engineering and Consulting) by calculating the percentage correct and incorrect items for congruent and incongruent questions. The questions belonging to a fact that was not responded to within three seconds during the scanning session were discarded. Also the questions that were not responded to in time during the test session were discarded. For the behavioral analyses, correct items were thus defined as all correctly answered questions and incorrect items were defined as all incorrectly answered questions that were responded to during encoding and retrieval. For tests regarding relations between the pre-test and the retrieval test, these measures were divided by their average confidence. For the MR-analyses, questions that were previously known and were correctly answered, but were indicated to be a guess, were additionally discarded. Correct items were thus defined as facts that were not missed during encoding, were not known in advance, and were confidently answered correctly on the retrieval test. Incorrect items were similarly defined, with the difference that also unconfident answers (guesses) were incorporated in the analyses. Based on these analyses, only participants with ten or more trials for either factor (schema hit, schema miss, non-schema hit, and non-schema miss) were used for subsequent analyses.

These measures were first tested in paired-samples T-tests probing the behavioral effects of schema (congruent versus incongruent) on memory during the pre-test and the retrieval test. Furthermore, one-sample T-tests were used to test differences from chance level (33%), and relations between pre-test and retrieval test were examined using a repeated measures ANOVA. Reaction times were analyzed using the same tests. Alpha was set at .05 throughout.

Grades

Participants were asked to provide us with their first-year grades of all courses when coming to the imaging center. Both first and repeated exams were used to calculate the average grade for each participant, and grades that were not denoted in numbers (such as “good” or “fair”) were not used in the calculation. After the end of the study year, the participants were again asked for their grades,

now of their second-year subjects. Of the thirty-one participants included in the final analyses, twenty-five responded. The amount of grades obtained per participant ranged from 11 – 19 in the first year and from 5 – 18 in the second year, due to differences in the amount of exams taken or repeated. The average of their grades was again calculated using the same method as mentioned above and average second-year grades were normalized individually by dividing with the average of the first-year grades. This measure was then used to correlate with brain activity for schema subsequent memory effects during the experiment using Pearson bivariate two-tailed correlation tests. Alpha was again set at .05.

MRI scanning parameters

Participants were scanned using a 1.5 Tesla Siemens Magnetom Avanto system equipped with a 32 channel phased array head coil (Siemens). For BOLD fMRI images, we used a T2* weighted gradient echo multi-echo EPI sequence [212] with the following parameters: TR: 2.64 s, TE1: 6.9 ms, TE2: 24.2 ms, TE3: 33 ms, TE4: 43 ms, TE5: 52 ms, 34 slices, ascending slice order, 3 mm slice thickness, .51 mm slice gap, matrix size: 64*64, FOV: 224*224 *119 mm, flip angle: 80°, voxel size: 3.5x3.5x3.0 mm. Slices were angulated in an oblique axial manner to reach whole brain coverage. To ensure reaching a steady state condition, the first seven scans were discarded. Additionally, T1 weighted anatomical scans at 1 mm isotropic resolution were acquired using an MPRAGE scan with TR of 2250 ms, TI of 850 ms, flip angle of 15° and FOV of 350 x 263 x 350 mm.

fMRI data pre-processing and analyses

Raw, multi-echo fMRI data were first combined into single-echo scans using in-house software written in Matlab 7.5 (The Mathworks, Inc., Natick, MA, USA), which used 29 separately acquired weighting scans to calculate the most optimal echo time for each voxel, and performed motion correction on the first echo by using iterative rigid body realignment to minimize the residual sum of squares between the first and all further functional scans. The combined scans were further preprocessed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Rigid body co-registration to corresponding individual T1 images was performed using mutual information optimization. Then, data were spatially normalized into a common space, defined by the Montreal Neurological Institute (MNI) 152 T1 image (voxel size = 2x2x2 mm), and smoothed by convolving the data with an 8 mm FWHM 3D kernel. Since the first seven scans were excluded, 914 scans were left for analysis.

After preprocessing, statistical parametric maps were generated by modeling the evoked blood oxygen level dependent (BOLD) response for each factor (schema correct, schema incorrect, non-schema correct, and non-schema

incorrect) as a delta function convolved with a hemodynamic response function (HRF). Furthermore, the derivative of the HRF for each factor, and the individual movement regressors were added as regressors of no interest to each first-level model. Contrasts of interest were created in these first-level models and subsequently random-effects one-sample t-tests were performed, testing the schema x memory interaction at the group level. These analyses were performed as whole-brain analysis, but the correction for multiple comparisons was limited to specific regions. Results in specific regions of interest (ROI) were additionally assessed using small volume correction (SVC) at $p < .05$ (bilateral MTL (hippocampus and parahippocampal gyrus combined) and right hippocampus, taken from the AAL-template [151], and masks of activity patterns in the mPFC as observed in memory retrieval tasks related to schema [118]). Additionally, post-hoc t-tests were performed on the effects of memory for both congruent and incongruent material by extracting the beta values from the peaks of the significant activity differences, and considered significant at $p < .05$. These extracted values were also used to correlate measures of brain activity (subsequent memory effect (schema correct – schema incorrect within both mPFC and MTL) with measures of study performance (baseline-corrected second year grades).Psychophysiological Interactions (PPIs) were calculated to assess functional connectivity between brain regions. These were executed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm) in combination with in-house software, written in Matlab 7.5 (The Mathworks, Inc., Natick, MA, USA). PPI analyses probe differences in coactivation of a certain seed region (physiological factor) with the rest of the brain modulated by an external factor (psychological factor). Here, we examined coactivation differences that were significantly larger for schema correct than for non-schema correct items and vice versa from a 6mm sphere around the mPFC peak [2,46,0]. Only voxels that were significantly active in an effect of interest analyses were used for this analysis. The single-subject GLM-model constructed for the previously described analyses was extended with two regressors: the general deconvolved signal from the seed region, and the deconvolved signal from the seed region for the contrast congruent correct versus incongruent correct items. For each subject, contrast estimates of this second regressor were used as input for the second-level random effects analysis. The seed region in mPFC was defined by taking the peak voxel obtained from the schema x memory interaction, surrounded by a 6mm sphere. Similar to the previously described significance values, connectivity was considered significant at $p < .001$ uncorrected at voxel-level and $p < .05$ corrected at cluster-level small volume corrected (SVC, [213] with right hippocampus as an independently determined ROI, taken from the AAL-template [151].

Results

Participants were first tested on knowledge during a pre-test, where they answered 20 questions for each discipline, randomly taken from the total stimulus set. Subsequently, participants were placed in the MR-scanner (Figure 1), where they encoded new information (100 sentences for each discipline) either related to their own discipline or to the other discipline. Participants then went home and were tested on their memory 24 hours later in a three-alternative forced-choice test (see experimental procedures for details).

Memory performance

Performance on the pre-test showed a significant effect of congruency ($t(30) = 6.71$, $p < .001$, congruent = 50,41% correct, incongruent = 34,15% correct), larger for the congruent information. Performance for the own discipline, was significantly different from chance ($t(30) = 7.146$, $p < .001$), whilst performance for the other discipline was not ($t(30) = .514$, n.s). At pre-test, participants did thus show better performance for the own discipline, and performed at chance level on pre-test knowledge for the other discipline.

Retrieval test performance showed a substantial effect of prior knowledge on learning of new information ($t(30)=12.55$,$p<.001$, congruent=70.3% +/- 0.09 correct, incongruent=50.6% +/- 0.09 correct). Both levels of performance were significantly different from chance (33%, congruent: $t(30)=21.96$,$p<.001$; incongruent: $t(30)=10.51$,$p<.001$) indicating the lower level of learning for the other (incongruent) discipline was not a floor effect. These measures indicate that participants learned information for both the disciplines, but showed better memory scores for congruent information at the retrieval test. Importantly, reaction times were not significantly different for congruent versus incongruent trials ($t(30)=.42$,n.s., congruent 0.99s, incongruent 1.01s), indicating no differences in time on task and thus suggesting equal attentional processing when encoding congruent and incongruent information. Performance on the retrieval test for schema-related items showed a positive relation to the grades obtained in the first year ($r(30) = .58$, $p = .001$) but not for grades in the second year ($r(30)=.26$, p=n.s.. These relations show that the experimental design was related to information learned in the curriculum, which is important when relating it to course-related measures.

Confidence levels (ranging from 1 (very confident) to 3 (guess)) were significantly better for schema-related information, both for the pre-test ($t(30)=9.92$, $p<.001$; schema-related: 2.15, schema-unrelated: 2.66) and for the retrieval test ($t(30)=13.82$, $p<.001$; schema-related: 1.67, schema-unrelated: 2.38), but increased more strongly for schema-related information

(F(1,30)=19.31, p<.001; schema-related: t(30)=10.37, p<.001; schema-unrelated: t(30)=6.30, p<.001)). Because of this significant interaction, we controlled for these confidence levels when relating pre-test and retrieval test by dividing each measure with its related confidence. Directly contrasting these measures showed a significant schema x congruency interaction (F(1,30)=38.13, p<.001) based on stronger increases in schema-related learning (t(30)=10.44, p<.001) than in schema-unrelated learning (t(30)=6.81, p<.001). Thus, our behavioral data shows that schema-congruent information was indeed better learned than schema-incongruent.

Neuroimaging results: Differential activity

The whole-brain analysis (Figure 2A) revealed only two effects for the congruency x memory interaction: one in the mPFC (peak [MNI2,46,0], 28 voxels, SVC for an mPFC mask taken from [118], p<.05) for congruent (correct>incorrect) > incongruent (correct> incorrect); and the other in the MTL (encompassing bilateral parahippocampal gyri and hippocampus) bilaterally (peaks [MNI -28,-18,-28], 43 voxels and [MNI 22,-16,-28] 74 voxels, SVC p<.05): for incongruent (correct>incorrect) > congruent (correct>incorrect). These findings indicate that the encoding signal corresponding to subsequently forgotten items subtracted from that for subsequently remembered items for the congruent sentences and vice versa for the incongruent sentences led to enhanced mPFC processing. The opposite comparison led to enhanced processing in MTL. To test whether this interaction was based on a singular, specific difference or rather on reliable set of differences, we performed post-hoc t-tests on the effects of memory for both congruent and incongruent material (congruent hits versus misses and incongruent hits versus misses) separately. These tests confirmed generally reliable differences, although two tests just failed to be significant (mPFC: schema hits > schema misses: p = .06, non-schema misses > non-schema hits: p < .001; schema hits > non-schema hits: p = .04; non-schema misses > schema misses: p < .001, MTL: schema misses > schema hits: p < .001; non-schema hits > non-schema misses: p = .06; non-schema hits > schema hits: p < .001; schema misses > non-schema misses: p < .001). This pattern of results indicates that the interaction is not solely driven by the subsequent memory effect for either congruent or incongruent trials. These results thus reveal that brain activation shows a schema-related interaction in both the mPFC and MTL. Separate analyses on the two student groups indicate that both groups contributed to this interaction.

Neuroimaging results: Differential connectivity

Next, we sought to examine the crosstalk between the MTL and mPFC with

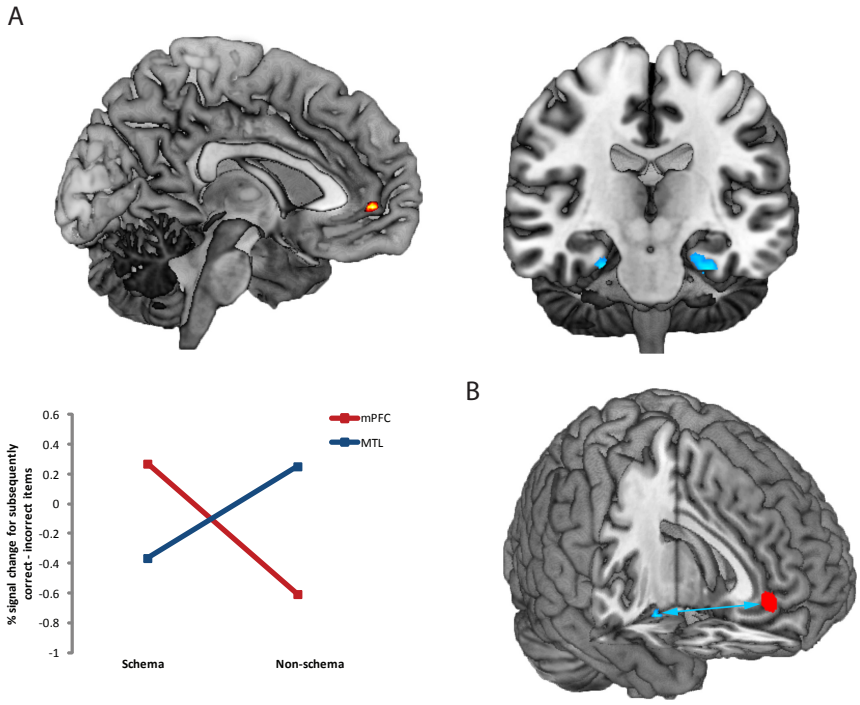

Figure 2: (A) Schema x subsequent memory interaction of brain activity during encoding revealed an interaction between mPFC and MTL regions, where mPFC (in red/yellow) was more active for congruent (subsequent correct items>subsequent incorrect items) > incongruent (subsequent correct items>subsequent incorrect items), and bilateral MTL (in blue/green) was more active for incongruent (subsequent correct items>subsequent incorrect items) > congruent (subsequent correct items>subsequent incorrect items). The graph shows the beta-values for the separate conditions, visualizing the interaction between the regions (mPFC and MTL) and schema. Note that this graph is purely for visualization purposes, statistically significant effects are reported for each of these regions in the text, and this graph just shows the interaction that is not again statistically tested. (B) Psychophysiological interaction revealed larger differential functional connectivity from the mPFC to the right hippocampus for non-schema correct items > schema correct items.

respect to the congruency of the new information (figure 2B). Our hypothesis predicts that functional connectivity is greater for incongruent information. This was assessed by PsychoPhysiological Interaction (PPI) analyses with the mPFC as seed region (as determined by the peak-voxel of the schema x memory interaction surrounded by a 6mm sphere). This revealed a differential coactivation with the right hippocampus (peak [MNI22,-12,-16], SVC right hippocampus $p<.05$) stronger for incongruent than for congruent correct items. No significant effects were observed for the opposite contrast. Thus, functional coupling between the mPFC and the right hippocampus was larger for the incongruent relative to congruent correct items.

Relation to course performance

Testing memory in an experimental retrieval test is one thing, but our use of course-related material created the opportunity of additionally asking whether there was any long-term impact on course-success. Our experiment might have, in part, mimicked gradual knowledge-accumulation supposed to occur in education. If so, brain-activation encoding patterns may be predictive of course-success. Our analysis of this possibility revealed a positive relation between mPFC-activity during learning of schema-related information and normalized grades (grades year 2 / grades year 1) obtained in the subsequent course-year ($r(24) = .431$, $p < .05$, figure 3), suggesting that activity in the mPFC during encoding is important for subsequent course performance. Interestingly, given the emphasis upon the MTL with respect to learning, no such relation was observed for MTL-activity ($r = .087$, n.s.).

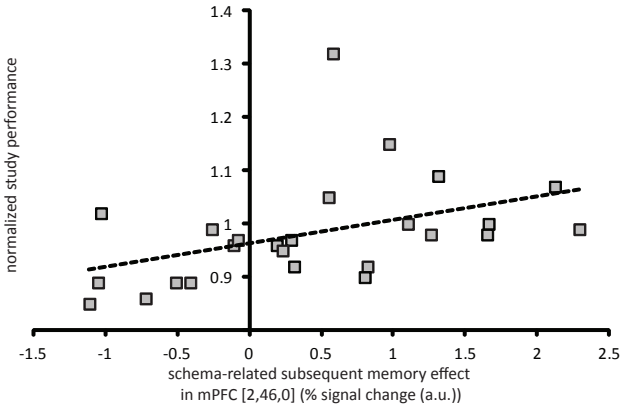

Figure 3: Correlation between mPFC activity for the schema subsequent-memory contrast (schema correct items > schema incorrect items) and progress in study performance (normalized grades) (r(24)=.431,p< .05).

Discussion

These results support the view that a pre-existing schema in the neocortex facilitates mnemonic processing during the encoding of new, educationally relevant information forming the basis of long-term knowledge. Behavioral results show that newly learned schema-related information was better remembered than similar information unrelated to a schema. Additionally, successful encoding of this information was found to be associated with enhanced mPFC-activity, while successful encoding of discipline-unrelated information was associated with enhanced MTL-activity and enhanced mPFC-hippocampus connectivity. As the binding of different parts of a memory-trace is proposed to shift balance from the MTL to the mPFC in time [56,57], mediated by schema [54,143,164], these results extend this hypothesis by showing that this shift in balance can occur at encoding already when new information is congruent with prior knowledge, and is related to subsequent memory performance. Moreover, schema-related

encoding activity in the mPFC was found to be predictive of study-grades obtained subsequently. Thus, these results show that a schema enhances encoding of new, educationally-relevant information through facilitation of the shift in MTL-mPFC balance, leading to long-term learning benefits. These findings are consistent with the idea of parallel encoding in mPFC and MTL (3), and increased efficiency of information processing (18) as a function of prior knowledge.

The mPFC is a brain region that has been attributed to diverse cognitive processes, including many with a mnemonic nature [55,56,60], but its exact role in these remains unclear. Even though the exact homologue of the mPFC in rodents and humans is still a matter of debate [60], studies in both species consistently support its role in memory. Regarding conceptual learning, the mPFC is thought to be related to conceptual knowledge integration [51], and conceptual comprehension [22,52,143]. More generally, the mPFC is also related to parallel encoding processes [54], remote associative memory retrieval [58,59,118] and retrieval of self-knowledge [214], and has been shown to actively replay learning-related neuronal spiking patterns during sleep in rodents [66,67]. Of specific relevance is that mPFC-lesions lead to an absence of memory enhancement based on semantic congruency [70], suggesting its importance in integrating or assimilating new information [60] into activated (or retrieved) existing semantic knowledge networks [51]. In that way, its contribution is to lay the foundations for enhanced future learning. Besides schema effects on memory, also novelty, or mismatches to a schema can show enhancing memory effects in specific cases [19]. This mismatching process has been consistently attributed to processing in the MTL [215,216]. We believe these findings are consistent with the model described above, when considering that newly learned information always either matches or mismatches to some extent with prior information. Based on earlier findings [52,54,131,143,164] and theories [163], and the results described here, we thus hypothesize that mPFC serves to assimilate new information into a schema by activating (or retrieving) the schema enabling integration of novel information, whereas MTL detects mismatches with a schema and serves to bind directly different parts of the memory trace into a specific episodic memory [for further explanation see: 217]. The true interactions we found in both mPFC and MTL, additionally showing enhanced activity for schema-unrelated and schema-related misses respectively, give rise to further speculation on the roles of the mPFC and MTL. These findings could be related to inappropriate classification of schema-unrelated information as relating to a schema (schema-unrelated misses) or when schema-related information is encoded via the MTL instead of being assimilated by the mPFC (schema-related misses). Further research will need to investigate these ideas.

Schema theory has been described as knowledge organized into an elaborate

network of abstract mental structures which represent one's understanding of the world [4]. Optimal construction and usage of a schema is thus recommended to lead to better structured learning [162,217], until and if one's existing schema no longer maps onto the known world. Until now, research on schema-theory has primarily focused on theoretical models aimed at explaining strictly behavioral findings. Now, using neurobiological techniques in animals and brain-imaging techniques in humans, we can pave the way to better understand the neural mechanisms underlying the previously hypothesized different sub-processes of schema-related learning (i.e. selection, abstraction, interpretation, and integration). Our findings focus on the interpretation and integration steps, indicating that distinct brain-regions are differentially activated during conceptual learning, but do not yet tap into selection and abstraction processes presumably represented in posterior, perceptual brain regions [218]. Future research should investigate these different sub-processes more explicitly.

Experiments that are more closely related to real-life situations are impossible to perform without taking into account inherent confounds. Therefore, we spent special caution to control for potential confounds related to the ecological validity of the design. First, we were particularly careful when constructing the sentences that were used as stimuli in this experiment. We extensively piloted the sentences, subsequently reconstructed them, made sure there were no differences in length and word frequency of the sentences, and corrected for sentences that were already known by the participants in the encoding stage of the experiment. In doing so, we counterbalanced the sentences across the two disciplines to our maximum capability. Furthermore, since the participants from the two different disciplines were analyzed together as one group, possible group differences beyond the traits we controlled for are not likely to have an effect on our results. Moreover, analyses were performed using a delta function model of brain activity, taking into account differences due to attention towards the end of the trial. Also, reaction time differences were not found to be significantly different for the different conditions. Thus, controlling for all these factors, we strongly believe that potential confounding differential effects on schema versus non-schema memory encoding did not influence our results.

In sum, the results reported here show that a schema, represented as prior conceptual knowledge in the brain, facilitates encoding of new conceptual information related to this schema in a university-setting. This facilitation leads to enhanced memory, more activity in mPFC as opposed to MTL, and less connectivity between these regions. Moreover, mPFC-activity is predictive of future performance. These results are of great importance for further understanding the fundamental neural principles of conceptual memory encoding and consolidation. Furthermore, as the acquisition and long-term

retention of conceptual knowledge is one of the main objectives of (academic) education, these and future endeavors investigating the role of prior knowledge in conceptual knowledge-acquisition could be of crucial significance for bridging the gap between neuroscience and education [134,136,217]. Next to investigating the schema-effect in general, future research might focus on schema-formation or adjustment according to newly learned information.

