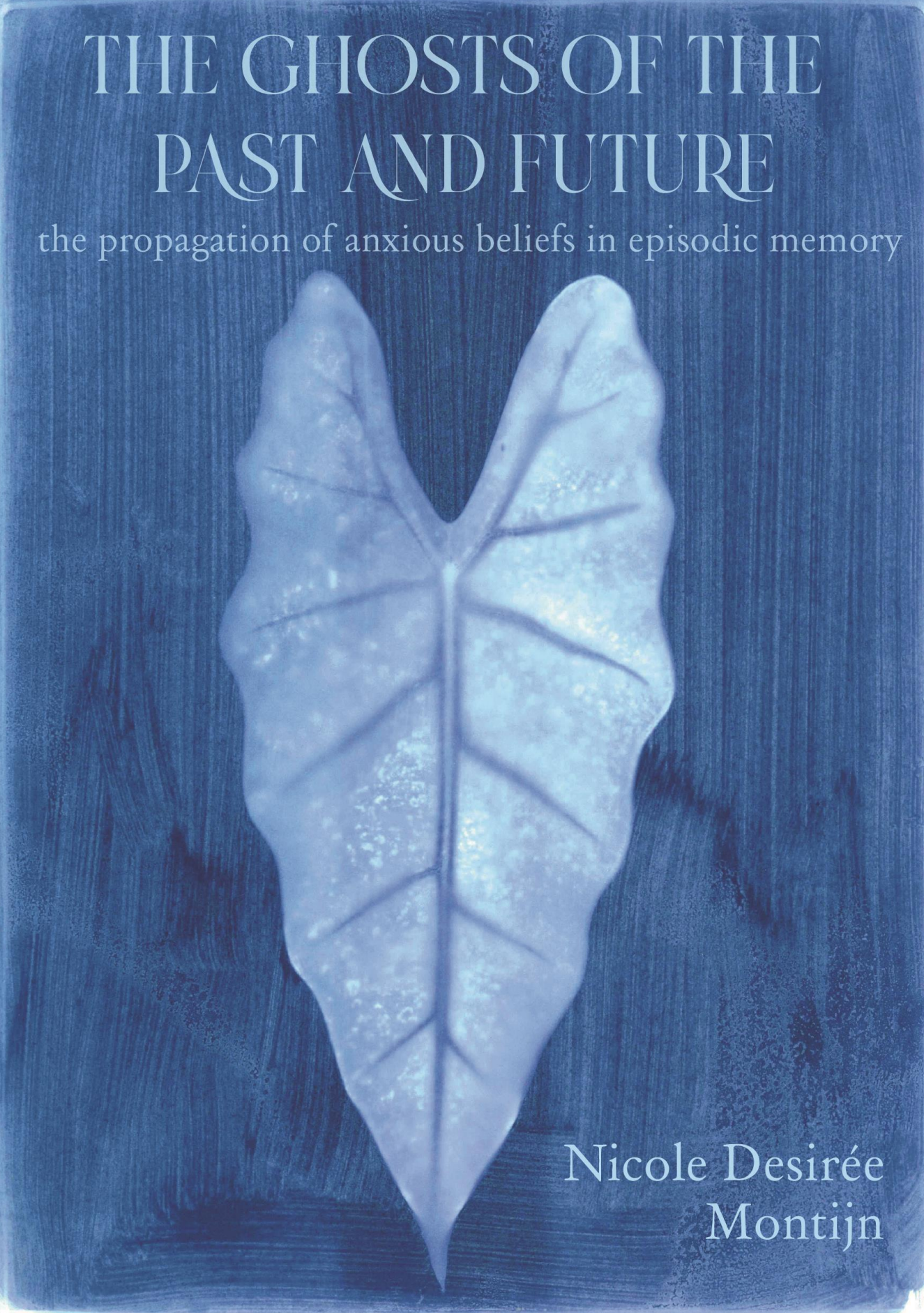
THE GHOSTS OF THE PAST AND FUTURE

the propagation of anxious beliefs in episodic memory



Nicole Desirée Montijn

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Geesten van het verleden en de toekomst

de verspreiding van angstige gedachten in episodisch geheugen

(met een samenvatting in het Nederlands)

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Nicole Desirée Montijn

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Promotor:

Prof. dr. I.M. Engelhard

Copromotor:

Dr. L. Gerritsen

Beoordelingscommissie:

Prof. dr. J.M.P. Baas
Prof. dr. M. Meeter
Prof. dr. G.T.M. Mooren
Prof. dr. D.J.L.G. Schutter
Prof. dr. T. Smeets

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I wish I would stop expecting
Don't know where I am heading
"You have so much potential,
thoughts far from sequential.."
But collections of the past
Don't prevent me getting lost
Connections fade too fast

Should stop relying on existing
For the sake of persisting
The present isn't continuous
The future feels ambiguous
But my body knows the danger
Of letting my mind become a stranger
The rise and fall of cognition
At the hands of sheer ambition

Please let me out of your head
Reconcile to what I could have had
Cause it's only sad,
when all is said and done with
the future is only as good as you remember it

- Nicole Desirée Montijn

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PROLOGUE

I am someone who is terrible at reading books. I much prefer to open them at random and see what the page gives me. I am someone who will point things out mid conversation, like how two ducks just landed in the office courtyard, because that just felt special to me. I am someone who cannot enter a room without immediately busting out a story about something that I saw on the way there. I love to wonder and wander. About what things are, what they were and what they could still be. And while not all the things I wonder about when my mind inevitably wanders are gems. They always reflect a part of who I am, who I was and who I could still be.

Chapter 1

General Introduction

Anxiety (related) disorders have long been characterized as primarily future oriented (1), as patients suffer from the anticipation of future threat (2). While the object of fear differs between anxiety disorders, patients share a hypersensitivity to impending threat and experience fear that is disproportionate to actual threat risk or severity (3,4). Individuals with anxiety disorders often go to extreme lengths to avoid these feared situations. Furthermore, in anxiety disorders, fear by definition is generalized to situations that are related to the original object of fear (5,6). Increasing our understanding of the mechanisms that drive memory generalization and future-oriented thought, as well as how these processes differ in anxious individuals, may be important in enhancing our understanding of the etiology and treatment of anxiety related disorders.

Current theoretical models and research on anxiety disorders focus largely on threat expectancy and maladaptive beliefs. These models are grounded in learning theory (7), with a rich history of classical conditioning, and do not typically consider anxiety in the context of episodic memory (8). Beyond recollection of past events, episodic memory drives constructive future-oriented processes that are important for prediction, guiding behavior and emotional responses. Episodic memory may therefore inform both the manner in which people anticipate future threat and the broader cognitive and behavioral impact. In recent years, the focus has started to shift towards incorporating insights from episodic memory into anxiety research (9), including the use of mental imagery in treatment (10). However, a detailed understanding of how episodic memory, and related processes like episodic future thinking, are affected and contribute to the maintenance of anxiety is still lacking.

In this introduction, and further chapters of this thesis, I will be discussing episodic memory for past and future events through the lens of psychopathology, particularly stress and anxiety-related problems. In the following sections, I will first provide an operationalization of how the concepts of stress and anxiety will be used throughout this thesis (see *Operationalization of Stress & Anxiety*). Next, I will give a brief history and the current standing with regard to theoretical models of episodic memory (see *Episodic Memory and Beyond*). In the sections thereafter, I will zoom in on specific aspects of episodic memory and their relevance to anxiety and stress. In order, I will be discussing

temporal contextualization of memory (see *About Time*), the abstraction of generalized knowledge structures called schema (see *Event Schema*) and how this drives constructive processes underlying future thinking (see *Constructive Episodic Simulation & Future Thinkin*g). Subsequently, I will discuss how these aspects of episodic memory relate to emotional biases in memory like the biased anticipation of future threat (see *Emotional Memory Bias*). Finally, I will provide the aim and general outline of the chapters presented in this thesis.

OPERATIONALIZATION OF STRESS & ANXIETY

Stress and anxiety play an important role in our survival as they aid in the identification and management of (potential) threats (3). They tend to be used somewhat synonymously in everyday speech. For example, saying 'I am so stressed about my exam' could equate to 'I am anxious that I am going to fail my exam'. In the context of this thesis, I will be referring to stress and anxiety as two distinct states based on their temporal orientation to a threat (11,12). Specifically, I will be referring to acute stress as the direct physiological and psychological response to an external threat, and to anxiety as the temporary (state) or chronic (trait) anticipation of a future threat.

Stress. Following a stressful experience, the peripheral physiological stress response is engaged to maintain and restore homeostasis in the body (13). The physiological effects of a stressor such as increased blood pressure, heart rate and glucocorticoid activity, can be measured with relative objectivity which make stress induction tasks a viable way to assess the effects of encountering threat in the lab (Box 2). The effects of stress inductions go beyond physiology. The effects of stress on cognition are complex, time-dependent and implicate multiple cognitive systems (14,15). Of particular relevance here are the effects of stress on attention, memory and emotional processing (16–18).

Anxiety. Beyond clinically diagnosed levels of anxiety, people can experience moderate levels of anxiety in daily life (19,20). Throughout the experiments presented in this thesis I will be referring to state and trait anxiety in healthy populations. Where state anxiety reflects a persons' current level of anxiety, trait anxiety reflects the typical level of

anxiety a person experiences viewed over a longer time period (e.g., over the past month) (21). In research, state anxiety levels can be experimentally manipulated, for example by exposing the participant to a stressor, while trait anxiety levels can inform personality based (i.e., trait) differences in performance on a task.

EPISODIC MEMORY AND BEYOND

As discussed in the introductory paragraphs of this chapter, episodic memory drives complex future-oriented behaviors. It is therefore very relevant to consider in the context of anxiety disorders, where understanding the etiology of the biased anticipation of future threat and generalization of fear across contexts and concepts is still of great importance. Not only from a theoretical perspective, but also to inform the development of treatment options. Before I go onto the specific aspects of episodic memory that I will consider in the context of anxiety and stress throughout the chapters of this thesis, I will first give a brief history of how episodic memory is and has been conceptualized.

Episodic memories are referred to as declarative, meaning we are able to voluntarily bring them to mind. Declarative memory has traditionally been studied as two distinct types of memory: episodic and semantic memory. This distinction was first described by Endel Tulving in 1972 and remained the most influential taxonomy of declarative memory over the following decades. The central tenet of Tulving's episodic-semantic distinction is the kind of information that each system processes. Episodic memory refers to memory for personally experienced events, that are bound to a specific spatial and temporal context. In other words, episodic memory captures what you were doing at a specific moment in time and at which location this took place. Furthermore, Tulving posited that this autonoetic displacement of the self in time, or mental time travel, did not only pertain to the personal past, but also to the personal future (22). Thus, episodic memory is a system responsible for both the recollection or re-experiencing of past events, and the simulation or pre-experiencing of future events (23,24). In contrast to the distinct temporal quality of episodic memory, semantic memories are not specific to one spatio-temporal context (25). Semantic memory refers to memory for factual information, or our general knowledge about the world, that is detached from the specific episodic context in

which this knowledge was acquired (26). Semantic memory is sometimes specified to personal semantics, such as autobiographical facts or self-knowledge (27).

While Tulving's definition of episodic and semantic memory is still widely accepted, his further proposal that they rely on functionally separate systems was met with a significant amount of criticism. With the emergence of cognitive neuroscience as a field, the advancement to modern neuroimaging techniques and a shifting focus towards naturalistic paradigms came increased recognition of the entanglement between episodic and semantic memory (28). Building on Bartlett's (1932) seminal work, cognitive research has focused on the transformative nature of episodic memory. Of particular interest here, is the transformation of episodic memories to complex structures of generalized knowledge, called schema, that are abstracted from multiple similar experiences (29–31). As such, contemporary models of human memory have reconceptualized episodic recollection as the product of a larger constructive simulation system where episodic, semantic and schematic information interact to enable a variety of the cognitive functions that rely on similar constructive properties (23,24,32).

In the next few sections, I will elaborate on the transformation from detailed episodic to generalized schematic memory as well as the constructive properties of episodic memory. Along the way, I will further describe their specific relevance and relation to anxiety and stress.

ABOUT TIME

Time is one of the most defining characteristics of episodic memory. In the context of anxiety, time may seem like the least important thing to consider. The focus tends to be on what someone is afraid of, not when as the answer to that tends to be 'well all the time'. However, even when time is not something we explicitly consider, the accurate retention of temporal context serves several important purposes. Temporal context captures both when episodic events occurred in time, as well as their temporal relationship to each other (e.g., event A came before B). Without memory for temporal context, our memories are unlikely to be very coherent as individual episodic events are part of an ongoing narrative that sequentially builds on itself. In relation to anxiety, wrongfully remembering temporal

order, for example that people laughed at your mistake instead of the laughing starting before the mistake, can lead to misattributions of causality that may contribute to your belief that you are a joke. Furthermore, these errors in temporal context memory can down the line inform wrongful interpretations of current events and predictions of the future, which I will discuss in the sections on Event Schema and Constructive episodic simulation. First, let's consider how we remember time in episodic memory under normal circumstances.

As I mentioned, episodic events are not just linked to a fixed moment in time, they have a temporal progression (33). Episodic events are part of a continuous sequence of events which in and of itself can be segmented at varying levels of temporal granularity (34,35) and grouped based on conceptual similarity (36). The (spatio-)temporal and conceptual relationship between episodic events can inform inference, contributes to the formation of schematic event representations and can ultimately enable us to make predictions about future events (37).

In episodic memory, the continuous flow of information is parsed into separate events based on significant conceptual or contextual shifts, such as a changes in location, goal, mood or activity (38). These shifts are referred to as *event boundaries* (39). This segmentation process can result in a sequence of discrete episodic events that can be recalled separately. How memory is segmented depends on the granularity of recall. For example, consider an episodic memory of knocking over a glass at a restaurant dinner. You may recount knocking over the glass on a moment-by-moment basis, such as physically hitting the glass, realizing you hit the glass and ultimately it spilling all over the table. However, this event sequence can also be considered one single event in a larger sequence when it is considered in the context of the entire day. The level of abstraction with which we recall a memory can thus determine how smaller events are clustered.

Thus far, most of the work on the temporal organisation of episodic memories has focussed on understanding the dynamics of event sequences (40). However, beyond sequence order, we can recall the approximate temporal distance between events. To illustrate, in a restaurant ordering food is followed by the food arriving, but the amount of time that passes between those two events likely determines how we evaluate the

experience. There are several competing theories as to how we achieve these estimates of temporal distance. One theory is that we infer time based on the amount of event boundaries that are perceived between two events. In the restaurant example, a longer wait time likely means that more events, and thus event boundaries, occur in between ordering and receiving your food than when the wait time is shorter. Indeed, episodes that contain more boundaries are remembered as longer (41,42), and the estimated time between events pairs that are separated by a boundary is typically judged to be longer (43). Alternatively, elapsed time between events may be encoded more passively through fluctuations in neural activity that are encoded as part of the memory trace (44–46). The latter account would imbue episodic memory with high-fidelity temporal markers that reflect not only sequence position, but also the distance between events in a sequence. Such high-fidelity memory for temporal context, would not only make our memories truer to the original timeline but also aid precise predictions for the future (see next section). We aim to investigate this specific hypothesis in **chapter 2** in a novel paradigm that allows us to dissociate time from sequence representations. Given that we currently do not know if and how fine-grained temporal information is retained in episodic memory, this study also provides a sense of how temporal context memory works in healthy participants which then allows comparisons to how it may be affected in clinical populations.

Indeed, poor contextualization of memory is known to play a role in various mood and anxiety (related) disorders (9,47). The accurate retention of temporal context, like sequence order and event time, ensures that information is interpreted within the appropriate contextual boundaries, and protects against overgeneralization of memory (48). This may be especially important for memories of highly emotional or stressful situations where context can act as a buffer to prevent prolonged negative impact of the experience (49). Following work on the role of emotion in sequence memory (38,50,51), highly arousing stimuli or stress may disrupt encoding of event boundaries, leading to deficits in sequence memory. However, it is unclear how emotion and stress affect temporal context memory beyond sequence order. Therefore, in **chapter 3**, we aim to investigate how stress might interfere with fine-grained temporal memory encoding by

combining our novel time paradigm (**chapter 2**) with an experimental stress induction (Box 2).

In the next section, I will discuss how memory for temporal context can inform the abstraction of general knowledge patterns about how similar events typically occur and elaborate how this might lead to incorrect predictions when temporal context is poorly retained.

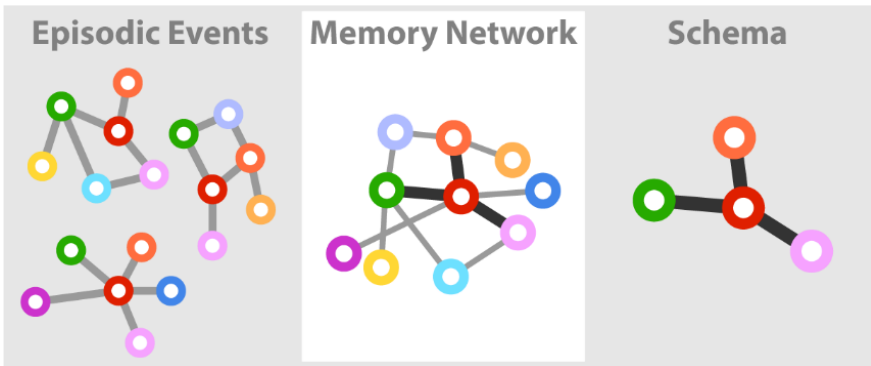

Figure 1. Network representation of episodic information. As multiple episodic experiences overlap the common associations in each network gain in relative strength compared to those that are unique to a single experience. This process facilitates the abstraction of schematic event representations that are purged of event specific details that are inconsequential to the general gist of this type of episodic event.

EVENT SCHEMA

As mentioned in the previous section, the accurate retention of temporal context serves another important purpose, namely predictions about similar (future) events. In order to make predictions for the future we need a sense of what is likely to occur. We develop this general knowledge, or schema, about predictable patterns (e.g., A always leads to B) through repeated experience. However, going back to the example from the previous section, when you don't retain the correct temporal context (i.e. laughing occurred before your mistake) this may lead you to make inaccurate predictions about how likely these people are to mock you for a mistake in the future. In addition to schematic influences on

future predictions (see next sections), schema can also (maladaptively) influence the perception and subsequent memory for current events, which I will discuss now.

Episodic experiences are by definition unique, but they can overlap with conceptually similar experiences (Figure 1). For example, while specific details may differ, your commute to work likely follows a similar event sequence every day. Because of this similarity you will have a good idea of what you can expect to happen during your ride, what you have to do to get there and how long it will take. Such commonalities across similar experiences are represented in associative memory networks called schema (52). Schema provide a template for what you can likely expect from any given situation. This makes them instrumental in the acquisition and interpretation of novel information, but also the mental simulation of potential future events.

While event schema are a form of generalized knowledge that is not bound to one specific spatio-temporal context, schema are not purely semantic either since the information retained in them can be context dependent or conditional on other factors (e.g. my commute is 10 minutes when the weather is nice). In addition, schema retain a link to and can facilitate recall of the specific episodic experiences from which they are derived (28,30). For example, you can recall what your typical commute looks like, and simultaneously be able to recollect the exact details of yesterdays' trip. Furthermore, unlike semantic memories, schematic memory representations are dynamic structures that adapt, and update based on ongoing experience (30). Schematic memory for predictable features of an event category can develop quickly (53), but it may take years to develop more sophisticated event schema. Preliminary work suggests that schema may start to develop alongside specific episodic memories, but that their impact on memory only becomes apparent as event specific memory details fade over time (53). Thus, schema representations remain stable while episodic ones do not, resulting in increased accessibility and reliance on event schema. In addition, schema facilitate the acquisition and retention of information that is congruent with the dominant schema (54). In the case of anxiety, this could lead to overly negative interpretations and memory of ongoing and future events, as we will discuss in a later section. Finally, schematic knowledge can systematically distort memory of current events towards a generalized category

representation (55,56), leading to inaccurate memory representations that are in line with the schema. Whether this schematic bias also pertains to temporal context memory is currently unclear.

Therefore, on top of the aims of **chapter 2 and 3** described in the previous section, we investigated if general knowledge of the average temporal structure of event sequences biased recall. In addition, we investigate whether such a bias may be amplified following acute stress, as memory accuracy, and thus the general knowledge that follows from it, is typically lower as a result of stress. If the latter is indeed the case, this may down the line offer a mechanistic explanation for why feared situations are recalled as more aversive than they objectively were.

Next, we will take a closer look at theoretical models of how schema enable the prediction and the construction of future events. In the section thereafter, I will discuss the consequences of this constructive process in cases where memory is emotionally biased, such as the increased anticipation of future threat in anxiety.

CONSTRUCTIVE EPISODIC SIMULATION & FUTURE THINKING

Episodic memories are not veridical records. Memory is closer to reconstruction than reproduction (57). As anyone who has ever assembled an Ikea closet before knows, such a constructive process can introduce errors. Similarly, some associations become weaker over time resulting in forgetting, like a pesky screw that rolled away. Other associations are so strong that they compete for recollection with the original memory trace, causing this information to get wrongfully included (58,59). Like that one shelf that seemingly fit perfectly until you see the lobsided finished product.

While this may seem problematic, the increased flexibility that comes with such a constructive system is considered adaptive. It allows us to move beyond mere reproduction of the past and facilitates the simulation of future events (23,32,60). The ability to flexibly construct events that may occur in your own future has been dubbed *episodic future thinking*. In Ikea terms, future thinking is like utilizing the fact that a lot of Ikea furniture has the same dimensions to build your own unique closet to fit all your needs out of parts from various styles and painting it your favorite color. Imagining what something would be like

without having to physically live through this experience has obvious benefits, it enables us to learn through other means than just trial and error (3). For example, you may imagine and practice your responses for an upcoming job interview ahead of time based on what you expect interviewers to ask, which may help you to perform better at the actual interview. This is especially a relevant ability in situations that the individual feels might present a risk, such as expected threat. Using future thinking, you can anticipate negative consequences ahead of time and try to prevent them. The downside of this will be discussed in the section on *emotional future thinking*.

To continue our story of schematic influences on memory, episodic memory and episodic future thinking can both be considered simulations of events. In both cases we flexibly combine pieces of information that we have learned share conceptual overlap or are likely to occur together. As outlined in the previous section, schema provide a relational framework on what one can logically expect from a specific situation. For example, when walking into a new office you will not go in blind; you have an idea of what you will normally find there, what you are expected to do and how to behave. As such, schema as well as semantic concepts provide the necessary structure to guide episodic simulation towards events that are reasonable given what we have previously learned (61,62). While both past and future simulations likely use schematic information as a scaffold during construction, future simulation likely relies on these structures more heavily (63). This is especially the case for simulations of events that are in the far future (64), because it differs more from your current situation, or situations that are highly novel (e.g., a vacation to a country you have not been to before) (24). Using schematic or semantic knowledge to aid constructive processes like episodic simulation has its benefits but can also be a pertinent source of bias, such as threat-focused biases in anxiety disorders (65). I will discuss the consequences of emotional and threat-focused biases in episodic future thinking in the next section.

EMOTIONAL MEMORY BIAS

Given that schema contain generalized representations and rules that are formed through previous experiences, they are generally biased towards scenarios or outcomes that we most consistently experienced and therefore expect to happen. This generalization is very

useful because it allows us to make quick decisions about how to (re)act without having to exert much cognitive effort (30,52). Schema also play a role in quickly determining relevance. We are bombarded with millions of stimuli every day, without a filter that guides our attention to the relevant information we would be utterly lost. Emotion, both positive and negative, plays an important role in determining this relevance. Schema and memory in general tend to be biased towards emotional information, such that stimuli that can offer a potential benefit or detriment to us are prioritized in memory (66,67). The anticipation of threat is a good example of this.

Emotional arousal can selectively strengthen mnemonic representations of an episodic event (68). In addition, emotional arousal during stressful experiences can direct attention towards emotionally salient information, meaning the resulting memory contains more emotional than neutral information (69). Because of these mechanisms that prioritize processing and retention of emotionally significant information, emotional experiences tend to be more formative in shaping our general expectations about the world than non-arousing experiences (70). So, rather than a schematic event representation building over multiple equally weighed experiences, a highly emotional experience can dominate an event schema and bias expectations towards an emotional outcome. For example, a bike crash on your way to work one day can lead to you be more vigilant towards a potential crash on that intersection in the future, even when all your other commutes were normal. Understanding the expression of emotional biases in memory, as well as how they can be counteracted is important for our understanding of anxiety disorders.

THREAT BIAS

Under normal circumstances these biasing mechanisms, even those focused on threat, would be highly functional. They guide attention towards relevant information and can help promote survival by helping the individual select the best course of action (e.g., being more careful to prevent a future bike accident). However, schematic biases may become more pronounced when they are focused on threat or intense emotion, as is the case for anxiety disorders (71). Over-representation of threat-related information in memory can create the illusion that the likelihood and impact of the occurrence of threatening events is higher

than they objectively are (72,73). These emotional biases are hard to correct. The memory system selectively prioritizes and retains information that aids survival (66). So, even repeated exposure to the positive alternative does not always outweigh the strongly formed mnemonic associations that underlie negative schema. In the treatment of anxiety disorders, even after successful gold standard treatments like cognitive behavioral therapy relapse rates can be as high as 14% (74). Thus, despite the relative efficacy of current treatment options, there is a need for new approaches to minimizing pervasive negative memory biases in anxiety disorders. Episodic future thinking might offer a means to do this, as I will discuss next.

