Chapter 6

General discussion

Research on future thinking is in its infancy and only recently have neuroscientists begun to direct attention to the asymmetry of mental time travel into past and future [92]. The current thesis aimed at elucidating differences between episodic memory and episodic future thinking in order to gain insight into the brain mechanisms involved in the dissociation of mental time travel into the past and future. A detailed discussion of the results of the four studies can be found at the end of the respective study chapters. The next sections briefly summarize the main results before embedding them into broader concepts and outlining directions for future research.

6.1 Summary of main results

All four studies revealed differences between mental time travel into the past and into the future, on the level of brain activation patterns using functional magnetic resonance imaging (fMRI, Studies 1 and 2) and electroencephalography (EEG, Study 3) and on the behavioral level in a patient investigation (Study 4).

6.1.1 Study 1

A direct comparison of brain activation patterns for episodic memory and episodic future thinking (Study 1 on page 19) revealed stronger activation during remembering in several regions of the visual processing stream presumably due to sensorial reactivation [77, 80, 83]. Stronger activation for episodic future thinking emerged in inferior temporal gyrus, potentially related to semantic detail generation. A whole brain interaction analysis uncovered that activation in right posterior hippocampus was strong during the early construction of past events, but subsided during the following elaboration, while the reverse was true for future events. An interaction of opposite
direction was observed in lateral prefrontal cortex (and other regions). These findings may be linked to an asymmetric predominance of associative and active retrieval processes for past and future event generation and suggest that memory and future thinking may differ in temporal activation patterns.

6.1.2 Study 2

FMRI parametric modulation analysis (Study 2 on page 37) revealed that subjective ratings of occurrence probability for future events modulate activation in the right anterior hippocampus: Activation increased with decreasing probability ratings. For unlikely future events, subjects presumably combine event details that never co-occurred before leading to elevated binding demands and thus increased hippocampal involvement. The study demonstrated the impact of inherent differences between mental time travel into future and past on brain activation.

6.1.3 Study 3

Electrophysiological investigation of past and future event generation (Study 3 on page 47) uncovered early differences in slow cortical potential amplitudes at temporo-parietal and parieto-occipital electrode sites, as well as late differences over right prefrontal cortex, presumably reflecting asymmetries in retrieval strategies and amount of sensorial and semantic detail retrieval. This differential recruitment of various processes, reflected in the time course differences, may help the brain tell apart memories from future thoughts.

6.1.4 Study 4

Study 4 (page 65) showed that patients with lesions in the medial dorsal nucleus of the thalamus, who were not impaired in an episodic memory task, exhibited a pronounced deficit for novel event generation. More precisely, imagination of impersonal and personal impossible events led to stronger impairments than episodic future thinking, probably linked to differences in recombination demands. The data suggested that lesions in the medial dorsal thalamus disrupt the ability to flexibly recombine information stored in episodic memory and demonstrate a difference in the cognitive processes required for mental time travel into the past and future.
6.2 Neural substrates of the past/future dissociation

When integrating the above-described results, it becomes obvious that a separation between episodic memory and future thinking can be observed in many regions of the core network (Figure 6.1). This is not in contradiction with the previously observed similarities (see section 1.2.1), which were confirmed in Study 1 (fMRI) and Study 3 (EEG). Differentiation takes place on a more subtle level, meaning that the activated regions for memory and future thinking do not extensively differ, but the strength and timing of activation seem to vary.

Studies 1 and 3 corroborated the notion of the reality monitoring framework that true memories evoke activation in posterior cortices due to the reactivation of sensory-perceptual details that were experienced during the original happening [77, 80, 82, 83]. In accordance with this, the assessment of phenomenological characteristics in the EEG examination (Study 3) revealed higher richness of detail for past than for future events; in the fMRI investigation (Study 1), on the other hand, detail scores were statistically indistinguishable for both conditions. The latter fact points to the problem that the richness of detail rating can comprise semantic and sensory details which are for practical reasons not separated during fMRI investigations like in behavioral studies [54, 84, 90]. Future-associated activation of lateral temporal cortex (Studies 1 and 3) may be linked to increased semantic detail generation which is used if sensory-perceptual information is missing.

