Chapter 7.

Summary and General Discussion
The main goal of this thesis is to understand the role of the default mode network (DMN) in episodic memory. This research was inspired by the intriguing finding that the DMN shows a negative memory success effect during episodic encoding but a positive effect during episodic retrieval, also referred to as the encoding/retrieval flip pattern. In chapter 2, we examined a possible consequence of the flip pattern, and found evidence for a competition between encoding and retrieval processes. From then on, we proceeded to investigate the functional implication of the flip pattern. We examined four different accounts based on previous research on the function of the DMN: the reallocation account (chapter 3), the reconstruction account (chapter 4), the orienting of attention account (chapter 5), and the respiratory account (chapter 6). None of the accounts we addressed appears fully conclusive as yet. Below follows first a comprehensive summary of the findings described in the different chapters. Then, I will discuss the findings in relation to the four accounts and I will also introduce a fifth account, the Attention to Memory (AtoM) account that potentially reconciles some of the findings. I will also discuss that the DMN does not always function as a single unit. Rather, in the studies described we found several functional dissociations among various DMN regions. I will also discuss the possibility that there are several factors and none of the four or five accounts can singlehandedly describe the role of the DMN. Finally, I will draw some overall conclusions and suggest avenues for future study.

**Summary**

In chapter 2, we showed for the first time the spatial overlap between the negative encoding success effect and positive retrieval success effect within the posterior midline region (PMR). This finding has now been confirmed in several other imaging studies (97, 100, 101). This pattern suggests that encoding and retrieval cannot occur at the same time and compete for DMN resources. We provided evidence that this competition indeed arises when both processes occur within a brief period of time and that it has direct consequences for memory. Critically, we showed that this effect cannot merely be ascribed to attentional processes, but is memory specific. Hence, encoding and retrieval compete. We also identified a specific region within the left ventrolateral prefrontal cortex (VLPFC) that appears to resolve the conflict between encoding and retrieval. Given that this region has been associated with rapid task-switching, the VLPFC may facilitate rapid switching between encoding and retrieval processes. Overall this study established that both the negative encoding success effect and positive retrieval success effect are closely linked to memory and both effects interact within the core of the DMN with direct consequences for memory.

In chapter 3, we used a continuous memory task to dissociate the difficulty of retrieval from retrieval success. This was inspired by the reallocation account of retrieval, which states that successful memory retrieval is less demanding than when retrieval is unsuccessful, which requires more effortful search and recurrent attempts. Thus, it is unclear if the retrieval success effect within DMN regions simply reflects reallocation of DMN resources to the more demanding conditions or relates to successful episodic retrieval. In order to distinguish between these alternatives, we manipulated the delay between encoding and retrieval during fMRI-scanning. The design was based on previous evidence indicating that retrieval at short delays is easier and leads to high-evidence mnemonic decisions, whereas retrieval at longer
delays is more difficult but also more hippocampus-dependent. Confirming previous findings, we found that retrieval decisions at short delays were more accurate and faster. With respect to fMRI results, the study identified three distinct patterns of brain activity within regions that commonly show a retrieval success effect. First, consistent with a role in episodic memory, the left and right hippocampus and the retrosplenial cortex – a subregion of the PMR - showed an increasing delay function. Second, consistent with increased difficulty, the precuneus and the superior parietal cortex (SPC), showed a decreasing delay function, consistent with the greater reallocation of resources. Critically, several cortical regions overlapping with the DMN – including mPFC, PCC, and IPC - showed a V-shaped delay function. This non-linear pattern of activity suggested that two different processes contributed to retrieval-related fMRI signals within the DMN. We interpret these findings as an interaction between the contributions of long and short-term memory. Regardless of the exact interpretation, the experiment clearly demonstrated that the PMR is functionally dissociated into three subregions: the retrosplenial cortex, precuneus and PCC – each contributing to retrieval in a distinct manner. Also, the mPFC, PCC, and IPC showed a coherent pattern of activity and were functionally dissociated from the hippocampus.