EMOTIONAL FUTURE THINKING

An avenue of research that has started to attract more attention to tackle this treatment gap is the use of episodic future thinking, or more broadly mental imagery. Future thinking may contribute to the preservation of these biases by drawing on schematic information to aid the construction of future events (10,24,75). Therefore, imagined future events are likely more congruent with the active schema including any emotional bias contained within it. In the case of anxiety disorders, patients have a higher propensity to imagine negative future events and anticipate the likelihood of occurrence of such events to be higher than their positive alternative (76). In addition, like past events, imagined future events can be remembered over time which can potentially lead to selective strengthening of the associative link between the (biased) memory elements. However, thus far little is known about the fate of emotional imagined future events and their impact over time. Early work suggests that like episodic recall, memory for future events may be biased towards positive situations such that positive future events are more accurately recalled (77). In **chapter 4**, we extend this work on positive future memory bias by assessing how specific event details of simulated future events fade over time using the Autobiographical Interview technique (78). Furthermore, given that people with anxiety tend to have a negatively biased view of the future (79,80), we examined if this future memory bias was reversed in highly anxious individuals.

Furthermore, emotional future thinking may exert an influence over the memory system that is more long lasting and far reaching than merely simulating the future. Positive episodic future thinking can positively bias the recollection of past events (81), as well as suppress recollection of similar past events (82). Given this broader impact of future thinking, it may be an attainable way to correct threat-focused biases in anxiety disorders. In **chapter 5**, we will therefore look at how we can use positive future thinking to exert temporary biases over encoding of new information in stressful experiences. While positive imagery interventions are already starting to be implemented in clinical practice (83,84), relatively little is known about the optimal way to use it and for whom it works. Therefore, we further set out to examine how the effects of positive future thinking interventions may vary based on individual differences, like the level of trait anxiety and emotion regulation efficiency, as well as whether task relevance of the positive imagery improved efficacy.

Next, I will describe the aim of this dissertation, and provide an outline of the empirical chapters.

BOX 1 – EXPERIMENTAL STRESS INDUCTION

Laboratory stress models typically aim to elicit a physiological stress reaction by exposing the participant to controlled physical and/or psycho-social stressors that activate the ANS (85). Physical stressors can include inducing pain or exposing the participant to extreme heat/cold. An example of a physical stressor is the *cold pressor test* (86) in which participants submerge their hand in ice cold water for several minutes. Psycho-social stressors are tasks that are typically experienced to be aversive like public speaking or negative social evaluation, such as the *Trier social stress test* (87) (chapter 5) where participants have to give an impromptu presentation. Combined methods apply both physical and psycho-social stressors to combat the problem that the physiological stress response can differ per person depending on the type of task. An example of a combined method is the socially evaluated cold pressor test (chapter 3).

Stress inductions in the lab are inherently noisy. Therefore, there are several factors that are taken into account to increase the likelihood of a discernable stress response. First, cortisol levels are naturally elevated in the morning which could lead to ceiling effects when attempting to increase cortisol levels experimentally (88). Therefore, to optimize the chance of a distinct response, stress experiments are typically conducted between 12:00 and 18:00. Second, natural cycling cis-gender women are typically required to be on birth control and free-cycling cis-gender women are preferentially tested in the luteal phase of their cycle (89). Other factors that are often controlled are caffeine and alcohol consumption as well as drug use within a certain window before the experiment.

AIM OF THIS DISSERTATION

In this thesis, I aim to elucidate the mechanisms that drive memory generalization and future thinking and their role in anxiety and stress related disorders. Regarding memory generalization, I will specifically look at the generalization of temporal context memory across similar experiences, due to the relevance of temporal context memory in generating precise predictions for the future. First, in healthy participants, to set a benchmark of normal encoding of temporal context (chapter 2). Followed by an examination of how stress can impact temporal context memory and potentially contribute to the poor contextualization of memory seen in psychopathology (chapter 3). Regarding future thinking, I aim to first examine the presence of structural emotional biases in the ability to simulate and retain future episodic events in anxious individuals (chapter 4). Despite the importance of negative anticipation in anxiety, little is known about how future-oriented thought is affected in this population. Subsequently, following recent trends to include future thinking in interventions for anxiety disorders, I aim to investigate how positive future thinking might be best applied to combat negative biases (chapter 5). Together, these chapters aim to further inform the emergence and cognitive behavioral impact of maladaptive biases in memory and future anticipation in anxiety.

GENERAL OUTLINE OF THIS DISSERTATION

Section 1 – When time is memory

In the first section we examined the transformation of episodic experiences to generalized event representations, how this may lead to structural biases in recall, and if generalization may be accelerated by high levels of stress during encoding.

In **chapter 2**, we examine how memory for the temporal structure of episodic event sequences generalizes across similar experiences and can bias recall. The temporal relationship between events is a defining aspect of episodic memory. Yet, we do not always have an exact record of when something occurred. The hippocampal-entorhinal region is centrally involved the retention of such temporal event structures. However, it is unclear whether these hippocampal event representations are reflective of objectively elapsing time between events, or of mnemonically constructed time based on a combination of

episodic and schematic information. To answer this question, we combined functional magnetic resonance imaging with a temporal learning task where participants had to mnemonically construct the temporal structure of four virtual days in which time was scaled. We investigated whether neural patterns of event representations in the hippocampal-entorhinal cortex were more reflective object time or mnemonically constructed virtual time distances using a representational similarity analysis.

In **chapter 3**, we examine how acute stress interferes with the temporal contextualization of episodic event sequences. Accurate retention of the temporal event context, e.g., the time of occurrence and order of events, ensures that information is interpreted within the appropriate contextual boundaries, and protects against overgeneralization of memory (48). The poor contextualization and lacking specificity of memory is known to play a role in anxiety-related disorders (9,47). It is possible that these distortions already occur during encoding as a consequence of physiological stress reactivity (90). Here, we subjected participants to the socially evaluated cold pressor test (SECPT; Box 1) before they had to learn the temporal structure of four virtual days (as in **chapter 2**). The aim was to investigate how stress before learning interfered with the ability to learn the temporal structure of these virtual days, and thus how stress may contribute to overgeneralization of memory.

Section 2 – When it is time for memory

In the second section, we look at the consequences of emotional biases in memory on episodic future thinking and goal directed behavior, and how we can remedy these biases by capitalizing on the mechanistic properties of the constructive simulation system.

In **chapter 4**, we examine how trait anxiety affects memory quality for imagined emotional future events. People regularly imagine detailed scenarios that could happen to them in the future. Accurate memory for these future events could benefit people's ability to update and achieve future goals over time. Emotion is known to play an important role in enhancing recollection. As future thinking relies on the same constructive system emotion, including any biases in that system, may affect memory for future events in a similar way. In healthy individuals, emotional memory tends to be positively biased.

However, individuals with anxiety tend to view the future in an overly negative light, which may result in enhanced recall of negative imagined future events. Here, we asked individuals with high and low levels of trait anxiety to imagine a series of episodic future events that were either positive, negative or neutral. The following day they returned to recall these imagined future events in as much detail as they could. The aim was to assess how memory quality, in terms of episodic specificity and emotional intensity, changed from simulation to recall and how this was affected by trait anxiety.

In **chapter 5**, we investigate whether imagining positive episodic future events can make a typically stressful situation feel less aversive. People form expectations of future events to help navigate complex social situations, but some expectations can be negatively biased. Since negative biases can lead to avoidance behavior and anxiety, it is important to find attainable ways of combatting them. Through its role in goal-directed behaviour and emotion regulation, positive future thinking may provide an accessible way to attenuate these negative biases. To assess this, we asked people to imagine a series of positive future events before engaging in a social stress task (Box 1). Furthermore, since expectations about events are represented in event schema, we examined if imagining task-relevant positive future events enhanced the effects of the intervention beyond those of positivity alone. Finally, we used electroencephalogram (EEG) to record neural oscillation patterns that are associated with emotion and stress regulation to map individual and group-based differences (91) in efficacy of the different future thinking interventions.

Finally in **chapter 6**, I summarize and discuss the results from the empirical chapters 2-5, and I will explain how the findings of these studies add to the understanding of memory generalization and biases in future thinking related to anxiety disorders.

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Section I

When time is memory

Chapter 2

Mnemonic construction and representation of temporal structure in the hippocampal formation

Jacob L. S. Bellmund
Lorena Deuker
Nicole D. Montijn
Christian F. Doeller

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Authors contributions

LD, and CFD conceived the experiment. NDM and LD developed the tasks and acquired the data. LD pre-processed the MRI data. JLSB analyzed the data and wrote the manuscript with input from CFD. All authors discussed the results and contributed to the paper.

Abstract

The hippocampal-entorhinal region supports memory for episodic details, such as temporal relations of sequential events, and mnemonic constructions combining experiences for inferential reasoning. However, it is unclear whether hippocampal event memories reflect temporal relations derived from mnemonic constructions, event order, or elapsing time, and whether these sequence representations generalize temporal relations across similar sequences. Here, participants mnemonically constructed times of events from multiple sequences using infrequent cues and their experience of passing time. After learning, event representations in the anterior hippocampus reflected temporal relations based on constructed times. Temporal relations were generalized across sequences, revealing distinct representational formats for events from the same or different sequences. Structural knowledge about time patterns, abstracted from different sequences, biased the construction of specific event times. These findings demonstrate that mnemonic construction and the generalization of relational knowledge combine in the hippocampus, consistent with the simulation of scenarios from episodic details and structural knowledge.

Introduction

Our memories are not veridical records, but constructions of our past[1]. When constructing scenarios of the past or future, we often combine specific episodic details with general, semantic knowledge[2–7]. For example, we can infer the time when an event took place not only from episodic details but also from associative or contextual information and general knowledge[8,9]. To answer the question when you left for work yesterday, you may combine knowledge about usually departing from home around 8:30 a.m. with the specific sequence of events that unfolded – eating breakfast while listening to the 8 a.m. news and arriving at work a few minutes late for the 9 a.m. meeting despite good traffic conditions on your commute. You infer that you left later than usual, at around 8:40 a.m. Thus, constructive mnemonic processes allow you to estimate when this event occurred, even if a specific event time is not part of the original memory[8,9]. Event representations in the hippocampal-entorhinal region carry information about sequence relationships[10,11], but whether this goes back to mnemonic construction is unclear. Next to its role in memory for specific sequences, the hippocampal-entorhinal region also generalizes across experiences via the abstraction of structural regularities and the recombination of information across episodes[12,13], suggesting you may use knowledge about comparable mornings to recall your departure time. Here, we ask whether temporal event relations are generalized across sequences that share a similar structure and address the question how mnemonic construction and generalization combine in the hippocampus and in participants' memory for event times.

In line with its well-established role in episodic memory, the hippocampal-entorhinal region is centrally involved in processing and remembering specific event sequences[10]. For instance, learning sequences recruits the hippocampus and entorhinal cortex[14,15], and hippocampal activity increases at event boundaries delineating sequences[16,17]. Hippocampal multi-voxel patterns are sensitive to objects shown at learned sequence positions[18], and recent work suggests that the hippocampus incorporates the duration of intervals between elements in sequence representations[19,20]. Further, pattern correlations in the hippocampus and entorhinal cortex relate to memory for temporal relations[21–26].

Hippocampal and entorhinal representations of events occurring in sequence reflect the temporal relations of these events. In one experiment, participants learned the spatial and temporal relationships of events encountered in sequence along a route through a virtual city[21,27]. After relative to before learning, pattern similarity in the anterior hippocampus and the anterior-lateral entorhinal cortex elicited by event images reflected the sequence relationships between pairs of events. Events closer in time elicited more similar activity patterns relative to events separated by longer intervals, resulting in negative correlations between pattern similarity and temporal distances[21,27]. Within the entorhinal cortex, this effect was specific to the anterior-lateral subregion[27], consistent with the involvement of this area in precise temporal memory recall[28,29]. Negative correlations between pattern similarity and distances are in line with sequence representations akin to cognitive maps of space – positions separated by low distances share similar representations, whereas positions with high distances between them are represented less similarly, i.e. pattern similarity scales with distance.

However, whether event representations in the anterior hippocampus and anterior-lateral entorhinal cortex reflect temporal distances based on constructed event times is unclear. Alternatively, these representations of temporal structure could go back to the order of events. For example, successive events could be linked together, resulting in representations of sequence order, where temporal distances are defined based on the number of associative links between events[30–32]. Another possibility is that temporal structure representations arise through elapsing time more passively. For example, the firing of individual entorhinal neurons changes with varying time constants in rodents and non-human primates, allowing time to be decoded from population activity[33,34]. Slowly drifting activity patterns could be incorporated into event memories as temporal tags, providing a potential mechanism for temporal memory[35]. Here, we tested whether event representations reflect temporal relations based on mnemonically constructed event times, even when accounting for event order and objectively elapsing time.

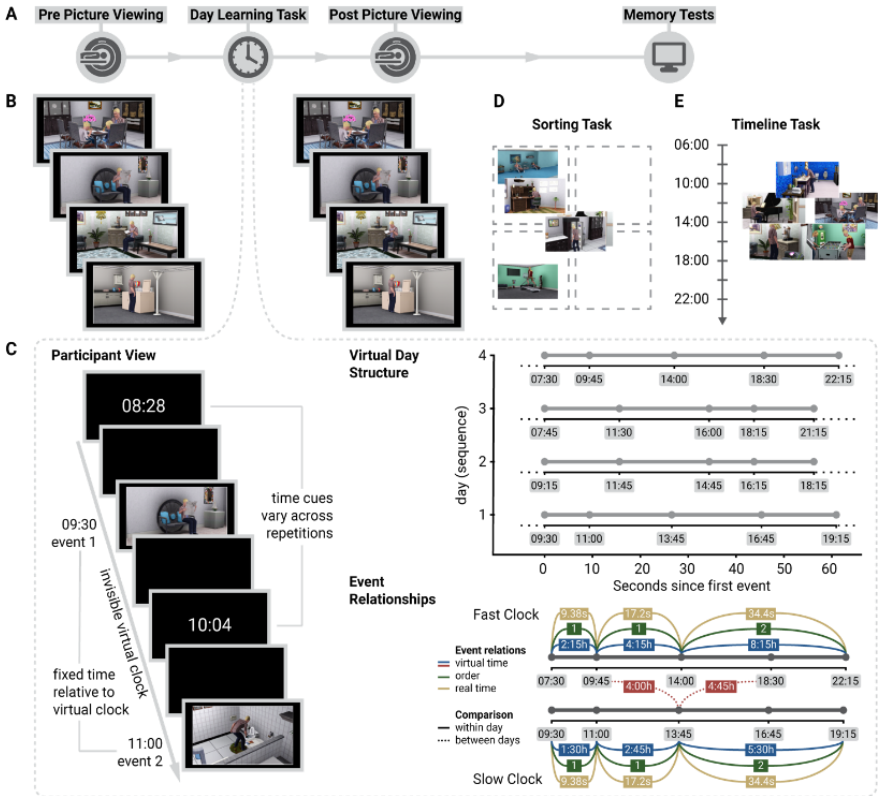

Figure 1. Experimental Design. A. Overview of the experiment. **B**. In the picture viewing tasks before and after learning, participants saw event images presented in the same random order and using identical stimulus timings. **C**. The day learning task took place in between the picture viewing tasks. Participants learned four sequences (virtual days) of five events each and inferred when events took place relative to a virtual clock. Left: The virtual clock ran hidden in the background for each sequence and was revealed only once in between successive events. These time cues varied across repetitions of a sequence, but events occurred at consistent points in virtual time. The duration of blank screen periods varied according to the interval between the indicated time and the event time. Thus, participants had to mentally construct event times by combining their experience of elapsing real time with the time cues. Top right: The hidden clock ran at a fixed speed relative to real time for a given sequence, but its speed varied between sequences. Bottom right: Different time metrics capture the temporal structure of the event sequences. Event relations can be quantified using temporal distances relative to the hidden clock (virtual time), sequence positions (order), and elapsed time in seconds (real time). While these metrics inevitably covary, they are partially dissociated by the clock speed manipulation. Virtual temporal distances can be quantified both within (solid lines) and across sequences (dotted lines). **D, E.** Participants' memory of the sequences was tested in two tasks. In the sorting task (**D**), participants sorted the scenes according to the four different sequences. In the timeline task (**E**), participants positioned the five event images of a given sequence next to a timeline to indicate constructed event times. **B-E**.The Sims 3 and screenshots of it are licensed property of Electronic Arts, Inc.

Mnemonic construction enables prospective cognition[2,5,36]. The hippocampal-entorhinal region integrates and recombines episodic details across experiences for future simulation, inferential reasoning and generalization[5,12,13,37–40]. Work in rodents and humans demonstrates that the hippocampus supports transitive inference, which requires inferring novel relations between stimulus pairs from knowledge about previously learned premise pairs[41–43]. Further, it combines separately learned associations, enabling inferences about shared associations[44–50]. Recent work suggests a central role for the entorhinal cortex in the abstraction of structural knowledge that is linked to sensory experience in the hippocampus[12,51]. Indeed, entorhinal activity patterns reflected structural similarities between choice options in a reinforcement learning task[52]. Furthermore, in an associative inference task, hippocampal activity patterns carried information about the shared internal structure of image triads such that the hippocampal representational geometry was generalized across triads[53]. Work in rodents suggests that hippocampal representations of events in a sequence generalize across comparable experiences in a different environment[54]. Applying abstract structural knowledge enables adaptive behavior through the generalization of relations to novel situations[12,51]. Whether representations of temporal relations of events in a sequence are constructed such that they generalize across sequences with a similar structure is unclear.

Knowledge about structural regularities and semantic associations closely interacts with episodic construction[4,7,38]. When estimating the size of studied images, participants' reconstructions were systematically distorted towards category averages[55,56]. For relatively small fruits like strawberries, participants tended to overestimate the studied size, whereas they consistently underestimated sizes of large fruits like pineapples. This resulted in an overall bias towards the category mean of all fruits[55]. Consistent with the notion that learned event structures contribute to event cognition[57–59], external and semantic details are used to furnish past and future scenarios when few episodic details are generated[60,61]. When estimating the times of events from a movie, which was terminated prematurely, participants underestimated when events took place for events close to the end of the presented section, possibly due to prior knowledge about the typical structure of movie plots[62]. These findings suggest that abstract knowledge about general patterns could

systematically distort constructions of specific event times. If, as in the introductory example, you usually leave for work at 8:30 a.m., this may bias the estimate of your departure time on the day you arrived late towards this time.

Here, we combine functional magnetic resonance imaging (fMRI) with a sequence learning task requiring the memory-based construction of the times of events forming different sequences. We show that event representations in the anterior hippocampus change through learning to reflect constructed event times rather than sequence order or passively elapsing time. Furthermore, the anterior hippocampus generalizes temporal relations across sequences, and structural knowledge about other sequences systematically biases the construction of specific event times. While within- and across-sequence relations are detected in anatomically overlapping regions of the hippocampus, the mode of representation differs depending on whether events belong to the same sequence or not. In contrast, the anterior-lateral entorhinal cortex uses one shared representational format to map relationships of events from the same and from different sequences.

Results

We asked participants to learn four sequences that consisted of five unique event images each (Figure 1). Participants were instructed that each sequence depicted events taking place on a specific day in the life of a family. Their task was to infer the time of each event relative to the temporal reference frame of a virtual clock (Figure 1C). Event images with minimal or no indication of time of day were randomly assigned to sequences and sequence positions for each participant. Thus it was impossible to infer specific event times or sequence memberships from the stimuli. The true virtual times of events were never revealed. Rather, the clock was running hidden from participants. It was uncovered only infrequently between event presentations to briefly show the current virtual time (see Methods). Participants had to combine their experience of objectively elapsing time (real time) with the virtual time cues to construct event times. Importantly, we manipulated the speed of the hidden clock between sequences so that different amounts of virtual time passed in the same real time intervals. With this paradigm, we partially dissociated the virtual time of events from the event order and real time to test whether mnemonically

constructed event times underlie participants' memory for the temporal structure of the sequences.

Successful construction of event times

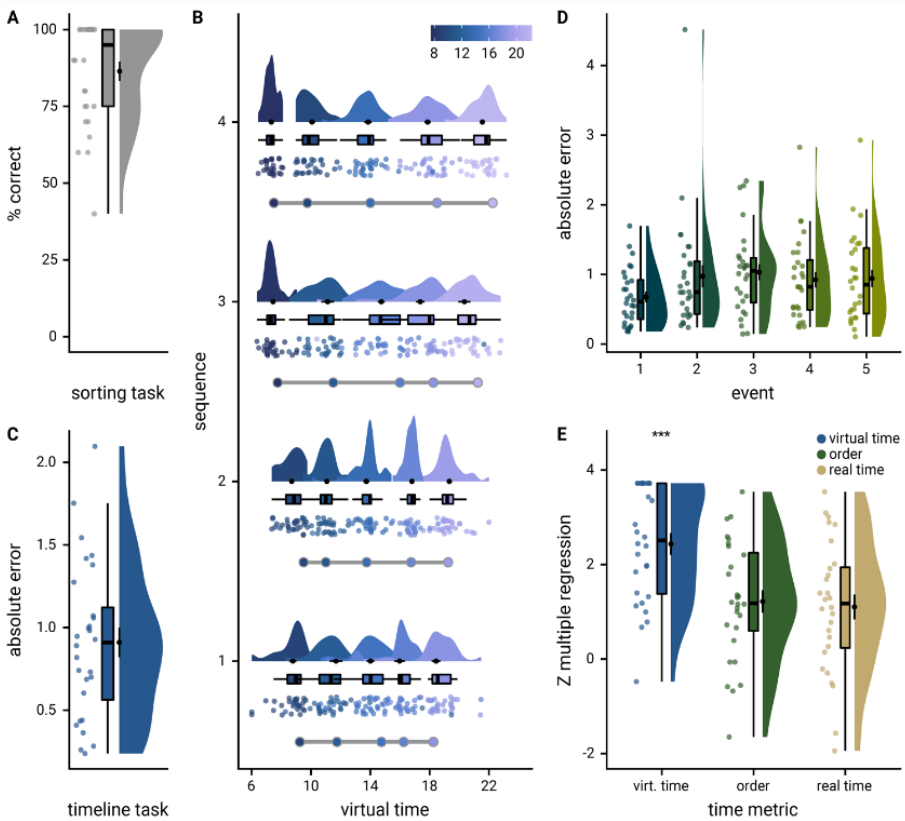

Figure 2. Participants learn the temporal structure of the sequences relative to the virtual clock. A. Plot shows the percentage of correctly sorted event images in the sorting task. **B.** Constructed event times were assessed in the timeline task. Responses are shown separately for the five events (color coded according to true virtual time) of each sequence (rows). Colored circles with gray outline show true event times. **C, D.** Mean absolute errors in constructed times (in virtual hours) are shown (**C**) averaged across events and sequences and (**D**) averaged separately for the five event positions. **E**. Z-values for the effects of different time metrics from participant-specific multiple regression analyses and permutation tests show that virtual time explained constructed event times with event order and real time in the model as control predictors. **A-E**. Circles are individual participant data; boxplots show median and upper/lower quartile along with whiskers extending to most extreme data point within 1.5 interquartile ranges above/below the upper/lower quartile; black circle with error bars corresponds to mean±S.E.M.; distributions show probability density function of data points. ***p<0.001

We assessed memory for the sequences using two behavioral tests administered at the end of the experimental session. First, participants sorted all event images according to sequence membership (Figure 1D). The high performance in this task (Figure2A; 86.43%±16.82% mean±standard deviation of correct sorts) demonstrates accurate memory for which events belonged to the same sequence. The distribution of sorting errors did not differ from uniformity across sequence positions (χ^2=2.55, p=0.635). Second, to probe constructed event times, we asked participants to position the events of a sequence on a timeline (Figure 1E). Remembered times were highly accurate (Figure 2B-D; 0.91±0.47 mean±standard deviation of average absolute errors in virtual hours). The accuracy of constructed virtual times differed between sequences ($F_{3,81}$=5.86, p<0.001), but not as a function of virtual clock speed (t_{27}=-0.82, p=0.423). We did not observe an across-subject relationship between the number of sorting errors and mean absolute errors in the timeline task. To test whether the constructed event times were driven by the virtual time of events, we regressed remembered times on virtual times with event order and real time as control predictors of no interest. We did so in a summary statistics approach based on multiple regression for each participant, combined with permutation tests, and using a linear mixed effects model (see Methods). The effect of virtual time on constructed event times was significant when controlling for variance accounted for by event order and real time (Figure 2E; summary statistics: t_{27}=10.62, p<0.001, d=1.95, 95% CI [1.38, 2.70]; mixed model: $\chi^2(1)$=115.95, p<0.001). Together, these findings demonstrate that participants formed precise memories of the different sequences and accurately constructed event times.

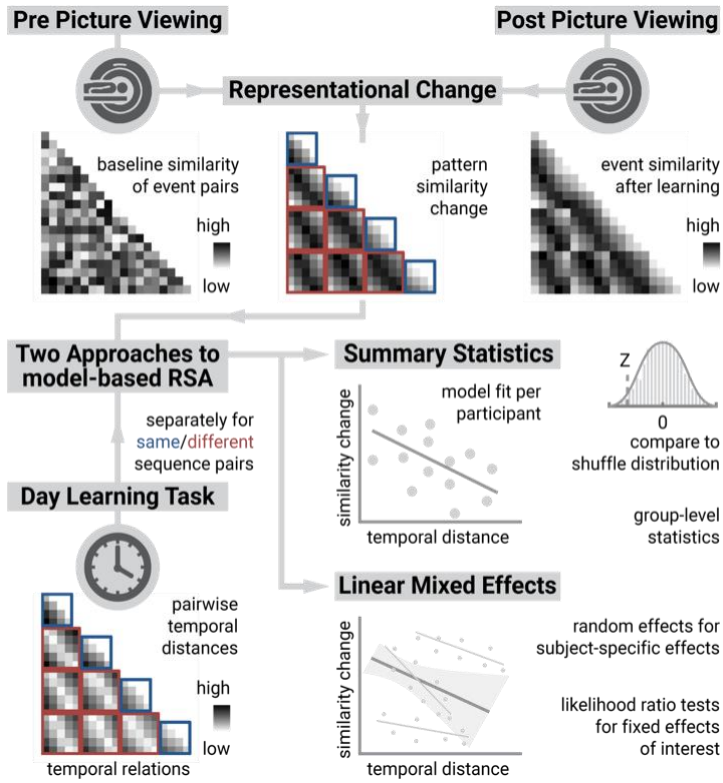

Figure 3. Representational Similarity Analysis Logic. We quantified the representational similarity of all event pairs before and after learning. Representational change was defined by subtracting pre-learning from post-learning pattern similarity (top row). Using two approaches to model-based representational similarity analysis (RSA, see Methods), we analyzed whether pattern similarity changes reflected the temporal structure of the sequences (bottom left). In the summary statistics approach (middle right), we regressed pattern similarity change on temporal distances between events using participant-specific linear models that were compared to null distributions obtained from shuffling similarity change against temporal distances. The resulting Z-values were used for permutation-based group-level statistics. In the mixed model approach (bottom right), we estimated the influence of temporal distances on pattern similarity change using fixed effects, with random effects accounting for within-subject dependencies. The statistical significance of fixed effects was assessed using likelihood ratio tests against reduced models excluding the fixed effect of interest.