Besides differing types of retrieved information (i.e., sensory-perceptual vs. semantic), the type of the retrieval operation itself is likely to differ between episodic memory and future thinking. For many past events, information can be retrieved in a fast associative manner that is dependent on the medial temporal lobe [137, 156, 184] and may be mirrored in the early past-associated hippocampal activation observed in Study 1. Future event generation, on the other hand, is presumably dependent upon active retrieval matching with early future-associated activation of the prefrontal cortex (Study 1) and is in accordance with the literature [23]. Asymmetries in the need for active and associative retrieval are further corroborated by past/future differences in the slow wave amplitudes over right prefrontal cortex during the late elaboration phase (Study 3). Finally, Study 4 showed that patients with lesions in the medial dorsal nucleus of the thalamus can vividly recall memories from their past, but are impaired in generating novel events. This is presumably

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1Ratings can be made inside the scanner; however, for time reasons this constrains the number of ratings that can be achieved. Ratings outside the scanner following the actual experiment have the disadvantage that the mental image of each event is no longer fresh and ratings on subcategories of richness of detail would likely be inaccurate.
Figure 6.1: Neural substrates of the past/future dissociation. The colored areas indicate brain regions in which the studies of the present project revealed evidence for a differentiation of mental time travel into the past and into the future.
caused by a deficient functioning of the medial dorsal-prefrontal circuit which is implicated in executive aspects of memory [95, 96]. In other words, active retrieval is hindered in these patients, while associative retrieval mediated by the medial temporal lobe may be unaffected thereby enabling the recovery of episodic memories.

The patient study (Study 4) further suggests an important function of the thalamus during mental time travel which has previously not been regarded. Especially studies with patients suffering from brain lesions have concentrated on the role of the hippocampus showing that this brain structure is important for binding together event details [34, 192]. This proposed function is in line with the interpretation of Study 2 that hippocampal activity modulation by occurrence probability may trace back to increased binding demands for unlikely events.

In summary, according to the data of this project the distinction between memories and future thoughts seems to be rooted in the different types of details that constitute mental journeys into the past and future (i.e., sensory and semantic) and different types of retrieval used to generate those details (i.e., active vs. associative). These differences expressed themselves in brain activation patterns, time courses of activation, and impairments following brain lesions.

6.2.1 Reconciling previous controversial results

The overview of previous neuroimaging studies on mental time travel and related abilities (see section 1.4.1) revealed mixed results with respect to unique past- and future-associated activation patterns. As mentioned previously, this may be partially caused by differing experimental designs and missing data about phenomenological properties (see section 1.4.1 and Addis et al. [77]). Study 2 revealed an additional factor that can help to reconcile inconsistencies with respect to the hippocampal involvement in mental time travel: Activation strength in parts of this brain structure is modulated by occurrence probability, which only exists for future events and thus impacts brain activation only in this and not in the past condition. Thus differing levels of occurrence probability in the studies may have led to a varying recruitment of the hippocampus.

The general trend toward strong prefrontal activation in future-directed thoughts [23, 25, 41, 76] could not be reproduced in Study 1 for reasons outlined in the respective discussion (page 35), but Study 4 indirectly hinted at the importance of the prefrontal cortex by showing the detrimental effects of lesions in the medial dorsal nucleus, which is strongly connected to the prefrontal cortex (see section 1.6). In addition, both Studies 1 and 3 (fMRI interaction analysis and EEG) showed that the involvement of many regions
of the core network is not an all-or-nothing phenomenon but fluctuates over
the course of event generation, thereby emphasizing the complex interplay of
various processes during mental time travel. Data from Studies 1 and 3 fur-
ther converge with observations of Addis and colleagues [77] that memories
for truly experienced events lead to stronger activation of sensory areas than
imagined events.

6.2.2 The prefrontal-thalamic-hippocampal axis

It is currently a matter of debate how different brain areas work together
in order to create predictions for the future. It is well established that the
hippocampus is important for relational memory, i.e., building associations
between stimuli [122, 125, 193, 194, 195] and suggested functions during men-
tal time travel include scene construction [35, 192] and recombination of de-
tails into novel events [141]. Merging neuroimaging studies in humans and
cell recording experiments in animals, Eichenbaum and Fortin [32] recently
proposed a more detailed model of how the hippocampus may subserve the
generation of predictions: Hippocampal neurons make up relational networks
in which distinct episodes are associated by common features and this over-
ap allows to derive relationships between elements that belong to different
episodes. In this model, the hippocampus only supplies the recovered memo-
ries, it does, however, not itself construct the future scenarios; logical process-
ning by the prefrontal cortex is required to evaluate the relationships between
elements.