In chapter 4, we performed an experiment that was derived from the reconstruction account. According to this account, the DMN supports reconstructive processes that one needs to reassemble an original event from memory. Similar processes are thought be involved in mental imagery. An open issue is to what extent DMN regions support successful vs. unsuccessful imagery and retrieval processes. Previous studies that examined regional overlap between imagery and memory used uncontrolled conditions, such as autobiographical memory tasks, that cannot distinguish between successful and unsuccessful imagery and retrieval. In this study, we used a memory-retrieval and a mental-imagery task to characterize the overlap and difference between these closely related processes. We identified three patterns of activity that indicated the majority of brain regions contributed in a similar manner to retrieval and imagery. First, we identified several regions overlapping with the DMN, including the hippocampus, mPFC, PCC and the posterior part of the IPC – the angular gyrus - that are associated with successful performance during both retrieval and imagery (positive success effects). Secondly, we identified a network including the anterior cingulate cortex, dorsolateral prefrontal cortex, dorsal precuneus and insular cortex that are more active during unsuccessful performance in both tasks (negative success effects). We interpret this pattern arises from more recurrent or increased attempts to retrieve items from episodic memory. Finally, we identified an extraordinary pattern in three regions, including ventral precuneus, the midcingulate cortex and supramarginal gyrus. These regions were associated with successful retrieval but unsuccessful imagery (interaction effects). We interpret this interaction in terms of reconstruction. Specifically, retrieval of past information is a necessary prerequisite for successful imagery. Thus, we speculate that these regions might aid the reconstruction of vivid imagery experience by integrating retrieved information. Regardless of our interpretation, our findings confirm that the DMN regions – including the hippocampus, mPFC, IPC and PMR - function similarly during memory retrieval and mental imagery, while several immediately adjacent regions contribute distinctly.
In chapter 5, we used resting-state fMRI in combination with the task from chapter 4. The experimental design allowed us to test if orienting of attention towards external vs. internal information could explain the encoding/retrieval flip pattern. According to the orienting of attention account, the negative encoding success effect should reflect beneficial orienting toward externally-presented information and coincide with deactivations, while the positive retrieval success effect should reflect orienting toward internal-mnemonic information and coincides with activations in the DMN. First, we found that DMN regions - including mPFC, PMR and IPC - as defined by resting-state fMRI - were more active during encoding of internally generated information (imagery), than externally presented information (perception). Thus, we confirmed that DMN regions show increased activity during mental imagery. Secondly, we confirmed that the encoding/retrieval flip occurs in the DMN. Thus the core DMN regions were activated during retrieval, but deactivated during encoding. However, counter to the orienting of attention account, the encoding activity was not modulated by whether items would benefit from internal or external orienting of attention. Third, we found that the hippocampus did not show an encoding/retrieval flip pattern, but a positive success effect for both encoding and retrieval, again regardless of orienting of attention. Moreover, we found that the hippocampus was functionally disconnected from the DMN during encoding, but connected during retrieval. Overall, these findings suggest that the memory related signals in the DMN are not critically dependent on the orienting of attention and that hippocampus is functionally dissociated from the DMN when new memories are formed.

In chapter 6, we combined a subsequent memory task with breath-hold manipulation to assess the influence of respiration on event-related fMRI. There is considerable evidence from resting-state fMRI studies that respiratory artifacts contribute substantially to fluctuations in fMRI signal within the PMR, because of its large blood vessels. Despite the fact that respiration has been strongly associated with arousal and attention, this aspect has been ignored in task-based fMRI studies. To test this issue, we used a breath-hold manipulation to remove respiratory fluctuations during learning and assessed the influence on the negative encoding success effects within the PMR. First, consistent with previous encoding studies, the left VLPFC showed a positive encoding success effect, while the PMR showed a negative encoding success effect (98, 249). Critically, the negative encoding success effect in the PMR was highly sensitive to a breath-hold manipulation, while the positive encoding success effect remained unaffected. Secondly, we found that the respiratory cycle changes relative to stimulus presentation and subsequent memory, indicating a link between physiological changes and cognitive performance. Finally, we found that the amplitude of the respiratory fluctuations was correlated with the magnitude of the negative encoding success effect. Thus, subjects who showed stronger respiratory fluctuations also showed stronger signal difference in the PMR, but not in the VLPFC. Overall, these findings demonstrate that fast event-related fMRI studies are far from insensitive to slow changes in respiratory physiology. Specifically, respiratory fluctuations can selectively influence the fMRI signal and confound specific cognitive conditions. Thus, when using the subtraction principle to isolate a specific cognitive process, it is necessary to consider a possible bias due to physiological differences, especially when using an experimental design that evokes
physiological responses. Overall, our results indicate that signals from the core of the DMN are particularly vulnerable to respiratory fluctuations.

**Box 3: Main findings**

1. Encoding and retrieval compete when both processes happen within a brief period of time. This competition leads to a conflict within the PMR with consequences for memory. The mid-ventrolateral part of prefrontal cortex (VLPFC) helps to resolve this competition and facilitates rapid switching between both memory states.