Hippocampal representations of within-sequence relations reflect constructed event times

Before and after learning the event sequences, participants viewed the event images in random order while undergoing fMRI (Figure 1AB). We quantified changes in the similarity of multi-voxel patterns between pairs of events from before to after learning (Figure 3, see Methods). Using two approaches to model-based representational similarity analysis, we tested whether changes in pattern similarity could be explained by the temporal relationships between pairs of events. Temporal distances between events were measured in virtual time, real elapsing time in seconds and as differences in sequence order position (Figure 1C). In the summary statistics approach, we compared the fit of linear models predicting pattern similarity changes from temporal distances to shuffle distributions for each participant and assessed the resulting Z-values on the group level using permutation-based tests. Second, we fit linear mixed effects models to quantify whether sequence relationships explained pattern similarity changes. Rather than performing inferential statistics on one summary statistic per participant, mixed models estimate fixed effects and their interactions using all data points. We used temporal distance measures as fixed effects while capturing within-participant dependencies with random intercepts and random slopes (see Methods). The converging results of these analyses demonstrate that our findings do not depend on the specific statistical methods employed. We centered our analyses on the anterior hippocampus and the anterior-lateral entorhinal cortex (see Methods) based on our previous work implicating these regions in representing sequence relations[21,27].

We first tested whether pattern similarity changes in the anterior hippocampus (Figure 4A) could be explained by the virtual temporal distances between event pairs from the same sequence. Surprisingly, we observed a positive relationship between similarity changes and temporal distances in both the summary statistics (Figure 4B; t_{27}=3.07, p=0.006, d=0.56, 95% CI [0.18, 1.00]; α=0.025, corrected for separate tests of events of the same and different sequences) and the mixed model approach (Figure 4CD; $\chi^2(1)$=9.87, p=0.002).

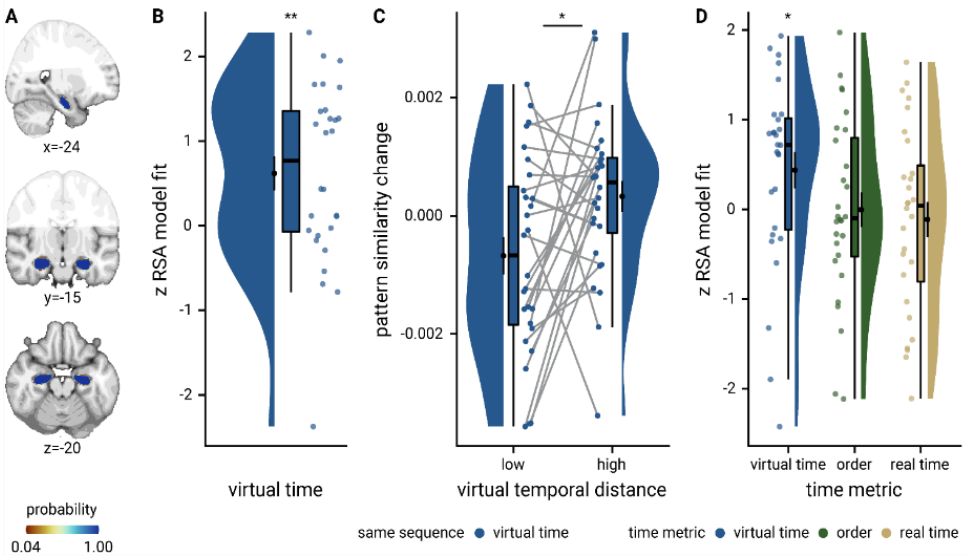

Figure 4. Sequence representations in anterior hippocampus reflect constructed event times. A. The anterior hippocampus region of interest is displayed on the MNI template with voxels outside the field of view shown in lighter shades of gray. Color code denotes probability of a voxel to be included in the mask based on participant-specific ROIs (see Methods). **B**. The Z-values based on permutation tests of participant-specific linear models assessing the effect of virtual time on pattern similarity change for event pairs from the same sequence were significantly positive. **C**. To illustrate the effect shown in **B**, average pattern similarity change values are shown for same-sequence event pairs that are separated by low and high temporal distances based on a median split. **D**. Z-values show the relationship of the different time metrics to representational change based on participant-specific multiple regression analyses. Virtual time predicts pattern similarity change with event order and real time in the model as control predictors of no interest. **B-D**. Circles are individual participant data; boxplots show median and upper/lower quartile along with whiskers extending to most extreme data point within 1.5 interquartile ranges above/below the upper/lower quartile; black circle with error bars corresponds to mean±S.E.M.; distributions show probability density function of data points. ** p<0.01; * p<0.05

This effect was further characterized by higher pattern similarity for event pairs separated by longer temporal distances than for pairs separated by shorter intervals Figure 4C, t_{27}=2.48, p=0.020, d=0.64, 95% CI [0.08, 0.87]). In contrast to our previous work[21], where we observed negative correlations of pattern similarity and temporal distances, participants learned multiple sequences in this study. They might have formed strong associations of same-sequence events on top of inferring each event's virtual time, potentially altering how temporal distances affected hippocampal pattern similarity (see

Discussion). The effect of virtual temporal distances on pattern similarity changes remained significant when competing for variance with a control predictor accounting for comparisons of the first and last event of each sequence (summary statistics: t_{27}=2.25, p=0.034, d=0.41, 95% CI [0.04, 0.82]; mixed model: $\chi^2(1)$=5.36, p=0.021, Supplemental Table 3). Thus, the relationship of hippocampal event representations and temporal distances is not exclusively driven by associations of the events marking the transitions between sequences.

Having established that hippocampal pattern similarity changes relate to temporal distances, we next assessed whether this effect was driven by virtual event times beyond sequence order and real time. We thus included the two additional time metrics as control predictors in the model. Virtual temporal distances significantly predicted pattern similarity changes even when controlling for the effects of event order and real time in seconds (Figure 4D; summary statistics: t_{27}=2.18, p=0.040, d=0.40, 95% CI [0.02, 0.81]; mixed model: $\chi^2(1)$=5.92, p=0.015). Further, the residuals of linear models, in which hippocampal representational change was predicted from order and real time, were related to virtual temporal distances (t_{27}=2.23, p=0.034, d=0.41, 95% CI [0.03, 0.82]), demonstrating that virtual time accounts for variance that the other time metrics fail to explain. Together, these data show that hippocampal representations of events from the same sequence changed to reflect mnemonically constructed event times.

The hippocampus generalizes temporal relations across sequences

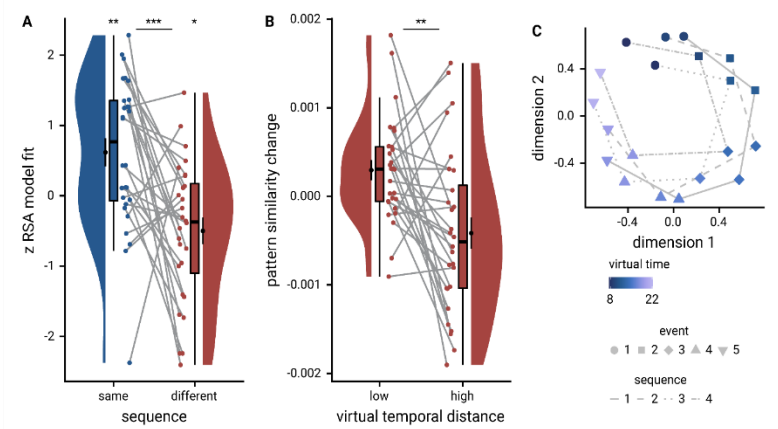

Figure 5. The anterior hippocampus generalizes temporal relations across sequences. A. Z-values show results of participant-specific linear models quantifying the effect of virtual time for event pairs from the same sequence (blue, as in Figure 4B) and from different sequences (red). Temporal distance is negatively related to hippocampal representational change for event pairs from different sequences. See **Error! Reference source not found.**EF for m ixed model analysis of across-sequence comparisons. The effect of virtual time differs for comparisons within the same sequence or between two different sequences. **B**. To illustrate the effect shown in **A**, average pattern similarity change values are shown for across--sequence event pairs that are separated by low and high temporal distances based on a median split. **C**. Multidimensional scaling results show low-dimensional embedding of the event sequences. Shapes indicate event order, color shows virtual times of events. The different lines connect the events belonging to the four sequences for illustration. *** p≤0.001; ** p<0.01; * p<0.05

We next tested whether similarity changes of hippocampal representations of events from different sequences mirrored generalized temporal distances. When comparing pairs of events belonging to different sequences, we observed a significant negative effect of virtual temporal distances on pattern similarity change (Figure5A, summary statistics t_{27}=-2.65, p=0.013, d=-0.49, 95% CI [-0.91, -0.10]; mixed model: $\chi^2(1)$=6.01, p=0.014; α=0.025, corrected for separate tests of events of the same and different sequences). This indicates that hippocampal representations of events from different sequences changed systematically to reflect generalized temporal relations. Events occurring at similar times relative to the virtual clock, but in different sequences, were represented more similarly than those taking place at more different virtual times (Figure 5B, t_{27}=-3.26, p=0.002, d=-0.89, 95% CI [-1.03, -0.21]). Virtual time was a significant predictor of hippocampal pattern similarity change for events from different sequences when competing for variance with order and real time (summary statistics: t_{26}=-2.62, p=0.015, d=-0.49, 95% CI [-0.92, -0.10], mixed model: $\chi^2(1)$=4.48, p=0.034, Supplemental Table 6; one outlier excluded). The relationship of temporal distances and representational change differed significantly between events from the same or different sequences (Figure 5A, summary statistics: paired t-test t_{27}=3.71, p=0.001, d=1.05, 95% CI [0.29, 1.13]; mixed model: interaction of sequence membership with virtual time $\chi^2(1)$=14.37, p<0.001). Similar interactions of sequence membership with order ($\chi^2(1)$=9.98, p=0.002) and real time ($\chi^2(1)$=9.27, p=0.002) were observed, but, crucially, the interaction of sequence membership and virtual time remained significant when including interactions of sequence membership with order and real time in the model ($\chi^2(1)$=8.57, p=0.003, Supplemental Table 8). Thus, the way

knowledge about virtual temporal relations was represented in the hippocampus depended on whether events belonged to the same sequence or not.

To explore how event sequences may be arranged in a low-dimensional representational space to give rise to the effects described above, we generated a distance matrix from the mixed effects model fitted to hippocampal pattern similarity change and subjected it to non-metric multidimensional scaling (see Methods). The resulting configuration in two dimensions (Figure5C), chosen for intuitive visualization, exhibited a c-shaped pattern for each sequence. Similar representational geometries have previously been described in parietal cortex[63–65]. Events occurring at similar virtual times occupy similar locations, in line with high pattern similarity for events from different sequences that are separated by low temporal distances. Thus, the generalization across sequences results in a comparable configuration for each sequence. While the observed configuration resulted in stress values significantly lower than those obtained in a permutation test (see Methods; z=-3.5, p=0.001), the high representational distances between temporally close events from the same sequence are not perfectly captured by the c-shaped arrangement. More than the two dimensions chosen for visualization would likely better capture the complex representational structure of the sequences.

Sequence representations differ between hippocampus and entorhinal cortex

In our second region of interest, the anterior-lateral entorhinal cortex (Figure 6A), the effect of virtual time on representational change did not differ statistically between event pairs from the same or from different sequences (summary statistics: paired t-test t_{27}=0.07, p=0.942). We thus collapsed across comparisons from the same and different sequences and observed a significant effect of virtual temporal distances on entorhinal pattern similarity change (Figure 6B; summary statistics: t_{27}=-2.31, p=0.029, d=-0.42, 95% CI [-0.84, -0.05]; mixed model: $\chi^2(1)$=4.39, p=0.036). In line with our previous work[27], events close together in time became more similar than those separated by longer temporal intervals (Figure 6C). The relationship of virtual temporal distances and entorhinal pattern similarity change was not statistically significant when competing for variance with distances based

on order and real time (summary statistics: t_{27}=-0.7, p=0.495, d=-0.13, 95% CI [-0.51, 0.25], mixed model: $\chi^2(1)$=1.18, p=0.278). We further corroborated that the temporal structure of the sequences was represented differently between the anterior-lateral entorhinal cortex and the anterior hippocampus (summary statistics: interaction between region and sequence membership in permutation-based repeated-measures ANOVA $F_{1,27}$=7.76, p=0.010, η^2=0.08, main effect of region $F_{1,27}$=3.10, p=0.086, η^2=0.02, main effect of sequence $F_{1,27}$=7.41, p=0.012, η^2=0.08; mixed model: three-way interaction between virtual time, sequence membership and region of interest $\chi^2(1)$=6.31, p=0.012). Whereas the hippocampus employed two distinct representational formats for temporal relations depending on whether events belonged to the same sequence or not, we observed consistent negative correlations between representational change and temporal distances when collapsing across all event pairs, but no statistically significant difference between representations of temporal relations from the same or different sequences in the entorhinal cortex.

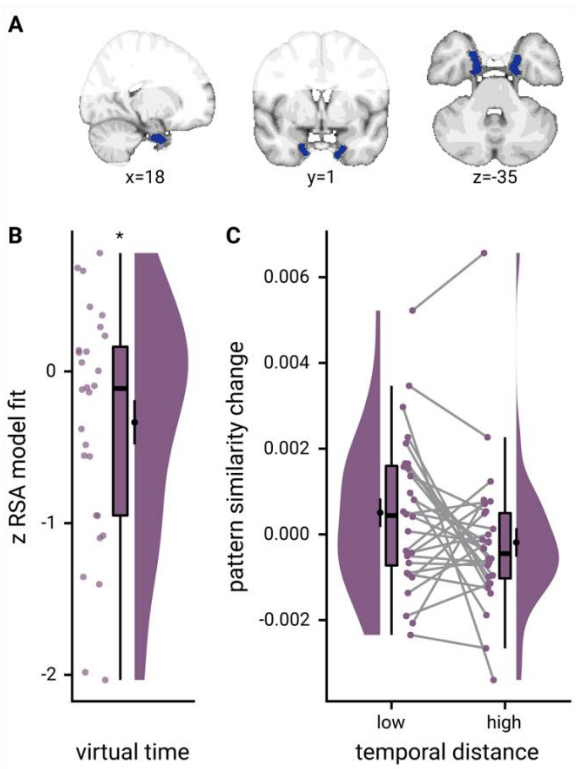

Figure 6. The anterior-lateral entorhinal cortex uses a shared representational format for relations of events from the same and different sequences. A. The anterior-lateral entorhinal cortex region of interest is displayed on the MNI template with voxels outside the field of view shown in lighter shades of gray. Color code denotes probability of a voxel to be included based on participant-specific masks (see Methods). **B**. Z-values for participant-specific RSA model fits show a negative relationship between pattern similarity change and virtual temporal distances when collapsing across all event pairs. **C**. To illustrate the effect in **B**, raw pattern similarity change in the anterior-lateral entorhinal cortex was averaged for events separated by low and high temporal distances based on a median split. * $p<0.05$

Anatomical overlap between representations of within-sequence relations and across-sequence generalization

We next asked whether representations of same-sequence relations are distinct from or overlap with the across-sequence generalization of temporal relations. For this purpose and to complement our region-of-interest analyses described above, we performed a searchlight analysis that revealed significant effects of virtual temporal distances on representations of events from the same sequence in the bilateral anterior hippocampus (Figure 7A; peak voxel MNI x=-24, y=-13, z=-20; t=4.53, p_{svc}=0.006). We used the same-sequence searchlight peak cluster to define a region of interest to test for the independent across-sequence generalization effect (see Methods). Indeed, virtual temporal distances explained pattern similarity change for events from different sequences in these voxels (Figure 7B; summary statistics t_{27}=-2.19, p=0.036, d=-0.40, 95% CI [-0.81, -0.03]; mixed model: $\chi^2(1)$=4.13, p=0.042), demonstrating an overlap between representations of within-sequence relations and their generalization across sequences.

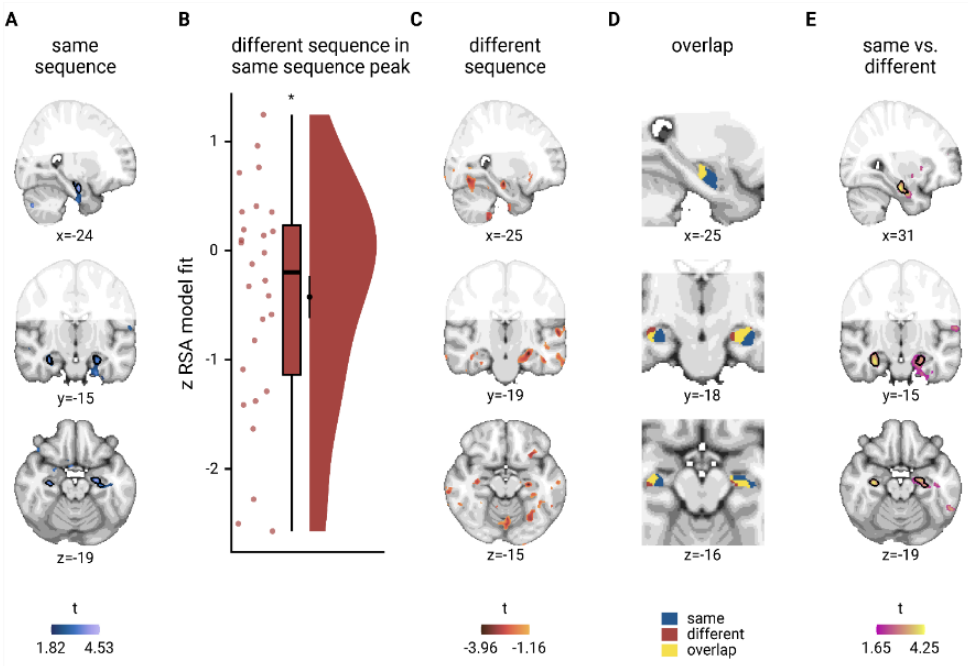

Figure 7. Overlapping representations of within- and across-sequence relations. A. Searchlight analysis results show a positive relationship between representational change and virtual temporal distances for event pairs from the same sequence in the bilateral anterior hippocampus. Statistical image is thresholded at $p_{uncorrected}<0.01$; voxels within black outline are significant after correction for multiple comparisons using small volume correction. **B**. In the peak cluster from the independent within-sequence searchlight analysis (**A)**, representational change was negatively related to virtual temporal distances between events from different sequences. Circles show individual participant Z-values from summary statistics approach; boxplot shows median and upper/lower quartile along with whiskers extending to most extreme data point within 1.5 interquartile ranges above/below the upper/lower quartile; black circle with error bars corresponds to mean±S.E.M.; distribution shows probability density function of data points. **C**. Searchlight analysis results show negative relationship between representational change and temporal distances for different-sequence event pairs. Statistical image is thresholded at $p_{uncorrected}$ <0.05. **D**. Within the anterior hippocampus, the effects for events from the same sequence and from two different sequences overlap. Visualization is based on statistical images thresholded at $p_{uncorrected}$ <0.05 within small volume correction mask. **E**. Searchlight analysis results show a bilateral interaction effect in the anterior hippocampus that is defined by a differential relationship of virtual temporal distances and representational change for events from the same and different sequences. Statistical image is thresholded at $p_{uncorrected}<0.01$; voxels within black outline are significant after correction for multiple comparisons using small volume correction. **A**, **C-E**. Results are shown on the MNI template with voxels outside the field of view displayed in lighter shades of gray. * p<0.05

Further, we conducted a searchlight analysis looking for negative correlations of temporal distances and pattern similarity change for events from different sequences. We detected clusters in anterior hippocampus that overlapped with the same-sequence searchlight effect (Figure 7CD), though this searchlight generalization effect did not survive corrections for multiple comparisons (peak voxel MNI x=-26, y=-19, z=-15, t=-3.96, p_{svc}=0.071, Supplemental Table 14). Lastly, we directly searched for brain areas in which pattern similarity change differentially scaled with temporal distances depending on whether events were from the same or different sequences. The two largest clusters in our field of view were located in the left and right anterior hippocampus (Figure 7E, peak voxel MNI x=31, y=-16, z=-21; t=4.25, p_{svc}=0.007, Supplemental Table 15). Taken together, these findings highlight that hippocampal representations carry information about the specific sequence in which events occur, and that these temporal relations are generalized across sequences.

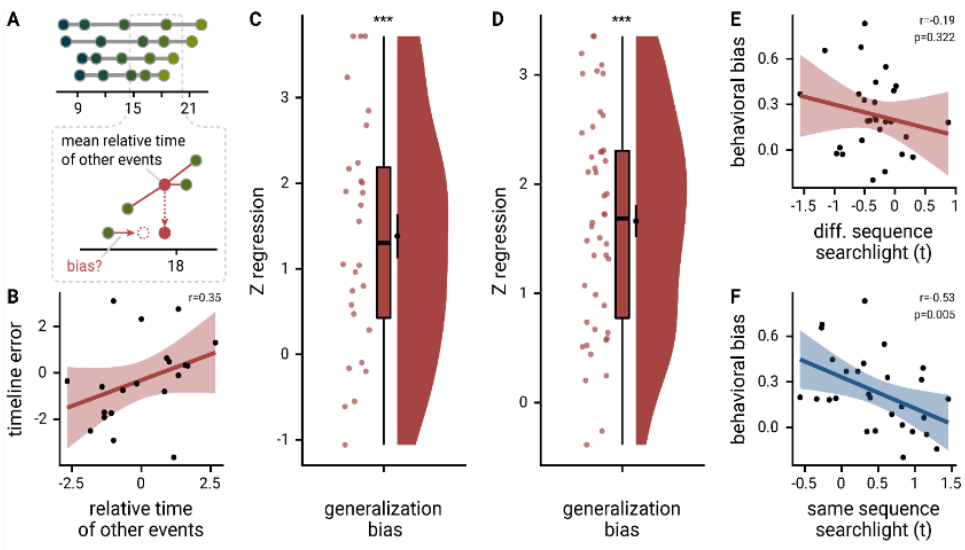

Figure 8. Structural knowledge biases construction of event times. A. The generalization bias quantifies the influence of structural knowledge on the construction of individual event times. For each event, the mean time of events at the same sequence position in the other sequences was calculated to test whether event times were biased towards the relative time of other events. **B.** The scatterplot illustrates the generalization bias for an example participant. Each circle corresponds to one event and the regression line highlights the relationship between the relative time of other events and the errors in constructed event times. The example participant was chosen to have a median-strength generalization bias. Correlation coefficient is based on Pearson correlation. **C.**

The relative time of events from other sequences predicted signed event time construction errors as measured in the timeline task. Positive values indicate that when other events took place late relative to a specific event, the time of that event was estimated to be later than when other events were relatively early. Circles show individual participant Z-values from participant-specific linear models (**B**); boxplot shows median and upper/lower quartile along with whiskers extending to most extreme data point within 1.5 interquartile ranges above/below the upper/lower quartile; black circle with error bars corresponds to mean±S.E.M.; distribution shows probability density function of data points. **D**. The generalization bias in event time construction through structural knowledge was replicated in an independent sample (n=46) based on Montijn et al.[66]. Data shown as in **B**. **E.** The behavioral generalization bias (regression coefficients from summary statistics approach) did not correlate significantly with the across-sequence generalization effect in the anterior hippocampus (searchlight peak voxel t-values). **F.** We observed a significant negative correlation between the same-sequence searchlight effect (peak voxel t-values) and the behavioral generalization bias (regression coefficients from summary statistics approach), suggesting that participants with strong hippocampal representations of the temporal relations between events from the same sequence were less biased by structural knowledge in their construction of event times. Statistics in **E** and **F** are based on Spearman correlation

Generalized knowledge about other sequences biases event time construction

Having established generalized hippocampal event representations, we explored whether knowledge about the general structure of event times in other sequences influenced the construction of individual event times. For each event, we quantified when it took place relative to the average virtual time of the events at the same sequence position in the other three sequences (Figure 8A; see Methods). We reasoned that the construction of a specific event time could be biased by knowledge about the general pattern of event times at that sequence position. Indeed, we observed positive relationships between the relative time of other events and signed errors in constructed event times as assessed in the timeline task (Figure 8BC; summary statistics: t_{27}=5.32, p<0.001, d=0.98, 95% CI [0.55, 1.48]; mixed model: $\chi^2(1)$=17.90, p<0.001). This demonstrates that structural knowledge about the sequences biased the construction of event times. The constructed virtual time of an event tended to be overestimated when the events occupying the same sequence position in the other sequences took place late relative to the event in question, and vice versa when the other events occurred relatively early. In an independent group of participants[66], we replicated this generalization bias (Figure 8D; summary statistics: t_{45}=11.30, p<0.001, d=1.64, 95% CI [1.23, 2.13]; mixed model: $\chi^2(1)$= 53.74, p<0.001), confirming the influence

of generalized knowledge about the sequences on event time construction. One possibility is that structural knowledge about the sequences biases the construction of specific event times, in particular when uncertainty about the virtual time of events is high. Indeed, we observed a significant negative correlation between how strongly pattern similarity changes in the anterior hippocampus reflected temporal relations between same-sequence events in the searchlight analysis and the strength of the behavioral generalization bias (Figure 8EF, Spearman r=-0.53, p=0.005; α=0.025 corrected for two comparisons; correlation with across-sequence effect: Spearman r=-0.19, p=0.322), suggesting that the construction of event times was less biased by time patterns generalized across sequences in those participants with precise representations of within-sequence temporal relations.