Acknowledgements

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Supplementary Information

Table S1: Example sentences (translated from Dutch)

Biology	Education
Fact: Clay is a sedimentary rock Question: What is a sedimentary rock? 1. magma 2. clay 3. marble	Fact: Selective attention is acquired Question: What is a feature of selective attention? 1. it is a combination of inborn and acquired factors 2. it is inborn 3. it is acquired
Fact: Darwin's finches belong to the micro-evolution Question: What is an example of micro-evolution? 1. Darwin's finches 2. the emergence of humans from apes 3. tadpoles	Fact: Iconic memory is visual short-term memory Question: What is iconic memory 1. auditive short-term memory 2. visual short-term memory 3. visual long-term memory
Fact: Light puts a brake on the growth of hypotocyls Question: What puts a brake on the growth of hypotocyls? 1. light 2. oxygen 3. sulfur hexafluoride	Fact: A non sequitur is a classical fallacy Question: What is a non sequitur 1. a circular argument 2. a precipitous generalization 3. a classical fallacy
Fact: A tundra is one of the primary biomes Question: What is one of the primary biomes? 1. a tundra 2. a bed of algi 3. a vascular plant	Fact: Piaget sees the child in principle as a small adult Question: How does Piaget see the child in principle? 1. as tabula rasa 2. as a small adult 3. as a machine
Fact: Plants send out a lot of biophotons Question: What sends out a lot of biophotons? 1. earth 2. plants 3. sedimentary rock	Fact: Sex segregation is a universal phenomenon Question: What kind of phenomenon is sex segregation? 1. a universal phenomenon 2. a sex specific phenomenon 3. a stigmatizing phenomenon
Fact: Histones are part of the nucleosome Question: What is part of a nucleosome 1. RNA 2. ribose 3. histones	Fact: Nativists state that intelligence is inborn Question: What do nativists state? 1. that intelligence is inborn 2. that intelligence is acquired 3. that intelligence is a combination of inborn and learning principles
Fact: Alpha-actins are present in muscles Question: Where are alpha-actins present? 1. in muscles 2. in fat 3. in the kidneys	Fact: The Wada-test measures language lateralization Question: What does the Wada-test measure? 1. language lateralization 2. restrictions in everyday life 3. quality of adherence in adults
Fact: Lipoma are benign tumors Question: What are benign tumors?	Fact: Duchenne and mental retardation are comorbid
1. amyloplasts 2. polysomes 3. lipoma	Question: Which which disorder is duchenne comorbid? 1. Prader-Willi syndrome 2. Angelman syndrome 3. mental retardation
Fact: Trehalose is an important disaccharide Question: What is an important disaccharide? 1. galactose 2. trehalose 3. apoptosis	Fact: Sleepwalking is a parasomnia Question: What is sleepwalking? 1. a hypersomnia 2. a dyssomnia 3. a parasomnia
Facts: Speedwell is an autotrophic organism Question: Which organism is autotrophic? 1. speedwell 2. reed-warbler 3. poisonous frog	Fact: Vygotsky is a representative of contextualism Question: What does Vygotsky represent? 1. psychoanalysis 2. contextualism 3. social learning theory

Chapter 6

Differential roles for medial temporal and medial prefrontal cortices in schema-dependent encoding: from congruent to incongruent

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(* = equal contributions)

Under revision

Abstract

Information that is congruent with prior knowledge is generally remembered better than incongruent information. This effect of congruency on memory has been attributed to a facilitatory influence of activated schemas on memory encoding and consolidation processes, and hypothesised to reflect a shift between processing in medial temporal lobes (MTL) towards processing in medial prefrontal cortex (mPFC). To investigate this shift, we used functional magnetic resonance imaging (fMRI) to compare brain activity during paired-associate encoding across three levels of subjective congruency of the association with prior knowledge. Participants indicated how congruent they found an object-scene pair during scanning, and were tested on item and associative recognition memory for these associations one day later. Behaviourally, we found a monotonic increase in memory performance with increasing congruency for both item and associative memory. Moreover, as hypothesized, encoding-related activity in mPFC increased linearly with increasing congruency, whereas MTL showed the opposite pattern of increasing encoding-related activity with decreasing congruency. Additionally, mPFC showed increased functional connectivity with a region in the ventral visual stream, presumably related to the binding of visual representations. These results support predictions made by a recent neuroscientific framework concerning the effects of schema on memory. Specifically, our findings show that enhanced memory for more congruent information is mediated by the mPFC, which is hypothesised to guide integration of new information into a pre-existing schema represented in cortical areas, while memory for more incongruent information relies instead on automatic encoding of arbitrary associations by the MTL.

Introduction

It has long been known that relating new information to prior knowledge can enhance memory for that information, and this has been interpreted mainly in terms of facilitated retrieval via a pre-existing schema [4,11,162,219]. More recently, the neural correlates of memory facilitation through activation of such schema have been found during both encoding [54,143] and consolidation [112,131,164], involving a functional interplay between the medial temporal lobe (MTL) and the medial prefrontal cortex (mPFC). From this neuroscientific perspective, a schema can be defined as a network of strongly-interconnected cortical representations, activation of which affects the processing of new, related information. Activated schemas are therefore presumed to facilitate all mnemonic stages: encoding, consolidation (e.g., through reactivation during offline periods such as sleep), and retrieval.

However, the specific roles of mPFC and MTL in this schema-dependent processing remain unclear. According to one recent theoretical framework [163], mPFC and MTL reflect distinct, complementary learning systems in the brain, whose relative influence on encoding depends on the congruency of new information with existing schemas. This framework, termed Schema-Linked Interactions between Medial prefrontal and Medial temporal regions (SLIMM) proposes that, when new information is perceived that is congruent with a schema, a coherent pattern of mutually-reinforcing activity arises across the cortical network associated with that schema. This resonating network drives activity within mPFC, which is then assumed to directly augment cortical plasticity, thereby facilitating the integration of new information with the pre-existing schema. This contrasts with conventional accounts that only MTL can rapidly learn new associations [40,44], but is consistent with recent evidence that such "cortical fast mapping" is possible in the presence of schema [220]. Furthermore, the increased mPFC activity is assumed to inhibit activity within the MTL, preventing simultaneous encoding of the new information by MTL. Only when the new information is not congruent with a dominant schema is the MTL able to encode that information, for example via indirect associations between hippocampal indices and the cortical representations activated by the new information [39,221]; see [163] for further details.

We designed an fMRI experiment to test predictions of the SLIMM framework. We scanned participants while they rated the degree of congruency of visual images of an object and a scene, and used these ratings to define three levels of subjective congruency for each participant (i.e, congruency was defined on an individual basis). On the day after their scan, each participant was presented with objects only, and asked to distinguish "old" objects they had seen on the previous

day from new ones (item recognition), and then, for the correctly remembered old objects, to indicate which of three alternative words described the scene that had been paired with that object on the previous day (associative recognition). This allowed us to return to the fMRI data during encoding of the object-scene pairs, and distinguish trials according to whether the association was subsequently remembered or forgotten to determine brain activity associated with successful associative encoding, as a function of the congruency of the pairing. If the SLIMM framework is correct, mPFC activity related to successful encoding should increase with congruency while MTL encoding-related activity should decrease with congruency. Furthermore, functional connectivity between mPFC and parts of the ventral visual stream that code the objects and scenes should also increase with congruency (reflecting stronger binding via a schema), while functional connectivity between mPFC and MTL should also be modulated by congruency [163].

Methods

Participants

Thirty-two native Dutch right-handed students (five male) participated in this experiment. All participants reported to be healthy, had normal or corrected-to-normal vision and were paid for their participation. Ethical approval was obtained from the institutional review board (CMO Region Arnhem-Nijmegen, The Netherlands), and all participants gave written informed consent. Four participants were excluded due to technical failure. Two other participants were excluded, because their behavioural performance did not yield a minimum of 9 trials for all categories included into contrasts of interest in the fMRI data analyses. Therefore, the data of these six participants were discarded and all analyses were performed on data of the remaining 26 participants (four male, age 18 - 27 years, mean 21.5 years). On average, participants reported to have slept 7.6 hours the night in between the two experimental days (range 6.5 - 9 hours).

General procedure

Participants performed an associative memory experiment, conforming to a 3x2 (congruency x memory) factorial design. Inside the scanner, on day one, they rated the congruency of, and intentionally memorized, 185 sequentially presented paired associates, each consisting of two colour photographs simultaneously presented next to each other, one scene and one object (Fig. 1). The congruency ratings, performed on a 33-point scale that appeared continuous to the participants, were subsequently used to divide the stimuli into three congruency

levels of identical trial counts (congruent, intermediate and incongruent). Before the encoding task, participants underwent a functional localiser experiment that lasted about ten minutes and after the encoding task, which lasted about 25 minutes, an anatomical scan was acquired, which lasted seven minutes. Participants then went home and returned the next day, approximately 24 hours later, when their memory was tested with an object recognition test and an object-scene associative memory test, which were administered outside the MR scanner.

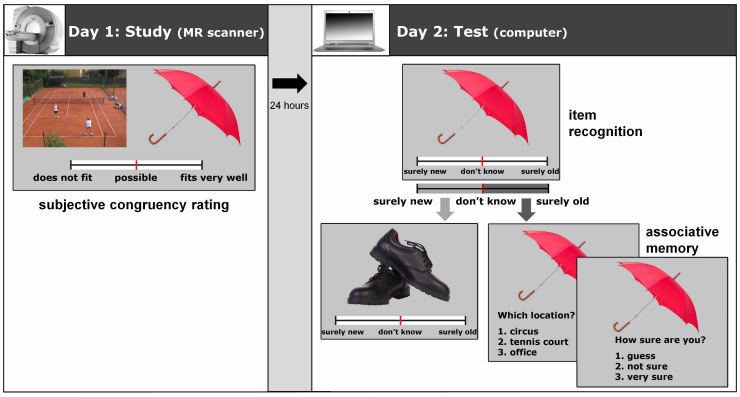

Figure 1: Experimental design. The experiment was conducted on two consecutive days. On day one, participants memorized a series of consecutively presented pairs of photographs in the MR scanner. Each pair of photographs contained one object and one scene, and participants were asked to indicate how well they thought the two photographs matched in terms of their co-occurrence in the real world, by moving the red bar on a congruency scale to a particular position. These ratings were used to assess subjective congruency, and then split into thirds to define three levels of participant-specific congruency. Participants returned 24 hours later to be tested on their memory. Participants were shown old and new object photographs sequentially and randomly intermixed, and indicated whether they had seen the object the previous day by moving the red bar on a confidence scale (item recognition). For objects judged as old, they were subsequently asked to choose one of three one-word descriptions of scenes that corresponded to the scene paired with the object on the previous day (associative memory). Finally, they were asked to rate their confidence on this decision (guess, not sure, very sure). Participants had to answer each question within six seconds.

Stimuli

Participants were instructed to memorize 185 paired-associates each consisting of two colour photographs, one scene and one object. We used both indoor- and outdoor-scenes (e.g. classroom, tennis court) which were easily recognizable and could be distinctively described by one or two words (as assessed in a pilot study, see 2.4). Pairs were predefined, such that object-scene associations would cover the whole range of the congruency scale and were unique, i.e. each picture was shown in only one pair. Ten percent of the pairs were constructed to be very incongruent (e.g. tennis court - soup ladle), while another 10% were constructed to be very congruent (e.g. classroom - chalk). To most optimally counterbalance

the design across participants, for half of the participants, the objects that were paired as very congruent before were re-paired within their subset to give very incongruent combinations, while the objects that were paired as very incongruent for the first half of participants were re-paired within their subset to give very congruent combinations. Thus, 20% of the objects and scenes were shown in either a very congruent or a very incongruent pairing, counterbalanced across participants, to control for biases resulting from our construction of the pairs. Consequently, 80% of the pairs were likely to be rated as more intermediately congruent, allowing subjective congruency ratings to be widely distributed.

Behavioural pilots

Prior to conducting the associative memory experiment in the MR scanner, we performed four behavioural pilots in a separate group of participants (n=26 in total). In these, we checked whether the pictures were easy to recognize and to describe and whether congruency of the constructed pairs fitted the intended distribution across the congruency scale (see section 2.5). During piloting we also confirmed that the number of trials was appropriate to attain behavioural performance above chance level while keeping enough trials in all conditions for our MR-analyses.

Associative memory encoding

The experiment was executed on two consecutive days (Fig. 1). On the first day, participants were instructed to memorize the 185 pairs while brain activation was measured using fMRI. Participants lay in the MR scanner supine and viewed the screen through a mirror mounted on the head coil while they responded with their right index and middle finger using a button box. Presentation 14.9 (NeuroBehavioural Systems Inc., Albany, CA, USA) was used to present the stimuli. Participants were instructed to remember the pairs for a test 24 hours later, but were not told what aspects they would be tested on. During the encoding task, the object and scene picture making up a pair were presented simultaneously and next to each other on a grey background for 3.5 seconds, followed by an intertrial interval of 2-6 seconds duration, during which a black fixation cross on grey background was shown. Pairs were presented pseudorandomly, with no more than three very congruent or very incongruent items following each other. All items (objects and scenes) were presented on two screen locations left and right of the centre. The side of the object and scene on screen (left or right) was randomized across trials. Additionally, 12 baseline periods of 10 seconds were interspersed evenly, during which a black fixation cross on grey background was shown. Due to technical problems, all durations were scaled by a factor of 1.5 for one participant, but because her results did not deviate we included her data in

the analysis. During pair presentation, participants had to judge the congruency of the pair by moving a red bar acting as cursor on a visual analogue scale (which was in fact a discrete scale with 33 parts that were not discernible for the participants), labeled on one end as does not fit, in the middle as possible and on the other end as fits very well (Fig. 1). The left/right orientation of the scale (well <> not well or not well <> well) was counterbalanced across participants.

Twenty-four hours later (standard deviation (SD) 1 hour), participants returned for the memory test (Fig. 1). On a computer screen, they were shown a set of 300 object pictures, consisting of the 185 pictures from day one as well as 115 new pictures that served as lures. These objects were not directly paired with learned objects, but were somewhat related to make the recognition task less easy. Participants were instructed to decide whether they had seen these objects the previous day by moving a red bar on a visual analogue scale (which was the same scale as used in the encoding experiment, see above), labeled on one end as surely new, in the middle as don't know, and on the other end as surely old. For items judged as old, participants had to indicate which scene was associated to it, choosing from three one-word descriptions. We used verbal descriptions instead of the original scene pictures to make the test harder and to eliminate recognition from idiosyncratic perceptual features of the photographs; instead testing more categorical-type memories. One correct answer and two other scenes from the studied set were provided in the three-choice question. To avoid the possibility of identifying the correct answer by solely remembering that the object had been shown with a congruent or incongruent scene, multiple choice options were manually arranged to have, additional to the correct answer, both one congruent and one incongruent incorrect option. All scenes were distributed to appear equally often as an option. Lastly, participants had to indicate how confident they were of their answer (three choices: guess, not sure, and very sure). Each response had to be given within six seconds, after which the next question was shown.

Localiser experiment

To determine brain regions that represent objects and scenes, a functional localiser experiment for objects and for scenes was conducted before the encoding task. Participants were shown colour photographs of objects, natural scenes, scrambled objects and scrambled scenes in a blocked design. The photographs used in the localiser experiment were different from the ones used in the associative memory experiment. Participants saw the same set of 24 pictures for each stimulus type five times, equaling 20 blocks with a total of 480 stimulus presentations. Blocks were presented in the same pseudo-random order for each participant. Each picture was presented for 0.7 seconds, followed

by an intertrial interval of 0.4 seconds duration, during which a grey background was shown. During the localiser experiment, participants performed a 1-back task. They were instructed to press a button if the same picture appeared twice consecutively. Participants were told that they would not have to remember the pictures shown during the localiser task.

Behavioural analyses

According to the congruency ratings given on day one, study phase trials were grouped into three congruency bins with approximately identical trial numbers labeled congruent, intermediate, and incongruent. Trials in which no congruency rating was given, i.e. the red bar was not moved, were excluded from the analysis. Reaction times were defined in two measures. First, we used the time it took participants to decide how congruent they thought a particular pair was (decision time), reflected in the time it took them to start giving a response, i.e. the duration from the onset of pair presentation until initiation of the answer. Second, we calculated the duration of the actual response (response time), i.e. the duration from the first until the last button press within a trial. The response time was necessarily related to a pair's congruency level, as the red bar was positioned in the middle of the scale at the beginning of each trial and had to be moved further towards the ends of the scale for more incongruent or congruent judgments, resulting in longer response times. By combining these two measures, we also calculated the overall reaction time per trial.

In the second day memory test, all responses on the object recognition question from scale part 1 (surely new) to 15 were classified as new answers, while all responses from scale part 19 to 33 (surely old) were classified as old answers, leaving out the intermediate (don't know) answers and the trials where the cursor was not moved. All trials with intermediate scores, i.e. scale parts 16 to 18, were discarded from the analysis, to exclude trials in which no choice had been made, i.e. the red bar had not been moved, as well as the adjacent very unsure decisions. Item recognition performance (d-prime) for each congruency level was then calculated as the z-transformed proportion of objects in each congruency bin included in the analysis that were correctly identified minus the z-transformed proportion of false alarms. Subsequently, associative memory performance was calculated as the proportion of correctly recognized objects for which the scene was correctly identified, irrespective of the associative memory confidence.

To analyze the behavioural measures, PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) was used. Student's t-tests were performed to assess whether memory scores differed from chance level (one-sample t-tests against 0 for item recognition accuracy and .33 for associative memory performance) and whether

memory scores, reaction times, beta weights (see below), and confidence of associative memory differed between congruency levels (paired-sample t-tests). For this purpose, the verbal confidence ratings of associative memory answers were transformed to an ordinal representation by scoring guess as 1 point, not sure as 2 points, and very sure as 3 points. To assess whether scores changed consistently across congruency levels, we ran repeated-measures analyses of variance (ANOVAs), testing for monotonic trends in the data. All measures were considered significant at a threshold of alpha=.05.

fMRI data acquisition

Participants were scanned using a 1.5 Tesla Siemens Magnetron Avanto system equipped with a 32 channel phased-array head-coil (Siemens AG, Erlangen, Germany). For blood-oxygen level dependent (BOLD) fMRI images, we used a T2*-weighted, gradient-echo, multi-echo EPI sequence [212] with the following parameters: repetition time (TR)=2.64 sec, echo time (TE)1=6.9 ms, TE2=24.2 ms, TE3=33 ms, TE4=43 ms, TE5=52 ms, 34 slices, ascending slice order, 3mm slice thickness, 0.51 mm slice gap, matrix size=64x64, field of view (FOV)=224 x 224 x 199 mm, flip angle=80 degrees, voxel size=3.5 x 3.5 x 3.0 mm. Slices were angled in an oblique axial manner to achieve whole brain coverage. To allow T1 saturation to reach equilibrium, the first three volumes were discarded. Additionally, T1-weighted anatomical scans at 1 mm isotropic resolution were acquired using an MPRAGE scan with TR=2250 ms, inversion time (TI)=850 ms, flip angle=15 degrees and FOV=350 x 263 x 250 mm.

fMRI data preprocessing

For both encoding task and localiser experiment, raw multi-echo fMRI data were first processed using in-house software written in Matlab 7.5 (The Mathworks, Inc., Natick, MA, USA), which used 32 separately acquired scans to calculate the optimal weighting of echo times for each voxel (i.e. by using a weighted measure of the contrast- to-noise ratio for each echo/scan). Motion correction was performed on the first echo by using iterative rigid body realignment to minimize the residual sum of squares between the first and all further functional images. Then the calculations of optimal echo time for each voxel were used to combine multi-echo fMRI data into single-echo images. The combined images were further processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to a mean functional image, and coregistered to the corresponding individual anatomical scan by using mutual information optimization. These images were subsequently spatially normalized and transformed to a common space, as defined by the SPM8 Montreal Neurological Institute (MNI) T1 template (voxel size = 2x2x2mm), as well as spatially smoothed by convolving them with

an 8 mm full width at half maximum 3D kernel.

fMRI data analysis

Localiser experiment

The blocked design of the localiser experiment yielded four conditions (objects, scenes, scrambled objects, and scrambled scenes), which we modelled by convolving the block durations with a canonical haemodynamic response function. In a general linear model (GLM), we included these four conditions and six motion parameters. We entered these statistical maps into a full factorial second level analysis (type x scrambling), and then calculated object (objects - scrambled objects) and scene (scenes - scrambled scenes) contrasts. Statistical maps for the localiser experiment were analyzed at a threshold of voxel level $p<.05$ whole-brain family-wise error (FWE) corrected.

Encoding task

According to the behavioural outcome from the retrieval test, we classified study phase trials as item misses (object not recognized), item hits (object recognized but associated scene incorrect) and associative hits (item recognized and associated scene correct) for each of the three congruency levels. For each level, trial categories were modelled by convolving a boxcar function of pair presentation duration (3.5 sec) with a canonical haemodynamic response function. In a GLM, we included these nine trial types, the baseline trials and six motion parameters. Additionally, we included decision time (the duration from the onset of the presentation of a new pair until the first button press within a trial) and response time (time from first button press until last button release within a trial) as parametric modulators for all trials, and confidence of associative hits (1, 2, or 3 points) as parametric modulators for associative hits only, forming a design matrix with 38 regressors.

Brain activation was first analyzed at a whole-brain level at a threshold of $p=.001$ uncorrected at voxel level and considered significant at cluster-level corrected $p(FWE)=.05$. For subsequent analyses on previously defined regions of interest (ROI), we adopted a small volume corrected (SVC) threshold of $p(FWE)<.05$ (at peak-level). The ROI for the mPFC was defined functionally, using an 8 mm sphere centered on the peak voxel (MNI [2,46,0]) in mPFC for the contrast of congruency x cued recall in our previous study [222]. The ROIs for ventral temporal cortical regions assumed to represent the current stimuli and used in the connectivity analysis (see hypotheses in Introduction) were derived from the independent functional localiser data of the present study; specifically, the peaks from the contrasts of scenes versus scrambled scenes, and objects

versus scrambled objects in lateral occipital cortex (LOC) and parahippocampal place area (PPA) (see Results), were used as the centres of spheres with a radius of 20 mm. Finally, the ROIs for the MTL were derived anatomically, from combining the Automatic Anatomic Labelling (AAL) definitions of the hippocampus and parahippocampal gyrus [151], separately in left and right hemispheres. All brain coordinates are given in MNI space.

Activity analysis

We calculated a subsequent memory contrast as the difference between associative hits and associative misses (the average of item hits and item misses), separately for each congruency level, within each participant. Subsequently, we entered the resulting contrast images into a multiple regression which included two regressors: a mean and linear function of congruency. The mean regressor therefore tested for the main effect of subsequent associative memory across participants, while the (orthogonal) linear regressor tested the interaction between subsequent memory and congruency (we also looked for a quadratic component in separate analyses, but nothing survived correction for our ROIs). This linear effect of congruency was tested either in the direction of congruency, i.e. linearly increasing from incongruent to intermediate to congruent, or in the direction of incongruency, i.e. linearly decreasing with increasing congruency. Beta weights for each original condition from the peak of the significant clusters identified by the above model were extracted using in-house software written in Matlab 7.11 (The Mathworks, Inc., Natick, MA, USA).