2. Reallocation or differences in task-difficulty cannot easily account for the retrieval success effect in the default-mode network. Several regions, commonly linked to retrieval success, show divergent patterns as a consequence of retrieval difficulty.

3. Mental imagery and memory retrieval activate the majority of brain regions in a similar manner. Yet, the ventral precuneus, midcingulate cortex and supramarginal gyrus show a divergent pattern of activity, indicating that these regions contribute differently to imagery and retrieval.

4. Orienting of attention toward internal vs. external information cannot easily account for encoding/retrieval flip pattern within the DMN regions. Rather, connectivity between the cortical DMN regions and the hippocampus determines the success of encoding and retrieval.

5. Physiological fluctuations in breathing predict memory formation and profoundly influence the negative encoding success effect in the PMR, but not the positive encoding success effect in the left VLPFC

**Discussion**

**A memory bottleneck**

The *encoding/retrieval flip* suggests a processing bottleneck within the PCC. Not only do encoding and retrieval show opposite levels of activity, but when both occur simultaneously, they compete with detrimental consequences for memory. The flip-pattern poses a challenge for virtually all contemporary theories of memory. Most theories of memory and the brain, assume that retrieval is “reactivation” of activity patterns present during encoding. These theories claim that neuronal “reinstatement” is the basic principle of memory and the more activity during retrieval resembles the state of encoding, the better memory is (250-252). However, the *encoding/retrieval flip* violates this principle and indicates that DMN regions contribute differentially to both memory phases. Our interpretation, in terms of a processing bottleneck, suggests that these differential contributions actually conflict.

However, given the indirect nature of the fMRI signal, one should remain careful when interpreting the *encoding/retrieval flip* in terms of a neuronal bottleneck. A single voxel can contain thousands of neurons, some of which can increase in their firing rate, while others decrease firing at the same time. Also, the fMRI signal is not only affected by local firing-rate
changes, but also by synaptic input from projecting brain regions (23). Combined, these neuronal changes could potentially result in an increase, decrease or sum to zero, in terms of the local metabolic demands. Overall, the global signal within a voxel cannot increase and decrease at the same time, but overlapping neuronal populations within a single voxel can, and the fMRI signal reflects the metabolic sum of these changes. Thus, we currently still need evidence to decide if the bottleneck between encoding and retrieval reflects competing processes within single neurons, local brain activity or cognitive processes at a much larger scale.

Interestingly, a recent study using electrodes implanted into the posterior cingulate cortex (PCC) of a monkey, has shown that single PCC neurons increased their firing rate during mental states that reflect “rest” and decreased their firing rate during states that require allocated attention (247). The results also indicated that changes in PCC activity reflected changes in local firing rate and not synaptic inputs. In addition, the authors argued that the firing rate of single neurons is both up and down regulated in consistent with the metabolic demands of the regions. Although this study does not provide data on the behavior of PCC neurons in episodic memory, it does indicate that both decreases and increases in fMRI signal can be linked to local firing rate changes in a manner consistent with the default-mode hypothesis. At this time, it remains unclear whether the encoding/retrieval flip occurs because distinct - but overlapping - populations of neurons compete or single neurons have a bipolar role in encoding and retrieval. Further experiments should investigate the neuronal contributions to the fMRI signal within the PMR during memory tasks and test how (or whether) the encoding/retrieval flip links to neuronal changes directly. Especially, because the PMR is particularly vulnerable to fluctuations in the respiratory cycle and fMRI signals can easily be confounded by physiological artifacts.

Independent evidence for a direct link between episodic memory and the encoding/retrieval flip has been provided by clinical studies investigating the onset of Alzheimer’s disease (AD). First, healthy elderly often show a diminished negative encoding success effect within the PCC (93, 95). Secondly, it has also been shown that amyloid plaques– a clinical marker of AD – initially deposit in the PCC and quickly spread to other DMN regions (4). Interestingly, these deposits directly correlate with the failure to suppress DMN activity during learning and coincide with problems with encoding (85). It is believed that these deposits precede the age-related decline of memory and are indicative of a pre-clinical stage of AD. In combination, these studies link the integrity of the PCC and a failure to suppress activity directly to episodic memory encoding. Yet, it remains unclear if the same individuals also have problems with activating their PCC in memory retrieval.