We further explored whether participants made systematic errors in the sorting task that might point towards generalization across sequences. Specifically, we searched for swap errors where participants interchanged events between sequences that occupied the same sequence position. Indeed, 57.5%±34.3% (mean±S.D) of sorting errors were swap errors and 12 of the 14 participants who made sorting errors also made swap errors (mean±S.D of 3.1±2.1 swap errors per participant with sorting errors). The proportion of swap errors in our sample was larger than expected from random sorting errors ($z=5.07$, $p<0.001$), indicating that participants systematically swapped events belonging to the same position between sequences. While we did not observe statistically significant relationships between swap errors and the generalization bias, the prevalence of these errors is compatible with the view that participants generalized across events occupying the same sequence position.

Discussion

Our findings show that hippocampal event representations change through learning to reflect temporal relations based on mnemonically constructed event times. Converging region of interest and searchlight analyses demonstrate that, on the one hand, the hippocampus forms specific representations of temporal relations of the events in a sequence that mirror constructed event times beyond the effects of order and real time.

On the other hand, temporal relations are generalized across sequences using a different representational format. In contrast, the similarity of event representations in the anterior-lateral entorhinal cortex scaled with temporal distances for events irrespective of sequence membership. The behavioral data demonstrates that the construction of specific event times is biased by structural knowledge abstracted from different sequences.

In our paradigm, participants mentally constructed the times of events relative to a hidden virtual clock. To do so, they needed to combine their experience of passing real time with infrequent cues about the current virtual time. Thus, real time was critical for the successful construction of event times, despite not being cued explicitly. Participants' responses in a memory test and the similarity structure of hippocampal multi-voxel patterns were explained by virtual event times beyond the effects of real time and sequence order, showing that sequence representations reflect mnemonically constructed time. Recent work demonstrated the scaling of time cell representations to different real time intervals in the rodent hippocampus[67]. Temporal scaling of hippocampal representations could potentially underlie our observation that temporal distances in virtual time are related to the similarity of event representations even when accounting for the effects of real time and order. This finding highlights that the anterior hippocampus maps relational knowledge derived from mnemonic constructions.

The hippocampus constructed an integrated representation that generalized temporal relations across sequences. Multi-voxel patterns of events taking place at similar virtual times, but in different sequences, were more similar than those of events occurring at different points in time. Thus, representations of events from different sequences changed systematically to reflect generalized temporal distances. Speculatively, this effect could be related to the observation that, in mice trained to run a number of laps on a maze to obtain rewards, lap-specific firing patterns in the hippocampus generalize across sequences of laps on geometrically distinct mazes[54]. While it is possible that the first and last events of the sequences are particularly important to sequence processing, our data show that virtual time explained representational changes when competing for variance with order and real

time also for events from different sequences. This makes it unlikely that the hippocampal generalization effect was driven exclusively by events at the first or last sequence position. The generalization of temporal distances across sequences in the hippocampus is in line with the contribution of constructive mnemonic processes to flexible cognition via the recombination of elements across experiences and statistical learning[13,40,43,46,48,49,68,69]. More generally, it is consistent with the role of the hippocampus in forming cognitive maps of relational structures and in generalizing structural knowledge to novel situations[12,38,51,53,57,70,71].

Structural knowledge and mnemonic construction are intertwined. In two independent samples, we show that general time patterns, abstracted from other sequences, bias the construction of specific event times. When events at the same sequence position, but in other sequences, took place relatively late to the time of an event, the time of that event was remembered to be later than when the other events occurred relatively early. This generalization bias shows that knowledge about events at structurally similar positions contributes to constructive memory for specific events. It is in line with biases resulting from the exploitation of environmental statistics when reconstructing stimulus sizes from memory[55,56], when estimating brief time intervals[72,73], or when discriminating the order of previously presented stimuli[74]. Likewise, prior knowledge can distort memories for short narratives[75], spatial associations[76] and temporal positions[62]. Consistent with the suggested role of grid cells in the representation of spatial structure, distortions in mnemonic reconstructions of spatial relations induced through boundary geometry follow predictions from models of grid-cell functioning[77]. Further, recombining information across episodes for associative inference can induce false memories for contextual details[68,78], illustrating that generalization impacts memory for specific associations. In line with the greater reproduction of episodic details by participants whose recall follows the temporal structure of an experience more closely[79], these findings highlight that structural knowledge and mnemonic construction are interwoven. More broadly, abstract semantic or schematic knowledge may provide a scaffold for the recall of episodic details[4,7,38,80,81]. Our findings show that structural knowledge not only facilitates, but also biases constructive memory.

The way temporal relations shaped hippocampal multi-voxel pattern similarity differed between pairs of events from the same and different sequences. We observed positive correlations between temporal distances and hippocampal representational change, which were characterized by relatively decreased pattern similarity for nearby compared to increased pattern similarity for more distant events from the same sequence. One possible explanation for the surprising direction of this effect could be that, compared to our previous work where participants encountered only one sequence[21], participants relied more on associative encoding strategies when learning multiple sequences in the present experiment. Possibly, the need to link events belonging to the same sequence altered how pattern similarity changes relate to temporal distances for these same-sequence events. In line with this interpretation, prior work has shown that the relationship of hippocampal pattern similarity and temporal memory can depend on factors like the use of associative encoding strategies and the presence of event boundaries marking switches between sequences of images from the same category[22,82,24]. Successful recency discrimination was associated with more similar hippocampal representations during encoding when participants were encouraged to use associative strategies to encode the order of image sequences from two alternating visual categories[22]. A different study found more dissimilar hippocampal representations for stimuli whose order was later remembered correctly[24]. Thus, the formation of associations between same-sequence events could explain why correlations of pattern similarity change were, in contrast to our previous work[21], positive. A second possible interpretation of this effect is based on observations that the hippocampus differentiates similar episodes[47,83–86]. Hippocampal differentiation could explain the relative decrease of pattern similarity for temporally close events from the same sequence. However, the generalization across sequences does not directly follow from a differentiation account.

The hippocampus supports constructive memory and generalization in concert with a distributed network of brain regions. In addition to medial temporal lobe structures, the mental simulation of past and future episodic scenarios recruits a core network including

medial prefrontal and retrosplenial cortex as well as lateral parietal and temporal areas[39,87]. Notably, this network overlaps with areas supporting the recombination of elements and generalization. For example, both the construction of novel experiences based on the combination of multiple elements[88] and memory integration across episodes[47] are supported by the medial prefrontal cortex and the hippocampus. In sequence processing, representational similarity is increased for items occupying the same position in different sequences in parahippocampal, retrosplenial and medial prefrontal cortices as well as in the angular gyrus[18,89]. Likewise, sequence positions can be decoded from magnetoencephalographic responses elicited by visual stimuli presented in scrambled order[90]. In line with the suggestion that the posterior parietal cortex supports generalization by projecting stimuli onto a low-dimensional manifold[91], neural magnitude representations that generalize across task contexts have been observed using EEG[63,92]. While we did not observe effects outside the hippocampal-entorhinal region that survived corrections for multiple comparisons, we note that, based on our prior hypotheses, we opted for high-resolution coverage of the medial temporal lobe at the cost of reducing the field of view of our MR images. As the events in our task can be conceived of as being arranged along one or multiple, parallel mental number lines, future research could test how the parietal cortex encodes event relations to explore commonalities with and differences to the generalization of event times observed in the hippocampus.

Our paradigm allows a highly-controlled read-out of representational change relative to a pre-learning baseline scan. Events are shown in the same random order before and after learning, ruling out that prior associations or the temporal auto-correlation of the blood-oxygen-level-dependent signal drives our effects. Future studies could extend the paradigm to investigate how hierarchically nested sequences are represented, for example by introducing higher-order relations between sequences – akin to different days being grouped in weeks. The precise temporal dynamics of the generalized hippocampal event representation pose another intriguing question. Based on the report that the temporal organization of memory reactivation relative to the hippocampal theta phase reflects semantic relations between items[93], a speculative hypothesis is that a theta phase code

could also underlie memory for temporal relations of events from the same and different sequences.

In conclusion, our findings show that the similarity of event representations in the hippocampus reflects relations between events that go back to mnemonically constructed event times, highlighting the impact of mnemonic construction on sequence memory beyond the effects of event order and real elapsing time. Temporal relations are generalized to events from different sequences, in line with hippocampal contributions to the abstraction of structural knowledge and the generalization across episodes. General time patterns abstracted from other sequences systematically influence the construction of specific event times, demonstrating that constructions of specific scenarios build on structural knowledge.

Methods

Participants

31 participants were recruited for this experiment. Participants gave written informed consent prior to participation. All proceedings were approved by the local ethics committee (CMO Regio Arnhem-Nijmegen). One participant aborted the experiment due to feeling claustrophobic when entering the MR scanner. Two participants were excluded from further analysis due to bad memory performance and technical difficulties during data acquisition. Thus, the sample consisted of 28 participants (21 female, age: mean±standard deviation 23.04±3.21 years, range 18-31 years).

Procedure

Overview

The experiment consisted of four parts (Figure 1A) and lasted approximately 2.5 hours in total. The first three parts were performed inside the MR scanner and comprised a learning task lasting around 50 minutes that was completed in between two blocks of a picture viewing task of around 25 minutes each. The tasks inside the scanner were presented on a rear-projection screen with a resolution of 800x600 pixels and implemented using

Presentation (version 16.2, Neurobehavioral Systems). Subsequently, outside of the scanner, participants performed two short memory tasks in front of a computer screen, implemented with custom Matlab code. The tasks are described in more detail below. Data analysis was carried out using FSL (version 5.0.4)[94] and R (version 3.6.1)[95].

Stimuli

The stimuli used throughout the experiment were created within the life-simulation computer game The Sims 3 (Electronic Arts) by taking screenshots. Each image featured a scene in the life of an affluent family. The main character, the family father, was visible in all scenes. In addition, the mother, son, daughter and family dog appeared in some of the images. All of the depicted events took place within the same family home, but showed activities in a number of different rooms. In an effort to design stimuli with minimal to no indication of day time, the house had constant artificial lighting, but no windows or clocks. The 21 pictures used in this study were selected from an initial set of 35 pictures based on an independent sample rating them as the most ambiguous with regard to the time of day they could take place. One image served as a target image for the picture viewing tasks (see below), while the other 20 event images were randomly assigned to different times and days for every participant.

Picture Viewing Tasks

In the picture viewing tasks (Figure 1B), participants viewed a stream of the event images. Their task was to look at the images attentively and to respond via button press whenever a target picture, which showed the father feeding the family's dog, was presented (pre-learning: 95.71%±7.90% mean±standard deviation of percentage of hits; 881.34ms±131.43ms mean±standard deviation of average reaction times; post-learning: 95.71%±6.90% mean±standard deviation of percentage of hits; 841.40ms±162.16ms mean±standard deviation of average reaction times). The task consisted of 10 mini-blocks. In each mini-block, the target image and the 20 images, which would later make up the virtual days (see Day Learning Task), were shown in random order. Mini-blocks were separated by breaks of 15 s. Stimulus presentations lasted 2.5 s and were time-locked to

fMRI volume acquisition onsets. Scene stimuli within a mini-block were separated by 2 or 3 repetition times (TR), randomly assigned so that both stimulus onset asynchronies occurred equally often.

For each participant, we generated a random stimulus order with the constraint that no scene was consistently presented at early or late positions across mini-blocks. Specifically, we compared sequence positions across mini-blocks between the images using a one-way ANOVA. We discarded randomizations where this ANOVA was statistically significant to exclude biases in presentation order. Crucially, the same, participant-specific random order of stimuli and inter-stimulus intervals was used in both the pre-learning and the post-learning picture viewing task. Thus, any systematic differences in the representational similarity of event pairs between the two picture viewing tasks do not go back to differences in the timing of stimulus presentations or the temporal auto-correlation of the BOLD-signal. Rather, we interpret such changes to be a consequence of the learning task.

Day Learning Task

In this task, 20 of the 21 scenes, which were shown in the picture viewing tasks, were presented repeatedly. This time, however, they were grouped into multiple sequences introduced to participants as “virtual days”. There were four different sequences, each comprising 5 events. Events from the same sequence were always shown in a specific order and with a specific time delay between them. Scenes were on screen for 1.5 s. At the end of each sequence, an image of a moon was shown for 5 s, then the next sequence began. Every sequence was presented 7 times. There were 7 mini-blocks in this task. Within each of these, every sequence was presented once. At the end of a mini-block, a 30-s break followed, then the next block started. The order in which the sequences were presented differed randomly across the 7 mini-blocks.

We instructed participants that the scenes depicted events from the life of a family and that the sequences of event images corresponded to different days in the family’s life. Participants were asked to memorize which events made up the different sequences (Figure 1C). We further instructed them to learn when during the respective sequence each event occurred. Specifically, we asked participants to learn event times relative to a virtual clock.

This clock was running hidden from participants and event images were shown whenever the hidden clock reached the specific event time (Figure 1C). The task was devised such that participants had to rely on their experience of passing real time and mnemonic construction to infer the times of events.

Specifically, to give participants an indication of virtual time, the hidden clock was made visible 6 times for every presentation of a sequence: once before the first event, once in between successive events, and once after the last event. Participants received no cues about elapsing real time, but had to use their experience of passing real time between virtual time cues to infer the event times relative to the hidden virtual clock. Importantly, the exposure of the hidden clock occurred at random times for each sequence presentation, with the constraint that it could not be revealed closer than 2 s to a preceding or subsequent event. Thus, participants saw different time cues in each repetition of a sequence. For example, while a specific event always happened at the same virtual time, e.g. 2:07 p.m., the virtual clock could be exposed at any time before the event, e.g. corresponding to 1:32 p.m. in the first repetition of the sequence, and corresponding to 1:17 p.m. in the second repetition. Because true event times were never revealed, participants could not exclusively rely on associative learning to solve the task. Time cues were visible for 1.5 s, but displayed only the time at the start of exposure, i.e. the displayed time did not change within the duration of its presentation.

In short, participants had to combine their experience-based estimates of passing time with the time cues provided by the exposures of the otherwise hidden clock to infer the time at which each event in each sequence took place. Crucially, we varied the speed of the hidden clock between sequences in an effort to partly dissociate real time (in seconds) from virtual time (in virtual hours). Thus, for two sequences more virtual time passed in a comparable amount of real elapsing time (Figure 1C). Correlations between the linearly increasing time metrics are inevitably high (Pearson correlation of virtual time with order $r=0.969$ and virtual time with real time $r=0.975$). Still this manipulation allowed us to determine using multiple regression whether virtual time explained constructed event times when competing for variance with real elapsed time and event order and whether hippocampal pattern similarity changes related to temporal distances in virtual time beyond ordinal

distances and real time distances. Regression models including collinear predictor variables do not result in biased parameter estimates[96,97].

Sorting Task

The day sorting task (Figure 1D) was performed in front of a computer screen. The 20 event images from the day learning task were presented on the screen in a miniature version. They were arranged in a circle around a central area displaying 4 rectangles. Participants were instructed to drag and drop all events of the same sequence into the same rectangle with a computer mouse. Participants freely chose which rectangle corresponded to which sequence as the sequences were not identifiable by any label and were presented in differing orders across mini-blocks during learning.

Timeline Task

In this task, participants saw a timeline ranging from 6 a.m. to midnight together with miniature versions of the five event images belonging to one sequence (Figure 1E). Participants were instructed to drag and drop the event images next to the timeline so that scene positions reflected the event times they had inferred in the day learning task. To facilitate precise alignment to the timeline, event images were shown with an outward pointing triangle on their left side, on which participants were instructed to base their responses.

MRI Acquisition

MRI data were recorded with a 3T Siemens Skyra scanner (Siemens, Erlangen, Germany). A high-resolution 2D EPI sequence was used for functional scanning (TR=2270 ms, TE=24 ms, 40 slices, distance factor 13%, flip angle 85°, field of view (FOV) 210x210x68 mm, voxel size 1.5 mm isotropic). The field of view (FOV) was aligned to fully cover the medial temporal lobe, parts of ventral frontal cortex and (if possible) calcarine sulcus. Functional images for the two picture viewing tasks and the learning task were acquired in three runs. In addition to these partial-volume acquisitions, 10 scans of a functional whole-brain sequence were also acquired to improve registration during preprocessing. The sequence settings were identical to the functional sequence above, but instead of 40 slices, 120 slices were acquired, leading to a longer TR (6804.1ms). A structural scan was acquired for each participant (TR = 2300 ms; TE = 315 ms; flip angle = 8°; in-plane resolution = 256x256 mm;

number of slices = 224, voxel resolution = 0.8x0.8x0.8 mm). Lastly, a gradient field map was acquired (for n = 21 participants only due to time constraints), with a gradient echo sequence (TR = 1020 ms; TE1 = 10 ms; TE2 = 12.46 ms; flip angle = 90°; volume resolution = 3.5x3.5x2 mm; FOV = 224x224 mm).

ROI Definition

Our previous work demonstrates representations reflecting the temporal relations of events from one sequence in the anterior hippocampus[21] and the anterior-lateral entorhinal cortex[27]. More generally, these regions have been implicated in temporal coding and memory (for review, see[10]). Further, the hippocampus has been linked to inferential reasoning and generalization[46,48,49,51,53]. We thus focused our analyses on these regions. Region of interest (ROI) masks were based on participant-specific FreeSurfer segmentations (version 6.0.0-2), which yielded masks for the entire hippocampus and entorhinal cortex. These were co-registered to participants' functional space. We defined anterior hippocampus using the Harvard-Oxford atlas mask (thresholded at 50% probability), selecting all voxels anterior to MNI y=-21 based on Poppenk et al.[98]. The resulting anterior hippocampus mask was also co-registered to participants' functional space and intersected with the participant-specific hippocampal mask from FreeSurfer. The mask for the anterior-lateral entorhinal cortex was based on Navarro Schröder et al.[99]. It was co-registered to participants' functional space and intersected with the entorhinal cortex mask from FreeSurfer.

Data Analysis

Behavioral Data Analysis

Sorting Task

For analysis of the sorting task, we took the grouping of event images as provided by the participants and assigned them to the four sequences to ensure maximal overlap between actual and sorted sequence memberships. While the assignment of groupings to sequences is unambiguous when performance is, as in our sample, high, this procedure is potentially liberal at lower performance levels. We then calculated the percentage of correctly sorted event images for each participant, see the raincloud plot[100] in Figure 2A.

In an exploratory analysis, we searched for systematic errors in the sorting task. Specifically, we looked for swap errors where participants interchanged events occurring at the same position between two or more sequences. We used a χ^2-test to assess whether the number of swap errors deviated from uniformity across sequence positions. To test whether participants made more swap errors than expected from chance we ran a permutation test where we introduced sorting errors for randomly selected events. For each of 10 000 iterations, we generated a surrogate sample of sorting results with the number of randomly introduced sorting errors matching the number of errors made by the different participants in our sample. We then quantified the proportion of swap errors across this surrogate sample. This resulted in a distribution of the proportion of swap errors that would be expected from random sorting errors. We assessed how many permutations yielded proportions of swap errors larger or equal to the proportion of swap errors observed in the fMRI sample to compute a p-value and further quantified a z-value as the difference between the observed swap error proportion and the mean of the chance distribution divided by the standard deviation of the chance distribution. We tested whether the number of swap errors was related to absolute errors in the timeline task (see below) using Spearman's correlation and a t-test for independent samples.

Timeline Task

We analyzed how well participants constructed the event times based on the day learning task. We quantified absolute errors across all events (Figure 2C) as well as separately for the five sequence positions (Figure 2D), the four sequences and as a function of virtual clock speed. Using two approaches we tested whether virtual time drove participants' responses rather than the sequence order or objectively elapsing time. For the summary statistics approach, we ran a multiple regression analysis for each participant with virtual time, sequence position (order), and real time since the first event of a day as predictors of responses in the timeline task. To test whether virtual time indeed explained participants' responses even when competing for variance with order and real time, included in the model as control predictors of no interest, we compared the participant-specific t-values of the resulting regression coefficients against null distributions obtained from shuffling the

remembered times against the predictors 10,000 times. We converted the resulting p-values to Z-values and tested these against zero using a permutation-based t-test (two-sided; α=0.05; 10,000 random sign-flips, Figure 2E). As a measure of effect size, we report Cohen's d with Hedges' correction and its 95% confidence interval as computed using the effsize-package[101].

Second, we addressed this question using linear mixed effects modeling. Here, we included the three z-scored time metrics as fixed effects. Starting from a maximal random effect structure[102], we simplified the random effects structure to avoid convergence failures and singular fits. The final model included random intercepts and random slopes for virtual time for participants. The model results are visualized by dot plots showing the fixed effect parameters with their 95% confidence intervals and marginal effects estimated using the ggeffects package[103]. To assess the statistical significance (α=0.05) of virtual time above and beyond the effects of order and real time, we compared this full model to a nested model without the fixed effect of virtual time, but including order and real time, using a likelihood ratio test. Supplemental Table 1 provides an overview of the final model and the model comparison.

To explore whether structural knowledge about general time patterns biases the construction of event times, we assessed errors in remembered event times. Specifically, when constructing the time of one specific event, participants could be biased in their response by the times of the events from other sequences at that sequence position. For each event, we quantified the average time of events in the other sequences at the same sequence position (Figure 8A). For example, for the fourth event of the first sequence, we calculated the average time of the fourth events of sequences two, three and four. We then asked whether the deviation between the average time of other events and an event's true virtual time was systematically related to signed errors in constructed event times. A positive relationship between the relative time of other events and time construction errors indicates that, when other events at the same sequence position are relatively late, participants are biased to construct a later time for a given event than when the other events took place relatively early. In the summary statistics approach, we ran a linear regression for each participant (Figure 8B) and tested the resulting coefficients for

statistical significance using the permutation-based procedures described above (Figure 8C). The regression coefficients from this approach were used to test for a relationship between the behavioral generalization bias and the hippocampal searchlight effects (see below). Further, we analyzed these data using the linear mixed model approach.

To replicate the results from this exploratory analysis, we conducted the same analysis in an independent group of participants. These participants (n=46) constituted the control groups of a behavioral experiment testing the effect of stress induction on temporal memory[66]. They underwent the same learning task as described above with the only difference being the duration of this learning phase (4 rather than 7 mini-blocks of training). The timeline task was administered on the day after learning. The procedures are described in detail in Montijn et al.[66]. The data from this independent sample are shown in Figure 8D.

MRI Preprocessing

Preprocessing was performed using FSL FEAT (version 6.00). Functional scans from the picture viewing tasks and the whole-brain functional scan were submitted to motion correction and high-pass filtering using FSL FEAT. For the two picture viewing tasks, data from each mini-block was preprocessed independently. For those participants with a field map scan, distortion correction was applied to the functional data sets. No spatial smoothing was performed. Functional images from the two picture viewing tasks were then registered to the preprocessed mean image of the whole-brain functional scan. The whole-brain functional images were registered to the individual structural scans. The structural scans were in turn normalized to the MNI template (1-mm resolution). Gray matter segmentation was done on the structural images, and the results were mapped back to the space of the whole-brain functional scan for later use in the analysis.

Representational Similarity Analysis

Representational similarity analysis (RSA)[104] was first implemented separately for the pre- and post-learning picture viewing task. It was carried out in ROIs co-registered to the whole-brain functional image and in searchlight analyses (see below). For the ROI analyses, preprocessed data were intersected with the participant-specific anterior hippocampus and anterolateral entorhinal cortex ROI masks as well as a brain mask obtained during preprocessing (only voxels within the brain mask in all mini-blocks were analyzed) and the

gray matter mask. For each voxel within the ROI mask, motion parameters from FSL MCFLIRT were used as predictors in a general linear model (GLM) with the voxel time series as the dependent variable. The residuals of this GLM (i.e. data that could not be explained by motion) were taken to the next analysis step. As the presentation of images in the picture viewing tasks was locked to the onset of a new volume (see above), the second volume after image onset was selected for every trial, effectively covering the time between 2270 and 4540 ms after stimulus onset. Only data for the 20 event images that were shown in the learning task were analyzed; data for the target stimulus were discarded. The similarity between the multi-voxel activity pattern for every event image in every mini-block with the pattern of every other event in every other mini-block was quantified using Pearson correlation coefficients. Thus, comparisons of scenes from the same mini-block were excluded. Next, we calculated mean, Fisher z-transformed correlation coefficients for every pair of events, yielding separate matrices of pattern similarity estimates for the pre- and the post-learning picture viewing tasks (Figure 3).