Functional connectivity analysis

We computed psycho-physiological interactions (PPI), using two seed regions: A sphere with a radius of 8 mm centred at the peak voxel in mPFC (MNI [-2,40,2]), which showed a positive interaction between memory and congruency in the activity analyses, and a cluster in left MTL which showed a negative interaction between memory and congruency, consisting of 51 voxels that survived $p<.001$ uncorrected (see Results). Note that changes in connectivity are not necessarily related to changes in mean activity, so this selection of ROIs based on experimental effects on activity does not bias the connectivity results [223]. Separately for all congruency levels, we computed the connectivity of the seed region with all other voxels, testing for regions that showed an interaction between the time course of the seed region's BOLD response (physiological variable) and the subsequent memory contrast for each of the three congruency levels, as used in the activity analyses (psychological variable). The resulting contrast images, indexing regions whose connectivity with the seed was stronger for hits than for misses for a given congruency level, were entered into further multiple regression analyses, again

probing an increase or decrease with congruency as described above. Hence, we tested for regions whose change in connectivity associated with hits versus misses varied with increasing or decreasing congruency.

Results

Behavioural measures

Item recognition accuracy

Item recognition accuracy (d-prime, Fig. 2A) was above chance level (0) for all congruency levels (incongruent pairs: $t(25)=18.19$, $p<.001$; intermediate pairs: $t(25)=16.99$, $p<.001$; congruent pairs: $t(25)=20.32$, $p<.001$). Item recognition measures increased linearly with congruency (linear component: $F(1,25)=15.37$, $p=.001$; quadratic component: $F(1,25)=3.61$, p=n.s.). Items from congruent pairs were better remembered than items from incongruent pairs ($t(25)=3.92$, $p=.001$) and intermediate pairs ($t(25)=3.79$, $p=.001$). Item recognition accuracy of incongruent and intermediate pairs did not differ significantly ($t(25)=0.35$, p= n.s.).

Associative memory performance

Associative memory performance (proportion correct, Fig. 2B) was above chance level (33%) for all congruency levels (incongruent pairs: $t(25)=7.79$, $p<.001$; intermediate pairs: $t(25)=13.77$, $p<.001$; congruent pairs: $t(25)=21.67$, $p<.001$). Associative memory performance increased monotonically with congruency (linear component: $F(1,25)=46.08$, $p<.001$, quadratic component: $F(1,25)=8.9$, $p<.01$) and differed significantly between all three levels (intermediate pairs - incongruent pairs: $t(25)=2.50$, $p<.05$; congruent pairs - intermediate pairs: $t(25)=7.13$, $p<.001$; congruent pairs - incongruent pairs: $t(25)=6.79$, $p<.001$).

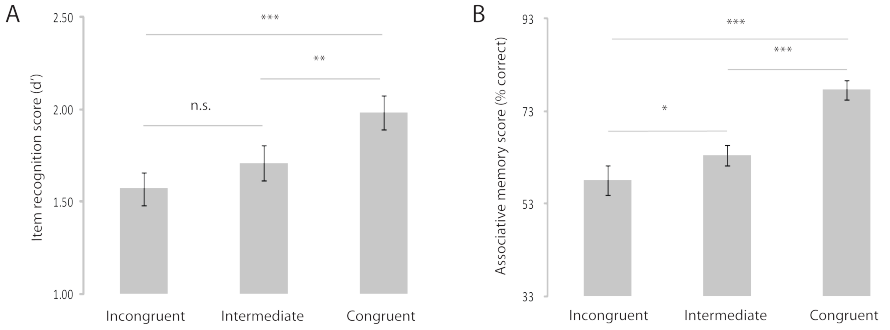

*Figure 2: Memory performance. A: Mean (and SEM) of item recognition accuracy (d-prime) for each congruency level. B: Mean (and SEM) of associative recognition performance (% correct) for each congruency level. Smaller horizontal bars indicate post-hoc paired-samples t-tests between two congruency levels; * p<.05; ** p<.01; *** p<.001; n.s. p>.05. SEM: standard error of the mean.*

Confidence measures

Confidence increased monotonically with congruency for item recognition hits (1-33; linear component: $F(1) = 23.94$, $p < .001$; quadratic component: ($F(1,25) = 8.64$, $p < .01$). For associative recognition, confidence (minimum 1 point, maximum 3 points) showed a significant linear increase with congruency, averaging across hits and misses (linear component $F(1,25)=37.80$, $p<.001$; quadratic component: $F(1,25)=1.11$, p=n.s.), but any interaction between memory (hits vs misses) and congruency failed to reach significance ($F(2,24)=2.47$, p=n.s.). Confidence for associations thus seems to be related to congruency in general, rather than to memory accuracy.

Reaction times

Reaction times during encoding showed a linear decrease with congruency (linear component: $F(1,25)=47.46$, $p<.001$; quadratic component: $F(1,25)=1.28$, p=n.s.) Congruent trials showed significantly faster reaction times than intermediate ($t(25)=3.15$, $p<.01$) and incongruent trials ($t(25)=6.89$, $p<.001$). Reaction times for incongruent and intermediate trials did not differ significantly ($t(25)=1.03$, p=n.s.). However, because the participants performed a congruency rating on a scale where the cursor always started in the middle and was moved by a series of button presses, the reaction times can be divided into two parts: Decision times (duration from the beginning of a pair presentation until the first button press within a trial) and response times (duration from the first to the last button press within a trial). As this measure is differentially affected by congruency due to the nature of the experiment (intermediate trials require less response times as the cursor always starts in the middle), we examined these two types of reaction time separately. Decision times differed significantly between congruency levels (incongruent pairs: mean=1.66 seconds, SEM=.04 seconds; intermediate pairs: mean=1.99 seconds, SEM=.06 seconds; congruent pairs: mean=1.57 seconds, SEM=.04 seconds; linear component: $F(1,25)=14.63$, $p=.001$; quadratic component: $F(1,25)=214.32$, $p<.001$), as did response times (incongruent pairs: mean=0.78 seconds, SEM=.03 seconds; intermediate pairs: mean=0.41 seconds, SEM=.04 seconds; congruent pairs: mean=0.71 seconds, SEM=.03 seconds; linear component: $F(1,25)=7.73$, $p=.01$; quadratic component: $F(1,25)=115.88$, $p<.001$).

Brain activity

Localiser contrasts

The localiser experiment revealed distinct, bilateral brain regions that were more strongly activated during processing of objects and scenes, respectively (see

Fig. 5). Activity in fusiform gyrus and LOC (peaks [-48,-78,2], [48,-70,-4]) was enhanced bilaterally in response to objects. Activity in the PPA was enhanced bilaterally in response to scenes (peaks [-26,-48,-8], [24,-40,-12]) (Fig. 5A, C). We used these results for small-volume correction of the connectivity analyses below (see Methods).

Main effect of subsequent associative memory

The contrast of greater activity for associative hits than associative misses revealed a main effect of subsequent memory, regardless of congruency, in left inferior frontal cortex, left fusiform cortex, left mid occipital cortex and left frontal inferior triangle ($p<.05$ whole-brain cluster-level corrected). Furthermore, a peak in left MTL (hippocampus; [-30,-16,-12]) survived correction for our left MTL ROI (see Methods), $p(SVC)<.05$ (Fig. 3).

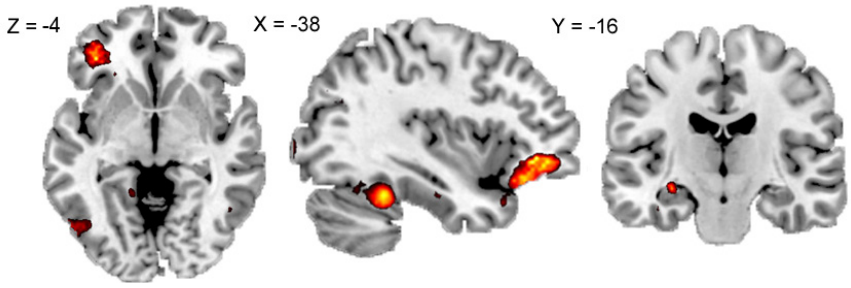

Figure 3: Main effect of subsequent memory for object-scene associations. The contrast between associative hits and misses, averaged across congruency, revealed (amongst others) activation in left inferior frontal gyrus (left and middle panel), left fusiform gyrus (middle panel), and left hippocampus (peak [-30,-16,-12], right panel). All maps are shown at p<.001 uncorrected, and all clusters survived whole-brain correction for their spatial extent, or small volume correction for their peak within pre-specified ROIs (see Methods).

Interaction between subsequent memory and congruency

We first tested for regions in which the subsequent memory effect increased (linearly) with congruency. Only one mid-cingulate cluster survived $p<.05$ whole-brain cluster-level correction. However, using our a priori mPFC ROI (based on our previous study, see Methods) the peak statistic at [-2,40,2] survived correction, $p(SVC).<05$ (Fig. 4A, C; but alo see Fig. S1A; Table S2). The opposite test for regions in which the subsequent memory effect decreased with congruency revealed no significant effects at whole-brain level, but a peak in left parahippocampal cortex ([-16,-18,-20]) survived correction for our left MTL ROI, $p(SVC).<05$ (Fig. 4B, D; but also see Fig. S1B; Table S2). Thus mPFC, as well as cingulate regions, showed activation associated with successful associative encoding that increased with the congruency of the association, whereas MTL showed encoding-related activation that decreased with the congruency of the association (i.e. that was greatest for incongruent pairs).

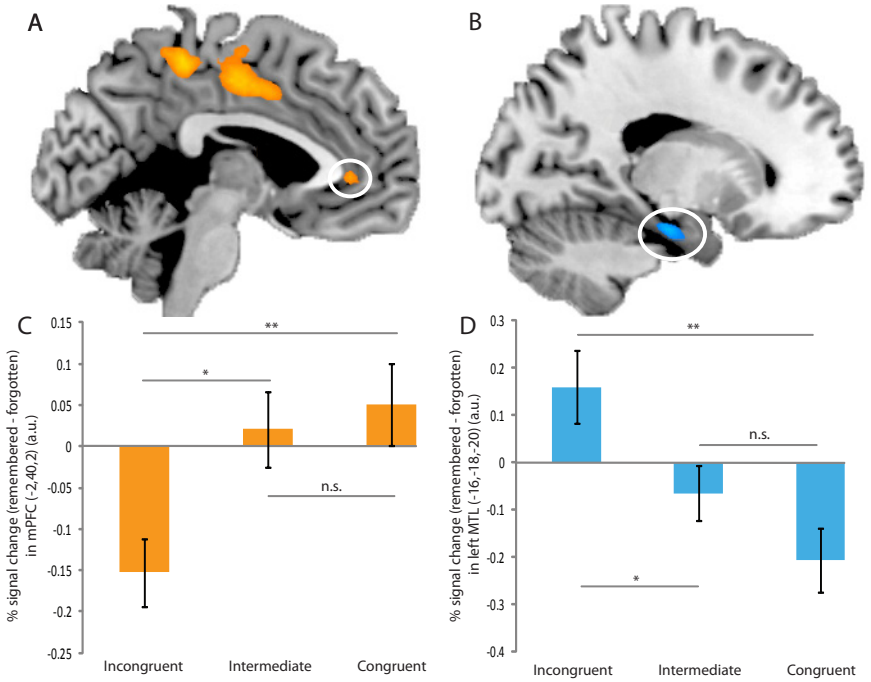

*Figure 4: Effects of congruency on subsequent associative memory. Statistical maps show the results of testing for brain regions that show an interaction between subsequent memory and congruency. Linear regression analyses were performed on the subsequent memory contrasts across the three congruency levels, either testing for an increase with congruency (A) or an increase with incongruency (B). A: Encoding-related activity in the medial prefrontal cortex (mPFC) ROI increased with congruency (peak [-2, 40, 2]). B: Encoding-related activity in the left medial temporal lobe (MTL) ROI increased with incongruency (peak [-16, -18, -20]). C: Mean (+/- SEM) of the subsequent memory contrast for each level of congruency extracted from the mPFC peak (A). D: Mean (+/- SEM) of the subsequent memory contrast for each level of congruency extracted from the MTL peak (B). Maps displayed at p<.005 uncorrected for the purpose of illustration. Peaks in mPFC and MTL are significant after small-volume correction for their respective ROIs, while the extent of the mid and posterior cingulate clusters survives correction across the whole brain. C+D Horizontal bars indicate paired-samples t-tests between two congruency levels; * p<.05; ** p<.01; n.s. p>.05 for illustrative purposes, since these p-values are biased by prior selection of the voxels to show a linear effect across all three congruency levels.*

Functional connectivity

To investigate how connectivity of the areas shown to be involved more strongly with the encoding of either congruent (mPFC) or incongruent (left parahippocampal) pairs differed across congruency levels, we ran psycho-physiological interaction (PPI) analyses. These tests revealed a peak within the right PPA ROI defined from the localiser, whose connectivity from the mPFC increased with increasing congruency during successful associative encoding ([12, -38, -8], p(SVC)<.05) (Fig. 5). When testing for the opposite contrast, we found decreased connectivity with increasing congruency from mPFC to more

dorsal medial prefrontal regions, and to an angular gyrus region, that survived whole-brain cluster-level correction. No voxel survived SVC for this contrast in our ROIs, though a hippocampal peak within our right MTL ROI ([32,-28,-6]) showed a trend, p(SVC).<.075. Finally, when testing for connectivity from the left parahippocampal seed, we did not observe significant interactions in the whole-brain or in our ROIs.

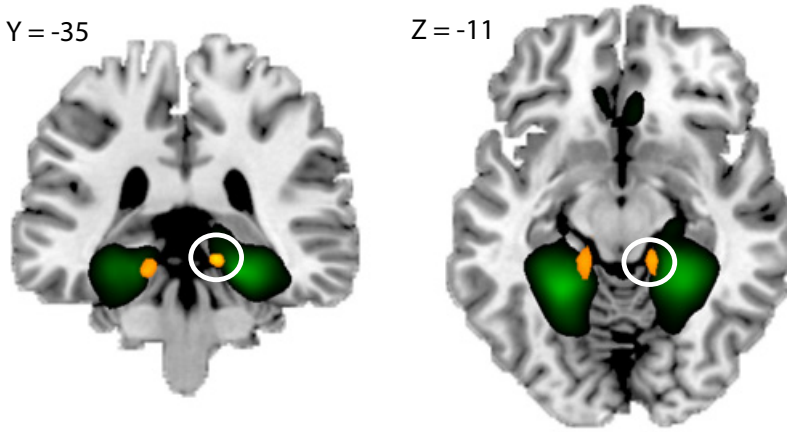

Figure 5. Effects of congruency on functional connectivity during successful memory encoding. Statistical maps show the results of a linear regression of the interaction between connectivity of a seed region and subsequent memory for each congruency level, imposed on localiser experiment results (green: scene localiser). Connectivity of the mPFC with right parahippocampal place area during successful encoding increased with congruency (shown in yellow, peak [12, -38, -8], on top of scene localiser (green) p(FWE)<.05 in coronal and axial views). Map displayed at p<.001 uncorrected at voxel level. The left PPA was also activated at this whole-brain threshold but did not survive subsequent small volume statistics.

Discussion

In this experiment, we investigated how brain activity during encoding of new associations is altered as a function of the subjective congruency of those associations with pre-existing schemas. The results replicate and extend earlier findings on schema effects during memory encoding [54,143,222], by using subjectively-defined congruency levels, and provide support for some of the predictions made by the recent SLIMM framework [163]. We explore these predictions in turn.

Behaviourally, we found that item recognition increased linearly and associative recognition increased monotonically across our three levels of congruency (Fig. 2), consistent with previous data on the memory advantage for congruent information [6,132,164,222]. Confidence levels also increased linearly with congruency for both memory measures, though there was no evidence that this increased confidence translated into higher accuracy for associative memory.

Consistent with earlier neuroimaging findings [93,224], main effects of subsequent associative memory (Fig. 3), averaging across congruency, were found in regions including the left hippocampus, left inferior frontal gyrus and left fusiform gyrus. The interaction between subsequent memory and congruency, on the other hand, revealed encoding-related activity in mid and posterior cingulate cortex that increased with congruency (Fig. 4A). These activations are often reported in memory retrieval tasks [225-227], and so this interaction may reflect congruent pairs, by their nature, having greater retrieval of associated information than less congruent pairs. More importantly, as predicted, mPFC also showed encoding-related activity that increased linearly with subjective congruency. This interaction is consistent with the SLIMM framework [163], in which mPFC is assumed to respond to the degree of resonance within cortical networks, and representations of congruent information will resonate more. This increased mPFC activity is then assumed to facilitate plasticity between the representations within those networks, enhancing later associative memory.

SLIMM also predicts that mPFC activity inhibits activity within MTL, and therefore MTL activity will show the opposite pattern, of increased activity with decreasing levels of congruency. This prediction was also confirmed, at least within a left parahippocampal region within our MTL ROI (Fig. 4B). This finding is also consistent with previous studies that found subsequent associative memory effects in parahippocampal cortex for tasks that required participants to learn arbitrary associations [224,228], which are analogous to the less congruent conditions of in the present design.

Furthermore, SLIMM predicts that the facilitation of cortical learning for schema-consistent information by mPFC is associated with increased functional connectivity between mPFC and the cortical regions that represent that information. In the present experiment, we used a localiser scan to identify a PPA ROI that was activated by our scene stimuli (where the PPA lay posterior to our anatomically-defined MTL ROI), and an LOC ROI activated by our object stimuli. Consistent with SLIMM's predictions, we found that connectivity from mPFC to PPA increased with increasing congruency (Fig. 5), suggesting that mPFC was influencing encoding-related activity associated with the scene stimuli (though we did not find this increased connectivity to the LOC ROI associated with the object stimuli). These results extend our previous finding of enhanced functional connectivity from the mPFC to a task-relevant somatosensory cortical area during retrieval of congruent information [164], in showing that functional connectivity between mPFC to such sensory representational areas is augmented by schemas during encoding, too.

Finally, SLIMM also predicts changes in connectivity between mPFC and MTL as a function of congruency, associated specifically with an inhibition of MTL

activity by mPFC for congruent information. However, how this inhibitory account translates into changes in functional dependencies between fMRI data remains unclear. Before, we argued that mPFC-MTL connectivity will in fact be greatest for intermediate levels of congruency, where there may only be partial activation of schemas, and hence of mPFC, so greater interaction between mPFC and MTL is necessary to resolve this "competition" [163]. We did not find evidence of this quadratic relationship across the present three levels of congruency. If anything, we found a trend for functional connectivity (from mPFC to a right hippocampal region) to increase linearly with decreasing congruency. This prediction therefore clearly requires further theoretical development (concerning how inhibitory interactions relate to fMRI connectivity measures) and further empirical data, specifically looking at mPFC-MTL connectivity with other, causal measures.

Note that we did not find any evidence of enhanced memory for incongruent information in this experiment. According to SLIMM, associations that are incongruent with a schema (i.e, highly novel) are encoded by an index (instance) in the MTL, and this "snapshot" should occur more often for low than for intermediate levels of congruency. Together with the aforementioned, mPFC-mediated advantage for highly congruent information, one might therefore expect a U-shaped function across the 3 levels of congruency used here. However, the prediction for behavioural performance also depends on the precise nature of the encoding and retrieval tasks, as discussed below.

Foremost is the issue of a "generate-and-recognise" strategy at retrieval [229], in which participants generate information from pre-existing schemas that is congruent with the retrieval cue (here, the picture of the object), and then detect whether such information seems familiar (recognised), as would occur if it had been paired with the cue at encoding. We tried to reduce the effectiveness of this strategy by using a forced-choice associative recognition test, in which names of three possible scenes were provided, so that participants need not generate possible scenes themselves. Additionally, we deliberately made one of the two incorrect choices match the (predefined) congruency level of the correct choice, so that merely remembering that an association was congruent or incongruent would not be sufficient to select the correct choice. Nonetheless, it remains possible that we could not fully prevent use of a generate-and-recognise strategy completely, which might have boosted performance for congruent trials, and masked any advantage for incongruent trials. Note however that this retrieval strategy would not directly affect the neuroimaging data at encoding, because the MTL could still show increased activity for remembered versus forgotten incongruent trials, even if this activity were not sufficient to overcome any retrieval bias towards congruent trials.

Secondly, a stronger test of MTL-encoding of incongruent items, according

the SLIMM framework, would be to test memory for incidental associations that were not directly relevant to the encoding task (e.g, the left-right location of the object and scene). This is because the MTL is assumed to take an episodic "snapshot" of all information present at encoding, so such incidental context should be better remembered for incongruent than congruent trials (where an active schema, and active mPFC, is predicted to actually filter out such unrelated information [163]). This is consistent with evidence that memory benefits for incongruent/unexpected information seem to generally arise under incidental encoding conditions [19,230], and particularly affect task-irrelevant contextual and perceptual details [as e.g. in 133]. Because participants in our study were aware that their memory would be tested later, they will have deliberately focused on trying to relate the object and scene, meaning that the scene targeted by our recognition test was not incidental. Future research should focus more specifically on testing task-irrelevant, incidental features of incongruent memories.

In conclusion, the present study revealed that the subjective congruency of new information with prior knowledge affected subsequent memory performance, activity in mPFC and MTL and functional connectivity between mPFC and sensory regions. These results provide support for the SLIMM framework, which proposes that two distinct neural mechanisms, instantiated in mPFC and MTL, interact during memory encoding, where the extent to which each contributes to encoding is governed by the congruency of the learned information with a pre-existing schema. Future research should focus on further specifying features of congruent and incongruent memory traces during and after encoding.