In summary, the encoding/retrieval flip presents a unique opportunity to help understand the function of the DMN regions in memory. This is especially so since it defies the fundamental principle of “reinstatement”. Most contemporary theories of memory state that successful retrieval requires the reinstatement of patterns present during encoding (57-59). Regardless of the precise explanations for the encoding/retrieval flip, the work within this thesis shows

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3The posterior cingulate cortex is a subregion of the posterior midline and part of the default-mode network.
that DMN regions contribute to memory in a manner distinct from regions – such as the hippocampus - that do show reinstatement. I will discuss five accounts that attempt to explain the function of the DMN and flip-pattern: (1) reallocation, (2) reconstruction, (3) orienting of attention, (4) attention to memory and (5) respiration. Each account has merits and flaws and I will discuss them below.

The reallocation account

The reallocation account states that decreases in DMN activity reflect reallocation away from default-mode processes (104, 105). The encoding/retrieval flip pattern can be explained in terms of reallocation: If we assume that successful encoding requires relatively more resources, then we can also assume that successful retrieval requires relatively fewer resources. Our findings in chapter 3 indicated a pattern inconsistent with a reallocation account of retrieval. Although we did observe task-induced deactivations, we also observed increased activity in the core DMN regions, when the task became more dependent on long-term memory. Combined, this resulted in a non-linear pattern of activity. One potential manner to rescue the reallocation account is to assume that our task did not demand more resources at the most difficult conditions. For example, if participants simply give up, they also stop allocating resources. As a consequence default-mode processes can increase activity for the most difficult conditions. Although not impossible, participants still showed very accurate memory performance, which makes this alternative interpretation unlikely. Rather, the non-linear pattern of activity suggests that two separate processes – one closely linked to short-term memory and another to long-term memory - act on the DMN at the same time.

Another challenge of the reallocation account is provided by several recent studies on mental imagery and prospective memory. These studies show that the DMN increases activity when a subjective (re-)experience is relatively elaborate and full of details (113, 187, 253). These findings are also difficult to reconcile with the reallocation account, given that construction of an elaborate mental scene should actually require more resources than retrieval without contextual details. Together with our findings, these results indicated that DMN activity cannot be explained by reallocation alone. Rather than only attributing DMN activity reallocation, it seems that DMN activity can increase, thus allocate resources, during processes related to memory retrieval. Finally, the reallocation account makes no claim on what default-processes actually are. Therefore, the account avoids the question, what occurs within the DMN, when resources are not reallocated? Yet, if we assume rest is an active state of mind, and given the similarity between the DMN and the regions that show a retrieval success effect, it is tempting to equate default-processes with memory retrieval. The next account is motivated by these observations and addresses this shortcoming of the reallocation account.

The reconstruction account

The reconstruction account states that increased DMN activity reflects reconstructive processes that are an essential part of memory retrieval (110). The reconstruction account emphasizes that remembering of past or imaginary events is not an automatic process but requires mental effort. Our experimental comparisons, in chapter 4, pose a slight challenge
for the reconstruction account. We found that DMN regions showed an activity pattern related to successful retrieval and imagery. In contrast, regions closely adjacent to the DMN, showed a pattern consistent with successful retrieval but difficult imagery. Given that poor or failed attempts coincided with more effort and recurrent attempts, it is tempting to interpret this pattern in terms of intensified reconstruction. This interpretation seems consistent with the observations that these latter regions are also closely tied to working memory (254). Nonetheless, the reconstruction account also claims that “reconstruction” can be divided into further sub-processes. Thus, overall our interpretation is not inconsistent with the reconstruction account. It simply suggests that the more “effortful” components of reconstruction do not occur within the DMN regions, but in regions closely adjacent.

The encoding/retrieval flip pattern can partially be explained in terms of the reconstruction account. The positive retrieval success effect is consistent with more reconstruction for remembering, but it is trickier to reconcile with the negative encoding success effect. We could interpret increased activity during encoding in terms of reconstruction, when we assume that this activity is actually “detrimental” and leads to forgetting (31). Under this assumption, decreases during encoding result from less reconstruction of mental representation. Already, this interpretation is at odds with the general view that associations benefit learning (42). Yet, if we also assume that these associations are predominantly intrusive, less activity should coincide with better performance. However, in those cases the reconstruction account would might also predict that subsequently forgotten items also activate DMN regions, when compared to a passive baseline. This is not the case, and encoding deactivations actually deviate from baseline, while activations for forgetting are indistinguishable from baseline (98). Overall, the reconstruction account makes an important statement regarding the reconstructive nature of memory retrieval (54, 55), but it is not very informative with respect to DMN activity during memory encoding or task-induced deactivations in general. The following account provides a full explanation for both increases and decreases in DMN activity by attributing them to differences in orienting of attention.