In order to assess changes in representational similarity between the two picture viewing tasks, we quantified pattern similarity changes as the difference of the respective correlation coefficients for every pair of events between the post-learning picture viewing task and its pre-learning baseline equivalent (Figure 3). Then, we analyzed how these difference values related to temporal relations between events, which we quantified using the absolute distances in virtual time ("virtual time") between events (Figure 1C, bottom right). We further tested whether the effect of virtual time on anterior hippocampal pattern similarity change persisted when including the absolute difference between sequence positions ("order") and the interval in seconds between events ("real time") as control predictors of no interest in the model. Time metrics were z-scored within each participant prior to analysis. We separately tested the effect of virtual time for event pairs from the same or different sequences and used a Bonferroni-corrected α-level of 0.025 for these tests. To implement these tests, we employed two approaches to model-based RSA that are described in detail below. We used a summary statistics approach, which uses permutation-based procedures on the subject-level as well as on the group-level, in line with recommendations for the analysis of multi-voxel patterns [105]. We also implemented

our statistical analyses using linear mixed effects models, which capture within-subject dependencies using random effects while estimating the fixed of interest on all data points. Mixed effects models are well-suited to test more complex interactions. The fact that the results of the two analysis approaches converge demonstrates that our findings are robust to the specific statistical technique. We used an α-level of 0.05 for both approaches because they are not independent as they are implemented on the same data and test the same hypotheses.

Summary Statistics Approach

In the summary statistics approach, we used the different time metrics as predictors for pattern similarity change. We set up a GLM with the given variable from the day learning task as a predictor and the pairwise representational change values as the criterion for every participant. The t-values of the resulting model coefficients were then compared to a null distribution obtained from shuffling the dependent variable of the linear model (i.e. pattern similarity change) 10,000 times. This approach to permutation-testing of regression coefficients controls Type I errors even under situations of collinear regressors[106]. Resulting p-values for each coefficient were transformed to a Z-score. The Z-scores were then used for group-level inferential statistics.

Group-level statistics were carried out using permutation-based procedures. For t-tests, we compared the observed t-values against a surrogate distribution obtained from 10,000 random sign-flips to non-parametrically test against 0 or to assess within-participant differences between conditions (two-sided tests; α=0.05 unless stated otherwise). We report Cohen's d with Hedges' correction and its 95% confidence interval as computed using the effsize-package for R. For paired tests, Cohen's d was calculated using pooled standard deviations and confidence intervals are based on the non-central t-distribution. Permutation-based repeated measures ANOVAs were carried out using the permuco-package[107] and we report generalized η^2 as effect sizes computed using the afex-package[108].

Linear Mixed Effects

Second, we employed linear mixed models to assess how learned sequence relationships were reflected in pattern similarity change using the lme4 package[109]. Mixed models have the advantage of estimating fixed effects and their interactions using all data, rather than performing inferential statistics on just one value per participant. We used the different time metrics as the fixed effects of interest. Factorial predictors (region of interest: anterior hippocampus and anterior-lateral entorhinal cortex; sequence: same vs. different) were deviation-coded. Within-subject dependencies were captured using random effects. Following the recommendation by Barr et al.[102], we always first attempted to fit a model with a maximal random effects structure including random intercepts and random slopes for participants. If these models did not converge or resulted in singular fits, we reduced the random effects structure. We always kept random slopes for the fixed effect of interest in the model to avoid anti-conservativity when testing fixed effects or their interactions[102,110]. The mixed effects models were fitted using maximum likelihood estimation.

We assessed the statistical significance of fixed effects of interest using likelihood ratio tests (α=0.05). Specifically, the model including the fixed effect of interest was compared against a nested, reduced model excluding this effect, but with the same random effects structure. Throughout the manuscript we report the results of these model comparisons (χ^2-tests with one degree of freedom) and refer to supplemental tables for summaries of the final mixed model parameters. We visualize fixed effect estimates with their 95% confidence intervals as dot plots and further illustrate effects using estimated marginal means[103].

Multidimensional Scaling

We aimed to explore how hippocampal event representations of the different sequences could be embedded in a low-dimensional representational space to give rise to the positive and negative correlations of pattern similarity change and temporal distances for same-sequence and different-sequence events, respectively. For each pair of events, we generated an expected similarity value using the fixed effects of the mixed model fitted to hippocampal pattern similarity that captures the interaction between virtual temporal

distances and sequence membership (c.f. Figure 5). Using the predict-method implemented in the lme4-package[109], we generated model-derived similarity values for all event pairs given their temporal distances and sequence membership. We chose this approach over the raw pattern similarity values to obtain less noisy estimates of the pairwise distances. Using the smacof-package[111], the model-predicted similarities were converted to distances and the resulting distance matrix was subjected to non-metric multidimensional scaling using two dimensions. We chose two dimensions to be able to intuitively visualize the results. Because MDS is sensitive to starting values, we ran multidimensional scaling 1000 times with random initial configurations and visualized the resulting configuration with the lowest stress value. Basing this analysis on the model-derived similarities assumes the same relationship of virtual temporal distances for all event pairs from different sequences, but we would like to note that not all solutions we observed, in particular those with higher stress values, resulted in parallel configurations for the four sequences.

We tested the stress value of the resulting configuration against a surrogate distribution of stress values obtained from permuting the input distances on each of 1000 iterations. Using the mean and standard deviation of the resulting null distribution, we obtained a z-value as a test statistic and report the proportion of stress values in the null distribution that were equal to or smaller than the observed stress value. Additionally, we contrasted the distances between pairs of events in the resulting configuration between distances separated by high or low (median split) input distances using a t-test for independent samples. Using a Spearman correlation, we quantified the relationship of the input distances and the distances in the resulting configuration.

Searchlight Analysis

We further probed how temporal distances between events shaped representational change using searchlight analyses. Using the procedures described above, we calculated pattern similarity change values for search spheres with a radius of 3 voxels around the center voxel. Search spheres were centered on all brain voxels within our field of view. Within a given search sphere, only gray matter voxels were analyzed. Search spheres not containing more than 25 gray matter voxels were discarded. For each search sphere, we

implemented linear models to quantify the relationship between representational change and the learned temporal structure. Specifically, we assessed the relationship of pattern similarity change and absolute virtual temporal distances, separately for event pairs from the same sequences and from pairs from different sequences. In a third model, we included all event pairs and tested for an interaction effect of sequence membership (same or different) predictor and virtual temporal distances. The t-values of the respective regressors of interest were stored at the center voxel of a given search sphere.

The resulting t-maps were registered to MNI space for group level statistics and spatially smoothed (FWHM 3mm). Group level statistics were carried out using random sign flipping implemented with FSL Randomise and threshold-free cluster enhancement. We corrected for multiple comparisons using a small volume correction mask including our a priori regions of interest, the anterior hippocampus and the anterior-lateral entorhinal cortex. Further, we used a liberal threshold of $p_{uncorrected}<0.001$ to explore the data for additional effects within our field of view.

To test whether within- and across-sequence representations overlap, we defined an ROI based on the within-sequence searchlight analysis. Specifically, voxels belonging to the cluster around the peak voxel, thresholded at $p<0.01$ uncorrected within our small volume correction mask, were included. The analysis of representational change was then carried out as described for the other ROIs above. The results observed using a threshold of $p<0.001$ were not statistically different from those obtained with a threshold of $p<0.01$ ($t_{27}=-0.95$, $p=0.338$; test against 0 using the ROI resulting from the $p<0.001$ threshold: $t_{27}=-1.98$, $p=0.056$).

Relationship to behavior

We used the regression coefficients quantifying the strength of the behavioral generalization bias to test for an across-subject relationship with the RSA searchlight effects. For each participant, we extracted the t-value of the across-sequence and the within-sequence searchlight effects from the peak voxel in our a priori regions of interest. We chose this approach because the searchlight analyses provide greater spatial precision than anatomically defined region of interest masks. We used Spearman correlations to test

for a relationship of the RSA searchlight effects and the behavioral generalization bias (α=0.025, corrected for two comparisons).

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Data & Code Availability

Analysis code and documentation is available on GitHub (https://jacbel.github.io/virtem_code/). Source data are provided with this paper. Data and code to reproduce the statistical analyses will be made openly available upon publication. These data and code can already be anonymously accessed by reviewers on the Open Science Framework (https://osf.io/zxnc8/?view_only=60edd0babf1e4a33b0892475f429ad53).

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Chapter 3

The effect of stress on memory for temporal context

Nicole D. Montijn

Lotte Gerritsen

Iris. M. Engelhard

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Author contribution

NDM, LG and IME designed the study; NDM collected the data; NDM and LG analyzed the data; all authors interpreted the data; NDM wrote the first draft of the article, and LG and IME provided critical revisions. All authors approved this version.

Abstract

Stress and emotional arousal interfere with encoding of temporal context memory for episodic events. However, it remains unclear how stress affects more fine-grained temporal memory, such as episodic events sequences and event times. Here, 86 healthy participants (M age = 22.5; 46% women, 54% men) were subjected to either a stress condition (socially evaluated cold pressor test) or a control condition, directly after or at a delay of 30 minutes they were presented the temporal structure of four virtual days. In these virtual days, time was scaled and participants could use clock cues to construe the passage of time within a day. We examined whether acute stress would interfere with encoding of episodic event sequences and temporal memory. Our results show that when learning took place directly after a stressor, virtual time estimates were more strongly biased towards a generalized timeline but temporal memory overall and event sequences were not differentially affected between the stress and control groups. Exploratory analyses suggest that memory accuracy improved in men and deteriorated in women as a function of subjective stress levels following acute stress. In conclusion, acute stress amplified memory generalization but we found no stress related differences in memory accuracy across levels of temporal granularity.

Introduction

Stress and arousal influence how well we remember events. Studies show that they typically enhance recall for emotional information at the detriment of contextual information, such as temporal context memory (1). These findings are generally in line with insights from stress research(2–4) that show selective attention and memory for material that is directly related to the stressor and thus might promote survival.

Interestingly, the same memory enhancing benefits that are typically imbued on emotional material also occur for neutral events (5,6). For instance, Tambini et al. (2017) showed that exposure to several blocks of emotional stimuli (IAPS pictures) induced a prolonged state of arousal that enhanced memory for neutral stimuli shown 9 to 33 minutes later. However, the same task was used for the emotional and neutral blocks, so it is unclear to what extent temporal context memory was also affected. A recent study that examined the effects of arousal on temporal order memory for neutral item pairs showed that sequence memory was enhanced for item pairs that followed an unrelated arousing stimulus, but it was impaired when the arousing stimulus separated the item pair (5). The latter effect may be caused by contextual-shift that is induced by the sudden onset of an emotional stimulus which induces an event boundary that separates the emotional experience from what came before (7). In contrast, as shown by Tambini et al. (2017) neutral information that follows an emotional event boundary may be unjustly lumped into the emotional experience.

The work we discussed thus far gives some insight into the likely fate of memories encoded during emotional arousal. Yet it remains unclear to what extent emotional arousal affects temporal granularity on a finer scale, and whether the effects remain over a longer time span (e.g., one day later). Temporal context captures when an episodic event occurred in relation to other events, such as event order and time distance between events, thereby providing a framework by which we can mentally organize and cluster events. Accurate retention of this temporal event context ensures that information is interpreted within the appropriate contextual boundaries, and it protects against overgeneralization of memory (8,9), and presumably the development of intrusive memories (e.g., 10,11).

Here, we investigated the time-dependent effect of stress on encoding the temporal structure of episodic event sequences using a 2-day paradigm. Participants were trained to

learn the temporal structure of four virtual days (12) either directly after stress or control task or after a 30-minute delay (wait and no wait condition). The wait manipulation allowed us to look at time dependent effects of stress on memory due to the direct release of noradrenaline and delayed glucocorticoid response (13–15). The next day, we assessed memory for the temporal structure of the virtual days. We expected that the control groups would retain a detailed representation of temporal structure, as was found in a previous study using this task (12), while the stress groups would retain temporal information at a higher level of granularity.

As a secondary objective, we sought to investigate whether possible stress-related reductions in temporal memory accuracy were directional. A previous study using the same temporal learning task found that individual event time estimates tended to be biased towards the average time of events in the same sequence position (12). This type of generalization bias was present in participants with relatively accurate temporal memory, but it appeared to be enhanced when memory specificity was low. If arousal reduces specificity of temporal memory, then this generalization bias should be more prominent in the stress groups compared to controls.

Methods

Participants

Participants were 86 cis-gender adults (40 female, 46 male, M age = 22.5, range = 18 – 32) with no self-reported current psychiatric disorders. They were recruited on campus using flyers, as well as through social media. Female participants were required to be on hormonal birth control to control for potential bias by fluctuations of female hormones (16). In the Netherlands, this is the most widely used form of contraceptives, especially amongst students (source CBS: https://www.cbs.nl/nl-nl/nieuws/2014/25/gebruik-pil-daalt-spiraaltje-wint-terrein). Participants were randomly assigned to one of four experimental groups; stress no wait, stress 30-min wait, control no wait, control 30-min wait (Table 1). All participants provided written informed consent. A power analysis (G*Power Version 3.1; Faul, Erdfelder, Buchner, & Lang, 2009) based on prior research (17) showed that a sample size of at least 20 per group was necessary to detect an effect of

stress and timing on memory encoding (power = .90, η_p^2 = 0,12). Taking potential missing values into account, we aimed to test 20-25 participants per group. They were remunerated with course credit or had the chance to win a gift card for their participation. The study was approved by the institutional ethical review board at Utrecht University (FETC16-090).

Table 1. Demographic information per group

Condition	*M age (SD)*	*Female*	*Male*	*Total*
Stress – no wait	21.3 (1.5)	11	9	20
Control – no wait	21.9 (2.6)	11	14	25
Stress - wait	23.4 (2.7)	10	10	20
Control - wait	23.4 (3.7)	8	13	21

Study Overview. The experiment was conducted on two consecutive days (Figure 1A), and had a 2 (stress/control) x 2 (wait/no wait) between-subject design. The first day consisted of a stress or control induction followed by a subjective stress questionnaire and an episodic learning task. The first session always took place between 12:30 and 18:00 to control for circadian cortisol rhythms. Participants either started the episodic learning task directly after the stress/control induction, or 30 minutes later, depending on the condition. Participants returned the next day for an unannounced memory test about the episodic learning task. The episodic learning task is effective in teaching participants a novel time scale and temporal structure of episodic material (Bellmund et al., 2021), and was slightly adapted. We reduced the number of trials per virtual day from 7 to 4, and administered the memory test a day later rather than shortly after learning. These changes were made to accommodate the task to the duration of the stress paradigm and to prevent potential effects of the stress induction on recall rather than just learning.

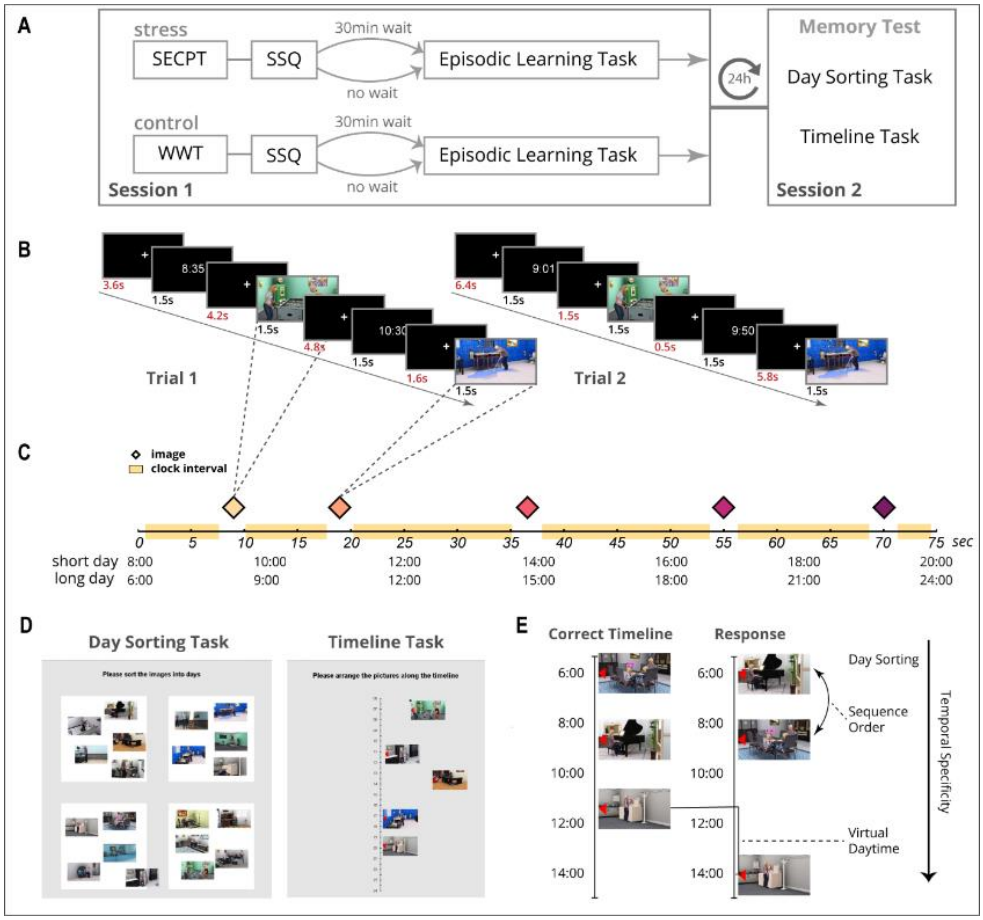

Figure 1. Experimental Design. A) Overview of study procedure for four experimental groups, over two sessions. **B)** Example of the trial structure of a virtual day, and the difference between two presentations of the same virtual day. **C)** Illustration of how the time scaling affects the virtual time distance between images for a short and long day with an identical structure. Diamonds indicate when an image is shown, and yellow blocks indicate the interval in which a clock will appear. **D)** Display of both memory tasks. **E)** Example of a response on the timeline task, and how temporal memory can be abstracted at different levels of specificity. **B-E)** The Sims 3 and screenshots of it are licensed property of Electronic Arts, Inc.

Socially Evaluated Cold Pressor Test

Stress induction. The socially evaluated cold pressor test (hereafter SECPT; 18) was used to induce physiological and social stress. Participants were instructed to submerge their non-dominant hand in a bucket of ice-cold water (0-2 degrees Celsius), for a maximum duration of 3 minutes. They were told that they could remove their hand from the water if it became unbearable, but to keep it in as long as they could. As a social stressor, the test leader wore a lab coat and took on a strict and highly formal demeanor. During the task, the test leader actively monitored participants while tracking the time using a stopwatch. Additionally, participants were told that their facial expressions would be recorded with a desk camera. After 3 minutes, or earlier when participants removed their hand from the water, they were given a towel to dry their hand and were asked to complete a short subjective stress questionnaire (SSQ). The SSQ asked them to rate how stressful, painful, and unpleasant they found the task on a 10-point Likert scale (0 – 100). Participants either proceeded directly to the episodic learning task or were asked to wait 30 minutes while reading unstimulating magazines (e.g. home improvement or sailing magazines). They were not allowed to use their phone.

Control induction. The control conditions followed the same procedure as the stress conditions. However, the SECPT was replaced by the Warm Water Test (hereafter WWT; 18). The WWT has the same general structure as the SECPT, but the water is lukewarm (20-23 degrees Celsius) and none of the social stressors are applied. The test leader stayed in the room with the participant during the task to track time, but did not actively monitor participants and stayed outside of their line of sight.

Episodic Learning Task

Scene images. We used 20 images, created using the life simulation video game The Sims 3 (The Sims 3 and screenshots of it are licensed property of Electronic Arts, Inc.), to construct virtual days for the episodic learning task. The images displayed everyday activities in the life of a Sim family (e.g. reading the newspaper or doing homework). All images depicted a unique scene, and they were independently rated by a sample of 40 students (Bellmund et al., 2021) as visually distinct, temporally ambiguous, and clear in

terms of content. Temporal ambiguity was of particular importance as each of the 20 images was randomly assigned to one of five fixed time-points within one of 4 virtual days.

Virtual days. The virtual day task was designed to model the way people experience and monitor the passage of time in daily life. For example, you look at a clock which says 15:00, do some activities and afterwards estimate that it must be about 17:00 now. The virtual days represent a scaled version of this process. In the virtual days, time moves faster but clocks can be used in the same way to estimate at what time events occurred within the day, and relative to each other.

Each of the four virtual days consisted of 5 images that were randomly assigned to specific time-points (Figure 1C) within the virtual day to create a 4 unique event sequences. The time-points at which an image took place were identical for all participants, only the image assignment was randomized between participants. Participants' task was to memorize which 5 images belonged to the same day, and to estimate at what time within the virtual day each image took place. To enable participants to estimate virtual time, a clock with the current virtual time was shown before and after each image at random intervals (Figure 1B and C). Image and clock trials were both displayed for 1.5 sec, and were interleaved by a fixation cross (Figure 1B). A 2 sec buffer between the onset of clock and image trials was used to prevent overlap due to the presentation time of the stimuli.

Clocks. Clocks appeared once at a random moment within specified intervals (yellow bars in Figure 1C). The time on the clocks represented the virtual time as the clock appeared on screen (see Instructional video in Supplemental Online Material), and did not change during the 1.5 sec display time. Clocks never appeared at the same moment across repetitions of the same day (Figure 1B). This allowed participants to get a closer estimate of the correct time with every repetition of a virtual day. The goal of this procedure was for participants to develop a sense of (virtual) time without relying on direct associations between clock time and an image.

Time Scaling. Within the virtual days, the passage of time was scaled so that each second represented a certain number of minutes in virtual time. The different time-scales allow dissociation between memory based on virtual time and real time. This feature was implemented as part of an earlier neuro-imaging study using the same task (Bellmund et al., 2021). We retained the two scales as it forced participants to learn the virtual time rather than for example counting the time in seconds. There were two short days, 8:00 – 20:00, and two long days, 6:00 – 0:00. The short and long days had the same duration in real time (75 sec) but differed in virtual time (12h and 18h). Thus, time passed more quickly in long days (1 sec = 14.4 min) than short days (1 sec = 9.6 min). In order to correctly estimate the time-point of each image, participants had to learn these time scales.

Episodic Learning Phase. Participants were instructed to learn the temporal structure of the 4 virtual days. They were informed that each of the images occurred at a specific time within a virtual day, and that their task was to learn which images belonged to the same day and at what time they took place using clocks. They received detailed instructions about the time scaling within the virtual days, and how they could use the clocks to estimate the time an image took place. All participants were asked to describe the task in their own words to verify that they understood the task before it started.

The episodic learning task consisted of 4 blocks of 4 event sequences (i.e. virtual days). Each virtual day was presented 4 times, once per block. An image of a moon was shown for 5 sec at the end of each virtual day as a visual boundary between the four event sequences (i.e. virtual days) in each block. The order of the four days was randomized within blocks, and there was a 30 sec break between blocks. The task took about 20 minutes to complete.

Memory test. One day later, participants returned to the lab for an unannounced memory test. They were told that they would do a similar task as in the first session, but the content was not disclosed. The memory test consisted of two parts (Figure 1D). In the first part, which we will refer to as the 'day sorting task' (Figure 1D left panel), participants were asked to recall which images belonged to the same virtual day. The 20 images appeared on the screen in a circular formation, in randomized order. Participants could drag and drop each image into one of four white squares that represented the four days. The virtual days were

not given explicit labels during the episodic learning task. So participants simply grouped the five images they thought belonged to the same day in one of the squares. This task assesses the ability to recall sequence membership of the individual events (coarse level of temporal granularity).

In the second part, which we will refer to as 'the timeline task' (Figure 1D right panel), participants were asked to reproduce at which time each image took place within the virtual day by placing it along a timeline. The four virtual days were presented separately. A timeline was presented on screen that ran from 6:00 till 0:00, as well as the 5 images that belonged to that day. A red arrow was embedded in each image to allow more precise placement along the timeline. When participants were finished with a day they could continue with the next day. This task assesses two levels of temporal granularity, namely (from highest to lowest) memory for event sequence (sequence order) and time of occurrence (virtual event time). The memory test took about 10 to 15 minutes to complete.

Statistical analysis

Subjective stress levels. To determine if the stress induction in the SECPT was successful and similar for both stress groups, we compared SSQ scores of the four experimental groups using a 2 (Condition: control, stress) x 2 (Wait: wait, no wait) between subjects ANOVA.

Memory test. For the day sorting task, we first tallied how many images from the same day were correctly grouped together in each square. Each square could only represent one virtual day. So if the top right square represented day 2 and contained three images of day 2, then the square received a score of 3. The scores for each day square were then added together. The maximum total score on the day sorting task was 20. This metric represents the highest level of temporal granularity (Figure 1E); clustering of events that belong to the same episode.

Performance on the timeline task was operationalized in two time metrics: sequence order and virtual daytime (Figure 1E). Scores for both metrics reflected the absolute deviation from the correct response. For both metrics, the scores were calculated per image and then averaged across all 20 images. Sequence order assessed memory accuracy for the order of

the event sequence, and was operationalized as the number of positions off from the correct response (e.g. image 1 placed at position 3 produces an error score of 2). Virtual daytime assessed the ability to accurately estimate event times and create an event timeline based on the new time scales learned through the task. The virtual daytime score was calculated by subtracting the correct image time from the participants' response (e.g. 12:40 – 12:00 = 40 virtual minutes). The time deviation was then converted from virtual minutes to seconds in real time (short days: VT / 9.6 * 60, long days: VT / 14.4 * 60) to correct for the different timescales of the long and short days (see 'Time Scales' above).
For both time metrics, an average score of 0 reflects perfect performance. This caused the response distribution to be skewed towards 0. Therefore, Mann-Whitney U tests were used to investigate the effect of stress induction and wait time on temporal learning. In addition to frequentist statistics, we employed Bayesian statistics to test for evidence for the null hypothesis.

Generalization bias

To assess the presence of a generalization bias in the virtual time estimates, we followed the analysis steps described in Bellmund et al. (2022) to produce a regression coefficient for the strength of the bias for each participant, followed by a (Condition: control, stress) x 2 (Wait: wait, no wait) between subjects ANOVA to assess group differences.

Exploratory analysis

To explore potential sex differences in the relationship between subjective stress and temporal memory, we conducted a linear regression in the two stress groups, with wait conducted (no wait/wait), sex (female/male) and subjective stress scores as predictors of memory performance.