Supplementary information

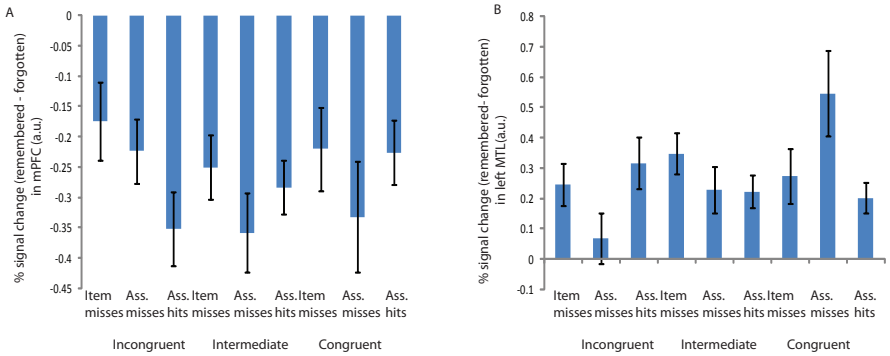

Figure S1: Effects of congruency on percent signal change in mPFC and MTL for all conditions separately.

Name region	Significance (FWE-corrected)	Voxel extent	Peak (MNI)
Left inferior frontal cortex	<.001 (cluster-level)	615	-38, 38, 4
Left fusiform cortex	<.001 (cluster-level)	520	-38, - 44, -24
Left mid occipital cortex	<.01 (cluster-level)	284	-44, -70, 28
Left frontal inferior triangle	<.05 (cluster-level)	254	-52, 24, 30
Left hippocampus	<.05 (SVC with left MTL; peak-level)	-	-30, -16, -12

Table S1: Regions significantly activated in the congruency-independent main effect of memory (thresholded at .001 uncorrected).

Positive interaction

Name region	Significance (FWE-corrected)	Voxel extent	Peak (MNI)
Mid cingulate cortex	< .001 (cluster-level)	2273	24, -36, 50
Medial prefrontal cortex	<.05 (SVC with sphere around [2,46,0]; peak-level)	-	-2, 40, 2

Negative interaction

Name region	Significance (FWE-corrected)	Voxel extent	Peak (MNI)
Left parahippocampal cortex	<.05 (SVC with left MTL; peak-level)	-	-16, -18, -20

Table S2: Regions significantly activated in the congruency x memory interactions.

Part IV:
Theoretical considerations and educational implications

Chapter 7

How schema and novelty augment memory formation

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Abstract

Information that is congruent with existing knowledge (a schema) is usually better remembered than less congruent information. Only recently however has the role of schemas in memory been studied from a systems neuroscience perspective. Moreover, incongruent (novel) information is also sometimes better remembered. Here, we review lesion and neuroimaging findings in animals and humans that relate to this apparent paradoxical relationship between schema and novelty. Additionally, we sketch a framework relating key brain regions in medial temporal lobe (MTL) and medial prefrontal cortex (mPFC) during encoding, consolidation, and retrieval of information as a function of its congruency with existing information represented in neocortex. An important aspect of this framework is the efficiency of learning enabled by congruency-dependent MTL-mPFC interactions.

Introduction

The existence of prior knowledge, to which new information can be related, generally improves memory for that information. Though the role of such schemas in learning has long been studied in psychology (see Box 1), only recently has this role been studied in neuroscience [112,130]. In particular, while structures within the MTL, such as the hippocampus, have long been implicated in the learning of declarative information [31], recent neuroscientific data have implicated an additional, time-dependent involvement of the mPFC [56,57], particularly when new information is congruent with a schema [54,143,164].

A second line of research has studied how the novelty of information can also improve its retention (see Box 2). This raises the question of when information conforming to a schema (congruent information) is remembered better or worse than information that does not (unrelated, or incongruent, information) [112,232]; a question that has important implications for optimising learning in educational settings [217]. Below, we review recent neuroscientific research addressing this question, before presenting a new framework that tries to explain the complex relationship between schema, novelty and memory.

Review of schema in systems neuroscience of memory

Several theories exist about how new information becomes consolidated into memory (see for review [42,92,111,112]). The so-called standard systems-level theory of consolidation [39] proposes that new (declarative) information is initially dependent on MTL structures like the hippocampus, but over time (possibly through reactivation [102], e.g, during sleep [101,104]), this information becomes relatively more dependent on the neocortex. This proposal is based on evidence that MTL-lesions not only impair the ability to form new memories (anterograde amnesia), but also impair the ability to retrieve memories formed within a period prior to the lesion (retrograde amnesia) [40]. After consolidation, long-term memories are believed to be represented by networks of interconnected neocortical brain regions representing the constituents of those memories; retrieval of which has become independent of the MTL (though see below; and [38]). More recently, an additional role has been suggested for the mPFC in such consolidation [43,58,232], consistent with evidence of offline replay of learning-related brain activity in mPFC (as well as MTL) [63,67,69] and by its prominent anatomical location within memory-related brain networks [55,233,234].

The presence of a schema, in terms of a pre-existing network of interconnected neocortical representations (see Glossary), has been suggested to accelerate

Glossary

Episodic/instance memory: a declarative memory for a specific event in space and time, which normally includes other contextual information present at that time (e.g, internal thoughts and states). We use instance to refer to a specific pattern of neocortical activity that is bound to an index in the MTL according to our SLIMM framework; we use episodic more generally to refer to memories with contextual information, which is often incidental (i.e. non-recurring, not part of an existing schema).
Declarative memory: memories that can be declared, i.e, have a propositional truth value (events or facts), normally associated with conscious recall, as distinct from procedural (non-declarative) memories like skill-learning, which cannot be verbalised and are often expressed unconsciously.
mPFC (medial prefrontal cortex): the medial aspect in the prefrontal cortex, encompassing Brodmann Areas (BA) 10, 11 and 32 in humans, and prelimbic, infralimbic and anterior cingulate cortex in rodents.
MTL (medial temporal lobes): part of the brain comprising hippocampus, perirhinal and enthorhinal cortices, and parahippocampal gyrus.
Neocortex: association cortex that stores elements of a memory trace (visual, spatial, auditory, somatosensory, emotional, etc). Note that the mPFC is part of the neocortex anatomically, but not considered to represent memory elements in the present framework.
Novelty: response to information that is not expected/predicted in a given context on the basis of prior experience. Note that we distinguish here between two types of novelty (Box 2): unrelated information that does not strongly match any schema, and incongruent information that is inconsistent with a dominant schema. Within the present SLIMM framework, only the latter improves memory, and note that this type of novelty cannot exist without a schema (i.e. the two concepts are intimately related).
Reactivation: reinstatement of a memory trace, either by online re-encountering of similar information, or by replaying the memory trace during offline periods.
Resonance: a neural state of co-activity of multiple mental representations (possibly across multiple brain regions), most likely bound via coherent (synchronous) activity.
Schema: a network of neocortical representations that are strongly interconnected and that can affect online and offline information processing.
Semantic/schematic memory: general, factual declarative memory that captures regularities extracted from multiple encounters (instances) over time, and divorced from accompanying, episodic details. We use schematic to refer to a (resonating) pattern of activity produced by strong connections within neocortex (i.e, an activated schema) within our SLIMM framework; we use semantic more generally to refer to acontextual knowledge that people possess.
Systems consolidation: the time-dependent and offline process by which connections between elements of a memory trace in the neocortex are strengthened so they are retained over the long-term, independently of MTL structures such as the hippocampus.

consolidation [130]. For example, a lesion study in rodents showed that memories congruent with a pre-learned spatial schema (Figure 1A) became hippocampally-independent after only 48 hours [131] (Figure 1B), while memories that lacked a prior schema were still hippocampally-dependent. Additionally, functional imaging in humans during a period of rest shortly after encoding revealed decreased hippocampal-mPFC functional coupling for more versus less congruent information [143] (Figure 1D), whereas successful retrieval of congruent information was associated with increased functional coupling between mPFC and a neocortical region coding that information [164]

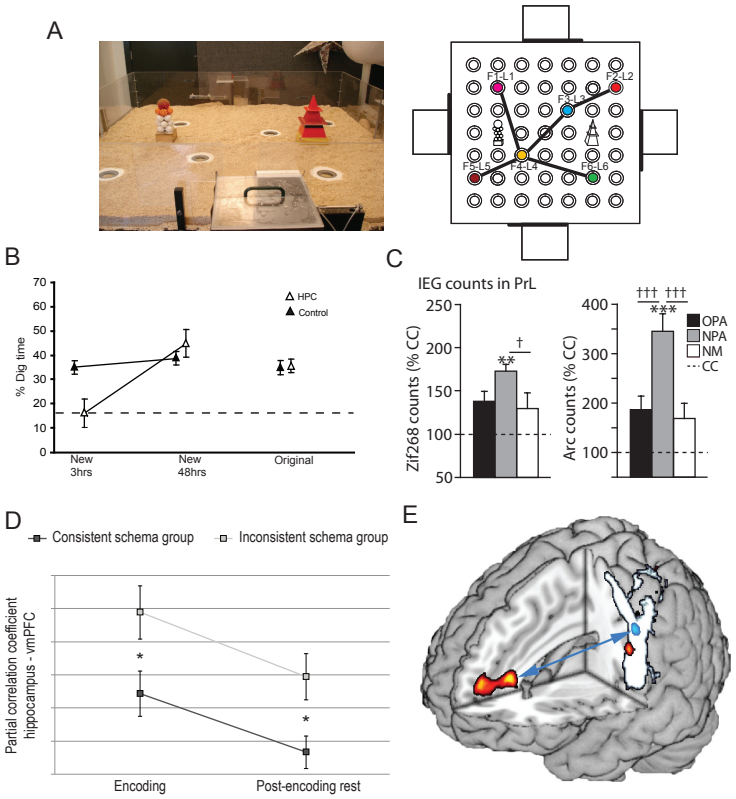

Figure 1: Overview of both rodent (A-C) and human (D-E) data on schema and memory. Rodent studies [54,131] have used an event arena (A), in which rodents initially learn a number of flavor-location associations. Left panel: Photo of the area. Right panel: Schematic of the 6 locations (L1-6) of the wells and their association with 6 different flavours (F1-6). The different landmarks used to navigate in the arena are also shown. (After learning such a schema, rats showed rapid hippocampal independence (after 48 hours, though not after 3 hours) of new flavor-location associations within the same arena [131] (B, hippocampally lesioned (HPC) versus control animals, represented in percentage dig time in the correct well). A separate group of rodents who had not learned the initial schema did not show such rapid consolidation of the new associations (data not shown). In a later study [54], the expression of two Immediate Early Genes (IEGs), zinc finger protein 225 (Zif268, left panel) and activity-regulated cytoskeletal protein (Arc, right panel), were higher immediately after encoding of the new associations (NPA = New Paired Associates) relative to retrieving the original associations (OPA = Old Paired Associates), learning associations in a completely new area (NM = New Map), and caged control (CC) animals, in prelimbic (PrL) structures (equivalent to human mPFC) and in the hippocampus (not shown). (C) In humans, mPFC-hippocampal connectivity was greater, both while participants watched a movie (i.e. during the encoding period) and during a resting period shortly afterwards (i.e. post-encoding rest period), the less congruent that movie was with the first part of the movie watched the previous day (i.e. the inconsistent schema group) [143]. (D) In a later study [164], mPFC activity, and connectivity between mPFC and a neocortical (somatosensory) region representing the schema-related information, was higher during retrieval of information congruent with a schema than information incongruent with a schema (E). For explanation of these different effects of congruency on regional activity and inter-regional connectivity, see Figure 2. Reproduced, with permission, from [131] (A,B), [54] (C), [143] (D), and [164] (E).

Box 1: History of schema research

The term schema was introduced from the philosophical work of Kant into developmental and cognitive psychology during the early 20th century by Piaget and Bartlett respectively [3,4], and refers loosely to an abstract, structured mental representation. This concept led to a cascade of both empirical behavioural research [10,162], and theoretical developments in artificial intelligence and connectionist modelling [12,25,261], as well as influencing educational theory [262].

A primary focus of the behavioural research concerned how schemas aid the retrieval of complex information; by providing a scaffold for organising retrieval of that information. This reconstructive aspect of memory offered a natural explanation of biases and false memories that occur from an over-reliance on schema [4]. Importantly however, schemas may also affect the encoding and consolidation of memories ([12]; see main text). For example, the superior recall of schema-congruent information cannot always be explained by facilitated retrieval [70] (e.g, by generation of schema-related information at test, followed by episodic recognition of information present at study [229]).

A primary focus of the connectionist modelling concerned the extraction of regularities from exposure to new information (instances) during learning [263]. A core problem here is the stability-plasticity dilemma; the degree to which a new instance should alter existing knowledge about a class of instances (schema) without destabilizing such knowledge. One solution to this problem (adopted by Adaptive Resonance Theory [253]) was a global parameter (vigilance) that determined whether or not a new instance needs to be represented separately, as a function of its similarity to existing schemas. Another solution was to appeal to different learning rules in complementary learning systems; in particular to appeal to a fast-learning system (in MTL) that stores unique instances, which can then be replayed in an interleaved fashion to a slower-learning system (in neocortex) that extracts their commonalities [25,110].

Enthusiasm for schema research waned since the 1980s, partly due to the over-extended definition of schema that arose from the explosion of interest, and partly due to some apparently contradictory behavioural results, where novel information (that does not conform to a schema) can sometimes be remembered well (see Box 2). Nonetheless, there has been a recent revival of interest in schema within the neuroscience community [54,112,131,143,164]. Here, the concept of a schema is simpler than in prior psychological research, operationalised for example as a familiar spatial layout, i.e. relationship between a number of locations within an arena in which a rat expects to find food [131], or as whether a word that must be associated with a novel visual stimulus is congruent with a simultaneously-presented tactile stimulus [164]. Our present (neuroscientific) conception of a schema therefore refers simply to a network of neocortical representations that are strongly interconnected, activation of which affects processing of new information, as expanded in the main text.

(Figure 1E). A schema thus appears to act as a catalyst for consolidation, affecting interactions between mPFC, MTL, and other neocortical regions, and possibly increasing the likelihood or effectiveness of replay of congruent information [110,112].

A schema can also influence processes occurring during initial acquisition. For example, functional imaging showed increased activity in mPFC for more versus less congruent information immediately after encoding in rodents [54] (Figure 1C) and increased MTL-mPFC coupling in humans, for less congruent information

Box 2: Novelty and prediction error

Novelty has long been suspected as an important factor in learning [19]. For example, people are often better able to remember an item that deviated from its prevailing context [264]. Conversely, there would seem little (e.g., metabolic) sense in the brain encoding information that is already fully predicted. For example, there is no need to encode the presence of your BathToy each time you enter your Bathroom (Figure 2A), assuming you always find it there. This is consistent with so-called predictive coding models of memory [26,98], where the key factor driving learning is the amount of prediction error (PE). Clearly, schemas still play an essential role, in that the predictions are based on such knowledge. This perspective seems to entail greater learning for incongruent than congruent information though; the opposite of schema theories (Box 1). However, the precise predictions depend on the nature of the learned information, and how it is subsequently retrieved, as expanded below.

From a Bayesian perspective, PE can be viewed as the divergence between prior and likelihood probability distributions. Thus, a familiar location would establish prior probabilities over the objects one expects to encounter there, while the (noisy) sensory input would provide the likelihood that certain objects are in fact present (Figure I). If one encounters a novel object in a novel location, such that both the likelihood and prior distributions are imprecise (flat), PE will be low (FigureIA), at least relative to a familiar object in a novel location (FigureIB). Thus maximal overall novelty does not necessarily entail maximal learning; indeed, novel stimuli are often less well associated with unpredictive contexts than are familiar stimuli [265].

Alternatively, when a familiar object (e.g, Cake) occurs unexpectedly in a familiar context (e.g, Bathroom) PE will be high (FigureIC). This situation corresponds to a maximal match-mismatch [97], where an initial match (recognition of a BathRoom) does not match other information (the Cake). High PE results in substantial learning, i.e. updating of the prior distribution to more closely match the posterior distribution. This can improve subsequent episodic recognition of the object, by virtue of reactivating a distinctive context (Bathroom) when that object is repeated [98,265]. However, memory will not always be improved: if cued with the location instead, the overlap between the new predictions (updated prior) and the object representation still may not be sufficient for the Cake to be recalled. This contrasts with finding a PlasticDuck in your BathRoom (Figure ID), where PE will be low (assuming PlasticDucks and

during encoding, related to strength of schema [143] (Figure 1D). These results are consistent with a large body of evidence that MTL-mPFC interactions, along with activity in other brain regions [132,235,236], are important for successful encoding and retrieval [51,62,64,66,177,237]. They are also consistent with more general claims that the mPFC is important for making online predictions (e.g, during perception [27,154]), enabled by schemas, whereas the MTL is important for detecting the type of novelty [97,238,239] associated with an incongruent schema (see Box 2).

While there is much debate about whether patients with MTL damage can form new memories [78], and in many situations they appear unable (anterograde amnesia), they can still show a congruency benefit [70], and there are certain situations where they appear able to learn new information [77,87,240-243]; situations possibly related to the existence of schemas. In particular, recent data have suggested that such patients can learn some information as well as

BathToys have similar representations), but the updated prior for your Bathroom will overlap with the PlasticDuck-representation, allowing it to be recalled. Thus, though incongruent information may produce greatest PE, the accuracy of subsequent retrieval of that information will depend on how it is cued. This may be one reason why an additional system (e.g, in the MTL) is needed to store incongruent instances, in case they recur and become important for extracting new schemas (see main text).

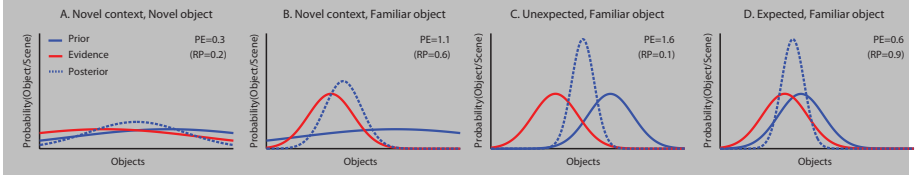

Figure I: Bayesian perspective on prediction-error driven learning (see [98]). The curves represent probability distributions, e.g. over a dimension of objects (ordered by similarity). The red line represents the likelihood of an object being present, given (bottom-up, noisy) sensory evidence; the solid blue line represents the prior distribution, given (top-down) predictions from the current context (e.g, location in the environment); the dotted blue line represents the posterior probability of objects being present (and resembles the updated priors that would result from the learning experience). PE refers to the prediction error – the divergence between prior and likelihood distributions – while RP refers to recall prospect – proportional to the posterior probability (from updated priors) of retrieving the object when cueing with the previous context (both PE and RP have arbitrary units). Panel A corresponds to a novel object in a novel context, with flat (imprecise) prior and likelihood (akin to the new sequence condition of [97], source memory for unfamiliar proverbs of [265], and unrelated case in the main text). Though maximally novel overall, PE is relatively low and little can be learned. Panel B corresponds to a familiar object in a novel context (akin to the familiar proverbs of [265]), where PE is increased relative to A. Panel C corresponds to a familiar object that is not expected in a familiar context, giving highest PE (akin to the changed condition of [97] and incongruent case in main text). Because of the residual divergence between posterior and likelihood distributions however, RP is lower than in Panel D, which corresponds to a familiar object that is expected in a familiar context (akin to the old sequence condition of [97], and the congruent condition in main text). This has low PE, but high RP, given high overlap between posterior and likelihood distributions.

controls [220,224,245] – so-called fast (cortical) mapping [39] – which may relate to schemas (see below). Damage to the mPFC, on the other hand, has been associated with reduced ability to filter and integrate incoming information, resulting in confabulation [73], a lack of a congruency benefit [70] and more errors during retrieval [74], which may reflect an inability to utilise schema (see Box 1, though see also [76]). These observations, along with lesion data in rodents [246], suggest that memories mediated by MTL and mPFC might be different in nature, ranging from more detailed, episodic memories (instances) supported by MTL, to more general, semantic (schematic) memories integrated by mPFC, as expanded below.

Memory for incongruent (novel) information can also be enhanced (Box 2). This novelty advantage has been associated with greater MTL-activity during encoding [96,216,247-249]. Moreover, the precise type of novelty is likely to be important [97], for example whether information is novel because it is

incongruent with an existing schema, or because it is unrelated to any existing schemas. Here we focus on enhanced memory owing to the former kind of novelty (or "prediction error"; Box 2), though the latter type of novelty (such as a completely new environment for a rodent [250]), might also improve memory through other means, such as arousal, reward and dopamine release [251,252]. While the role of novelty has been acknowledged by some schema theorists (e.g, in terms of schemas being used to direct attention to novel aspects of an experience [12]), there is no clear consensus, at least within neuroscientific theories, about the precise conditions under which memory is superior for congruent or incongruent information. Below, we outline a framework termed SLIMM (Schema-Linked Interactions between Medial-prefrontal and Medial-temporal regions) that appeals to two complementary modes for learning new information, determined by MTL-mPFC interactions, in order to reconcile the facilitatory effects of schema and novelty on memory.

A new framework relating schema and novelty to memory

SLIMM extends standard consolidation theory, in terms of a time-dependent shift from MTL to neocortical representations, by adding a third component – the mPFC – that acts to accelerate direct neocortical learning independent of the MTL. Within SLIMM, the main function of the mPFC is to detect the congruency of new information with existing information in neocortex, which we term resonance (akin to Adaptive Resonance Theory (ART) [253]), in the sense that congruent information resonates with existing information. Greater resonance leads to greater mPFC activity, which in turn is assumed to potentiate direct connections between neocortical representations (e.g, through phase synchronization [254]). Note that these are the same connections assumed to be more gradually strengthened in the absence of such mPFC input, as in standard consolidation theory; the mPFC thus enables faster neocortical learning [220]. Importantly, mPFC is assumed to have a reciprocal relationship with MTL, such that mPFC activity inhibits MTL activity (as reviewed in [255,256]). This relates to the assumption that MTL automatically captures new experiences [257], except, according to SLIMM, when inhibition from mPFC means that the new information can be related via a schema. Only when there is low resonance (or high prediction error, see Box 2), as occurs for incongruent information, the MTL will bind those elements into an instance (e.g, via a unique index in hippocampus, given its pattern separation capability [221]).