**The orienting of attention account**

The orienting of attention account states that activity in the DMN network decreases when attention is oriented to the external environment, but increases when attention is oriented to internally generated representations (4, 28). The encoding/retrieval flip pattern can be explained in terms of orienting of attention under the assumption that successful encoding requires focus on the external environment, while successful retrieval is aided by internal attention (116). In summary, DMN activity reflects a virtual axis of internally versus externally oriented attention (internal = more DMN activity / external = less DMN activity). Thus, according to the orienting of attention account, the levels of activity during encoding and retrieval are a byproduct of the state of attention and not directly linked to memory.

Our findings in chapter 5 indicated a pattern of activity that was inconsistent with the orienting of attention account. Consistent with the account, we observed that the DMN is activated by mental imagery and that rich mental imagery benefits learning. However inconsistent with the account, we found that at the same time decreased DMN activity still predicted encoding regardless of whether items was internally imagined or externally
presented. Thus, these findings indicate that orienting of attention alone cannot explain the activity patterns within the DMN related to memory. One way to defend the *orienting of attention account* is to assume that our encoding/imagery task did not require sufficient internal attention to completely reverse DMN activity. However, when comparing internal to external encoding, we did observe significant DMN activity (internal > external). Thus, such an explanation is not likely. Also, mentioned above, we found that successful imagery benefited memory encoding. Rather, the pattern of activity - again - suggests that two processes act on the DMN at the same time. Consistent with this idea, several recent studies have also showed that individual regions of the DMN – or overlapping regions - contribute to various cognitive processes in different manner (63, 96, 255). Thus, although DMN regions are less active during conditions that require external attention versus those that require internal attention, not all patterns of DMN activity – including the *encoding/retrieval flip* - can be explained in terms of the *orienting of attention*.

**The respiratory account**

The *respiratory account* – introduced within the thesis - claims cognitive processes coincide with physiological responses and can result in respiratory fluctuations that affect the fMRI signals. Critically, the *respiratory account* does not disprove any of the earlier mentioned accounts, nor does it singlehandedly account for the activity differences within the DMN. Rather, it attempts to isolate and explain the contributions of a single component of the fMRI signal. By doing so, the *respiratory account* assumes that the DMN regions mediate several independent processes that contribute to signal differences. In retrospect this idea seems almost trivial, but it has an important implication. From here, we consider the possibility that we require multiple accounts in order to explain the role of the DMN.

In chapter 6, we provided evidence that the negative *encoding success effect* within PMR can be largely explained by respiratory contributions. In contrast, we did not find this effect in other DMN regions. Yet, we cannot exclude - by the absence of an effect – that respiration has no influence in other DMN regions. Instead, it is known that respiratory fluctuations have various effects on the fMRI signal in different parts of the cortex (118, 238). Therefore, we assume that the contribution of respiration varies in different DMN regions. Importantly, the results also demonstrate that effects of respiration are not automatically removed by a simple contrast between two cognitive conditions. In contrast, cognitive conditions can differ with respect to respiration. Finally, we should emphasize that the negative *encoding success effect* did not disappear entirely in the absence of respiratory fluctuations. The residual effect that cannot be explained by respiration is consistent with the earlier mentioned findings of single PCC neurons that change their firing rate in a manner consistent with the default-mode hypothesis (247). Recently, similar results using intracranial measurements in humans have been reported and established the neuronal origin of the DMN (248). Consistent with these findings, we interpret the residual negative *encoding success effect* as a conventional cognitive-based signal differences resulting from neuronal processes.

Overall, the data in chapter 6 demonstrates that it is probably impossible to construct a single cognitive axis that captures the various functions of the DMN. Actually, the results of chapters 2, 3 and 5 illustrate the exact same point: the fMRI signal within DMN regions
reflects the combination of multiple processes. Yet with the respiratory account, we can still attempt to construct a single theory for the PMR. For example, we could interpret increased activity in terms of reconstruction and decreased activity in terms of ongoing respiratory fluctuations. Yet, given that we observe the influence of respiration mostly in PMR, such a combinatory account would not automatically apply to signals in other DMN regions. Thus, although respiratory changes might account for some of the cognitive findings within - and outside – of the data published within this thesis, it cannot account for the signals within the DMN alone. I will now introduce a final cognitive account, that still attempts to singlehandedly explain the role of the DMN. This account was originally intended to explain signals within the parietal cortex and does not incorporate - or exclude - the contributions of respiratory fluctuations.