Results

Subjective Stress. To examine whether the stress induction was successful, group differences were compared in self-reported subjective stress using a 2 (Condition: control, stress) x 2 (Wait: wait, no wait) between subjects ANOVA. We found a main effect of

Condition, $F(1, 82)= 286.14$, $p < .001$, $\eta_p^2 = .78$, indicating that the SECPT indeed induced more subjective stress than the control induction (Stress: $M = 160.8$, $SD = 59.9$, Control: $M = 11.5$, $SD = 18.6$). However, there was also a significant interaction between Condition and Wait, $F(1, 82)= 6.41$, $p = .013$, $\eta_p^2 = .073$. This interaction was due to higher subjective stress scores in the Stress – Wait group ($M = 183.0$, $SD = 62.7$) compared to the Stress – No Wait group ($M = 138.5$, $SD = 49.0$), $t(38) = -2.499$, $p = .017$. This difference limits direct comparisons between the wait and no wait stress groups, and was likely due to chance given the randomized group allocation, the same protocol for both groups, and measurement of subjective stress directly after completing the SECPT. Finally, we found no sex differences in subjective stress between the stress and control group, $F(1,82)= .5$, $p = .481$, $\eta_p^2 = .006$, and between the stress no wait and wait group, $F(1,36)=.016$, $p = .901$, , $\eta_p^2 = .000$.

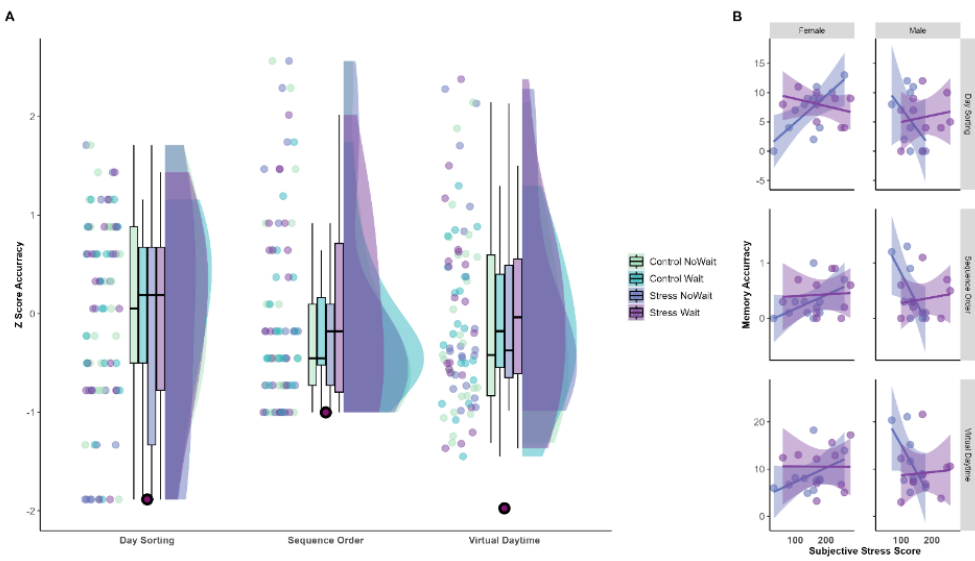

Figure 2. Memory performance per outcome measure per group. **A)** Data distribution of Z scores for performance on day sorting, sequence order, virtual daytime. Black dots represent the Z-score that indicates perfect performance on each measure (i.e. a score of 0). **B)** Memory accuracy as a function of subjective stress separated by sex and outcome measure, only for the stress condition. Sex interacts with subjective stress for the no wait group but not the wait group, leading to impaired memory in women when subjective stress is higher and improved memory in men when subjective stress is higher.

Day Sorting Task. A Mann-Whitney U test was used to examine the effect of stress on encoding of episodic context, as indexed by which event images belong to the same virtual day. There was no significant difference in performance between the stress and control group in both the No Wait (Control: *M* (*SD*)= 12.84 (3.3); Stress: *M* (*SD*)= 13.85 (4.4)), *U* = 216.5, *p* = .442, and Wait condition (Control: *M (SD)*= 12.95 (3.4); Stress: *M (SD)*= 13.20 (3.4)), *U* = 195, *p* = .694. Furthermore, there was no difference in performance between the stress – wait and stress – no wait groups, *U* = 184.5, *p* = .678.

Timeline Task. First, the Stress groups with their respective Control group (e.g. stress wait with control wait) were compared to examine the effect of stress on memory for temporal structure. No significant differences were found between the stress and control groups for sequence order and virtual time (No Wait: all *U* > 192, *p* > .185; Wait: all *U* > 177, *p* > .389). Second, the Stress groups were compared to examine the effect of the interval between stress and learning on memory for temporal structure. Again, no group differences were found (all *U* > 178, *p* > .552).

Bayesian independent-sample t-tests were performed in JASP (JASP Version 0.14.01) to assess evidence for the null hypothesis (i.e. no difference between the stress and control groups). A default Cauchy prior of 0.707 was used as it was difficult to determine an informed prior. Comparing the stress no wait and the control no wait group, showed anecdotal to moderate evidence for the null hypothesis across all outcome measures: Day Sorting B_{10} = .403, 95% CI [-.756, .314], Sequence order B_{10} = .307, 95% CI [-.603, .451], Virtual Daytime B_{10} = .321, 95% CI [-.641, .416]. Comparing the stress wait and the control wait group, there was again anecdotal to moderate evidence for the null hypothesis across all outcome measures: Day Sorting B_{10} = .313, 95% CI [-.605, .485], Sequence order B_{10} = .314, 95% CI [-.612, .478], Time Deviation B_{10} = .31, 95% CI [-.496, .593].

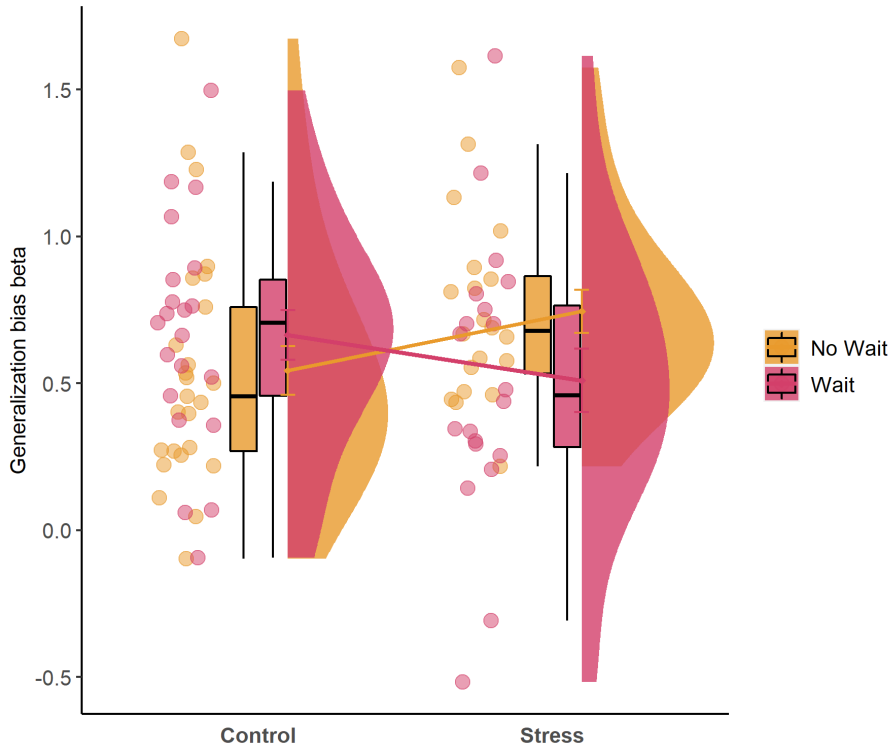

Figure 3. Group differences in strength of generalization bias. Higher beta indicates that participants were more likely to bias their time estimates of individual events towards a general timeline averaged across the virtual days.

Generalization Bias. Next, we examined whether stress before sequence learning amplifies the generalization bias reported in Bellmund et al. (2022). Replicating the analysis performed by Bellmund et al. (2022), a linear regressions for each individual participant was conducted to assess to what degree estimated event times were predicted by the average distance to other events in the same sequence position. For example, if the average virtual time of event 5 in day sequences 2-4 was relatively late compared to event 5 in day 1, did participants systematically overestimate the virtual time of the latter. To assess the presence of this bias in the individual groups, the resulting p-values from these participant-level linear models were converted to Z-scores, and tested against 0 using a permutation-based t-test. All four groups showed significant levels of this generalization bias: Control No

Wait $t(24) = 7.81$, $p = .000$, $d = 1.51$, 95% CI [.98, 2.19], Control Wait $t(20) = 7.80$, $p = .000$, $d = 1.63$, 95% CI [1.04, 2.42], Stress No Wait $t(19) = 11.82$, $p = .000$, $d = 2.53$, 95% CI [1.73, 3.67], and Stress Wait $t(19) = 5.78$, $p = .000$, $d = 1.23$, 95% CI [.70, 1.93].

Then a 2 (Condition: control, stress) x 2 (Wait: wait, no wait) between subjects ANOVA was conducted on the regression coefficient (beta) of the participant-level linear models, to assess whether the generalization bias was stronger for the stress groups. There was a statistically significant interaction effect, $F(1, 82) = 4.08$, $p = .046$, $\eta_p^2 = .047$. The Stress No Wait group displayed a stronger, but not statistically significant, generalization bias than the Control No Wait group, $t(43) = -1.7809$, $p = 0.082$, $d = .54$, and Stress Wait group, $t(38) = 1.809$, $p = 0.07$, $d = .57$ (see figure 3). So, in line with Bellmund et al. (2022), all groups showed a significant generalization bias, but this bias tended to be slightly stronger (i.e. virtual time estimates were skewed more towards the average timeline) when learning took place directly after stress induction.

Sex differences. To explore sex differences, linear regressions were conducted to assess the interaction between wait time, sex and subjective stress on memory performance for all four time metrics in the two stress groups (wait/no wait). These analyses revealed a significant three-way interaction between wait group, sex and subjective stress predicting memory performance (see Figure 2B) for Day Sorting ($\beta = .14$, $p = .012$, 95% CI: .03, .24) Sequence order ($\beta = .0138$, $p = .011$, 95% CI: .003, .0243) and Virtual Daytime ($\beta = .15$, $p = .03$, 95% CI: .011, .292). Follow-up analyses, using subjective stress and sex as predictors, showed that this interaction is explained by a main effect of sex as well as the interaction between sex and subjective stress (see Supplementary table 1) in the stress no wait group (Day Sorting $F(3,16) = 2.929$, adjusted $R^2 = .23$, $p = .06$, Sequence order $F(3,16) = 3.916$, adjusted $R^2 = .31$, $p = .02$, Virtual Daytime $F(3,16) = 3.294$, adjusted $R^2 = .26$, $p = .04$), but not in the stress wait group (all $F(3, 16) < .84$, $p > .48$). The interaction pattern is quite consistent between different measures (Figure 2B).

Discussion

This study aimed to provide a first examination of the effect of a validated stress paradigm on encoding of temporal context in episodic memories, using a fine-grained temporal

memory task for episodic events sequences and event times. Following a stress or control task, participants completed an episodic learning task that has previously been proven effective in teaching participants a novel time scale and temporal structure of episodic material (12). While subjective stress scores indicated that the stress manipulation was successful, the results did not show a pronounced effect of stress on temporal memory. Performance was best for the sequence order metric across groups, which seems to indicate that participants generally focused on learning the event sequence rather than the virtual time and still required a strong cue (i.e. being given the correct items per day to access that knowledge). However, we did find a slight amplification of the previously reported generalization bias effect (12) in the stress no wait group, compared to control no wait. Finally, our data support earlier work that found that the effect of acute stress on memory is differentially moderated by stress reactivity for men and women (19,20). When learning took place directly after stress induction, memory accuracy improved as a function of subjective stress in men, but it deteriorated in women.

Contrary to earlier work on the effects of arousal on memory for neutral event sequences we did not find that stress enhanced (5,6), or interfered with (1) sequence memory. First, as suggested by Clewett et al. (2019), the enhancement of neutral sequence memory following arousal may be contingent on the neutral and arousing event sharing a task context. In the current setup, there was a clear task separation between the stress induction and the learning task. Thus, even though these tasks were performed in the same room and directly followed each other in the no wait groups, participants may have perceived a clear event boundary between the two tasks.

Second, regarding the potential negative effects of stress on sequence memory, it is possible that this effect depends on the presence of emotionally arousing or stress relevant stimuli in addition to neutral stimuli (21,13,15,22). The physiological stress reaction generally biases attention towards information related to the stressor, which is innately emotionally arousing (2,23). This attentional bias is known to disrupt encoding of information that is deemed less relevant in the current situation in favor of information that promotes immediate survival. Previous work has shown that this attentional bias towards threat, likely mediated by noradrenergic activity, is stronger in women and leads

to improved memory for negative material (24,25). In contrast, using neutral material, our exploratory analyses showed that memory was impaired for women as a function of subjective stress. It is possible that this memory impairment is indicative of a stronger attentional bias in women that promotes memory for negative over neutral material. Future work may examine whether this effect is indeed reversed when the temporal learning task includes emotional stimuli. An exciting example of how a temporal learning task can act as the stressor is a recent study that examined temporal clustering in memory by having participants walk through a haunted house (26,27).

In line with Bellmund et al. (2022), our data show a pronounced generalization bias across all groups in the estimation of specific virtual event times. Responses systematically deviated towards the average virtual time of events that shared the same sequence position. To illustrate this effect, if you are asked which time you left for work today, and you don't know exactly, you are more likely to guess a time that is closer to when you typically leave than one that is further away. Participants showed a stronger generalization bias for event sequences learned directly after acute stress. Previously, this generalization bias had been explained as people relying more on general knowledge to aid recollection when memory specificity is low (e.g. 'I always leave around 8am so maybe I left around 8:05am') (12). However, this interpretation was based on a sample with high task performance, meaning that if participants lacked memory for a specific virtual event time they could indeed rely on their intact knowledge of the other event sequences. In the current study, performance across groups was quite poor which makes a 'general knowledge' based explanation of this bias less likely. Perhaps the stronger bias in the no wait stress group was caused by a change in learning strategy whereby participants focused on learning the general gist of the sequence structure rather than the specific event times, as participants may have been more distracted by the stress task directly prior. This might similarly lead to a generalized timeline in memory for virtual event times, as all sequences are encoded following the same gist-like template.

This interpretation, i.e. following acute stress participants rely on simpler heuristics to solve a task, corresponds with findings that in high pressure situations participants are more likely to rely on simpler problem-solving strategies thereby reducing their performance

accuracy (28,29). Evidence from work on math proficiency has shown that stress and time pressure impair performance by overloading working memory (30,29). Demanding computations, such as those required to deduce virtual time in this task, are more difficult to achieve when working memory resources are low and can in and of themselves introduce pressure (31). Finally, stress affects working memory performance differentially in men and women. Similar to our findings, research has shown that acute stress enhances response time on an n-back working memory task men and deteriorates response time in women (32). While we did not directly manipulate or assess working memory in the current experiment, the generalization bias pattern and sex interaction following acute stress are in line with a working-memory based account.

Furthermore, our data suggest that the level of subjective stress modulates the effect of acute stress on memory, and that it does so differently for men and women. Specifically, acute stress impaired memory in women and enhanced memory in men as a function of subjective stress. While our sample size does not allow us to draw stark conclusions, this finding does mirror previous work on sex differences in noradrenalin activity (19) and its relation to memory performance. When yohimbine, a noradrenalin antagonist, was administered prior to learning, performance on a memory generalization task with neutral stimuli was impaired in women and improved slightly in men (20). Speculatively, this could suggest that stress reactivity, both physiological and subjective, differentially affects learning in men and women but this modulation does not appear to be specific to a particular type of memory nor did it induce a discernible shift in learning strategy.

A limitation of the current study is that both the control and stress groups had high error scores on the virtual time measure (mean error of about 1.5 – 2.5 virtual hours) compared to earlier work using the same task (12). This difference in performance may be due to changes in the timing of the memory test, which was conducted a day later in the current experiment instead of directly after learning (12). The reason for this change was to limit the effects of the stress task on learning. If the memory test was performed directly after learning, stress might also interfere with recollection (33). This larger delay between learning and recall may have affected the accuracy of temporal memory across groups,

which may have obscured stress-related effects. Future work using this paradigm could increase the number of learning trials to increase sensitivity of the task at delayed recall.
A further limitation is the lack of an objective measure of stress reactivity. Both subjective stress and cortisol responses are known to vary widely between people due to factors like sex, age, menstrual cycle and chronic stress (34,35). In addition, subjective stress and physiological stress reactivity do not always correlate well (36,37). Therefore, future work should consider including both salivary cortisol as measures of stress reactivity next to subjective stress measurements. Indeed, one study demonstrated that endogenous cortisol secretion moderated the impairing effect of stress on implicit spatial learning (38).

In summary, this study examined the effect of stress on encoding of temporal context information in episodic memory. The results do not show a discernible impact of stress on the ability to remember temporal context, across levels of temporal granularity. We did observe opposing effects of acute stress on general memory ability for men and women depending on the level of subjective stress. Future work should consider including tasks that are more sensitive to subtle changes in temporal context memory and measures of physiological stress reactivity to further disentangle this interaction between sex, (subjective) stress reactivity and memory performance.

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Open Practices Statement

The experiment reported in this article was not preregistered. Requests for raw data and materials can be e-mailed to the corresponding author. Pre-processed data that were used for the main analyses can be found at:
https://osf.io/85g3x/?view_only=6171b06689924bf6aba88a1d393ba1aa .

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Section II

When it is time for memory

Chapter 4

Forgetting the future: Emotion improves memory for imagined future events in healthy individuals but not individuals with anxiety

Nicole D. Montijn

Lotte Gerritsen

Iris M. Engelhard

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NDM and IME designed the study; NDM performed the research; NDM and LG analyzed the data; and NDM wrote the first draft of the article. All authors approved the final version of the manuscript for submission.

Abstract

Negative thoughts about future events form a central aspect of anxiety disorders. Considering the impact of negative future thoughts in anxiety, it is important to gain a deeper understanding of how these imagined events are retained over time. Prior research indicates that emotional intensity fades faster for negative than positive memories in healthy individuals. This so called fading affect bias could extend to recall of imagined future events. Furthermore, several studies have suggested that this bias may be reversed in anxious individuals. In the current study, we examined whether highly anxious individuals (N = 23), relative to non-anxious individuals (N = 30), show faster decay for positive than negative future event simulations. The results show that emotion facilitates cued recall for imagined future events in the non-anxious group, but not in the highly anxious group. In addition, highly anxious individuals show decreased episodic specificity during recall across all emotional conditions.

Introduction

Negative thoughts about the future form a central aspect of anxiety disorders. More specifically, patients with anxiety tend to imagine more negative future events and judge those events as more likely to occur compared to non-anxious controls (e.g., 1–4). In contrast, future simulations tend to be more positively biased in healthy individuals (5,6). While much research has focused on the construction of future images, relatively little is known about whether and how they are retained.

Recent research has shown that future images can indeed be remembered over time (7), and can influence perception and memory beyond their initial construction. Notably, future thinking can influence the way novel events are remembered (8), can inhibit recall of topically similar memories (9), and can increase false memories (10). Furthermore, future thinking has been shown to benefit goal maintenance and to reduce impulsive decision making (11,12). The accurate retention of imagined future events may be pivotal in the behavioral maintenance and updating that are required to achieve the desired outcome of these future events over time (13,14). Therefore, it is important to gain understanding about how imagined future events are remembered, especially considering their impact in anxiety disorders.

It is well documented that episodic memory and episodic future thinking rely upon similar neural mechanisms (15,e.g., 16). Patterns of remembering and forgetting found in episodic memory may therefore provide clues about the fate of imagined future events. For instance, an important determinant of memorability is the emotionality of the event: emotional events tend to be remembered better than neutral events (17,18). Like memory content, the strength of the emotional affect that is associated with an episodic event ('emotionality'), is subject to change over time. A large body of literature indicates that negative affect fades faster over time than positive affect in healthy individuals, which has been coined the Fading Affect Bias (FAB; for a review see 19). While the exact purpose of the FAB is unclear, it has been speculated that it serves in favor of a positive life narrative (19). This explanation fits with the positivity bias that is found in healthy individuals (5). Given the aforementioned role of negative thoughts in anxious individuals, it has been suggested the FAB may be decreased in anxiety disorders, leading to faster fading of

positive affect than negative affect. This decrease has indeed been found in individuals with high trait anxiety for past episodic memories (20).

To the best of our knowledge, the FAB has not been directly studied in imagined future events. However, (21) found that memory details of negative future events are forgotten at a faster rate than those of positive future events in healthy individuals. This pattern is identical to the FAB, which suggests that fading affect and forgetting may be connected. Szpunar et al. (2012) hypothesized that emotionality might serve as a binding factor to connect the episodic details that form the future event. If the emotionality fades over time, the connections between event details are broken, which leads to reduced recall. Because the FAB has not been studied in future simulations, it is still unclear whether faster fading of affect is indeed related to more forgetting in imagined future events. Furthermore, (7) were unable to replicate this enhanced recall for positive future events in healthy individuals, but their data were biased towards positive events which may have obscured possible effects of emotional valence.

In the current study, we aimed to investigate whether the FAB occurs for remembered future event simulations, and whether it is reversed in anxious individuals. Additionally, we examined whether there is a parallel relationship between reductions in emotionality (fading affect) and recall accuracy of imagined future events. We compared individuals with low and high trait anxiety on their retention of core event details, and subjective emotional intensity for positive, negative and neutral future events. We used an adapted version of the experimental recombination procedure to aid the construction of episodic future events (21), in conjunction with the Autobiographical Interview to enhance event elaboration (22,23). We expected the highly anxious group to show stronger reductions in emotional intensity for positive than negative future simulations, and the opposite for the low anxious group. As fading affect is suggested to be linked to reduced recall, we expected the highly anxious group to have better memory for negative events, and the low anxious group for positive events.

Methods

Participants. Participants were 23 high trait anxious (23 female, M age = 21,7, range = 18 - 26) and 30 low trait anxious (8 male/22 female, *M* age = 22, range = 19 - 26) adults, with no self-reported current psychiatric impairment. They were selected based on a pre-screening of 250 university students, using the State-Trait Anxiety Inventory – Trait Subscale (24,25). Cut-offs were set at a score of <35 for the low trait anxiety group (*M* = 28.8, *SD* = 3.1, range = 20 - 34), and >46 for high trait anxiety (*M* = 52 , *SD* = 5.2, range = 47 - 69). While none of our participants reported being diagnosed with an anxiety (-related) disorder or receiving psychological treatment the trait anxiety scores of our highly anxious group fell within the range of scores that is generally found in clinical populations (25–27).

A power analysis (G*Power; 28) was conducted to estimate the sample size. We chose to use a relatively conservative effect size for our power analysis, η_p^2 = .05 compared to η_p^2 = .15 reported by Szpunar et al. (2012), to correct for the reduction in trials. Using these parameters, a sample size of 30 per group was deemed necessary to detect a conservative effect of anxiety on emotional future thinking (power = .80, η_p^2 = .05). However, due to difficulties in the recruitment of the high trait anxiety group we ultimately decided to stop data collection at an earlier stage. This led to a power of .77.

All participants provided written informed consent. They were remunerated with course credit or money for their participation. The study was approved by the institutional review board at Utrecht University (FETC17-103). It consisted of three sessions.

Session 1: Stimulus collection. In the first laboratory session, participants were asked to provide lists of 40 people, 40 places and 40 objects that they knew from personal experience in the past 10 years. This method was adapted from the experimental recombination procedure (29) and was previously used in this fashion by (21). We used a listwise method for stimulus collection rather than extracting items from personal memories, because this was more time-efficient and proved to be equally effective in earlier studies (21,30). For lists of people, participants were instructed to provide first and last names of people they knew personally. They were allowed to use social media outlets as a reference. For lists of places, participants were instructed to provide specific places

("The lake in central park" rather than "New York") they had visited in the past 10 years. The objects needed to be portable and highly specific ("My blue Moleskine notebook" rather than "notebook"). Participants were instructed for all lists to choose items they knew well and could easily picture. The lists were examined for quality (e.g. objects that were too similar or a-specific places) and the 30 best items from each list were selected. All three lists were randomized separately, and then combined to form 30 cue word triads with a person, place and object in each. This session took about 30 to 45 minutes to complete.

Session 2: Future event simulation. Lab session 2 took place one week later. Participants were asked to imagine 9 positive, 9 negative and 9 neutral future events. They were instructed that each event should be plausible within the next 5 years of their lives. All events should be specific in time and place, meaning they had to transpire within the course of one day in one location. To elicit each future simulation, participants were shown a cue triad consisting of a randomly selected person, place and object provided during stimulus collection. The cue words were shown in blue, red or green, which indicated that the future simulation needed to evoke respectively a neutral, negative or positive emotion.

There were three practice trials (one for each emotion) directly after the task instruction to familiarize participants with the task. Practice trials were identical to test trials, but the task paused after every practice trial so the instructor could provide feedback. For the 27 test trials, the task continued automatically. The experiment was split into 3 blocks of 9 simulations separated by a 5-minute break. Each block included 3 trials per emotional condition. Practice trials were not included in the analysis.

Each trial lasted 3 minutes, in which participants were asked to envision and verbally describe a future event that featured all three cue words (person, place, object), and evoked the cued emotion strongly. The cue triad remained on screen the entire time. Regarding the verbal description, participants were instructed to vividly describe anything they imagined about the event, including what they are doing, seeing, feeling or thinking. If necessary, the experimenter would use general probes from the Autobiographical Interview (22,23) to elicit a more specific or detailed account. Probing ceased when participants started to repeat information. A countdown appeared on screen in the last 5

seconds to indicate the end of the description time. Descriptions were audio recorded using a desk microphone placed in front of the participant. Next, participants were asked to complete three 0-100 visual analogue scales on screen regarding the emotional valence (negative – positive), emotional intensity (not at all – very much) and vividness (not at all – very much) of the imagined event. This session took about 2 hours to complete.