Encoding

For example, imagine that you encounter a model duck (PlasticDuck) in your

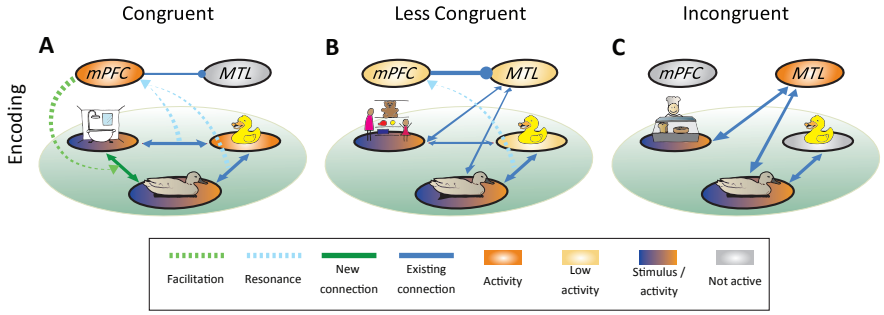

Figure 2: Schematic depiction of the SLIMM model during encoding. Interactions between the mPFC, MTL and neocortical (indicated by the grey-green plan1e during encoding of associations between a familiar object (PlasticDuck) and a familiar environment, which is either (A) a BathRoom, providing a congruent schema by virtue of a similar BathToy that one keeps there, (B) a ToyShop, for which the schema is less congruent, in that a BathToy is only loosely related, or (C) a Bakery, in which a BathToy is not part of the schema. In the Congruent case (A), the neocortical representations of PlasticDuck and BathRoom are activated by their perception, and the BathToy is activated by its existing associations to both. The mPFC is activated by the resonance (synchronous co-activity) of these representations, and therefore potentiates neocortical connections between all of them, resulting in a new direct connection between PlasticDuck- and BathRoom-representations (while other connections in the schema may have already asymptoted at maximal strength). The mPFC additionally inhibits the MTL (indicated with the vertical arrowhead). In the incongruent case (C), the lack of resonance between activated neocortical representations means that mPFC is not activated, MTL is not inhibited, and the new association between the PlasticDuck and Bakery is stored instead via a separate instance in MTL. In the less congruent case (B), where there is only a weak connection between BathToy- and ToyShop-representations (indicated by a less strong arrow), there is only partial activation of the BathToy-representation, hence partial resonance, and greater inhibition from mPFC to MTL is required to resolve this intermediate state. Hence, memory encoding is less effective.

bathroom (Figure 2A); a duck that resembles your favourite rubber bath duck (BathToy), but that has not been encountered in your bathroom before. According to SLIMM, your memory for this new (congruent) pairing of the PlasticDuck and BathRoom is likely to be good, because you already possess an association between the BathToy and PlasticDuck and between the BathToy and BathRoom (the schema), to which the new PlasticDuck can be related. The simultaneous perception of PlasticDuck and BathRoom activates their corresponding neocortical representations, and this activity spreads to other strongly connected neocortical representations, such as the BathToy, owing to previously learned associations. These strong connections mean that the BathToy-, BathRoom-, and PlasticDuck-representations resonate (e.g, via synchronous oscillations [258]). This resonance is detected by the mPFC [52,54], which then potentiates the strengthening of neocortical connections between the resonating representations, leading specifically to fast learning of a new, direct connection between BathRoom and PlasticDuck (i.e., good learning). The high activity in mPFC also inhibits activity in MTL [143], such that no indirect

association is made between PlasticDuck and BathRoom via a new MTL-instance.

Conversely, the same PlasticDuck encountered in a Bakery (Figure 2C) will produce a strong novelty effect (prediction error; Box 2), because such objects are not normally expected there. In this (incongruent) case, SLIMM predicts that you are also likely to remember the pairing of the PlasticDuck and Bakery, but for a different reason. The lack of any strong pre-existing connections, direct or indirect, between PlasticDuck- and Bakery-representations leads to little resonance in the neocortical network. Thus mPFC is not activated, MTL is not inhibited, and the MTL serves to bind the active representations of the PlasticDuck and Bakery via a new instance. This leads to good (episodic) encoding [54], that is sensitive to MTL disruption [70,87,220].

Finally, if you encounter the PlasticDuck in a ToyShop (Figure 2B), assumed to be only loosely related to the BathToy (less congruent), neither a specific schema nor a prediction error is likely to be evoked strongly, and memory for that encounter is predicted to be poor. This is because there is weak resonance, requiring increased MTL-mPFC interactions in order to resolve, as both try to encode the memory [143]. Consequently, neither is strongly activated, and there is neither good schematic (mPFC-mediated) nor good instance (MTL-mediated) encoding, leading to poor memory.

Retrieval before consolidation

Imagine walking back into the BathRoom shortly after encoding the congruent case. Activation of the BathRoom-representation will lead to processes similar to those at encoding, i.e., reactivation of BathToy (schema) and hence PlasticDuck-representations, resonance, mPFC activation and further strengthening of the direct neocortical connection between PlasticDuck and BathRoom. Note that concurrent activation of other elements of the schema (e.g, BathToy) can explain the bias towards remembering schematic aspects of the PlasticDuck. Similar processes are assumed to happen during replay, when the BathRoom-representation is reactivated by internal processes, rather than by sensory input [110].

In the incongruent case, walking into the Bakery leads to retrieval of an instance from the MTL, which entails reactivation of not only of the PlasticDuck-representation, but also of other incidental (episodic) representations that were present at encoding (see below and Figure 3D). Walking into the ToyShop, on the other hand, only leads to weak reactivation of the PlasticDuck, given only weak neocortical connections and low likelihood of the MTL having encoded an instance. Note however that if the PlasticDuck and ToyShop are repeatedly experienced together, the gradual strengthening of neocortical-neocortical connections can eventually lead to effective storage in long-term memory (see

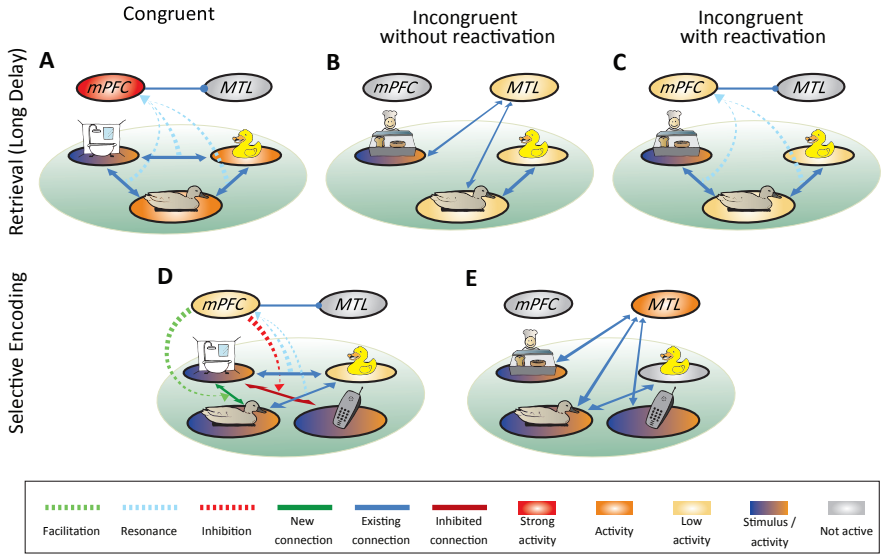

Figure 3: Schematic depiction of the SLIMM model during memory retrieval (A-C) and selective encoding (D, E). Panels A-C show mPFC, MTL and neocortical interactions during retrieval of associated objects after consolidation, when cued by perception of the familiar BathRoom (A), or Bakery (B and C), from Figure 2. In the congruent case (A), the PlasticDuck is likely to be recalled owing to high activity of its representation following activation spread from the BathRoom (and indirectly from the BathToy) representation. In one "incongruent" case (B), recall of the PlasticDuck can occur through retrieval of the MTL-instance (episodic recall), though this may be rare (see text). Alternatively, if there have been repeated reactivations of the PlasticDuck- and Bakery-representations during the delay (C), for example by their repeated co-occurrence in the environment, recall of the PlasticDuck can occur owing to a direct connection from the Bakery-representation (i.e.. the PlasticDuck has now become part of the Bakery schema). Panels D-E illustrate how associations with incidental, unrelated events (e.g, one's mobile phone ringing) are suppressed when not consistent with the dominant (eg. BathRoom) schema in the congruent case (D), hence not well encoded, unlike in the incongruent case (E), when all activated representations are bound into the same instance, encoded by the MTL.

next section), as in standard consolidation theory.

Retrieval after consolidation

After a longer delay, the outcome depends on whether consolidation has occurred, i.e, whether there has been repeated reactivation of the critical representations, either by re-exposure to both, or by offline replay. Such reactivation is particularly likely for the congruent case, resulting in the connection between the PlasticDuck- and BathRoom-representations asymptoting (Figure 3A). In this case, cueing with the Bathroom still activates mPFC through resonance [54,57,164], but since no further neocortical strengthening is needed, mPFC is not necessary for retrieval.

For the incongruent case, there are two possibilities. If the PlasticDuck and Bakery have been repeatedly reactivated (Figure 3C), multiple instances will

be encoded by the MTL (in addition to gradual cortical learning). The greater number of such MTL-instances also increases the likelihood of offline reactivation of these representations, allowing commonalities across instances to effectively be extracted by gradual learning (e.g., as in [25,110]). Thus eventually the PlasticDuck is no longer incongruent, but has become part of the Bakery schema. However, even if the PlasticDuck and Bakery have not been reactivated, such that no direct neocortical-neocortical connection exists (Figure 3B), retrieval of the PlasticDuck can still occur after a long delay, via retrieval of the MTL-instance. Though not predicted by standard consolidation theory, this possibility is consistent with other theories and evidence that some remote episodic memories are MTL-dependent [38,55].

Selective encoding and interference

If memories can be retrieved via indices within the MTL system, as in Figure 3C, why is an additional mPFC system needed? Our proposal is that an additional learning system is necessary to overcome the high levels of interference resulting from multiple MTL-instances sharing common elements. The function of the mPFC is then to select the most relevant elements of an experience (those congruent with existing schema), during both encoding and retrieval. Thus the mPFC not only detects resonance, but also amplifies activity in congruent representations by additionally suppressing activity in representations inconsistent with the dominant schema (possibly through an attractor-type mechanism [259]). Imagine for example that, while encountering the PlasticDuck in one's BathRoom, one's mobile phone rings (Figure 3D). Because telephone calls are not particularly related to the BathRoom schema, any connections between the MobilePhone-representation and the other active representations are de-potentiated (Figure 3D). In this way, only information that is related to the dominant (active) schema is effectively selected for direct neocortical learning. This automatic highlighting of schema-relevant information is likely to maximise the efficiency of learning new information [260]. In contrast, when experiencing the PlasticDuck and MobilePhone call in the Bakery, where there is no dominant schema activated (Figure 3E); all of these elements are bound into a single instance by the MTL (i.e, incidental, episodic details, such as the phone call, are better remembered in the incongruent case). This mPFC-amplification is also important for reducing interference during retrieval, by focusing on representations congruent with existing knowledge. This might explain why patients with mPFC-lesions often confabulate, retrieving semantic or episodic information not directly relevant to the retrieval cue [73].

Predictions of SLIMM

SLIMM provides several predictions for future experiments, both for healthy subjects, and for subjects with MTL or mPFC damage. Foremost, it predicts that memory performance in healthy subjects can be a non-linear function of congruency, with better (schematic) memory for congruent items (mediated by mPFC), and better (instance) memory for incongruent items (mediated by MTL). However, because the nature of the memories underlying performance at either end of this congruency dimension differs, the precise shape of this function will depend on the nature of the retrieval test. Free recall or cued recall, for example, may show only an advantage for congruent items (particularly if a generate-and-recognise strategy is used; see Box 1), whereas tests of incidental episodic detail (unrelated to a schema), such as recognition or source memory tests, may show an advantage for incongruent items.

For future neuroimaging experiments, the framework predicts that MTL and mPFC will show differential activity patterns and functional coupling (both between each other and with neocortical regions representing components of the memory) as a function of congruency, during encoding, offline replay, and retrieval. During encoding and replay, mPFC-activity is predicted to increase with congruency, MTL-activity is predicted to decrease with congruency, while mPFC-MTL coupling is predicted to be maximal for partially congruent conditions, when mPFC and MTL are both partially activated (Figure 2B). After consolidation, initially incongruent information will engage mPFC (since it has effectively become incorporated in the schema), while successful retrieval of unconsolidated incongruent information will still engage MTL (Figure 3).

Damage to either the mPFC or the MTL is expected to disrupt the balance between the two types of learning described above. Selective MTL-damage is predicted to disrupt episodic encoding, and produce complete retrograde amnesia for instances [38], along with temporally-graded retrograde amnesia sparing those memories that have already been consolidated [40]. However, the still-functioning mPFC will continue to encode information congruent with prior knowledge (producing congruency effects [70]), via strengthening neocortical connections between novel information and existing schemas. Conversely, mPFC-damage will disrupt schematic encoding of information, and hence lead to an absence of a congruency effect, as all memories will be stored as instances by the MTL. This will result in difficulties integrating new information into a schema, and increased interference during retrieval of information (confabulation). For information acquired shortly before the mPFC-lesion (recent memories), there will still be a congruency effect, since congruent information has been consolidated into neocortical networks in an accelerated manner relative to

Box 3: Outstanding questions

- How precisely does the mPFC detect resonance, amplify congruent representations and suppress less congruent representations? How does it then potentiate synaptic changes between resonating neocortical representations (e.g, in terms of synaptic tagging or neurotransmitters)?
- How precisely do the mPFC and the hippocampus interact: does the mPFC only inhibit the MTL, or is there mutual competition? Do they interact differently during online experience and during offline replay (when instances may be retrieved from MTL)?
- Why do temporary lesions of the hippocampus impair encoding of schema-congruent information [266]? Does this happen only when the schemas are spatial, given evidence that hippocampus also represents spatial information in the rodent?
- How does the role of MTL in SLIMM relate to other theories of MTL function, such as scene construction [267], and future simulation [268]? Is reconsolidation related to integration of new information into schemas, and will blocking of reconsolidation thus also affect schema-related memories? [111]
- Do different subparts of the mPFC have different functions? And how are the mPFC subparts in the rodent related to those in human mPFC?
- What are the precise memory deficits following mPFC-lesions, e.g, in terms of interference, transient retrograde amnesia (for congruent information), and possibly even encoding of greater episodic detail than in controls?
- How do the effects of schemas vary across development? For example, given the relatively slow maturation of PFC, relative to other brain regions [269], does the ability to use schema change from childhood to early adulthood? And does healthy ageing reduce the mPFC efficiency in learning new schema-congruent information?
- How are more complex/structured schema represented in the brain, and how can their formation be manipulated (both during encoding, consolidation, and retrieval) to optimize learning and education?

incongruent information. However, there may be a brief period of retrograde amnesia for highly congruent information acquired very shortly before the mPFC-lesion, when no instances were likely to be encoded and consolidation has not yet occurred. For more remote memories already consolidated in neocortex, the mPFC-lesion should have no effect (unlike, for example, damage to anterior, lateral temporal lobes [88]); nor should mPFC-lesions affect long-term instances still indexed by the intact MTL. In sum, MTL and mPFC-lesions will produce specific problems encoding new instance versus schematic memories respectively, and differential retrograde amnesia gradients for recent and remote memories, as a function of congruency.

Conclusions and future directions

Our aim has been to integrate research and theories on schema, novelty, and the contributions of the MTL and mPFC to memory formation, within a single framework (SLIMM). SLIMM is broadly consistent with a number of other consolidation theories [38,92,111], but makes the role of schema, mPFC and mPFC-MTL interactions more explicit. We accept that the framework is simplistic (eg. when assuming mechanisms that are not yet fully empirically tested, such

as resonance detection by mPFC), and faces problems with some existing data (see Box 3). Nonetheless, at a minimum, SLIMM should help to better understand and inter-relate previous, sometimes paradoxical, findings in the neuroscientific and psychological literature. We hope it will also prompt future behavioural, neuroimaging and lesion studies that test the predictions outlined above. We believe that these developments will be of fundamental importance for optimising life-long learning and education, and for treating learning and memory disorders.

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Chapter 8

How to achieve synergy between medical education and cognitive neuroscience? An exercise on prior knowledge in understanding

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Abstract

A major challenge in contemporary research is how to connect medical education and cognitive neuroscience and achieve synergy between these domains. Based on this starting point we discuss how this may result in a common language about learning, more educationally-focused scientific inquiry, and multidisciplinary research projects. As the topic of prior knowledge in understanding plays a strategic role in both medical education and cognitive neuroscience it is used as a central element in our discussion. A critical condition for the acquisition of new knowledge is the existence of prior knowledge, which can be built in a mental model or schema. Formation of schemas is a central event in student-centered active learning, by which mental models are constructed and reconstructed. These theoretical considerations from cognitive psychology foster scientific discussions that may lead to salient issues and questions for research with cognitive neuroscience. Cognitive neuroscience attempts to understand how knowledge, insight and experience are established in the brain and to clarify their neural correlates. Recently, evidence has been obtained that new information processed by the hippocampus can be consolidated into a stable, neocortical network more rapidly if this new information fits readily into a schema. Opportunities for medical education and medical education research can be created in a fruitful dialogue within an educational multidisciplinary platform. In this synergetic setting many questions can be raised by educational scholars interested in evidence-based education that may be highly relevant for integrative research and the further development of medical education.

Introduction

Cognitive neuroscience attempts to understand how knowledge, insight and experience are processed in the brain and to clarify their neural correlates as demonstrated by various electrophysiological and imaging techniques [270]. There are many reasons why cognitive neuroscience should convey important information to and interact with education (TLRP Commentary 2008, www.tlrp.org). First of all, the brain is the principal organ involved in learning. Secondly, improving education, especially in children, is a priority in many countries. Thirdly, increased knowledge of brain function can inform and improve educational practice. Fourthly, neuroscience is rapidly progressing which is accompanied by a great momentum. Fifthly, and quite relevant, a scientifically based approach may prevent the introduction of questionable educational practices in the classroom (TLRP Commentary 2008). Sixtly, a multimedia revolution is going on that will enable further probing and promoting of a broad spectrum of human learning [271]. Seventhly, a new generation of learners is emerging that should survive the technological alterations of the modern mind [272]. In light of this overwhelming rationale it is paradoxical that cognitive neuroscience so far has had only limited influence on education, let alone medical education. A plausible explanation for this phenomenon is the presence of gaps between cognitive neuroscience and education. A major challenge therefore is how to fill these gaps and achieve synergy between medical education and cognitive neuroscience.

During the past 30 years fruitful interaction between education and cognitive neuroscience has been hampered by the presence of gaps. Bruer, only a decade ago even stated that this interaction was a bridge too far [273]. From the relevant literature [274,275] two gaps emerge, i.e. one between (cognitive) neuroscience and education, and another between practice of education and educational research. The first gap mentioned is based on different levels of abstraction between (cognitive) neuroscience and education, and epistemical differences between explanation theories and action theories. The latter represents the contrast between basic science on the one hand and practicing science on the other hand [275]. These involve *scientific* concerns, i.e. in-principle differences in methods, data, theory, and philosophy [274]. Another set of concerns is *pragmatic*, i.e. consideration of costs, timing, locus of control, and likely payoffs [274]. Furthermore, over-simplification of findings from neuroscience, over-interpretation their outcome and premature introduction into the classroom have given rise to so called “neuromyths” that subsequently yielded an adverse effect on the interaction between cognitive neuroscience and education [270,276]. Despite the presence of these obstacles several prominent researchers, both from cognitive neuroscience and education, currently believe that bridging the gaps is

possible, leading to a fruitful mutual interaction, i.e. synergy [136,270,274-276].

Recently a number of constructive approaches has been proposed in order to be able to bridge the gaps mentioned. As the gaps include scientific and pragmatic aspects, successful bridging involves a complex and multi-step approach. According to Ansari and Coch [136] a concerted effort is needed to think about the goals and benefits of connecting education and cognitive neuroscience. This is currently undertaken in the new field of mind, brain, and education (MBE), that should provide realistic information about the potential outcomes of interactions between cognitive neuroscience and education [136]. Coch and Ansari strongly propose to train teachers in neuroscience and to train cognitive neuroscientists in basis educational theory and methodology in order to reach a proper integrative approach [136]. Mason advocates bridging, at least as the first step, by educational psychology [277]. Hereby a two-way path is foreseen in which educational psychologists are the integrative scholars as indicated by Coch and Ansari [136]. In this two-way path the initiating role of educationalists should be strong, raising salient issues and questions for neuroscientific research [278]. It was even suggested by Greenwood and Meltzoff et al that educators, together with those working in other disciplines, develop the science of teaching, or the new science of learning, respectively [137,279]. The new science of learning arises from several disciplines, i.e. developmental psychology, machine learning, neuroscience and education and it has great promise for transforming educational practices [137]. This proposal is in line with the earlier mentioned new field of MBE and educational psychology, but it is more comprehensive and ambitious. In order to further elucidate the potential benefits of this integrative approach two considerations are important [280]. Firstly, it should be explored how educational principles, mechanisms, and theories could be extended or refined based on findings from cognitive neuroscience. Secondly, it should be explored which neuroscience principles, mechanisms, or theories may have implications for educational research and could lead to new interdisciplinary research ventures. A recent report on explorations in learning and the brain [280] concludes that a) the time has come to design new types of research that will provide us with adequately detailed and applicable guidelines for educational design based on neuroscientific data, and b) a starting point is given for an agenda for educational science research that incorporates neuroscientific theories and techniques. Fruits of a constructive dialogue between cognitive neuroscience and education include a common language and understanding about learning, more educationally-focused scientific inquiry, and multidisciplinary research projects (TLRP Commentary 2008).

Much of the foregoing considerations on education can be directly translated to medical education. Medical education beside it has its own dimensions

such as particular educational characteristics, preclinical and clinical learning environments, a culture (attitude) of strong commitment, and organizational dynamics and constraints [281-285]. In addition, since medical neuroscience (e.g. neuroanatomy, neurophysiology, clinical neurology, medical psychology) is an important part of the medical curriculum many opportunities for interactions with medical education are available, as noted earlier by other authors [286]. Highly interesting research topics from a view point of medical education, that also could have relevance for implementation in educational practice, include the importance and mechanisms of prior knowledge for learning, the effects and mechanisms of multimodal learning, the effects and mechanisms of learning metacognitive and regulative skills, and the optimal development of expert know-how [280]. As the focus of this paper is on the question how to achieve synergy between medical education and cognitive neuroscience we would like to give an in-depth discussion on only a few of the previously mentioned research topics as an example and not present a more global discussion on several topics. For this purpose we have chosen the topic of the importance and mechanisms of prior knowledge for understanding, based on its great promises for medical education and medical education research [161,282], and our own current research interest [57,129,143]. We first will discuss basic aspects of prior knowledge from cognitive psychology, subsequently make a translation to cognitive neuroscience, followed by a discussion on the opportunities for medical education and medical education research. Finally our conclusions and recommendations how to stimulate the synergy between medical education and cognitive neuroscience in a broader perspective are presented.