The attention to memory account

The attention to memory account (AtoM) claims that activity in the DMN network decreases when attention is under control of top-down memory processes, but increases when attention is under the influence of bottom-up memory processes (63, 158, 256). This account is inspired by perceptual models for control of top-down versus bottom-up attention (96, 202). Also, the AtoM model specifically applies to the role of the inferior and superior parietal cortex (SPC). However, since the inferior parietal cortex (IPC) is part of the DMN, I consider therefore the AtoM account as a potential interpretation for DMN activity. As such, the AtoM account explains the encoding/retrieval flip pattern in terms of bottom-up versus top-down memory processes. During encoding, top-down control of memory benefits learning and as a consequence DMN deactivations predict success. In contrast, during retrieval, bottom-up memory processes coincide with success and activate the DMN regions.

Most findings within this thesis can be explained in terms of the AtoM account. The bottleneck within our memory system, presented in chapter 2, can be explained in terms of competition between bottom-up attention benefiting retrieval, and top-down attention benefiting memory encoding. In chapter 3, the non-linear patterns of activity could also reflect competing top-down and bottom-up memory processes: the very short delay might be reflecting spontaneous retrieval resulting from a lack of task difficulty, while the very long delays are dominated by bottom-up recognition, since these delays are no longer supported by the short-term memory buffer. Activity in the DMN regions might reflect this interaction between top-down and bottom-up memory processes by a V-shaped pattern of activity. In chapters 4 and 5, the increased activity for imagery might reflect bottom-up contributions of retrieval. While at the same time the negative encoding success effect might again reflect top-down contributions to memory encoding. Each time, a combination of bottom-up and top-down memory processes can explain the complex pattern of activity.

Despite the validity of AtoM account with regard to the work presented within this thesis, it remains a post-hoc explanation. Also, although the AtoM account can explain most findings presented within this thesis, it remains relatively unspecified what bottom-up and top-down memory processes precisely are. AtoM borrows its terminology from experiments on perception and top-down versus bottom-up attention (257). When people focus their attention, they place cognitive processes under top-down control, while sudden distractions
are the consequence of bottom-up processes. These studies emphasize that bottom-up
distractions are not necessarily bad, since they can benefit perception of an approaching car
or a sudden fire alarm. The main point of the AtoM account is that bottom-up signals do not
originate from the external environment alone, but can also spontaneously arise from our
memory system. Again, the claim is that spontaneous retrieval is not necessarily bad, but can
also benefit recognition memory or mental imagery (63). Very recently, some new
experimental data has been published in support of AtoM account and on the separation of
top-down versus bottom-up contributions to memory. (258) Still, it remains an open
question to what extent the AtoM account is relevant for DMN regions beyond the parietal
cortex.

Multiple accounts

To conclude, no single account – including AtoM – can sufficiently explain all findings with
regard to the DMN. Within this thesis and in several recent studies, the DMN has been
linked to mental imagery, thinking about others, autobiographical memory, self-reflection,
prospection, navigation and more (e.g. 114, 165, 253, 259). Also, the DMN shows
abnormalities in many pathological states, including AD, schizophrenia, ADHD, and
depression (e.g. 4, 81, 82, 84). Interestingly, it has been shown the macaque brain hosts a
similar default-network (260). Thus far, it has proven impossible to find a single basic
explanation that can account for all these observations. In contrast, the data within this thesis
shows that individual brain regions can flexibly couple and decouple from the DMN. Also,
individual DMN regions can show signal related to multiple cognitive processes at the same
time. In line with our findings, it has recently been shown that the DMN can be fractionated
into functionally distinct components (255). Thus, although it remains desirable to find a
single basic explanation, this might simply prove impossible. Our own data suggests that
multiple accounts are necessary to explain the versatile signals with the DMN. Before I draw
final conclusions regarding the validity of each account, it is useful to drop the notion of a
single coherent default-network and characterize some differences between the core DMN
regions (i.e. the hippocampus, mPFC, PMR, and IPC).