It is still unclear whether the hippocampus mediates only retrieval and
binding of details\(^2\) or whether recombination itself and thereby generation
of novel events takes place in this medial temporal lobe region [196], poss-
ibly in the anterior hippocampus [141]. The animal literature shows that
hippocampal neurons are capable of predictive coding [196]. Buckner [36]
recently proposed that hippocampal cell assemblies can re- and preplay event
sequences, which can also be chained together in order to create extended
sequences. A certain amount of randomness in the chaining process may lead
to new sequences producing flexible behavior. It has to be noted, however,
that electrophysiological investigations in animals address predictions on a
much shorter time scale than mental time travel spans in humans [7, 10] and
it is still a matter of debate whether and in what way human mental time
travel and animal foresight abilities differ [4, 5, 6, 7, 8, 9, 10, 11].

The data from the present patient study (Study 4 on page 65) clearly sup-
port the view that the hippocampus does not carry out all necessary func-

\(^2\)There is good evidence that the hippocampus mediates at least two functions during
episodic memory recall: It serves as an index that reinstates a set of details stored in the
neocortex and it integrates details into a coherent whole [192].
Figure 6.2: Anatomical connections between prefrontal cortex, thalamus, and medial temporal lobe. Connections are simplified according to Aggleton and Brown [197]. See left part of figure for anatomical localization of structures (medial temporal lobe components following Bird and Burgess [198]). EC: Entorhinal cortex; PC: Perirhinal cortex; PHC: Parahippocampal cortex.

Tions for novel event generation. Patients with intact hippocampi were able to remember past episodes but had marked problems imagining novel events. The present data thus show that an intact prefrontal-thalamic-hippocampal axis (Figure 6.2) is required for novel event generation. Opitz [195] proposed that different kinds of binding may be subserved by the prefrontal cortex and the medial temporal lobe regions (see Figure 6.2 for medial temporal lobe anatomy) and Barbey et al. [187] point to the important role of the prefrontal cortex for event sequence knowledge (see discussion of Study 4 on page 104 for more details). In accordance with this, Hassabis et al. identified a whole network responsible for scene construction [72] and Summerfield et al. showed that the hippocampus does not exhibit tonic activation while elements are added to the scene [73]. Like other areas – for instance the dorsolateral prefrontal cortex and thalamus – it was engaged and disengaged as needed.

The role of the thalamus in the interaction between prefrontal and medial temporal lobe regions has remained elusive so far, but it became clear from Study 4 that its integrity is essential for novel event generation. As outlined in the discussion of Study 4 (page 105), the medial dorsal nucleus of the thalamus seems to play an active role in memory by modulating the activity of neurons connecting the medial temporal lobe and prefrontal cortex [190]. Human patient studies have indicated a role for the thalamus in prospective memory\(^3\) [199], creativity [177], and especially for the medial dorsal thalamus.

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\(^3\)Prospective memory describes the process of remembering to carry out a certain action in the future.
in relational memory [98]. All of these functions are related to the generation of novel events by the processes of planning (prospective memory), integrating information about different elements (relational memory), and divergent thinking (creativity), but it is as yet unclear how exactly the thalamus contributes to these functions.

Although clearly more research is needed to understand the contribution of different areas to the recombination process, it is evident that complex interactions between medial temporal lobe, prefrontal cortex, thalamus, and further brain regions are involved and that thalamic contributions may be as important as intact hippocampal functioning (Study 4).

6.3 The plausibility of imagined events

Previous studies have blurred the dissociation between future, atemporal plausible, and implausible events partially because these different types of imagination seem to recruit a highly similar set of brain regions [23, 24, 26, 72, 77] and because amnesia seems to disrupt both future thinking and imagination of atemporal novel events [34, 59, 60, 62, 65]. As noted by Szpunar, there is nevertheless an important difference between "imagining encountering a stray elephant on the way to work tomorrow, and imagining seeing an elephant during a trip to the zoo that one intends to take next week" [159, p. 145]. In line with this claim, imagination of implausible (i.e., fictitious) events in Study 4 was behaviorally differentiated from imagining plausible future events. The impact of occurrence probability on brain activation (Study 2) additionally hinted at a neural differentiation. Disentangling the different types of imagination or unraveling a continuous influence of plausibility on behavioral and neural measures will be an interesting task for the future (see section 6.4).