Insights from cognitive psychology on prior knowledge in understanding

A critical condition for the acquisition of new knowledge is the existence of previously acquired relevant knowledge, i.e. of a well developed mental model or *schema* [6,12]. The term schema is most often used to refer to the general knowledge a person possesses about a particular domain. Weaving the strands of information into a coherent schema will facilitate students' understandings of content [287]. A schema allows for the encoding, storage, and retrieval of information related to that domain [12]. Alba and Hasher propose a modal theory by which schema-driven encoding of complex information is characterized by four basic processes: selection and reconstruction, abstraction, interpretation, and integration [12]. They consider reconstruction as the central retrieval process of schema theory, and reduction of the amount of information as an important element, but recognize that memory representation is far richer and

detailed than schema theory would suggest. Based on recent social and cultural perspectives McVee et al have revisited schema theory and as a result thereof consider schemas as transactional and embodied constructs [13]. They view schema and other cognitive processes or structures as embodied, i.e. who we are as biological beings determines our sensorial interactions with the world and thus the nature of the representations we construct. Further, they consider knowledge to be situated in the transaction between world and individual. Finally, according to these authors these transactions are mediated by culturally and socially enacted practices carried out through material and ideal artifacts. Following their interpretation, a schema therefore has an embodied, transactional and cultural nature. This interpretation has implications for the definition, the formation, the processing, and transformation of schemas [13]. Formation of schemas is a central event in student-centered active learning, by which mental models are built of whatever is being learned, consciously and deliberately testing those models to determine whether they work, and then repairing those models that appear to be faulty [282,288]. Students learning in this way are more likely to be achieving meaningful learning. Michael has presented evidence supporting active meaningful learning that includes: a) Learning involves the active construction of meaning by the learner, b) Learning facts and learning how to do something are two different processes, and, c) Some things that are learned are specific to the domain or context in which they were learned, whereas other things are more readily transferred to other domains [282]. This elaboration by active learning opens up the possibility for reflection and better understanding [161].

These insights from cognitive psychology on prior knowledge in understanding have relevance for the education process, as they can inform educators about best teaching and learning practices and their impact on the evaluation process [161,288]. Teaching of science implies a task of understanding how things work [141]. Testing of conceptual understanding will require deeper forms of assessment than those used in traditional evaluations. The above mentioned insights also involve student learning, performance and professional competence, as well as recommendations for reform of medical curricula [161]. Student learning of science involve changing one's mental model or schema how something works, which involves a conceptual change [289]. A mental model or schema is a cognitive representation of the functional parts of a system and the cause-and-effect relations showing how a change in the state of one part affects a change in the next one [290]. According to Mayer three important steps in conceptual change are: a) Recognizing an anomaly, realizing that one's current mental model is not able to explain the facts observed, b) Constructing a new model, that can explain the facts, and c) Using a new model, that makes and tests predictions of the model in new situations [141]. Interestingly, each step can be

used as a starting point for teaching and learning: a) Confronting misconceptions, b) Providing a concrete analogy, and c) How to test hypotheses, respectively [141]. All of the above considerations are based on facts and insights from research in cognitive psychology that is shifting its focus from decontextualized sterile laboratory tasks to contextualized realistic tasks [141]. So, teachers should be more aware of what students learn and how they learn [282,291-293].

These are goals of *evidence-based education*, a recent intention promoted by, amongst others, the European Commission (Council of the European Union 2007). Evidence-based education tries to bridge the gap between the practice of learning on the one hand, and the development of learning and educational research on the other hand [294,295]. In order to implement these goals it has, for example, been advised to: a) Review how educational professionals, both practitioners and policy-makers, mediate and apply knowledge in their daily work, b) Promote a positive culture of evaluation that improves the connection between learning objectives and educational practices; and c) Share new ways of improving accessibility of all types of evidence, so that they inform research, policy and practice (Council of the European Union 2007). In the practice and research of medical education several of these recommendations have already been implemented as a result of fruitful collaborative efforts such as Best Evidence Medical Practice, which have most probably promoted excellence in medical teaching [296]. This will be discussed later.

From the scientific platform created by cognitive psychology and educational psychology including evidence-based education we now will engage in an overture for the translation to cognitive neuroscience. Following the ongoing line of reasoning we will focus on the importance and mechanisms of prior knowledge in understanding. We will try to disentangle various aspects of prior knowledge that could be used as individual components subject to behavioral studies. Results from the behavioral studies subsequently could serve as a starting point for cognitive neuroscientific research, which illustrates the multi-step approach in bridging the gaps between medical education and cognitive neuroscience (see Figure 1). The aspects of prior knowledge to be discussed are selected for their potential relevance in medical education. For medical education, two types of learning in which the importance of prior knowledge is expressed, are multisensory learning [293] and the acquisition of expertise [286]. These types now will be discussed in more detail.

Meaningful learning occurs when a learner selects relevant material from an array of information, organizes it into a coherent representation in a limited capacity working memory, and integrates it with existing knowledge in long-term memory [288,297]. These steps are involved in multimedia learning in which multiple modality information is presented [297]. Multiple mental

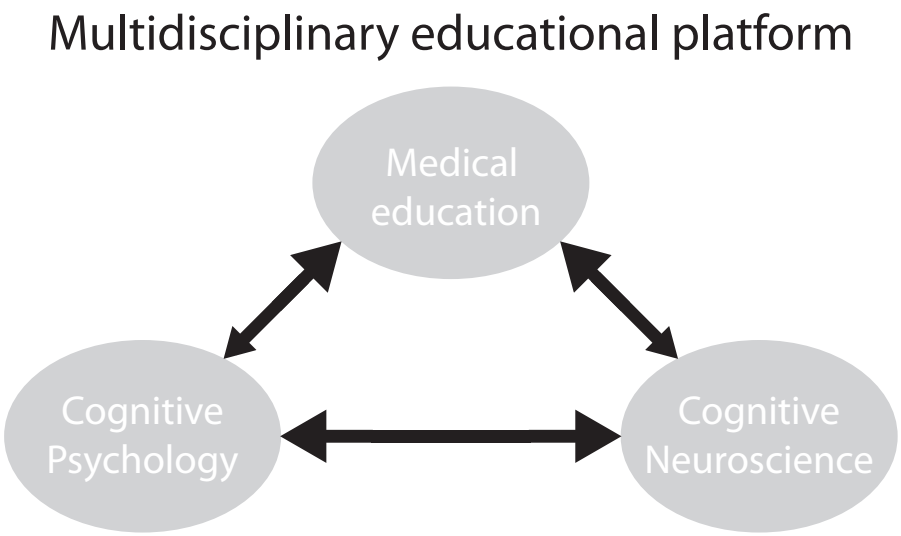

Figure 1: Synergy between Medical Education and Cognitive Neuroscience can be achieved by creating a multidisciplinary educational platform, in which Cognitive Psychology is included.

representations can enhance problem-solving abilities, completing each other, resulting in a more authentic portrayal of a problem than any single source of unimodal information [298]. In line with this, Lasry and Aulls propose a theoretical model of multiple internal mental representations, which they name n-coding [160].The n-coding construct is developed to demonstrate the independence of information processed along different modalities such as verbal, visual, kinesthetic, logico-mathematical, and social modalities. The authors have shown that the construct is useful in designing context-rich environments and can be used to increase learning gains in problem solving, conceptual knowledge, and concept confidence. In addition, it is useful in guiding which additional dimensions in the learning environment need to be attended [160].In the rich learning environment in medical education multimodal learning certainly is present. Therefore, a proper insight of the various modalities to meaningful learning in terms of their quality, quantity and sequence (timing) is important. In such a setting, a previous representation would act as prior knowledge for subsequent representations. Multisensory-training protocols, as opposed to unisensory protocols, can better approximate natural settings and therefore, produce greater and more efficient learning [144]. However, the extent to which this facilitation occurs depends on appropriate relations, i.e. congruency, between the information coming into each of the senses. Congruency of new information with prior knowledge can be interpreted as a fit with a schema. More research on multisensory learning paradigms is needed to better understand

the mechanisms and processes of learning within natural settings. This also includes the better understanding of the modality effect, the educational practice of presenting to-be-learned graphical information visually, and related textual information through an auditory mode [299]. Especially relevant to medical education is multisensory learning through visual and tactile stimuli in order to develop three-dimensional insight of human anatomical structures, and haptic competences for surgical interventions [300,301].

Experts are often able to recognize the key features of a problem rapidly, mainly using perceptual cues. This perceptual expertise enables them to be highly selective in their search and to solve routine problems without exploring many alternatives [302]. It takes a long time of intense dedication to become an expert- at least ten years in many domains-, including medical specialization and subspecialization [286]. Remarkably, transfer seems to be minimal from one domain of expertise to another. In the development of expert competences schemas are acquired incrementally and automatically [302]. Gobet and Simon have described a computational model providing a mechanisms explaining how schemas are created in this situation [303]. A schema or template is created if a node meets specific criteria related to its connectivity with other nodes in the discrimination network. They are created in situations where the context presents both constant and variable information. An important consequence for education is that without variation of chunks and links connecting them, schemas cannot be created [302]. Further implications for education are the difficulty of transferring knowledge from one domain to another, the effect that curriculum sequence may have on learning, the conditions best suited for the acquisition of schemas, and a computational definition for the difficult notion of conceptual understanding. These theoretical considerations from cognitive psychology, as already promoted by Regehr and Norman, foster scientific discussions that may lead to salient issues and questions for research in cognitive neuroscience [288].

Translation to cognitive neuroscience

In order to understand processing in the brain and their neural correlates it is important to acquire some of the theoretical background on learning and memory. Miyashita in an excellent review has described the cellular and network machineries of cognitive memory in the brain and their top-down control [83]. The types of explicit memory identified in humans and in animals studied are episodic (event) memory and semantic (fact) memory. The cognitive memory system is composed of three major subsystems, i.e. the medial temporal lobe, the temporal cortex, and the frontal cortex. The medial temporal lobe, which includes the hippocampus, plays a critical role necessary for memory storage

to take place. The hippocampus is involved in memory encoding and retrieval [44,112]. However, the ultimate storage sites for explicit memories appear to be in the neocortex [83,112]. The unique configurational association between environmental stimuli and behavioral context, which is likely the basis of episodic memory, depends on neural circuits in the medial temporal lobe. Memory traces representing repeated associations likely are the basis for semantic memory that is consolidated in domain-specific regions in the temporal cortex. These regions are reactivated during remembering and contribute to the contents of a memory. Two types of retrieval signal reach the cortical representations, one runs from the frontal cortex for active retrieval (top-down), and the other spreads backward from the medial temporal lobe for automatic retrieval. The existence of top-down signaling from the frontal cortex to the temporal cortex was directly demonstrated in monkeys [83]. The challenge is to clarify hierarchical interactions or couplings between multiple cortical areas as initially demonstrated by an effective connectivity analysis or a correlation analysis with functional Magnetic Resonance Imaging (fMRI) in humans. The fMRI technique is now discussed in more detail as it is highly instrumental in cognitive neuroscience and may be so in research on learning.

A wide range of fMRI study designs is available for research in cognitive neuroscience, as elucidated in a comprehensive review by Amaro Jr and Barker [304]. The strategy in an fMRI experiment is based on an intervention in the brain and observation of the modulation of the system response. The MRI method most often used to produce information related to brain function is called BOLD (Blood Oxygenation Level Dependent), and is based on MR images made sensitive to changes in the state of oxygenation of the hemoglobin. Areas with a high concentration of fully saturated oxygen give a higher signal than areas with a low concentration. The practical implication is that BOLD signals are an indirect measure of the increase in neuronal activity at the moment a subject performs a particular task while the person is inside the scanner. BOLD sensitivity is directly proportional to the magnetic field strength. Every one to three seconds images are made and the brain areas in which the brightness changes relative to the task can then be determined using statistical analyses. For neuroimaging other techniques such as positron emission tomography (PET) may be used but the discussion of these techniques is beyond the scope of this paper. Before embarking on neuroimaging it is important to realize whether the scientific question may or may not be suitable for this technique [304]. Therefore, ideally a working hypothesis including a neuroanatomical substrate has to be formulated, and adaptations in the cognitive task experiment have to be made that make it suitable for the neuroimaging environment. Several designs are possible of which the factorial and parametric designs are most commonly used,

both single and combined. In the first mentioned design cognitive conditions are processed in a factorial manner, thus allowing tests for interactions between each component. This technique relies upon neuropsychological evidence for precise definition of the task components, and if possible, complementary behavioral data. The principle is to have the participant perform a task when the cognitive components are intermingled in one moment, and separated in another instance of the paradigm [304]. The idea of increasing the cognitive demand associated with a particular cognitive task, without modifying its intrinsic nature is the basis of parametric design. Stimulus presentation strategies include the blocked design, the event-related design, and a mixed design. In the blocked design the stimuli of the same condition are presented subsequently, and the BOLD response represents a steady state actually composed from individual hemodynamic response functions from each stimulus, and is generally of higher magnitude. In the event-related design each stimulus hemodynamic response function(s) is detected, and can be analyzed in detail. Finally, the mixed design consists of a combination of events closely presented, intermingled with control condition providing the technical needs for analysis event-related analysis as well as cognitive state information. The various image acquisition techniques and additional computational exercises to analyze brain connectivity are beyond the scope of this paper.

Now we would like to discuss prior knowledge and learning against the background of the hippocampal-neocortical interactions theory [112,130]. This theory attempts to map existing neuropsychological ideas about the determinants of episodic memory onto the neural circuits and synaptic processes in both hippocampus and neocortex that have been identified as relevant to memory formation. It encompasses the following important elements: a) The critical role of mental models or schemas in systems consolidation, i.e. consolidation of memory traces in the neocortex, and b) Memory updating as a key factor for memory consolidation in the hippocampus. Based on elegant studies in rats Tse et al found that prior knowledge on the correct location in a so called complex event arena plays a causal role in system consolidation [131]. They also showed that system consolidation using a schema based on prior knowledge occurs rapidly, i.e. within 48 hours in this study. This contrasts with the previously widely accepted opinion that it takes a long time before intercortical connections become strong enough to support unaided memory retrieval. The crucial new insight from these results is that new information processed by the hippocampus can be consolidated into the cortex more rapidly if this new information is relevant to prior knowledge, i.e. a schema in which the new information can be assimilated [131]. This implies that the hippocampus is only required for rapidly updating any new event in relation to these schemas [112]. This updating may

occur through memory reconsolidation, i.e. the process by which the act of memory retrieval appears to destabilize previously stored memory traces and thereby enable them to be strengthened or to incorporate new information [112].

Reports of multisensory interactions in various perceptual tasks and settings indicate that these interactions are the rule rather than the exception in human processing of sensory information [305]. There exists a rapidly growing literature of the neuroanatomical, electrophysiological and neuroimaging studies that show that multisensory interactions can occur throughout processing [306]. According to Shams and Seitz multisensory facilitation of unisensory learning occurs, based on the observation that the learning advantage of auditory-visual training over visual-alone training was substantial [144]. Similar results were found by Von Kriegstein and Giraud, showing that implicit multisensory associations influence voice recognition [155]. Regarding the implications and neural mechanisms involved they state that even under conditions of unimodal sensory input, crossmodal neural circuits that have been shaped by previous associative learning become activated and underpin a performance benefit. The key difference between unisensory and multisensory training exists during encoding, whereby a larger set of processing structures are activated in the multisensory paradigms. Shams and Seitz present three possible neural mechanisms as an explanation for multisensory facilitation of unisensory learning. These mechanisms comprise of: a) Alteration of unisensory structures, b) Alteration of multisensory structures that interact directly, and c) Alteration of multisensory structures that are coordinated by a separate multisensory structure. An important aspect of multisensory facilitation of unisensory learning is that facilitation is more pronounced in the congruent condition [144]. The degree of congruency thereby is clearly relevant for learning. This means that the relationship between the stimuli that are consistent with the prior experience of the individual or the relationships between the senses found in nature is important to facilitate learning [144]. Recent results from our group [164] demonstrate that successful retrieval of congruent compared to incongruent visuo-tactile associations is related to enhanced processing in a medial prefrontal somatosensory network. This suggests optimized memory consolidation by facilitation of neocortical integration when new information fits a preexisting schema. Further research is needed to study how the integration of complex multisensory object information in the human neocortical networks takes place.

Recent studies suggest that the semantic relationship between multimodal input streams might be a relevant factor in the way different areas are recruited during multimodal integration [307]. Willems et al report that the integration of speech and co-speech gestures in the (pre) motor cortical brain areas involved represent the matching of two input streams for which there is a relatively

stable common object representation, whereas integration in the prefrontal cortex is better characterized as the on-line construction of a new and unified representation of the input streams [307]. Co-speech gestures embody a form of manual action that is tightly coupled to the language system. Interestingly, the (pre) motor cortex can be activated to action words [308]. Ruschemeyer et al compared activations to action verbs with "complex verbs" that had the action verb as its stem, but did not have an action-related meaning [309]. For example, the German verb "greifen" (grasp) was compared to "begreifen" (to understand, to comprehend). The rationale was that if action verbs automatically activate parts of the motor cortex, this should also be the case in complex verbs that include an action verb, such as "begreifen". They found that action words did activate premotor cortical areas compared to abstract verbs. No such activation was however found in response to the complex verbs. It is not well known whether complex verbs such as "begreifen" are stored with "greifen" (to grasp) as their stem. Still, these intriguing findings raise an interest to further study the neural mechanisms of embodiment, as they may have relevance for multimodal learning. In a much broader sense, the heart of the matter of understanding could be to embody that matter [13,310].

Opportunities for medical education and medical education research

The overall goals of medical education are a) The acquisition of the knowledge, skills, attitudes and values required to perform professional medical tasks competently and safely, and b) The development and continuous refinement of the basic clinical skills that are required to provide competent care throughout a lifetime of professional work (AAMC Report 2004; AAMC Report 2005, to be downloaded at https://www.aamc.org/). As indicated by Regehr and Norman, and Patel et al, and already touched on in the previous paragraphs cognitive and learning sciences theories have great relevance in informing the process of medical education evaluation, including its impact on student learning, performance and professional competence, as well as recommendations for reform of medical curricula based on such theories [161,288]. This includes the insights from cognitive psychology on prior knowledge in understanding on the one hand, and the attempts to translate these to cognitive neuroscience on the other hand. Against this background we now will illustrate how such integrative approach may create opportunities for medical education. In order to create such opportunities it is important for medical education to formulate firm ambitions in terms of excellence and to set high standards for medical education research [285,296]. Aspects of medical education and those of medical education research will be discussed separately.

Cognitive neuroscience has driven educational progress that also is highly relevant for medical education [270]. The discovery of mirror neurons has enforced the insight that imitating helps learning [311]. Excellent teachers that act as role models may enhance learning this way [296]. The recognition of prolonged brain development during adolescence has consequences for learning and teaching of our, especially male bachelor students, as their integrative cerebral functions have not fully matured yet [312]. On the other hand, brain plasticity may induced by extensive learning of medical students [313], and it may happen until older age [314], yielding good physiological perspectives for long life learning [310,313,314], which is an important feature of keeping up professional medical competences. Experiences are better stored when learned in an emotional or arousing setting and increased motivation [44], which is often the case in medical education. The presence of multiple intelligences necessitates splitting up intelligences helping developing one at a time [315]. Insights into consciousness in the brain helps to analyze learning [316]. Last but not least, these new findings and insights driven by cognitive neuroscience have enriched all the biomedical disciplines that deal with normal brain function and structure and their clinical counterparts. This implies integration of recent advances in neuroscience into e.g. undergraduate neuroscience and physiology courses [317]. In addition, research training on psychiatry and neurosciences to medical students has been introduced [318].

In order to reach excellence in medical education Ramani proposed a number of recommendations, including establishing explicit learning and teaching outcomes, implementing best evidence medical education (BEME), and evaluating teaching and impact of teaching [296]. These recommendations not only have great relevance for the insight in learning efficacy of students, but they also challenge the teaching faculty in its role of an educational scholar that is interested in what students learn and how they learn. This scholarly attitude is a prerequisite to be able to create opportunities to use insights from cognitive psychology in understanding student's learning and to be able to improve the curriculum on a scientifically sound basis. Assessment of learning efficacy provides a means to obtain consistent data to feed curriculum improvement and to formulate questions for educational research. Assessment in medical education currently involves an integrated approach of formative and summative assessments and regular evaluation of competences that is recorded in a student portfolio [285,319]. An important goal of assessment is to optimize the capabilities of all learners and practicioners by providing motivation and direction for future learning [319]. Such assessment thus can be viewed as an educational tool that provides useful information for both students and faculty [320]. Recently, the role of interim assessments a a third type of assessment in a

comprehensive assessment system of US school districts was described, that a) Evaluate student's knowledge and skills relative to a specific set of academic goals, typically within a limited time frame, and b) Are designed to inform decisions at both the classroom and beyond the classroom level (see Perie et al., 2007, to be downloaded at http://www.achieve.org/files/TheRoleofInterimAssessments.pdf). As the results of interim assessments can be meaningfully aggregated and reported at a broader level they could serve as input for evidence-based education that could be useful for scientific elaboration. In addition, repeated assessments may enhance learning, known as the testing effect [321]. So, next to the scholarly attitude of the teaching faculty, data generated by interim assessments could involve the teachers in scientific discussions with peers, students, and cognitive psychologists. Translation of salient issues and questions to cognitive neuroscience can be stimulated by structured discussions that take place in a multidisciplinary educational research platform (Figure 1). This is an extension of the close collaboration between doctors and educationalists as proposed by Schuwirth and Van der Vleuten [285]. It is important to share new ways of improving accessibility of all types of evidence, so that they inform research, policy, and practice (Council of the European Union 2007).