Session 3: Cued recall. One day after session 2, participants returned to the lab for an unannounced memory test. In this recall task, for each trial, participants were presented with two of the three cue words from the original cue triads (person, place and object). The cue words were presented in the original configuration to ensure participants knew whether the person, place or object was missing. The emotional valence cue was no longer provided. Participants were given three minutes to verbally identify the missing cue word and to recollect the associated future event in as much detail as possible. Similar to the previous session, probe questions were used to ensure participants verbalized every detail they mentally re-envisioned about the event. A counter appeared on screen in the last 5 seconds to indicate the end of the description time. All event descriptions were audio recorded using a desk microphone. Finally, participants were asked to complete the same three visual analogue scales on screen. They were specifically instructed to answer each question as they felt about the imagined event now, rather than how they remembered feeling the day before.

The structure of the experiment was identical to the previous session, but trials were randomized within each block to minimize the effect of context on recall. Each type of cue word (person, place and object) was omitted from the cue triad an equal number of times per block and per emotion condition. The same three practice trials as in the previous session were used to limit loss of data. Like session 2, this session took about 2 hours to complete. All stimulus materials were presented using Presentation software version 20.0.

Data pre-processing. First, to examine recall accuracy, the number of correctly identified cue words in each condition was counted for each participant. A recall score of 9 indicated that all cue words were recalled correctly. Only answers provided before onset of the event

description were considered. Answers that captured part of the cue word were seen as correct (e.g. 'my green purse' instead of 'my green purse with flower pattern'). Second, all recorded event descriptions, for both the simulation and recall phase, were scored based on the level of episodic specificity with which they were described. Ratings were assigned a score of 0 – 6, using the rating scale for Episodic Richness outlined in the AI manual (Levine et al., 2002). On this scale, 0 points reflect that no episodic information was described, while 6 points mean that description evoked a sense of true (pre-)experiencing, was rich in detail, and contained at least 2 elaborations. Difference scores were calculated for each event (recall score minus simulation score). A negative score reflects a loss in episodic detail (i.e. forgetting of details, or impoverished description during recall), while a positive score reflects an increase in episodic detail (i.e. more event elaboration during recall). Finally, for the analysis of fading affect, difference scores were calculated for the subjective emotional intensity ratings (cued recall – event simulation). A positive difference score reflects that there was an increase in emotional intensity from the simulation phase to the recall phase, whereas a negative difference score reflects a decrease in emotional intensity. Statistical analyses were performed using SPSS version 25.

Results

Subjective valence ratings. We ran a 2 (trait anxiety: low, high) x 3 (emotion: negative, positive, neutral) mixed ANOVA on subjective valence in the simulation phase to ensure that participants were following task instructions for the emotional valence conditions. Higher valence scores reflect more positive valence. This showed a main effect for emotion, $F(1.235, 62.997) = 500.04$, $p < .001$, $\eta_p^2 = .91$ [CI: .869, .927], but not for trait anxiety, $F(1, 51) = .089$, $p = .767$, $\eta_p^2 = .002$ [CI: .00, .056], and no significant interaction, $F(1.253, 62,997) = 3.079$, $p = .076$, , $\eta_p^2 = .057$ [CI: .00, .163]. This confirmed that both anxiety groups imagined future events that were of the appropriate valence within each emotionality condition (see Table 1).

Table 1. Mean (SD) Subjective Ratings during Future Event Simulation and Recall, separated by trait anxiety group and emotion condition. Higher valence scores reflect more positive valence.

		Simulation			Recall		
	Subjective Ratings	Negative	Positive	Neutral	Negative	Positive	Neutral
High Trait Anxiety	Valence	28.79 (7.2)	74.16 (8.5)	53.74 (2.3)	50.49 (5.1)	53.60 (7.7)	51.66 (6.1)
	Intensity	60.67 (10.2)	61.12 (12.6)	43.07 (13.3)	50.63 (11.1)	48.10 (11.8)	47.15 (13.0)
	Vividness	65.31 (10.4)	71.35 (12.4)	66.81 (14.5)	60.42 (13.8)	59.14 (16.9)	58.58 (15.2)
Low Trait Anxiety	Valence	24.66 (9.2)	77.77 (7.8)	53.59 (3.9)	50.17 (7.4)	52.10 (6.2)	52.5 (6.9)
	Intensity	61.09 (13.8)	63.07 (12.2)	42.03 (15.9)	49.31 (16.5)	48.13 (16.6)	49.43 (15.6)
	Vividness	67.58 (13.7)	72.53 (11.8)	67.45 (13.8)	62.02 (17.7)	61.48 (18.1)	64.02 (16.8)

Recall accuracy. To investigate the influence of anxiety on recall of memory details for imagined emotional future events, we conducted a 2 (trait anxiety: low, high) x 3 (emotion: negative, positive, neutral) mixed ANOVA. A main effect was found for trait anxiety, $F(1, 51) = 4.78$, $p = .033$, $\eta_p^2 = .09$ [CI: .003, .219]; but not for emotion, $F(2, 102) = 1.33$, $p = .27$, $\eta_p^2 = 0.025$ [CI: .00, .081], and a significant interaction between trait anxiety and emotionality was found, $F(2, 102) = 3.83$, $p = 0.025$, $\eta_p^2 = .07$ [CI: .004, .149].[1] Post-hoc independent-samples t-tests revealed that, compared to the low trait anxiety group, the high trait anxiety group had a lower recall accuracy for both positive, $t(51) = -2.79$, $p = 0.007$, $d = .77$ [CI: .206, 1.33], and negative, $t(51) = -2.296$, $p = 0.026$, $d = .64$ [CI: .076, 1.19], but not for neutral future events, $t(51) = -0.624$, $p = 0.536$, $d = .17$ [CI: -.372, .716] (see Figure 1).

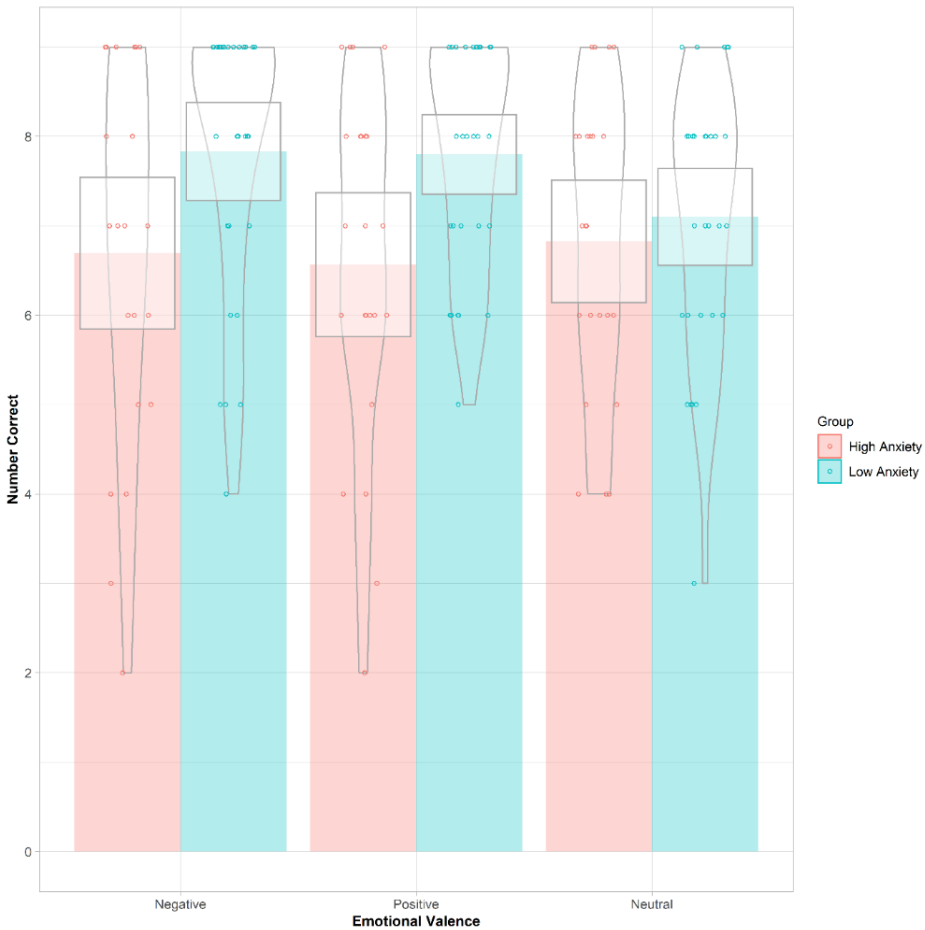

Figure 1. Mean, 95% CI, and data distribution of the number of correctly recalled cue words (maximum score = 9) per emotion condition and trait anxiety group.

Episodic Specificity. First, we examined pre-existing differences in the detail with which the future events were simulated. We ran a 2 (trait anxiety: low, high) x 3 (emotion: negative, positive, neutral) mixed ANOVA on the episodic specificity scores for the simulation phase. We found a main effect for emotion, $F(2, 102) = 5.345$, $p = .006$, $\eta_p^2 = .095$ [CI: .016, .18], but not for trait anxiety, $F(1, 51) = .300$, $p = .586$, $\eta_p^2 = .006$ [CI: .00, .08], and no significant interaction, $F(2, 102) = .648$, $p = 0.525$, $\eta_p^2 = .013$ [CI: .00, .054]. This confirmed that both anxiety groups simulated future events with an equal level of episodic specificity (see Table 2).

Second, we conducted a 2 (trait anxiety: low, high) x 3 (emotion: negative, positive, neutral) mixed ANOVA to investigate the effect of anxiety and emotion on the change in episodic specificity between the simulation and recall phase (difference score: recall minus simulation). We found a main effect for trait anxiety, $F(1, 51) = 4.46$, $p = .04$, $\eta_p^2 = .08$ [CI: .002, .21], but not for emotion, $F(2, 102) = 1.50$, $p = .23$, $\eta_p^2 = 0.029$ [CI: .00, .087], and no statistically significant interaction between trait anxiety and emotion, $F(2, 102) = 0.192$, $p = 0.825$, $\eta_p^2 = .004$ [CI: .00, .025]. Post-hoc independent-samples t-tests revealed that, compared to the low trait anxiety group, the high trait anxiety group showed a larger reduction in episodic specificity for positive events, $t(30.338) = -2.09$, $p = 0.045$, $d = .60$ [CI: .021, 1.13]. Similar but non-significant trends with medium effect sizes were observed for negative, $t(51) = -1.688$, $p = 0.097$, $d = .46$ [CI: -.085, 1.01], and neutral events, $t(33.725) = -1.727$, $p = 0.093$, $d = .49$ [CI: -.074, 1.02] (see Figure 2).

Table 2. Mean (SD) Episodic specificity (AI) scores for future event simulation and recall, separated by trait anxiety group and emotion condition. Scores could range from 0 to 6.

		Negative	Positive	Neutral
High Trait	Simulation	4.79 (.65)	4.81 (.67)	4.62 (.63)
Anxiety	Recall	4.09 (.89)	3.97 (.90)	3.82 (.92)
Low Trait	Simulation	4.66 (.79)	4.67 (.73)	4.58 (.76)
Anxiety	Recall	4.26 (.78)	4.20 (.78)	4.11 (.86)

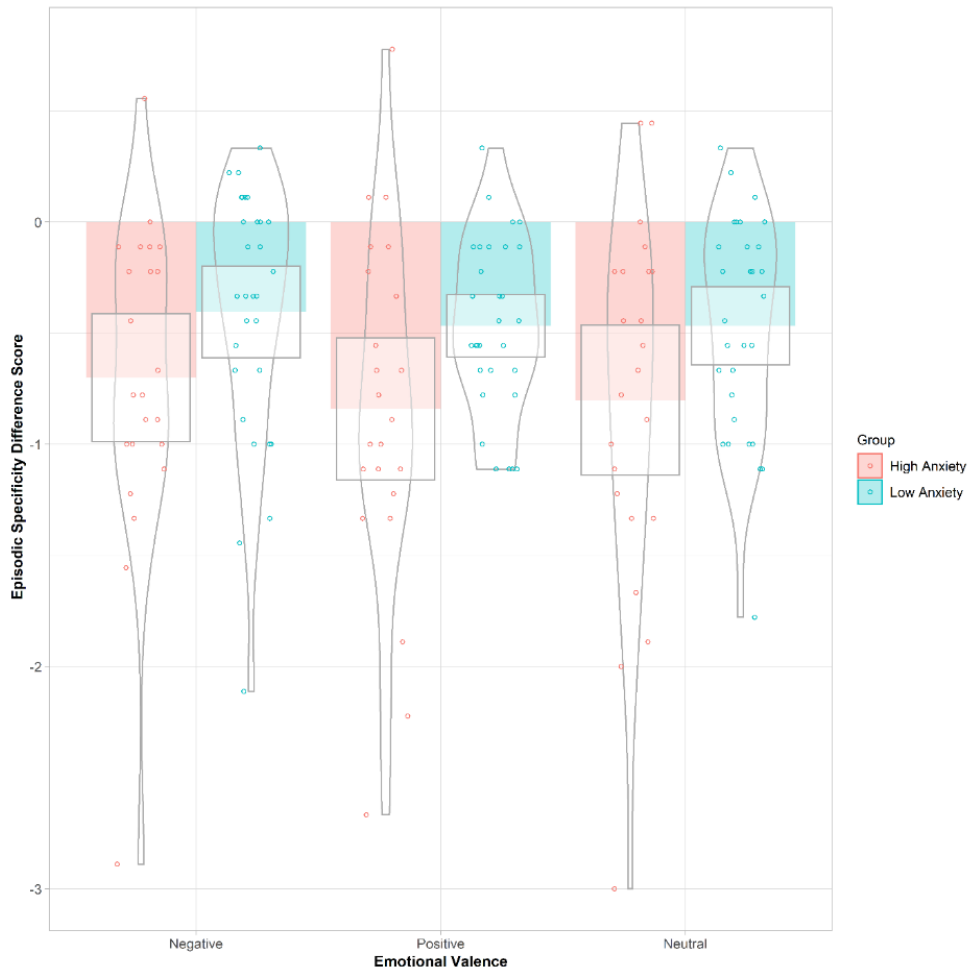

Figure 2. Mean, 95% CI, and data distribution of the episodic specificity difference scores (recall minus simulation) per emotionality condition and trait anxiety group. Negative scores reflect decreased episodic specificity during recall, while positive scores reflect increased specificity during recall.

Fading Affect measures. To assess the presence of a FAB, the difference scores (recall minus simulation) of subjective emotional intensity were subjected to a 2 (trait anxiety: low, high) x 3 (emotion: negative, positive, neutral) mixed ANOVA. Scores below zero reflect fading of emotional intensity, while positive scores reflect increased emotional intensity. The results revealed a significant main effect for emotion, $F(2,102) = 60.02$, $p < .001$, $\eta_p^2 = .54$ [CI: .42, .61], but not for trait anxiety, $F(1,51) = .002$, $p = .97$, $\eta_p^2 = .00$ [CI: .00, .00], and

no significant interaction between trait anxiety and emotion, $F(2,102) = 1.19$, $p = .31$, $\eta_p^2 = .023$ [CI: .00, .076].[1]

Further examination of the main effect of emotion using repeated measures ANOVA's (time: simulation phase, recall phase) revealed a decrease over time of subjective emotional intensity for both negative ($M = -11.03$, $SD = 13.44$), $F(1, 52) = 35.67$, $p < .001$, $\eta_p^2 = .41$ [CI: .23, .53], and positive ($M = -14.11$, $SD = 12.27$), $F(1, 52) = 70.04$, $p < .001$, $\eta_p^2 = .574$ [CI: .41, .66], future events, and an increase of emotional intensity for neutral events ($M = 5.96$, $SD = 13.77$), $F(1, 52) = 9.91$, $p = .003$, $\eta_p^2 = .16$ [CI: .035, .30]. The mean decrease in emotional intensity was higher for positive than negative events, but this did not reach statistical significance, $F(1, 52) = 3.44$, $p = .069$, $\eta_p^2 = 0.062$ [CI: .00, .18]. Together, these analyses do not show a difference in fading affect between high and low trait anxiety groups, and do not show proof of a FAB in imagined future events.

Table 3. Results for the hierarchical regression analyses for recall of positive, negative and neutral events.

Recall Positive	*B*	*SE B*	*β*
Step 1			
Constant	7.033	.396	
Group	1.304	.431	.384**
Difference score Positive	0.036	.018	.256*
Step 2			
Constant	7.272	.488	
Group	.883	.659	.260
Difference score Positive	.054	.028	.392
Group * Difference score Positive	-.031	.036	-.217

Recall Negative	B	SE B	β
Step 1			
Constant	6.907	.415	
Group	1.175	.495	.316*

Difference score Negative	.021	.018	.152
Step 2			
Constant	6.711	.494	
Group	1.483	.650	.399*
Difference score Negative	.002	.032	.011
Group * Difference score Negative	.029	.039	.195

Recall Neutral	B	SE B	β
Step 1			
Constant	6.691	.326	
Group	.163	.428	.052
Difference score Neutral	.033	.016	.290*
Step 2			
Constant	6.648	.334	
Group	.279	.465	.089
Difference score Neutral	.044	.023	.383
Group * Difference score Neutral	-.020	.031	-.136

Parallel fading. To investigate whether emotional intensity and recall deteriorate at a similar rate for simulated future events, we conducted three separate hierarchical regressions for each of the emotionality conditions. The dependent variable was the number of correct cue words, and predictors were group (trait anxiety: high = 0, low = 1), difference scores of emotional intensity (recall – simulation), and their interaction. The regression showed a significant relationship between group and recall for positive and negative future events, but not for neutral future events (see Table 3), which was also indicated by means of the mixed ANOVA. Furthermore, for positive and neutral future events, we found a positive relationship between the difference score of emotional intensity and recall accuracy. This indicates that less emotional fading was associated with higher recall accuracy for positive (β = .259, p = .046) and neutral (β = .290, p = .038) future events, but not for negative events (β = .152, p = .259). In all three analyses, the interaction

term could be rejected. The remaining two predictors accounted for a modest amount of the variance for positive, $F = 6.205$, $R^2 = .199$, $p = .004$, and negative, $F = 3.302$, $R^2 = .117$, $p = .045$, future events. Finally, we tested whether emotional valence (negative; neutral; positive) interacted with the difference score of emotional intensity on cued recall across emotionality conditions using the Neutral condition as a reference, the three-way interaction between group (low/high anxiety), emotional valence and difference score was not significant (Negative: $\beta = .04$, $p = .314$; Positive: $\beta = -.01$, $p = .84$). Based on these findings, we conclude that there was no parallel relationship between reductions in emotional intensity and recall accuracy of imagined future events.

Discussion

The aim of this study was to examine whether the FAB can be observed in memory for imagined future events, and whether it is reversed in anxious individuals. Additionally, we sought to uncover whether there is a parallel relationship between reductions in emotionality and recall accuracy for imagined future events. Our results do not indicate a bias in fading affect for imagined future events in the low or high anxiety groups and do not replicate earlier reports of enhanced recall for positive future events (21). Instead, our results indicate enhanced recall for both negative and positive future events, compared to neutral future events, in the low anxiety group during cued recall. Interestingly, the high anxiety group did not show this enhanced cued recall accuracy for emotional future events. Furthermore, compared to the low anxiety group, the high anxiety group showed greater decay in episodic specificity across all emotion conditions. While this effect is subtle, this does underline a potential negative relationship between anxiety and memory for imagined future events. Finally, reductions in emotional intensity were not significantly associated with reductions in recall accuracy.

The finding that emotion improves cued recall of imagined future events in low trait anxious individuals fits well with prior work on emotional memory enhancement. This enhanced memory for emotional events is thought to be facilitated by the arousal induced release of noradrenaline and cortisol, which aid memory encoding and consolidation (31,e.g., 32). Even though this emotional memory enhancement does not appear to affect episodic

specificity of the recalled event, it does suggest that emotional future events are more readily available for recall. Interestingly, our results show that highly anxious individuals may lack this emotional memory enhancement. Indeed, earlier work using a perceptual oddball task shows a similar effect in trait anxiety: high trait anxiety individuals did not benefit from emotionality of the oddball whereas low anxious controls did (33). The authors contributed this finding to a moderating effect of trait anxiety on the association between the release of noradrenalin in the amygdala and emotional memory encoding. While our data does not allow us to contribute to this mechanistic discussion, it does highlight that trait anxiety can interfere with the beneficial effect that emotion has on memory encoding. Together with the finding that anxious individuals showed reduced episodic specificity during recall, this lack in emotional facilitation may impede the adaptive-value of future thinking in anxious populations.

As noted by Ingvar (1985), future thoughts are generally believed to promote goal-directed behavior (34,35). Our emotional reaction to a simulated future event is thought to be an important motivating factor in setting goals to achieve or avoid these future events (6). It is important to highlight that both negative and positive future thoughts hold adaptive benefits with regards to goal-directed behavior (36). The heightened retention and mental availability of these emotional future simulations will ultimately benefit maintaining and updating of these goals. The finding that highly anxious individuals do not show this emotional memory enhancement and in general show faster memory decay for future events could possibly lead to reductions in effective goal-directed behavior (13).

Furthermore, our findings indicate that low trait anxiety individuals benefit from the emotionality of the future event only with respect to the structural integrity of the memory. The subjective emotionality and valence that was connected to the future events during encoding dissipates quickly and reverts to a neutral state. Heightened retention of emotional future events in the absence of the re-experience of the emotion may indicate that emotional experience does not serve a purpose beyond encoding in future thinking. Thus, emotion can lead to stronger memory formation but does not depend on explicit maintenance of the emotion for its positive effect on recall. Moreover, the apparent absence of a positive or negative bias in future memory recall suggests that both valences

may be equally important to retain once they have been simulated. Therefore, we posit that the remembered future is goal-oriented rather than “rosy”.

Our results seem to contrast with past research that found a positive memory bias in healthy controls and pessimism for future events in anxious individuals. One reason for this may be that we fixed the number of future events for each emotional condition, instead of leaving the emotional valence up to the participant. Additionally, we instructed participants to provide cue words that did not have a strong emotional association. In contrast, earlier work on emotional memory bias in anxiety disorders has mostly relied on emotional cue words (for review see, 37). These studies could therefore reflect a bias in attention and spontaneous future thinking rather than a bias that affects memory encoding as was assessed here.

The present study may be limited by its use of a general negative condition rather than a fear-specific one. While the literature on anxiety disorders often reports a negative memory bias, other work exemplifies that this memory bias is limited to anxiety-provoking events. However, our results are in line with recent work showing that high social anxiety is not associated with enhanced recall for imagined negative social situations (38). Combined with our results, we postulate that anxiety may be related to the selective retrieval of anxiety-related memories but not to enhanced recall accuracy for such memories. Another limitation is that we examined a

relatively small, non-clinical student sample, which may limit generalizability of the findings to a clinical population. Finally, while the AI analysis offers novel insights into episodic specificity of remembered future simulations for anxious populations, it is unclear whether this reduction in detail indeed leads to problems in adaptive functioning (39,40) and whether naturalistic future thinking follows a similar pattern of decay.

In conclusion, while prior research has shown that highly anxious individuals have a stronger tendency to imagine negative future events in a naturalistic setting, the current results suggest that this bias does not translate to the type of emotional facilitation that survives consolidation. Ultimately, the combination of increased negative future thinking and faster (emotional) memory decay for future thoughts may still lead to an overrepresentation of, albeit poorly encoded, negative information in memory in high trait

anxiety. Gaining a deeper understanding of the way these future events are represented in memory can inform treatments that target maladaptive fear.

Notes.

1. To investigate if the unequal gender distribution between the trait anxiety groups impacted our results we ran all major analyses again excluding all male participants. The results were not significantly affected.

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Chapter 5

Positive future thinking without task-relevance increases Anxiety and frontal stress regulation

Nicole D. Montijn

Lotte Gerritsen

Dana van Son

Iris M. Engelhard

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Author contributions

NDM, LG and IME designed the study; NDM collected the data; NDM, DvS and LG analyzed the data; all authors interpreted the data; NDM wrote the first draft of the article, and DvS, LG and IME provided critical revisions. All authors approved the final version of the manuscript for submission.

Abstract

Negative anticipatory biases can affect the way we interpret and subjectively experience events. Through its role in emotion regulation, positive future thinking may provide an accessible way to attenuate these biases. However, it is unclear whether positive future thinking works ubiquitously, independent of contextual relevance. Here, we used a positive future thinking intervention (task-relevant; task-irrelevant and control condition) prior to a social stress task to adapt the way this task was experienced. We assessed subjective and objective stress measures and also recorded resting state electroencephalography (EEG) to assess intervention related differences in the level of frontal delta-beta coupling, which is considered a neurobiological substrate of stress regulation. Results show that the intervention reduced subjective stress and anxiety, and increased social fixation behavior and task performance, but only if future thinking was task-relevant. Paradoxically, task-irrelevant positive future thoughts enhanced negative perceptual biases and stress reactivity. This increase in stress reactivity was corroborated by elevated levels of frontal delta-beta coupling during event anticipation, which suggests an increased demand for stress regulation. Together, these findings show that positive future thinking can mitigate the negative emotional, behavioral and neurobiological consequences of a stressful event, but that it should not be applied indiscriminately.

Introduction

Anticipatory anxiety and stress are as much a part of everyday life as they are of certain mental disorders. Such anxiety is associated with negatively biased expectations and interpretations that can cause emotional distress (1,2). Expectations have an important role in guiding behavior and the interpretation of novel information. They are typically shaped by prior experience (3), which provides a perceptual filter that influences attention (4,5), perception (6,7) and ultimately memory (8,9). Negative expectations do not just protect an individual from threat but also help moderate emotional responses to unpleasant situations, or prevent them altogether (10). However, it can bias processing of novel experiences, so negativity can over time become disproportionate to the situation (11).