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<th>Box 4. Some issues regarding each account</th>
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<td><strong>Reallocation account:</strong></td>
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<td>- Only explains the role of the DMN in encoding, not retrieval</td>
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<td>- Does not clarify the cognitive content of default-processes</td>
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<td>- Cannot account for the results in chapters 3, 4 and 5</td>
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<td><strong>Reconstruction account:</strong></td>
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<tr>
<td>- Only explains the role of the DMN in retrieval, not encoding</td>
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<td>- Requires further decomposition of reconstructive processes</td>
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<td>- Cannot account for results in chapter 4</td>
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<td><strong>Orienting of attention account:</strong></td>
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<tr>
<td>- One a function for the DMN</td>
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<td>- Explains the encoding/retrieval flip</td>
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<td>- Seems to fit with most of the literature</td>
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<td>- Cannot account for results in chapter 5</td>
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<td><strong>Respiratory account</strong></td>
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<td>- Shows that DMN signals are composed of multiple components</td>
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<td>- Applies to the PMR but does not extend to other DMN regions</td>
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<td>- Neurons in monkey PMR fire consistent with the DMN hypothesis</td>
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<td><strong>Attention to memory account:</strong></td>
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<td>- Explains the encoding/retrieval flip</td>
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<td>- Seems to fit with most of the literature</td>
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<td>- Unclear if account applies to regions outside the parietal cortex</td>
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The hippocampus

The hippocampus is indisputably linked to memory, although its specific function remains debated. Animal studies – mostly in rats – link the hippocampus particularly to spatial navigation. Although place cells have also been found in the human medial temporal lobe (e.g. 112, 261), studies in humans predominantly link the hippocampus to episodic memory (e.g. 59). Several theories try to reconcile this apparent discrepancy, by emphasizing that the rat hippocampus is also critical for upcoming non-spatial events and might help generate predictions based on memory (e.g. 53, 102) Recent animal studies have shown that brief sequences of hippocampal place-cell activity are chained together to represent extended episodes (262). These patterns form both retrospective and prospective codes and are more pronounced when animals make exploratory decisions (263). Although the precise function of this prospective activity is heavily debated, the patterns clearly demonstrate that hippocampal activity is not only triggered by current events, but also anticipates future behavior. Consistent with this prospective view, it was shown in recent clinical studies that hippocampal damage can also lead to impairments when imagining novel events (166, 264). More general, it is often reported that patients with impaired memory - for example in Korsakoff’s syndrome – often show an absence of imagination and flexible thinking (265, 266). Taken together, these findings suggest a flexible role for the hippocampus. The hippocampus provides elements that can be constructed – by interacting with other default-mode regions – to remember past events, explore novel possibilities and encode information to guide future behavior.

Box 5. Schema of activity patterns in the core default-mode regions during encoding and retrieval

In orange, the hippocampal formation (HF) which shows a positive success effect during encoding (ENC) and retrieval (RET). In blue, the medial prefrontal cortex (mPFC), inferior parietal cortex (IPC) and posterior midline regions (PMR) which show the encoding/retrieval flip pattern. In red, an estimated contribution of respiration to the negative encoding effect within the PMR. The contribution of respiratory fluctuations to the retrieval success effect has not been investigated. (HF is not in plain).
The inferior parietal cortex

The lateral regions of the inferior parietal cortex (IPC) are implicated in a wide range of cognitive functions including perception, attention and working-memory (e.g. 202, 254). The lateral IPC receives and sends information to the sensory–motor systems, the hippocampus and prefrontal cortex (177). Unilateral lesions in the parietal cortex commonly result in attention deficits that result in a neglect of part of the external environment (267, 268). Also, neuroimaging studies have consistently implicated the IPC in memory (12, 98) and recently, it was also shown that bilateral lesions of the IPC can result in deficits in episodic memory (61, 62). Several recent studies try to reconcile the versatile role of the IPC by segregating distinct subregions - within close proximity - into separate functional modules (e.g. 141, 144, 269). However, the mapping of functional modules to precise anatomical locations has proven difficult, due to relatively large individual variations and a lack of precise anatomical definitions (270). This lack of definitions is the result of the relative absence of a precise IPC homologue in the macaque monkey (271) and the relative difficulty of tracking white matter fibres in diffusion images of the IPC (1). To circumvent these difficulties, new segregation schemas are being proposed that incorporate data from resting-state connectivity (272). These schemas might serve as roadmaps for investigating the IPC and settle some of the current controversies (96, 99). The data within this thesis clearly verifies the role of the IPC in memory. Also, via the functional dissociations within close proximity, it also exemplifies the need for better functional/anatomical definitions. Despite the debate on precise localization of subregions within the IPC, the view has emerged that the IPC integrates perceptual information from the environment with information from our memory system (63, 96). Taken together, these theories postulate that the mechanisms that operate on perceptual attention can also be applied to help our understanding of memory. In sum, the IPC provides an arena for bottom-up and top-down interaction between information from the hippocampal-memory systems and sensory brain regions.