Research on medical education, especially problem-based learning [322], should contribute to a better understanding of why and how the concepts of constructive, self-directed, collaborative and contextual learning do or do not work and under which circumstances [292]. As we have elucidated in previous paragraphs, prior knowledge built in a schema, greatly facilitates contextual learning if the new information can be assimilated in the schema. Medical education makes use of several schemas in which knowledge and understanding is constructed and reconstructed and they are of different magnitude [288]. Such schemas may vary from the three dimensional structure of an organ, to the complex function of (a component of) an organ, to a certain reaction pattern characteristic to a group of diseases, and, to the rationale of a diagnostic or therapeutic intervention. It would be fascinating to understand the critical conditions to build a biomedical schema, and to reconstruct it following assimilation of new knowledge. This may be highly relevant for the integration between clinical experiences and the basic science courses [161,323], and for the process of illness script formation [284,324]. Related questions include: Does the degree of congruency with prior knowledge influence learning efficacy? Does the type of schema, e.g. unimodal or multimodal, influence the neural mechanism of processing and coordination? How does multimodal learning enhance insight into three dimensional proportions such as in human anatomy [325]? Which neocortical areas are involved in schema consolidation and in which hierarchy [83,112]? Which factors interfere with schema formation? It

would be very challenging seeing the learning efficacy in educational conditions in which schema driven learning is manipulated in order to improve learning efficacy. Related questions include: Is there a difference in learning effect of a meaningful schema and a memory aid schema? What is the optimal time interval to add new knowledge to a schema? What is the maximal qualitative (complexity) and quantity (load/overload) of a schema? How long does a schema lasts and in which condition (decay?)? How are schemas reconstructed during the development of expertise? Can embodiment enhance schema formation? Does schema formation concern both explicit and implicit memory? How can we avoid incoherence of new knowledge with a schema, leading to interference with learning as observed in multitasking and repetitive task shifting [272]? Can we use schemas as connecting elements in designing or remodeling individual courses, series of courses, or curricula? Can they be related to concrete learning objectives as used in a *learner outcome oriented* curriculum? And, can the use of schemas facilitate problem formulation by helping students to recognize the nature of the problem [326]?

We hope that the fruits of these research efforts may strengthen the bridges between medical education and cognitive neuroscience, thereby achieving synergy. And like Albert Einstein we believe that integrated research of the two domains should be driven by an ongoing *urge to understand* [327].

Conclusions and recommendations

From the foregoing discussion the following conclusions and recommendations can be made:

1.Based on the promising results of initial integrative research between cognitive neuroscience and education research, and the great potential for medical education and medical education research, synergy between medical education and cognitive neuroscience should be possible.

2. Cognitive psychology plays an important role as a scientific interface between medical education and cognitive neuroscience.

3. As formation of schemas is a central event in student-centered active learning and has relevance for both medical education and cognitive neuroscience the topic seems particularly suitable for integrative research efforts.

4. (Medical) teachers should be more aware of what students learn and how they learn, which are goals of evidence-based education that tries to bridge the gap between the practice of learning on the one hand, and the development of learning and educational research on the other hand.

5. In order to understand processing in the brain and their neural correlates it is important to acquire some of the theoretical background on learning and

memory. Before embarking on neuroimaging, it is important to realize whether the scientific question may or may not be suitable for the different imaging techniques.

6. Recent neurocognitive research in human subjects shows evidence for multisensory facilitation of unisensory learning, which facilitation is specific to the congruent condition. Congruency between stimuli may reflect whether they can be readily integrated in a schema.

7. The dialogue on interesting research alleys on the crossroad of medical education including medical education research, and cognitive neuroscience should proceed along a research agenda designed by a multidisciplinary educational research platform, in which cognitive psychology is included.

8. In order to increase opportunities for this research, the medical educational field should further promote evidence-based education in order to create a platform for having an optimal dialogue.

9. Instead of bridging preexisting research domains a new learning-centered domain could be opened: a field of mind, brain, and education, or, alternatively, of educational psychology, or even a new science of learning.

10. Opportunities to study interesting research topics in medical education should be explored, e.g. the role of prior knowledge in understanding, multimodal learning, and the development of expertise.

11. Integrative training to professionals with interdisciplinary competences in the domain of mind, brain and education, who share the same language and theoretical frameworks, is strongly advocated.

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Part V:
Discussion and appendices

Chapter 9

Discussion

9.1 Summary

The experiments described in this thesis yield a consistent picture of the neural mechanisms underlying the enhancing effects of schemas on memory in humans. Information congruent with a schema that is successfully learned by the brain is generally found to be related to enhanced activity in the mPFC, both during encoding (chapters 5 and 6) and retrieval (chapter 2), while learned information that is incongruent or unrelated to a schema is associated with enhanced activity in the MTL (chapters 5 and 6). Moreover, connectivity between these regions is enhanced during processing of subsequently remembered schema-incongruent or unrelated information (chapters 4 and 5). During retrieval, schema-related information is not only found to lead to enhanced activity in the mPFC, but also to enhanced connectivity between mPFC and sensory regions presumably representing part of the memory trace (chapter 2), and is moreover found to differentially affect specific memory measures during consolidation (chapters 3 and 4). In sum, these results convincingly show that the neural mechanisms underlying formation and retrieval of new memories are modulated by its congruency with a preexisting schema, balancing between enhanced involvement of the mPFC in case information is more congruent or the MTL in case it is more incongruent. These findings are of crucial interest for theories on encoding and consolidation [19,31,38,92], and the nascent field of educational neuroscience, which tries to use neuroscientific findings to improve classroom learning [134-137].

The effects described in the empirical experiments (chapters 2-6) are placed in a broader and more applicable context in chapters 7 and 8. In chapter 7, we elaborated on the seemingly contradictory distinction between schema and novelty effects on memory and the underlying neural mechanisms by providing a framework that explains existing data and forms new hypotheses that can be tested in future experiments. In chapter 8, we specified the implications of this type of research for the growing field of educational neuroscience, and listed applications for the classroom and questions for further research into the schema effect on memory that can affect classroom learning and development of curricula. These concluding chapters therefore act both as a summary and a guideline for future research into both more fundamental and more applicable neuroscientific schema research.

9.2 Uses for schemas in the cognitive neuroscience of memory

The (cognitive) neuroscience of memory is an interdisciplinary research field that combines molecular and cellular research in animals with systems level

approaches (both electrophysiological and hemodynamic) in healthy humans and patients [78,125], complemented by computational models that further test brain mechanisms and behavioral effects [25,221,328] (see chapter 1.3). In the past decades, this research field has made tremendous advances by finding neuronal bases of learning, brain regions that are involved in different types of learning, investigating the differences and commonalities between memory mechanisms and other cognitive processes such as perception and attention, and trying to understand the nature of memory representations in the brain and how these evolve over time. These findings have shaped our thinking about memory and gave rise to treatments for diseases such as Alzheimer's disease [329], semantic dementia [88], and amnesia [31], along with educational applications [134], and knowledge structures in software programs [14,221,328]. What can neuroscientific research into schema effects on memory, as described in this thesis, add to this body of literature?

9.2.1 Encoding

As described in the introduction (chapter 1.3.5), memory encoding refers to learning through the online processing of information so it can be stored into long-term memory. Previous research on memory encoding has often implicitly assumed that newly encoded memories were placed upon a tabula rasa, suggesting they would be processed similarly irrespective of their consistency with preexisting memories. The research described in this thesis shows that this assumption is invalid. To the contrary, memory encoding processes appear to be affected by the relation between new memories and old memories that are present in preexisting associated schemas (chapters 4, 5 and 6), and can be predictive for future performance (chapter 5). This is represented by a shift in balance between more mPFC-mediated encoding for memories congruent with a schema and more MTL-mediated encoding for memories that are more incongruent with a schema. The experiments described in this thesis thus strongly suggest that the way new memories are processed is dependent on their congruency with a schema.

Memories were long thought to be stored preferably when they were novel enough [19] (see 1.3.5), a statement challenged by the research described in this thesis. In the experiments reported in this thesis, memory formation and retrieval rather appear to be enhanced by the consistency of a new memory with a preexisting schema, as also stated in the schema theory [4] (see 1.2, but also 1.5). We discussed the apparent controversy between these theories in chapter 7, where we described two complementary encoding mechanisms that can compete to store a memory either as part of an existing schema through

mediation of the mPFC or as a separate memory trace bound through the MTL. Importantly though, both processes can lead to improved storage of a memory but for a different reason. Memory traces are thus suggested to be different in nature such that memories stored by the mPFC are more semantic in nature, while MTL-mediated memories are more episodic in nature. These putative statements will need to be further tested in future experiments, along with other statements raised in chapter 7.

9.2.2 Consolidation and retrieval

The initial hypothesis that a schema specifically affects consolidation of memory traces [112,131] (see 1.4) is partly countered by the discovery of differential encoding processes in chapters 4 and 5. Nevertheless, these findings do not contradict the option that schema-dependent consolidation processes can still influence storage of memories that are differentially congruent with a preexisting schema. Chapters 2-4 have looked into schema-dependent consolidation and retrieval processes and showed that both during early consolidation as is thought to occur during post-encoding rest (chapter 4) and at retrieval at different time points after encoding (chapters 2 and 3), schema-related differences are apparent that can transform memory traces over time (chapter 3). Thus, consolidation processes, next to encoding processes, are also found to have profound, perhaps complementary, effects on the schema effect on memory.

The findings reported in this thesis are generally consistent with both the consolidation theories described in chapter 1.3.6, the systems consolidation theory [42] and the transformation theory [92]. The main difference between these two theories is that the latter assumes that there are two different types of memories that transform into an hippocampally independent trace over time (semantic memories) or stay hippocampally dependent (episodic memories), and that these memories can both exist at the same time such that the preservation of an episodic memory does not exclude the possibility of it affecting semantic memories related to it. As postulated in chapter 7, memories that are congruent with a preexisting schema could already be more semantic (or schematic, see chapter 7) from the start, as they are readily integrated into the schema, mediated by the mPFC. This proposal further allows the possibility that schema-congruent memories are inherently more semantic than schema-incongruent memories, a feature that will facilitate their consolidation into neocortical networks and thus represents a promising novel way to investigate consolidation processes without confounds such as forgetting and interference.

As described in chapter 3, whether consolidation processes are necessary for the schema affect to arise depends on the way a memory is tested. In this

experiment, we found the schema effect on item recognition to be specifically affected by consolidation, while associative memory already showed a schema effect right after encoding that persisted through consolidation. These findings show that the way memory is cued along with its remoteness are important factors to consider when investigating the schema effect on memory, and can furthermore account for some of the controversial findings in behavioral schema literature [12,17,18]. Investigating a particular schema-congruent or schema-incongruent memory more extensively, such as examining its confidence, the amount of details, its resistance to interference and the tendency to represent false memories, can shed more light on the nature of these memories. Testing these memories and their neural underpinnings at different points in time can additionally inform consolidation theories in the future, giving a more complete view on how memories evolve over time as a function of its congruency with a preexisting schema.

Overall, research on the schema effect on memory can inform the debate between existing consolidation theories, ultimately reaching a consistent view of memory consolidation. Moreover, investigating how schema-congruency changes the nature of memory traces during and after consolidation, will lead to valuable insight into the way memories are represented in the brain and how they interact with each other. Additional to initial effects of schema-dependent encoding, examining effects of consolidation can thus give more insight into memory development over time.

9.2.3 Schema and novelty

The effects of a preexisting schema on memory can be placed in a larger body of evidence that relate to general functioning of the brain. The predictive coding theory [26] (see 1.3.5) states that the brain continuously tries to predict what will happen in the world around it based on prior experience and acting to minimize the prediction error, the difference between the prediction and the incoming information. Based on this theory, large prediction errors are expected to lead to enhanced memory [98], a hypothesis that is in line with the novelty encoding hypothesis, but contradictory to the schema theory (see chapter 7). On the other hand, when it is the brain's main purpose to minimize prediction error (e.g. to reduce metabolism), congruent information should also be vital to update and strenghten subsequent predictions that might otherwise deteriorate and is thus expected to be stored accordingly.

In the framework we describe in chapter 7, we explain this apparent contradiction by illustrating two encoding mechanisms that act to either enhance congruent or incongruent memories, mediated by the mPFC or the

MTL respectively. Congruent associations, mediated by the mPFC, are in this framework suggested to be more readily integrated into the schema. This process is expected to rapidly expand and strengthen a schema when it is validated, so a new memory can readily assist predicting future input itself, but is stripped from accompanying contextual details (by selective encoding, see chapter 7). Incongruent memories, on the other hand, are bound through analogous links with the MTL preserving contextual details, but only slowly consolidate, such that they can only start predicting future input when repeated multiple times. This way, the brain can optimally and most efficiently make use of incoming information by using both congruent and incongruent information to construct a representation of the world that on the one hand allows predicting of the future but is conversely only slowly altered when this representation becomes erroneous. Nevertheless, unpredicted instances that evoke a prediction error, such as very salient or emotional experiences, can still be very important and will thus be directly stored by the MTL so it does not affect the carefully built schema of the world directly.

Evolutionary, such a role for different schema-dependent processing modes in the brain is intuitive. On the one hand, it does not make sense to explicitly store information that is not very salient, but on the other hand, the brain needs to store important aspects of this information to help predict what will happen in the future. Information that is salient, however, needs detailed storage (e.g. to be evaluated later on), but should not merge with a schema that predicts future input before it has reliably been established (e.g. through reactivation) that this information does in fact represent an important and reliable part of the outside world. The brain thus needs these two processing modes to build on the one hand a reliable model of the world, but also to be able to flexibly adjust this model without too much bias when this world happens to change.

9.3 Dynamic memory

The research reported in this thesis points to one common direction: that of a dynamic nature [330] of declarative memory traces, dependent on congruency with preexisting knowledge, both during encoding, differential offline consolidation processes, and cueing during retrieval. These factors should be investigated in future research because they, as shown in this thesis, largely determine the way memories will be processed. Taking into account the modulatory effect of preexisting knowledge structures thus paves the way for a new approach to investigate mnemonic processing, considering a newly encoded memory as being placed on a (presumably) continuous scale ranging from very episodic to very semantic. Memories on either of these outer ends of

the scale have their own particular traits and are modulated by factors such as congruency and (re)consolidation (but also e.g. motivation and emotion, see 1.3.3 and 1.3.7), dynamically and continuously shaping these features. When viewing memories in this way, differences in strength, familiarity, and vividness during retrieval, along with involvement of different brain regions can more easily be explained. Moreover, assumed sharp dissociations between e.g. declarative and non-declarative [80], semantic and episodic [84], and consolidated and unconsolidated memory traces [42] might be smoothed when considering a more continuous modulation by congruency [81].

9.4 Open questions and future research

This dynamic view on memory, considering memories as continuously changing and interacting entities, even when already fully consolidated, allows for old questions to be resolved and novel questions to be addressed. I will briefly concentrate on a few of these novel questions in this concluding section.

9.4.1 How is a schema constructed in the brain?

Behavioral and neuroscientific theories about the physical representation of a schema are relatively different, mainly because many of the behavioral definitions on schema representations were constructed when there was not yet much known about brain functioning. Now that cognitive neuroscience is flourishing, and we gradually unravel more about the functional architecture of the brain, a successful combination of behavioral and neuroscientific notions on schemas is forthcoming [112,130]. Considering the brain as a prediction machine [26] where previous experiences, stored as weighted connections between individual neurons and neuronal populations, act to predict future experiences, allows for a broader view on schemas and how they influence behavior in a more general way. As already mentioned in the introduction (1.1) and elaborated on in chapter 7, our definition of a schema is as follows: *a framework of acquired knowledge, skills or attitudes implemented within a network of connected neurons in which memory traces of associated information have been stored that, when activated, can alter the manner in which information is processed, including memory encoding, consolidation and retrieval.* Such a definition allows for both behavioral and neuroscientific tests on different hierarchical levels, ranging from simple information processing to higher cognitive processes such as decision making and reasoning.

A question arising from this definition is how these knowledge networks (or the engram [30]) of connected neurons that represent associated information are constructed and remodeled by the brain. Understanding the world around

us, and acting appropriately to irregular information is inevitably related to stored representations of this world. Understanding how this consistent schema of the world is build, and how it subsequently affects new learning, is of crucial importance for implementation in educational programs and for treating patients who show distortion or inconsistency of schema build-up, e.g. in autism [331-333] or semantic dementia [88].

9.4.2 The functional role of the mPFC and its relation to the MTL

Even though the mPFC is consistently found to be active for congruent mnemonic processing in our experiments, a clear understanding on what this region is doing exactly and what its relative contribution is alongside the mnemonic functions of the MTL is still lacking. As discussed in chapter 7, what would be the added value of an encoding mechanism mediated by the mPFC when the MTL already stores all information perfectly well? One answer to this question is described in chapter 7 and elaborated on above (9.2.3), that of selective encoding of only information relevant for the schema. This way, irrelevant information is automatically inhibited, allowing the brain to store more information because irrelevant information is not stored or forgotten rapidly. This suggestion allows for a more evolutionary perspective on why a region such as the mPFC acts to assimilate information (chapter 7), allows for inference detection [53], and extracts regularities [110].

The mPFC is a region that is active in many cognitive tasks (more for dorsal parts) [49] and even more so during rest (i.e. when there is no cognitive task at hand; more for ventral parts) [117]. A task for future research is to combine all these functions of the mPFC in a common task that relates to emotional, social, decision making, and mnemonic processing that persists offline, and that can inform theories within these different research fields (such as described in [49]).

9.4.3 Development

Our brains change continuously, but during development these changes are more profound than in adulthood [334]. During the years preceding adulthood, e.g. during childhood and adolescence, different brain regions develop to full maturation at different rates. The prefrontal cortex, for example, develops until well within our twenties, while other brain regions are found to be fully developed by adolescence and adulthood [335]. How this relatively late maturation affects the processes described in this thesis is an intriguing question that is of extreme importance for educational applications during childhood, adolescence and adulthood [134].

The large plasticity related to this late maturation of the prefrontal cortex could lead to easier building of schemas during early life, but one could also

argue that a prefrontal cortex that is not functioning to its full extent might lead to more episodic-like memories because all information will be processed by the MTL (see 8.2.3). Data from patients suffering from developmental amnesia, a disorder where the hippocampus is damaged early in life, shows that these children still do well early in life, but run into problems when they become older [240,336], possibly because their prefrontal cortex matures. These theories need to be further investigated in healthy participants and patients.

9.4.4 Applications to education

As argued in chapter 7, many of the findings in behavioral and neuroscientific investigations into the schema effect on memory can be very beneficial for education [134-137]. Specifically, this type of research can inform the construction of curricula, the use of particular types of teaching methods, and it can inform teachers and students on how they can retain specific information most optimally (see also chapter 1.6). Before this fundamental research can be effectively applied however, the questions mentioned above need to be further examined. For example, understanding more about the functioning of the mPFC and how it develops is crucial for educational applications. Additionally, further understanding the differing memory enhancing effects of congruent and incongruent memories, and how these evolve over time will lead to fundamental insights regarding what type of memories are enhanced by congruency-dependent learning. This knowledge can subsequently be used to provide students with the right information at the right time, depending on their schema of a certain subject, and teaching them how to best study this information.

9.5 Conclusion

In summary, the human research and general theories presented in this thesis, together with the earlier studies on rodents [54,131], can serve as a solid basis for further neuroscientific research on the schema effect on memory. This schema research has the potential to unite disciplines such as educational neuroscience and the cognitive neuroscience of memory, and can aid to solve unsettled issues regarding memory encoding, (re)consolidation and retrieval while linking them to long-term learning problems that are of crucial interest to educational organizations. I therefore hope that the data discussed in chapters 2-6, the theories posed in chapters 7 and 8, and the future questions raised in chapter 9.4, have laid a foundation that will be able to inform future research into the schema effect on memory. This future research is then expected to inform theories on the cognitive neuroscience of memory to better understand the memory system in our brain. Additionally, it can aid educational aims to reach optimal learning

situations; situations that are most optimally based on mutual understanding between educational theories and neuroscientific theories. This way, by knowing and understanding how to build, extend, and alter the schemas in our brain, we might get a better grip on what we remember and forget and, most interestingly, how this is related to the knowledge we gathered throughout our past.

Appendices

- Nederlandse samenvatting
- References
- Acknowledgements
- Curriculum Vitae
- List of publications
- Donders Graduate School for Cognitive Neuroscience series

Nederlandse samenvatting

Introductie

We verzamelen een heleboel kennis tijdens ons leven. Kennis over de mensen om ons heen en hoe we met ze omgaan, kennis over de wereld, natuurwetten, politiek en economische systemen en kennis over onszelf en wat we allemaal hebben meegemaakt. Deze kennis heeft effect op hoe we de wereld benaderen en welke informatie we uiteindelijk het beste onthouden. Informatie die aansluit bij je voorkennis wordt over het algemeen beter onthouden omdat het gemakkelijker geïntegreerd kan worden in het kennisnetwerk in je brein, terwijl informatie die niet aansluit bij je voorkennis moeilijk een plaatsje kan krijgen. Een belangrijke theorie in de psychologie en de pedagogiek is de *schema theorie* die zegt dat informatie die past bij onze voorkennis (het schema) beter wordt opgeslagen dan als informatie niet past bij onze voorkennis [4]. Deze theorie is uitgebreid onderzocht over de jaren en dit heeft geleid tot controversiële bevindingen. Informatie blijkt over het algemeen beter opgeslagen te worden als het past bij je voorkennis, maar dit is niet altijd het geval omdat soms informatie die tegenovergesteld is aan je voorkennis ook beter onthouden wordt [12,18]. Stel je maar eens voor wat er zou gebeuren als je ineens een roze olifant zou tegenkomen, dit is tegen je verwachtingen in en je zal dit dus ook goed onthouden. Door deze controversiële bevindingen is de schema theorie over de jaren minder populair geworden, omdat onderzoekers het moeilijk vonden om alle bevindingen te verklaren in een overkoepelende theorie.