6.4 Open questions

Given the short history of future thinking research, much remains to be explored in order to understand the exact relation between mental time travel into the past and into the future. The following proposals for future research questions thus cover only those that result from the experiments of the present project.
6.4.1 Role of medial dorsal thalamus and prefrontal cortex for mental time travel

Study 4 implicated the medial dorsal nucleus of the thalamus in mental time travel; however, it is not yet clear whether this is due to a disconnection from the prefrontal cortex or from the medial temporal lobe or due to a disturbance of an intrinsic thalamic function. Testing the patients with additional standard tests for executive functions [22] would be a first step to characterize their impairments in more detail; another interesting approach would be to relate the capacity for novel event generation to more abstract concepts like creativity. A comparison of imagination and memory skills of patients suffering from different brain lesions in the prefrontal-thalamic-hippocampal axis may, however, be best suited to resolve this question.

6.4.2 Influence of event plausibility

As outlined in section 6.3, previous research did not distinguish plausible and implausible events. During fMRI, subjects could be prompted\(^4\) to imagine events that are already planned, events that are not planned but likely to happen, unlikely events, and impossible events. Conditions could be compared directly or parametric modulation analysis (similar to Study 2) could be conducted using subjective ratings of plausibility, which would allow to model linear and non-linear influences of plausibility on brain activation. Parametric modulation could reveal whether implausible events represent only one end of a plausibility continuum (linear influence) or whether there is a general discontinuity between plausible and implausible events (non-linear influence). Based on the data of Studies 2 and 4, target regions for this investigation would comprise the hippocampus, thalamus, and prefrontal cortex.

6.4.3 Relation between future thinking and decision making

The discussion on the functional advantage of the capacity to simulate the future has led to the proposal that decision making processes may benefit from mental time travel [147]. Peters et al. recently reported that future reward discounting\(^5\) can be diminished by episodic future thinking [201]. That means that imagining the situation in which one receives a reward in the future helps

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\(^4\) Cue words could be specifically designed to facilitate imagination of the different event categories (e.g., Christmas vs. outer space) or subject-specific information from a prescanning session could be used.

\(^5\) A reward is assigned lower value when promised for the future compared to immediate delivery [200].
to appreciate the value of that reward. It would be interesting to see whether
the influence on discounting can be manipulated by the probability of the
imagined events. In other words, does the imagination of a highly likely event
(e.g., receiving money as a birthday present from the parents) diminish the
delay discounting more than imagination of a highly unlikely scenario (e.g.,
meeting Bill Gates who spontaneously decides to give money to strangers)? A
relation between reward and probability processing would strengthen the idea
that future thinking is behaviorally relevant for present decisions and could
further explain the modulation of caudate nucleus\(^6\) activity by occurrence
probability in Study 2.

### 6.4.4 Methodological considerations

The present project introduced several methodological advancements with
respect to previous experiments, which may be interesting to implement in
future studies as well. Future studies should consider to take advantage of the
high temporal resolution of EEG, given that Studies 1 and 3 revealed strong
evidence for differences in the temporal brain activation patterns for memory
and future thinking.

Experimental designs for fMRI studies have already been advanced over
the last years by introducing construction and elaboration subphases [23].
Study 1 additionally introduced investigating memory and future thinking for
one on the same event in order to keep temporal distance and content similar
across conditions. This rules out factors that may potentially elicit differences
in brain activation patterns that are not truly caused by the past/future
distinction. Together with previous investigations [78, 115], Study 2 stressed
the importance of assessing the phenomenological properties and considering
them in the interpretation of the data. For future studies it will be even
more important to estimate the novelty of events since it was shown that
past/future differences in the phenomenological features only emerge if future
events are truly novel [90].

Finally, Study 4 suggested that working with patients suffering from brain
lesions that only mildly or not at all impair memory functions opens new
ways for the mental time travel research.

### 6.5 Conclusion

The present project aimed at investigating the differences between mental
time travel into the past and into the future in order to gain insight into the
brain mechanisms which help to tell apart memories from future thoughts.

\(^6\)The caudate nucleus is commonly implicated in reward processing [202, 203].
Using functional magnetic resonance imaging, electroencephalography, and the investigation of patients suffering from ischemic brain lesions, the studies revealed a differentiation of the brain activation patterns, the time courses of activation, and the processes recruited during episodic memory and episodic future thinking. More precisely, the present data suggest that both processes may be distinguishable based on the predominance of sensory-perceptual or semantic details and by the predominance of associative or active retrieval mechanisms.

While many of the here reported results speak in favor of the constructive episodic simulation hypothesis by replicating previously reported similarities between remembering and imagining [16, 17], it is important to note that strong evidence exists that future thinking draws on additional processes compared to episodic memory. Future studies will characterize these additional resources in more detail and will help to elucidate the functional significance of the capacity to simulate the future for daily life, for instance during guiding our decisions.