The medial prefrontal cortex

Although the medial prefrontal cortex (mPFC) is consistently implicated in memory and the DMN (105), it still remains a relative poorly understood region of the human brain (273). Patients with damage in the mPFC can suffer from impaired recall of detailed events, while retaining normal recognition memory (274). Also, damage to the ventral part of the mPFC can result in a tendency to confabulate during retrieval of autobiographical memories (275). The mPFC is activated during spontaneous self-referential thought (276) and judging the similarity of another person to oneself (277). Several recent imaging studies have shown that the mPFC is activated when judging whether retrieved information is referring to oneself or not (165, 188, 278). Overall, these observations suggest that the mPFC helps in evaluating the self-relevance of memories (255, 279). This idea is consistent with studies that link the mPFC to evaluation of past, current and upcoming options (e.g. 280-283). Combined, these findings support a prospective memory function for mPFC, in which memories of past experiences are used to generate predictions of upcoming events (9, 187, 284). In sum, the mPFC helps to assess the relevance of memories and evaluate the episodic exploration of possibilities.
The posterior midline

The posterior midline region (PMR) shows the patterns of activity that have defined the DMN (67) and is considered the central node of the DMN (285). The PMR is composed of the retrosplenial cortex, posterior cingulate cortex (PCC) and anterior part of the precuneus. Each region has differential connections and the data within this thesis shows that these regions contribute to different aspects of memory (2, 190). The retrosplenial cortex has dense connections to the hippocampus and is associated with episodic memory and spatial navigation (286). Also, neurological disorders that impair memory - such as AD and post-traumatic stress disorder – often compromise the integrity of the retrosplenial cortex (287). The posterior cingulate cortex has the strongest reciprocal projection to the mPFC and thalamus and has been associated with emotional content of memory (2, 288). Finally, the precuneus is most densely connected with the IPC and sensory regions and is often associated with the perceptual-like experience of mental imagery (15). Despite these minor differences, their strong interconnections (2) and the fact that these regions often (de)activate in synchrony suggest that these regions are functionally related. (28). However, given that the PMR has proven particularly sensitive to respiratory fluctuation, some previous cognitive findings might require reinterpretation. For example, uncontrolled cognitive processes such as mind-wandering or lapses of attention may well coincide with changes in the respiratory cycle (229, 289). As a consequence, the PMR might prove functionally far more diverse than we observed until now. To conclude, given its central location, the PMR is perfectly equipped to integrate and control the communication between various DMN regions.

Future studies

The DMN covers the most metabolically active regions of the brain and during rest it consumes roughly 40% more glucose compared to the hemisphere average (67). Currently, we lack a functional explanation why these regions consume the most energy. Within this thesis I argue that cognitive default processes - that consume energy and recruit neurons within the network – are responsible for this consumption. Evidence for the cognitive involvement of DMN regions in memory and during spontaneous rest is abundant (53, 229, 289-291). Although this can explain increased activity during rest, it cannot explain why their metabolism exceeds other regions – for example, the visual cortex (28). Novel studies should investigate whether this metabolic property of the DMN reflects underlying functional-anatomical properties - such as the proportion of interneurons or the average spiking rate of all pyramidal cells. A better understanding of the local anatomical properties and how they affect the fMRI signal should help decide the validity of the theoretical accounts that explain the functional role of the DMN. For example, the AtoM account states that DMN activity is functionally up-and-down regulated, while the reallocation account proposes only functional deactivations (63, 104). Increased understanding of the functional properties of the fMRI signal in combination with the anatomical properties of these cortical regions should help decide the validity of various accounts.
In conclusion, the work in this thesis has provided a number of new insights into episodic memory and the role of the default-mode network. First, it provided the first direct evidence for the contrasting role of DMN during encoding and retrieval. Secondly, the experimental findings eliminate several possible explanations for the role of the DMN, including a simple reallocation account and the orienting of attention account. Moreover, the present work sheds light on the contribution of different processes - including respiratory - to the fMRI signal. Finally, the work clarifies the flexible nature of the DMN, for example, the distinct role of the hippocampus during encoding. Overall, the work within this thesis has clearly indicated that the individual DMN regions provide distinct contributions to learning and remembering.