De opzet van dit proefschrift was in eerste instantie om bovengenoemd *schema effect* (beter geheugen voor schema-gerelateerde informatie) te relateren aan geheugen mechanismen in het brein. Hoe informatie wordt opgeslagen in ons brein is een eeuwenoude vraag waar nog steeds erg veel onderzoek naar wordt gedaan. Door eerder onderzoek weten we dat we het geheugen kunnen opdelen in verschillende soorten. Het soort geheugen wat in dit proefschrift centraal staat in het *declaratieve geheugen*, wat feitenkennis en kennis van gebeurtenissen representeert. Twee gebieden in het brein zijn erg belangrijk zijn voor dit declaratieve geheugen: de *hippocampus* en de *mediaal prefrontale cortex (mPFC)*. Over het algemeen wordt verondersteld dat de hippocampus stukjes van het geheugen die in het hele brein verspreid liggen met elkaar verbindt. Deze hippocampus is dus ook voornamelijk actief tijdens het leren (*encoderen*) van nieuwe informatie en het terughalen van recent opgeslagen informatie [31]. Over de tijd, door *consolidatie* van het geheugen tijdens rust en slaap, neemt de invloed van de hippocampus af, omdat de verschillende stukjes van het geheugen beter verankerd worden in de rest van het brein en de hippocampus deze niet meer hoeft te verbinden [43]. Tegelijkertijd wordt de mPFC actiever bij het terughalen van informatie over de tijd [57,68], wat impliceert dat dit gebied voornamelijk

belangrijk is voor het terughalen van oudere herinneringen en misschien wel de functie van de hippocampus overneemt (zie figuur 1.4). Recenter onderzoek heeft echter laten zien dat de mPFC en de hippocampus al tegelijkertijd actief zijn tijdens en na het encoderen van nieuwe informatie en dat de mPFC dus misschien ook belangrijk is voor het opslaan van nieuwe herinneringen [62,64].

De invloed van een schema op deze hersenprocessen is pas kortgeleden voor het eerst onderzocht in ratten door Richard Morris en zijn onderzoeksgroep. Deze onderzoeken lieten zien dat ratten die eerder een ruimtelijk schema geleerd hadden veel makkelijker nieuwe informatie die aansloot bij dit schema konden leren dan informatie die niet aansloot bij dit schema. Daarnaast bleek dat de hippocampus minder lang nodig was om de informatie terug te halen [131] en dat naast de hippocampus de mPFC actief was tijdens het encoderen van nieuwe, schema-gerelateerde informatie [54]. Deze resultaten laten zien dat de hippocampus belangrijk is voor het opslaan van nieuwe informatie terwijl de mPFC, in samenwerking met de hippocampus, specifiek belangrijk is voor het opslaan van schema-gerelateerde informatie. Dit proefschrift onderzoekt deze theorie in menselijke proefpersonen met toegepaste geheugenexperimenten en functionele magnetische resonantie imaging (fMRI), een beeldvormende techniek waarmee hersenactiviteit tijdens het leren en herinneren van informatie kan worden gemeten. Daarnaast koppelt het onderzoek in dit proefschrift de bevindingen aan toepassingen voor het onderwijs.

Schema effecten tijdens en na geheugen consolidatie

In de eerste twee hoofdstukken van dit proefschrift werden de effecten van schema's op consolidatie en retrieval (terughalen van informatie) besproken. Hoofdstuk 2 en 3 bespreken hetzelfde experiment, waarbij proefpersonen combinaties van woorden, stofjes en patroontjes leerden die wel (congruent; bijvoorbeeld een zijden stropdas) of niet (incongruent; bijvoorbeeld een stropdas van ruw materiaal) gerelateerd waren aan voorkennis. In hoofdstuk 2 werden de proefpersonen een dag na het leren in de MRI-scanner getest op hun kennis over de geleerde informatie. Hieruit bleek dat hun geheugen voor de congruente informatie beter onthouden was en dat dit gerelateerd was aan een verhoogde activiteit in de mPFC en de somatosensorische hersenschors, waar het geheugen voor hoe het patroontje voelde waarschijnlijk opgeslagen ligt. In hoofdstuk 3 worden de geheugentests beschreven nadat dit experiment was uitgebreid met twee nieuwe groepen die of gelijk na het leren werden getest, of twee dagen na het leren. Deze tests laten zien dat er bij herkenning van het patroon pas een schema effect ontstaat na consolidatie, terwijl bij het leggen van de congruente associatie tussen het patroon en het woord al verbeterd is gelijk na het leren van

de informatie en dus geen consolidatie nodig heeft om versterkt te worden. Er zijn dus verschillende invloeden op het schema effect: het soort geheugen dat getest wordt en de tijd die verstreken is tussen het leren en het testen hebben beide effect op hoe het schema effect zich manifesteert.

Schema effecten tijdens encodering

In het tweede gedeelte van dit proefschrift werden schema effecten op encoderen onderzocht. In hoofdstuk 4 hebben we hiervoor een film gebruikt die in twee stukken was verdeeld. Het eerste deel van de film werd op dag 1 aan de proefpersonen getoond, waarbij de helft van de proefpersonen de film in normale volgorde zag terwijl de andere helft de film door elkaar gehusseld zag. Het idee hierbij was dat de proefpersonen in de eerste groep een duidelijk schema zouden opbouwen terwijl de tweede groep hier moeite mee zou hebben. Dit zagen we inderdaad terug in een test die we de volgende dag deden; de proefpersonen van de twee groepen waren even goed in het herkennen van scenes uit de film, maar de tweede groep was duidelijk slechter in het reconstrueren van het verhaal: onze schema-manipulatie was dus gelukt. Vervolgens keken de proefpersonen het laatste gedeelte van de film in de MRI-scanner, waarbij we de communicatie tussen de hippocampus en de mPFC maten tijdens het kijken van de film en tijdens een rustperiode daarna. We vonden dat de communicatie tussen deze twee gebieden tijdens allebei deze periodes verhoogd was voor de groep die de gehusselde film had gezien ten opzichte van de andere groep. Deze proefpersonen moesten harder hun best doen om de nieuwe informatie van het laatste deel van de film te integreren met hun slecht opgebouwde schema en deden dit met versterkte communicatie tussen de hippocampus en de mPFC tijdens het encoderen van informatie en vlak daarna.

Hoofdstuk 5 bouwde voort op deze bevindingen, maar in een meer educationeel kader. In dit experiment leerden tweedejaars proefpersonen van twee verschillende studies (biologie en pedagogiek) korte zinnetjes met nieuwe informatie die ofwel aansloten bij hun eigen ofwel bij de andere studie in de MRI-scanner. We konden met dit experiment dus goed vaststellen of informatie specifiek aansloot bij het schema van de proefpersonen. De volgende dag werden de proefpersonen getest op wat ze nog wisten van wat ze hadden geleerd de dag ervoor en hieruit kwam duidelijk naar voren dat ze de informatie die aansloot bij hun studie-schema beter hadden onthouden. Deze verbetering van het geheugen hing samen met hogere activatie van de mPFC tijdens het leren, terwijl schema-ongerelateerde informatie samenhing met activatie in de parahippocampus, vlak naast de hippocampus, en met verhoogde communicatie tussen de hippocampus en de mPFC. Daarnaast was de sterkte van de mPFC activiteit voor schema-

gerelateerde informatie voorspellend voor hoe studenten het in het tweede jaar van hun studie deden: hoe meer activiteit, hoe beter ze werden ten opzichte van hun eerste jaar. Het gebruik maken van je mPFC om nieuwe informatie te integreren hangt dus samen met toekomstig studiesucces.

In hoofdstuk 6 hebben we deze wisselwerking tussen de hippocampus en de mPFC uitgebreider onderzocht door te kijken naar drie subjectief bepaalde schema categorieën (congruent, ongerelateerd en incongruent) in plaats van twee. Daarnaast keken we in dit experiment naar een simpeler schema als in de eerdere hoofdstukken: associaties tussen objecten en locaties, zoals ook beschreven in hoofdstuk 7. Proefpersonen kregen steeds een object en een locatie tegelijkertijd te zien die ze moesten leren. Ook gaven ze op een schaal aan hoe goed ze deze bij elkaar vonden passen (van incongruent tot congruent). De volgende dag kregen ze een test waar ze werden getest op herkennen van de objecten en de associatie met de lokaties. We vonden dat de congruente associaties het beste werden onthouden en dat hoe congruenter deze correct onthouden associaties waren, hoe meer mPFC activiteit daaraan gerelateerd was. Daarnaast was er ook meer koppeling tussen de mPFC en gebieden waar het geheugen opgeslagen werd. Andersom was de parahippocampus wederom actiever hoe incongruenter de associaties waren. Deze resultaten laten zien dat er een lineaire relatie is tussen subjectieve congruentie van een herinnering en welk hersengebied actief wordt, de mPFC meer voor congruente associaties en de parahippocampus meer voor incongruente associaties. Deze resultaten zijn consistent met de resultaten uit hoofdstuk 4 en 5 en geven meer inzicht in de specifieke relatie tussen schema-congruente en schema-incongruente herinneringen en de gerelateerde hersengebieden in het licht van de theorie beschreven in hoofdstuk 7.

Theoretische en praktische implicaties

Hoofdstuk 7 bood een theoretisch model om de resultaten beschreven in hoofdstuk 2 tot en met 5 verder te verklaren en te verbinden met andere bevindingen in de literatuur. In dit hoofdstuk beschrijven we een model dat verklaart waarom naast informatie die congruent is met een schema ook incongruente informatie vaak goed wordt onthouden en wat de rollen van de mPFC en de hippocampus (of mediaal temporale lobule MTL, dat een iets breder gebied representeert) hierin zijn. Het model gaat ervan uit dat een nieuwe gebeurtenis altijd de MTL activeert die vervolgens de verschillende stukjes van deze informatie met elkaar verbindt, tenzij de MTL wordt tegengehouden door de mPFC, die geactiveerd wordt door de activatie van een schema. De mPFC zorgt er dan voor dat specifieke informatie van een gebeurtenis geintegreerd word in dit schema. Herinneringen

die worden opgeslagen door de mPFC worden dan dus direct geintegreerd in het schema en niet als losse stukjes gekoppeld door de MTL, waardoor informatie relevant voor het schema beter kan worden gefilterd en versterkt. Incongruente informatie, opgeslagen door de MTL, kan dus ook goed onthouden worden, net als congruente informatie, maar wel met andere karakteristieken: meer details en sterkere contextuele relaties. Congruente informatie daarentegen is volgens dit model minder gedetailleerd en specifiek omdat het wordt opgeslagen door de mPFC. Dit model biedt een verklaring voor onze data, eerdere experimenten en specifieke hypotheses voor toekomstig onderzoek.

In hoofdstuk 8 gingen we uitgebreider in op de toepasbaarheid van schema onderzoek in het onderwijs, specifiek het medische onderwijs. Dit hoofdstuk betoogt dat onderzoekers in de cognitieve neurowetenschappen en het medisch onderwijs beter moeten samenwerken om neurowetenschappelijke bevindingen in de onderwijspraktijk te kunnen gebruiken. Dit kan via andere disciplines, zoals cognitieve psychologie, maar het is ook nuttig om een nieuw onderzoeksveld op te zetten die deze verschillende disciplines kan verenigen (*new science of learning* [137]). Door dit soort onderzoek kunnen onderwijzers en studenten zich bewuster zijn van hoe je het beste kan leren en onderwijstechnieken baseren op wetenschappelijk onderzoek (*evidence based education*). Door onderzoek in de cognitieve neurowetenschappen te baseren op onderwijskundige vraagstukken en door het stellen van onderzoeksvragen die interessant zijn voor de onderwijspraktijk kan neurowetenschappelijk onderzoek in de toekomst bijdragen aan het verbeteren van curricula en leertechnieken.

Conclusie en discussie

Tot slot vatte hoofdstuk 9 alle voorgaande hoofdstukken samen. De MTL (waaronder de hippocampus) en de mPFC zijn gebieden die belangrijk zijn voor het leren van nieuwe informatie, waarbij de MTL specifiek belangrijk is voor het detecteren van nieuwe informatie die incongruent is met een schema en die vervolgens als losse stukjes opgeslagen worden. De mPFC is daarnaast belangrijk voor het detecteren van informatie dat congruent is met een geactiveerd schema en zorgt er vervolgens voor dat deze informatie wordt geïntegreerd in het schema, waardoor het goed wordt opgeslagen. Hierbij wordt informatie dat minder relevant is voor het schema (zoals specifieke details en context informatie) echter minder goed opgeslagen. Hoe informatie gerelateerd is aan een schema is dus van cruciaal belang voor hoe het zal worden opgeslagen in het brein. Deze inzichten zijn belangrijk voor verder onderzoek binnen de cognitieve neurowetenschap en vormen een basis voor toekomstige toepassingen in het onderwijs. Verdere vragen die in de recente toekomst behandeld kunnen worden

zijn: hoe is een schema precies gerepresenteerd in het brein, wat is de precieze rol van de mPFC in combinatie met de MTL en hoe is de ontwikkeling van deze processen bij kinderen en adolescenten wiens brein nog in ontwikkeling is? De experimenten beschreven in dit proefschrift geven een goede basis en bieden specifieke hypotheses en vragen voor dit vervolgonderzoek.

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Dirk, wat hadden we moeten doen zonder jouw innovatieve ideeën? Jij leek wel overal wetenschappelijke inspiratie te hebben, van de badkamerwinkel tot tijdens het geven van anatomie onderwijs: jij zag overal schema's! Ik bewonder je brede en oprechte interesse in wetenschap en ik vind het een eer om een van jouw laatste PhD-studenten te zijn. Je ondersteuning en eindeloze ideeën voor vervolgonderzoek hebben mij erg gestimuleerd en ik zal dit proberen mee te nemen in de rest van mijn carrière. Heel erg bedankt voor dit alles en voor het creëren van een mogelijkheid om nog wat langer te blijven voordat ik (hopelijk) mijn carrière in het buitenland voortzet. Voor nu wens ik je een vreedzaam pensioen, ook al denk ik dat je nooit echt afscheid zal kunnen nemen, en ik hoop dat we in de toekomst ideeën kunnen blijven bespreken.

Mark, jij bent zo intensief betrokken geweest dat ik niet weet waar ik moet beginnen. Ik kon altijd bij je binnenlopen voor brandende vragen over experimentele designs en data analyse, en jij had altijd een nuttig antwoord. Ik zal nooit onze SPM sessies vergeten waar we probeerden om een beter overzicht van de resultaten van ons 3x3x2 design the krijgen door de SPMs op de grond te leggen (wat uiteindelijk niet echt geholpen heeft, maar het was wel vermakelijk). We bleken uiteindelijk niet alleen van M&Ms te houden, maar het ook te zijn (jij de bruine en ik de blauwe)! Toen je me vertelde dat je wegging vond ik het jammer, maar ik ben blij dat je nog steeds aan de overkant van de straat zit en we nog steeds soms kunnen bijkletsen. Bedankt dat je er altijd was als ik je nodig had en ik wens je een geweldige toekomst met Ingrid en Eva. We houden contact!

Erno, tijdens mijn stage heb je me alles geleerd wat wetenschap te bieden heeft: van de dagelijkse ergernisjes met net-niet-werkende matlab en presentation scripts, scanner perikelen en niet-significante pilot resultaten, tot de lol van het "verkopen van sexy data", het tegen elkaar "uitspelen" van reviewers en presenteren en feesten op conferenties. Ik denk dat geen van ons verwacht had dat onze CroCo-analyse uiteindelijk in PNAS en Science terecht zou komen, wat natuurlijk voornamelijk aan jouw matlab-kunsten te wijten is! De laatste jaren was je voornamelijk mijn mentor en vraagbaak voor onderzoeks- en carrière-advies en daarnaast gewoon een koffiemaatje voor het bespreken van alle andere relevante dingen (Rosa). Bedankt voor al je advies, je geniale ingevingen, nuttige discussies en biertjes ik hoop dat er nog velen mogen volgen!

Rik, I couldn't have chosen a better person to spend my time abroad with. You warmly welcomed me to the CBU and helped me to broaden the view on my thesis topic by relating it to your ideas and other related research. I was amazed by the time you were willing to spend just sitting in your office and "hurting our brains" to make sense of it all, thereby teaching me how to construct a plausible framework, think through its predictions, and deal with critical comments. I believe we did a good job making some sense, and I hope we will be able to extend that sense in the future by collaborating on the many remaining questions that we raised. Bathducks (or rubber ducks, whatever) will never be the same again!

David, you were the one that initiated the idea of an fMRI experiment with a movie and I believe we succeeded quite nicely. Even though we haven't collaborated since, I am grateful for your contributions to this project, and I really enjoy your occasional typically British humouristic remarks at the coffee machine!

Sarah, as I already said when you got your diploma: you were a model student. At first, I envisioned teaching you all kinds of stuff, but I soon noticed that you already knew all the practical stuff and had enough prior knowledge to be able to disagree with me. We thus ended up jointly running our experiment, a way better siutation. Thank you for your help and company, I hope we will keep in touch!

The **Memory and Emotion (former Cognitive Neurology of Memory)** group members have changed significantly throughout the years, so I hope I can mention everyone. For all the lab meetings, stress meetings, schema meetings, and pizza meetings, many thanks to **Ruud, Mariët, Marieke, Isabella, Nils, Klodiana, Jan-Willem, Linda, Silvy, Susanne, Floris, Tim, Noortje, Yu, Atsuko, Eelco, Marijn, Guido, Shaozheng, Hein, Lindsey, Marloes, Jenny, Heiko, Mirre, Gesa, Carly, Frauke, Sabine, Ingrid, Vincent, and Olga.** The hippocampus and education meetings brought memory researchers from the whole Donders together. Thanks to **Joost, Esther, Anne, Janneke, Alex, Sander, Sasha, Christian, Bruce, Ludo, Eliane, Marc and Jan** for all the interesting discussions!

I spent the last five-and-something years at the Donders sharing office with many different people. Thanks to **the interns in room 0.98, Krissie, Miriam, Shanti, David, Mirjam, and Daniel** for sharing frustrations, joy and lots of coffees!

The Donders is an extremely well-functioning and very pleasant environment to perform research. Thanks to all who make this possible on a daily basis: **Tildie, Sandra, Nicole, Arthur, Marek, Sander, Erik, Ed, and Paul.** For the Donders, I participated in the "Dagje uit" committee together with **Esther, Ed and Anne**, the OC together with **Marek, Floris, Joost, Miriam, and Guido**, and the Donders Discussions together with **Saskia, Sybrine, Niels, Rick, Terry, and Noortje**. Thank you all for these collaborations!

And then I have spent quite some time enjoying the fun part of doing your PhD: your young, entertaining and incredibly intelligent colleagues. I spent countless hours in the coffee room, the pub, and at conferences with you guys, always trying to justify myself by claiming that peer-to-peer (or beer-to-beer) networking, casually discussing research stuff, and selective pruning are beneficial for your career. I like to think that this thesis provides at least a little support to these claims, but most of all it was just for fun of course. Thanks to many of the people already mentioned before and **Rick, Floris and Roel (the initial FAD committee), Robert, Ben, Laura, Hubert, Peter (x2), Hanneke, Marieke, Martine, Verena (x2), Jurrian, Stan, Rene, Eelke (x2), Egbert, Arjen, Lennart, Inge, Stephen, Tessa, Matthias (x2), Anke-Marit, Loek, Jeanette, Ruben, Flora, Jolien, Wincke, Til, Frank, Roemer, Tom, Iske, Tim, Tobias, Andre, Pawel, and Sean (our FAD poet)** for making the FADs and all the other Donders social events so amazing!

Also during my time in Cambridge, I had the pleasure to share useful and fun meetings, coffee, and pub hours with the Memory & Perception group and other people from the CBU. Thanks in particular to **Bernhard, Pierre, Maria, Andrea, Elisa, Jason, Roland, Ruud, Ian, and my roomies** for making my Cambridge experience so constructive and entertaining!

A bright mind once said: "If I have seen further it is by standing on the shoulders of giants". I wish to thank some of these giants here: memory researchers that paved the way and that I've had the pleasure to exchange thoughts with. In particular **Richard Morris**, and his group in Edinburgh, who started the whole schema research line and who has ever since been an extremely valuable collaborator. Additionally, I would like to thank the following giants: **Morris Moscovitch, Lynn Nadel, Paul Frankland, Eleanor Maguire, Penny Lewis, Alison Preston, Mick Rugg, Jeff Karpicke, Lucia Talamini, and Anthony Wagner.** Your research and your constructive comments during visits and conferences clearly shaped the research in this thesis.

Miriam en Sasha, my dear paranimfjes! In 2006 begonnen we gezamenlijk aan de CNS master en sindsdien zijn we alle drie blijven hangen in Nijmegen. Bedankt dat jullie me willen begeleiden tot het doctor zijn. **Mir,** je bent mijn liefste vriendinnetje in Nijmegen en ik geniet altijd heel erg van onze biertjes-drink, vegetarische-eet en bijklets-avondjes. Je bent geweldig en superlief, vergeet dat niet! **Sasha**, jouw nuchtere geest helpt me altijd weer relativeren; zo erg is het allemaal niet, het komt wel goed! Daarnaast ben je gewoon een enorme schat, en ik hoop dat je dat nooit zult veranderen.

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Mijn floorball-maatjes van de **Hot Shots** en de **Flames** brachten de afgelopen jaren de nodige sportieve afleiding buiten het onderzoek om. Dank aan alle leden en teamgenootjes waar ik de laatste paar jaar mee heb mogen trainen, wedstrijden en toernooitjes spelen en borrelen!

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Curriculum Vitae

Marlieke van Kesteren was born on August 14th 1983 in Zwolle, the Netherlands. In 2001, she graduated from high school at the Gymnasium Celeanum in Zwolle. She then spent a year in San Diego and Boston, USA to study English. In 2002 she returned to the Netherlands to start a bachelor program in Artificial Intelligence at the University of Groningen. During these studies, her interest in Cognitive Neuroscience started to grow and in 2006, after obtaining her bachelor degree, she decided to switch to a master's program in Cognitive Neuroscience in Nijmegen, the Netherlands. During this master's program she followed an internship at the Donders Centre for Cognitive Neuroimaging (then F.C. Donders Centre) in the group of Professor Guillén Fernández and supervised by dr. Erno Hermans, studying the effects of schemas on memory encoding and post-encoding rest. After this, she started a research assistantship with dr. Erno Hermans followed by a PhD position on schema consolidation at the end of 2008, funded by Professor Dirk Ruiter at the UMC St Radboud. As part of this PhD, she spent three months at the MRC Cognition and Brain Sciences Unit in Cambridge, UK in 2011, to write an opinion paper together with Professor Richard Henson on their joint research interests. From February 2013, she works as a post-doctoral researcher at the UMC St Radboud and the Donders Centre for Cognitive Neuroimaging.

List of publications

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