Expectations of an event may be expressed and evaluated through episodic future thinking. This involves the mental simulation, or pre-experiencing, of future events by recombining elements from previous experiences (12). Future thinking is important for a range of cognitive functions including planning, likelihood estimation, decision making, and emotion regulation (13). Its role in emotion regulation is also reflected on a neural level. Future simulation relies on functional connectivity between the hippocampus and prefrontal cortex during event construction (14–16), an area that has been related to emotion regulation processes and cognitive control. Because episodic future thinking takes a role in both the expression of anticipatory bias and the regulation of the accompanying emotional response, it may provide an accessible way to attenuate negatively biased cognitions.

Indeed, recent work shows that future thinking can positively bias the interpretation of neutral narratives (17), and inhibit the recollection of contextually similar scenarios (18). Furthermore, increasing the level of episodic detail with which future events are simulated enhances emotion regulation strategies and improve psychological well-being towards worrisome future events (19,20). Beyond future thinking, positive imagery interventions have been developed to reduce anticipatory anxiety and stress (21). Interventions that use personally or contextually relevant imagery appear to produce consistent effects (e.g. 22,23). However, it is unclear whether they work ubiquitously, independent of context or trait predisposition, and if these effects go beyond subjective experience. Of particular interest is whether task-relevance is indeed a boundary condition for the effect of positive

interventions, and whether trait anxiety may limit efficacy as it is associated with deficits in emotion regulation (24,25).

Here, we addressed those questions by having participants imagine positive future events before being subjected to the Trier Social Stress Test (TSST; 26), which is an aversive task that involves an impromptu presentation in front of a jury panel. To address the notion that efficacy might depend on task-relevance of the intervention, we compared no-intervention controls to participants who imagined either positive task-relevant or task-irrelevant future events. The goal was to mitigate the negative emotional response that is generally triggered by the TSST using positive future thinking, and skew subjective perception towards more positive interpretations of this stressful task. We expected both intervention groups to benefit from the intervention compared to controls, but expected that the task-relevant group would show the most improvement. We used a combination of self-report measures, eye tracking, and electroencephalography (EEG) to assess intervention-related differences in stress reactivity and emotion regulation.

Emotion regulation depends on connectivity between the pre-frontal cortex and limbic areas, like the hippocampus and amygdala (27). Cross-frequency coupling, or the interaction between two different neural oscillation frequencies, can be used as a measure for such functional connectivity (28). Of interest is the level of coupling between delta (1 – 4 Hz), associated with affective processing and anxiety (29,30), and beta (14 – 30 Hz) oscillations, associated with cognitive control (31,32). Frontal delta-beta amplitude-amplitude coupling has been proposed as a marker for trait level stress regulation efficiency, as it could differentiate between low and high levels of social anxiety in anticipation of a social stressor (33). Furthermore, and of particular interest for this study, frontal delta-beta phase-amplitude coupling (PAC) has been proposed as a neural marker for emotion and stress regulation (34,35). Earlier reports, that used a similar task design as the current study, showed that in individuals with low levels of social anxiety delta-beta PAC typically increases when state nervousness and anxiety increase (33,36). Therefore, delta-beta PAC specifically could be a viable measure for differences in stress and emotion regulation in a low anxiety sample like we present here. However, these earlier studies do not include measures that reflect whether higher PAC is associated with more effective

regulation of stress, merely that PAC increases as a response to stress. Thus, it remains unclear whether increases in delta-beta PAC during stress anticipation are reflective of adaptive stress regulation, or rather stress reactivity.

Methods

Participants

We tested 65 students recruited at the Utrecht University campus, none of whom self-reported any current psychiatric impairment (i.e. no current diagnosis with an anxiety (related) disorder, major depressive disorder, or manic episode. Furthermore, female participants were required to be on hormonal birth control to control for potential bias in the hormonal stress response due to fluctuations of female hormones (37). Participants were randomly assigned to one of three experimental groups: task-irrelevant positive, task-relevant positive and control. All participants provided written informed consent. A power analysis, G*Power Version 3.1 (38), based on prior research (17,18) showed that a sample size of at least 18 per group was necessary to detect an effect of the positive future intervention on task appraisal (power = .80, η_p^2 = 0,16). Taking potential missing values into account, we aimed to test 20 participants per group. They were remunerated with money or course credit for their participation. The study was approved by the institutional ethical review board at Utrecht University (FETC19-053).

Three participants were excluded due to technical problems that forced us to quit the test session prematurely. This led to a sample size of 62 before data pre-processing (21 task-irrelevant, 21 task-relevant, 20 control). Furthermore, 6 participants (4 task relevant, 1 task-irrelevant and 1 control) were excluded from the eye-tracking analyses due to missing data (see Eye tracking pre-processing for further details on exclusion criteria), and 3 participants (one of each group) were excluded from the EEG analysis due to poor data quality.

Procedure

Data acquisition took place over two consecutive days. The first session took place in the lab between 12:00 and 18:00 to limit variability in stress reactivity due to the circadian cortisol rhythm. Participants started by filling out a battery of trait and state questionnaires

followed by 5 minutes of eyes closed resting state EEG. This was followed by the positive future thinking intervention (see Positive Future Thinking), and then the Trier Social Stress Test (see TSST). For the control group, the order of these two tasks was reversed. Regardless of experimental group, the TSST was always directly followed by a questionnaire on task appraisal and memory for the preceding event. The second session consisted of a follow up questionnaire that consisted of the same items as the Task Appraisal Self-Report and a debriefing. This session was completed at home.

Positive Future Thinking. Participants were subjected to a positive future thinking intervention either before (task-irrelevant and task-relevant) or after (control) the TSST. For all groups, the intervention consisted of vividly imagining 15 positive episodic future events that could occur within the next five years of their lives. Participants were instructed to imagine the event in as much detail as they could, and to envision scenarios that evoked a highly positive emotion. For each trial, participants were shown a positively valanced cue word, e.g. successful or confident (see Materials section for the full list), that they could use as a starting point to imagine an event. All participants, irrespective of intervention group, were shown the same 15 cue words (one for each of the 15 trials), but the order was randomized between participants. Participants in all conditions were instructed to imagine a different event for each trial. While the cue words ensured differentiation to some degree, we asked participants to type a short title (3 – 5 words) for each event to ensure task compliance and diversity in the imagined events.

In the task-relevant condition, participants were instructed to imagine positive future events that could occur within the next 5 years based on the displayed cue word that involved them giving an oral presentation in front of 2 or more people. For example, for the cue word ‘successful’ someone might envision themselves giving a poster presentation at a conference and successfully convincing a skeptical researcher. To allow more diversity between scenario’s any event involving some type of public speaking, such as receiving an award or a thesis defense, was accepted as ‘presenting’ as long as they were the one speaking.

In the task-irrelevant condition, participants were instructed to imagine positive future events that could occur within the next 5 years based on the displayed cue word that they

would generally experience to be positive. For example, for the cue word 'successful' someone might envision themselves getting the news that they finally got their dream apartment after much searching.

The task started with two practice trials to familiarize participants with the procedure. Practice trials were 3 minutes each, and required participants to describe the imagined event. The experimenter would use questions from the Autobiographical Interview to guide the participant to envision an event that had the appropriate level of episodic detail and emotional intensity. For the remaining 13 trials, per trial one cue word was presented in the middle of the screen for 45 seconds. The experimenter was in the room with the participant during the intervention to further ensure that participants adhered to the task instructions. Trials were separated by a 5 second break, and a longer break of one minute halfway down the task.

TSST. The presentation part of the Trier Social Stress Test (26) was used as the aversive episodic event that all participants were subjected to. Right before onset of the task, participants were informed that they would have to give an impromptu 5 minute presentation as if it were a job interview in front of a jury panel, whom they would be able to see through a video call. Participants were led to believe that the jury panel would be evaluating both their presentation and behavioral characteristics, and that their entire presentation would be recorded for subsequent analysis. In reality the 'video call' was a prerecorded video (see SI Appendix). To further standardize the presentation, all participants had to give a presentation on Climate Change and were given a list of 10 facts about this topic which they had to memorize and incorporate in their presentation. The specific topic was only revealed once they received the fact sheet.

The task could be divided in five phases: task instruction, fact sheet reading, mental preparation, presentation and recovery. EEG was recorded during the mental preparation and recovery phase, and eye tracking was recorded during the presentation phase.

After the task instruction, participants were given 2 minutes to study the fact sheet followed by 5 minutes to mentally prepare their presentation. The fact sheet was not available during the preparation time and participants were not allowed to talk or take notes. Following the preparation time, participants completed the PASA questionnaire (39)

to assess anticipatory stress and could click to place the video call to the jury panel to start their presentation. During the presentation, the test leader scored the amount of facts from the fact sheet that were included in the presentation. If participants ran out of material, the test leader could give predefined content prompts (e.g. What have you done to impact or benefit the environment?). After 5 minutes of presentation time, the experiment continued automatically to a 5 minute recovery phase where participants had to sit in silence and fixate on a fixation cross. Following the recovery phase, all participants completed the STAI-S, and a set of 11 visual analogue scales at assessing subjective task appraisal.

Materials and Stimuli

Cue words intervention. Cue words were selected from a subset 25 positively valanced cue words that are commonly used as part of the Autobiographical Memory Task (40). An independent student sample (N = 21) rated all 25 words on subjective valence and arousal, as well as ease of simulation for both generally positive events and events involving an oral presentation. Words that rated highest across all four measures were selected for use. The following 15 cue words were used in all three conditions: successful, confident, friendly, enthusiastic, proud, smart, cheerful, respected, liked, peaceful, relaxed, interested, happy, comfortable, admired.

Baseline Self-Report. Measures of key traits underlying the current tasks (i.e. anxiety, stress, memory and imagery) were taken to assess a priori group differences, as well as a baseline measure for state anxiety. Specifically we assessed state and trait anxiety levels using the State Trait Anxiety Inventory (STAI-S and STAI-T; 41), trait worry using the Penn State Worry Questionnaire (PSWQ; 42), stress reactivity using the Perceived Stress Scale (PSS; 43), and vividness of mental imagery using the Vividness of Visual Imagery Questionnaire (VVIQ; 44). Scores for all questionnaires were computed using their respective scoring manual.

Task-Appraisal Self-Report. A second battery of questionnaires was administered right after the recovery phase of the TSST to assess post event state anxiety and task appraisals. For state anxiety we again used the STAI-S.

For post-event task appraisals, we used a combination of the visual analogue scales that are part of the Primary Appraisal and Secondary Appraisal scale (PASA; 39) and items that were designed specifically for this study. The first part of the PASA was administered right before the presentation phase of the TSST, and consists of 16 items on anticipatory stress that are rated on a 6 point Likert-scale (1 strongly disagree – 6 strongly agree).

The second part of the PASA is administered after the stress-inducing event (in this case the TSST presentation) and consists of four visual analogue scales (0 not at all – 100 totally) on the level of experienced stress during and level of experienced control over the event. We elaborated on this scale with 7 more items. Of the novel items, two related to the level of physical and emotional discomfort ("The past situation was embarrassing for me" and "I felt physically uncomfortable in the past situation") and two to confidence in their own performance ("I think my presentation went well" and "If I were asked to give the presentation again I would do it exactly the same way"). These items were rated on the same scale as the original PASA items (i.e., 0 not at all – 100 totally). Furthermore, three items assessed subjective appraisal of the jury panel. Of these three, one used the original scale ("I thought the jury panel was intimidating") and two were rated from negative to positive (0 – 100; "I think the judges evaluated my presentation" and "I felt the facial expressions of the jury panel were"). After reverse scoring positively worded items, all ratings were summed and averaged with the three jury-items forming their own category.

TSST video. In the original protocol for the TSST (26), the presentation participants give is held in front of a live audience of judges that are in the same room with the participant. However, several video based adaptations of this procedure have been developed over the years to accommodate the use of specific measures or manipulations. These adapted versions, even animated VR environments (e.g. 45), are generally found to be equally as effective as the original in-vivo setup. Here, we opted to use a pre-recorded video of the jury panel both to standardize the experience between participants and to accommodate the recording of EEG and eye-tracking during the TSST.

Three actors were recruited as jury members. Actors were instructed to wear professional attire. The recording started with a brief introductory statement *("Welcome, thank you for preparing this presentation. You may start now."*) by the head jury member, seated in the middle, to sell the idea of a live video connection. This was followed by 5 minutes of silent observing as if the jury were actually listening to a presentation. As per the official TSST protocol, the jury was asked to refrain from giving verbal or non-verbal feedback during the entirety of the recording. However, taking notes and attentive listening were encouraged. Jury members looked directly into the camera to make it look like they were making eye contact from the participants perspective. After 5 minutes the head jury member notified the participant that their presentation time was up and that they would disconnect the call *("Well time is up, thank you for your presentation. We will now close this connection."*). Following this statement, one of the other jury members pressed a button on their laptop and the video switched to a black screen.

Eye tracking recording and pre-processing

Eye tracking was recorded using a Tobii T120. Calibration was done right before the task instructions of the TSST, using a 9 point fixation calibration.

Pre-processing of the eye tracking signal was performed in Tobii Studio. First, participants were rejected if gaze detection was less than 60 percent during the presentation phase. For the remaining dataset, areas of interest (AOI) were set as ellipses around the faces of the three jury members. The number of fixations and fixation duration (in ms) were calculated for all AOI's and non-AOI using the automatic detection mechanism in Tobii Studio. The average fixation duration and total amount of fixations on each area were calculated per 1 minute interval to assess changes in fixation behavior throughout the 5 minute presentation.

EEG recording and software

EEG recording was done using 64 Ag/AgCl electrodes placed in an extended 10-20 montage and collected at a 1,024 Hz sampling rate using the ActiveTwo BioSemi system (BioSemi, The Netherlands). Biosemi Common Mode Sense (CMS) active electrode and Driven Right

Leg (DRL) passive electrode replaced the conventional ground electrode, and CMS was used as the online reference. Vertical EOG was measured with two Ag-AgCl electrodes placed above and below the right eye. Offline pre-processing (see SI Appendix) of the EEG time series was performed using MATLAB (The Mathworks, Version 9.6.0.1472908, R2019a) with EEGLAB (Version 2020).

EEG pre-processing

The EEG signal was downsampled to 512 Hz. Data was re-referenced to the average of all 64 electrodes and offline band-pass filtered between 1 and 40 Hz (24dB/oct), with a 50-Hz notch filter (zero-phase shift). Noisy channels were interpolated. Ocular artefacts were removed from the non-resting state data (mental preparation and recovery) using the ocular correction ICA method in EEGLAB. For each condition, data was then segmented into 8-second non-overlapping epochs (4,096 time samples), to have sufficient low-frequency cycles to detect dPAC (46). The first and last 15 epochs of both tasks were manually inspected for gross artifacts and excluded if necessary. Out of those, three early and three late clean epochs were selected for use in further analysis. These three early and three late epochs of the resting state, mental preparation, and recovery were exported to ASCII files for further analyses.

The focus of this study includes frontally mediated delta-beta PAC, to allow comparisons with relevant studies (33,47) and to reduce the risk of the multiple comparisons problem. F3, Fz and F4 were selected for further analysis.

PAC analyses were performed as in Poppelaars et al. (33) using custom scripts. The selected EEG epochs were down-sampled to 128 Hz, and band-pass filtered separately for delta (1–4 Hz) and beta (14–30 Hz) using a Butterworth IIR bandpass filter by using a zero phase-shift filtering method (with a filter order of 8 for delta and 34 for beta; which doubled after using both a forward and a backward filter). A Hilbert transform was applied to the delta and beta filtered epochs to isolate the phase and amplitude information (48). The first and last 16 samples – equal to the order of the lower frequency's filter (cf., 36) – were cut from each epoch to remove edge artefacts originating from filtering (46,49).

Debiased Phase-Amplitude Coupling Analysis

PAC analyses between delta phase and beta amplitude were performed using the debiased PAC (dPAC) method (50,51) with custom-written scripts (as in 33), to fit the current data specifications and research interests. Delta-beta dPAC and the accompanied Z-values were calculated for each participant and electrode, over the six epochs, and were thereafter averaged over three frontal electrodes (F3, Fz and F4), yielding one dPAC and Z-value per participant, per condition. dPAC was calculated by removing the phase clustering from the traditional PAC method (cf., 52) via a simple linear subtraction (50,cf., 51). PAC can be defined as:

$$PAC = \sum_{t=0}^{n} \alpha_t \, e^{i\varphi_t}$$

where a_t represents the amplitude of the modulated frequency (i.e., beta amplitude), and ϕ_t represents the phase of the modulating frequency (i.e., delta phase), *t* is time, and *n* is the total number of time samples. The phase clustering (PC) is calculated by averaging the complex vector of phase angles ($e^{i\varphi t}$), from which the magnitude (or strength) and angle of clustering can be determined:

$$PC = \frac{1}{n} \sum_{t=1}^{n} e^{i\varphi_t}$$

It should be noted that by not including the beta amplitude *a*, all complex numbers have the same length, and, therefore, all angles have the same weight in the averaging process. This allows for determining the average angle, or PC. For dPAC, the aforementioned complex numbers, $a_t e^{i\varphi}$ (combining beta amplitude *a* and delta phase *φ*) are averaged for all time samples, correcting the phase angle of the complex numbers by the earlier obtained PC:

$$dPAC = \frac{1}{n} \sum_{t=1}^{n} a_t \, (e^{i\varphi_t} - PC)$$

The dPAC value is expressed as the magnitude of the averaged complex number, where zero indicates no coupling, and values greater than zero indicate coupling. The significance of the coupling was established by comparing the dPAC values to surrogate dPAC values that were obtained via a non-parametric permutation testing approach (53) by randomly

shuffling epochs for phase information, while amplitude remained intact. This shuffling process was repeated 1,000 times, yielding a distribution of surrogate dPAC values as expected under the null hypothesis of no coupling. This method not only allows for significance testing but also accounts for possible outliers (50). Significant dPAC was determined by comparing dPAC to their surrogate counterparts ($dPAC_{null}$) to obtain *Z*-values (dPACz):

$$dPACz = \frac{dPAC - mean(dPAC_{null})}{std(dPAC_{null})}$$

These *Z*-values were used for hypothesis testing due to their straightforward interpretation (i.e., standard deviation units; 54).

Results

Subjective measures

No baseline group differences

Participants started with a baseline assessment of state and trait anxiety levels (STAI; 41), as well as trait based levels of worry (PSWQ; 42), stress reactivity (PSS; 43) and imagery ability (VVIQ; 44). Group comparisons (see Table 1) revealed no significant baseline differences on any of the measures: trait anxiety (STAI-T), $F(2, 61)= .073$, $p = .93$, state anxiety (STAI-S), $F(2, 61)= 1.07$, $p = .350$, worry (PSWQ), $F(2, 61)= .092$, $p = .912$, stress reactivity (PSS), $F(2, 61)= 1.939$, $p = .153$, and visual imagery ability (VVIQ), $F(2, 61)= 1.000$, $p = .374$. This suggests that the randomization of participants across conditions was successful.

Table 1. Demographics and Baseline Questionnaire scores (Means and SD) per experimental group.

	Task-Irrelevant	**Task-Relevant**	**Control**	**Total**
N participants (F/M)	21 (16F/5M)	21 (12F/9M)	20 (13F/7M)	62 (41F/21M)
Age	23.5 (3.1)	23.5 (2.5)	24.5 (3.6)	23.8 (3.1)
STAI-State Baseline	31.7 (4.4)	34.6 (9.7)	31.9 (6.1)	32.7 (7.1)
STAI-Trait	38.3(8.3)	38.7 (9.9)	37.7 (8.3)	38.2 (8.8)
PSWQ	46.5 (10.5)	46.7 (13.6)	45.2 (11.8)	46.2 (11.9)
PSS	16.1 (5.5)	16.2 (6.1)	12.9 (6.6)	15.1 (6.2)
VVIQ	58.4 (13.7)	55.8 (7.7)	60.3 (8.8)	58.2 (10.5)

Note. *No significant group differences were found for any of the measures.*

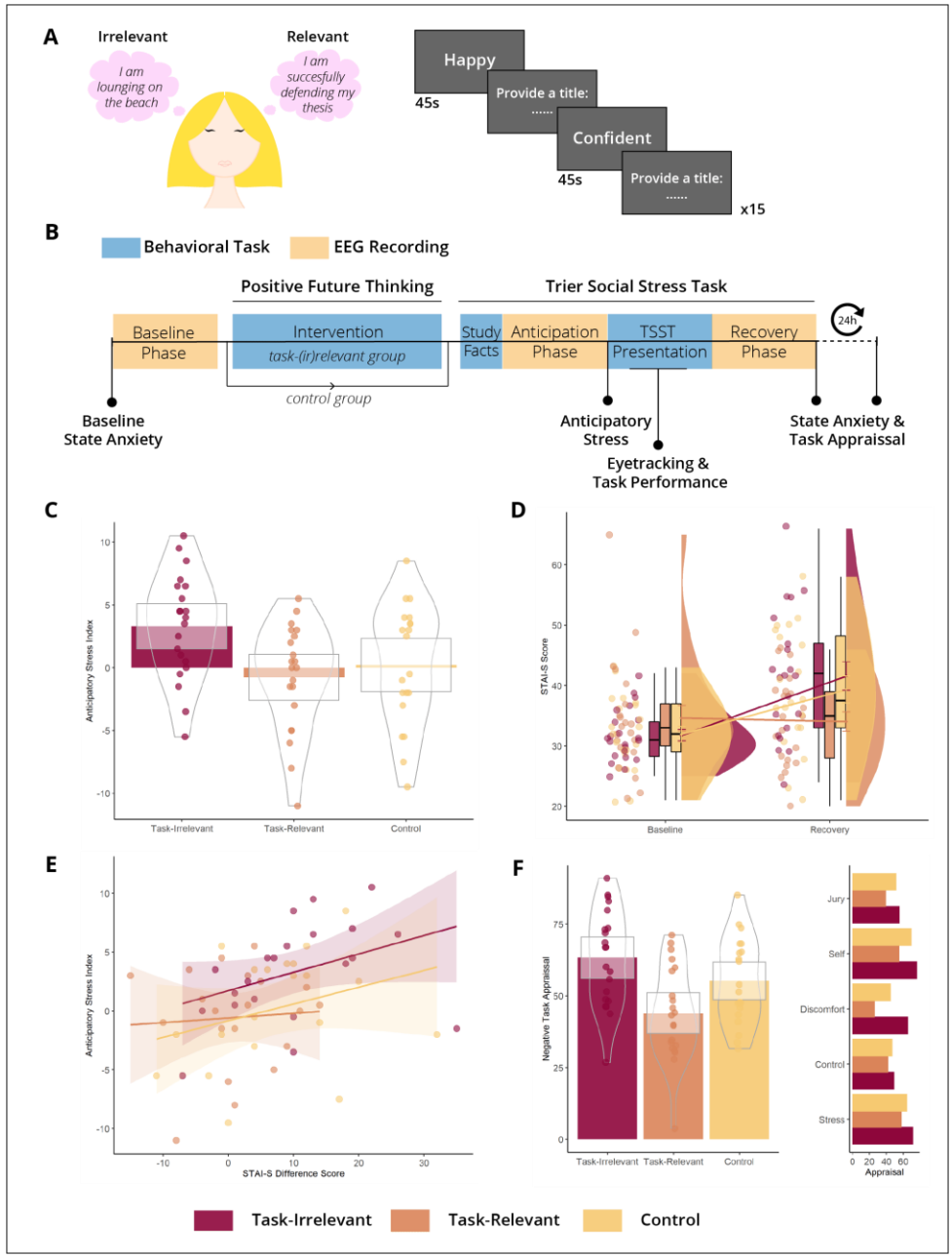

Figure 1. Design and Subjective Data. **A)** Task design Positive Future Thinking intervention. Participants either imagined 15 generally positive future events (Task-Irrelevant Group) or 15 positive future events where they gave a presentation (Task-Relevant Group). Positively valanced cue words were presented to aid event construction. Participants were asked to provide a title for every

imagined event to ensure task-compliance. **B)** Study design including timepoints at which specific measures were taken. **C)** Response distribution for Anticipatory Stress Index. Colored bars represent group mean, white squares show 95% CI, violins and points show distribution of individual participants. Positive scores reflect maladaptive stress while negative scores reflect adaptive stress. **D)** Between groups response distribution and group means of STAI-S scores at Baseline and post-TSST Recovery. Graph shows an increase in State Anxiety for the Task-irrelevant and Control group, but not for the Task-relevant group. Scores on the STAI-S range from 20 to 80. **E)** Correlation between Anticipatory Stress levels and task-related changes in State Anxiety. **F)** Subjective task appraisal scores separated by experimental group. Bars represent mean scores, violin and points show response distribution, boxes represent 95% CI. To the right, appraisal scores are separated by both experimental group and appraisal sub-scale. Scores ranged from 0 (not negative at all) to 100 (very negative).

Task-irrelevant positive future thinking leads to more stress reactivity during anticipation

After the anticipation phase (see Figure 1B), we assessed subjective levels of anticipatory stress using the Primary Appraisal (situational threat and challenge) and Secondary Appraisal (situational control and self-confidence) scale (PASA; 39). A positive Stress Index (primary – secondary) reflects that the perceived threat or challenge outweighs the perceived ability to control the situation. We found a significant main effect of group, $F(2, 59)= 4.815$, $p = .012$, $\eta_p^2 = .14$, that was driven by a higher Stress Index in the task-irrelevant group compared to both the task-relevant and control group (see Figure 1C).

Task-relevant positive future thinking prevents event-related negativity and anxiety

Directly after the TSST, participants completed the STAI-S again to assess changes in State Anxiety following their presentation. A 2 (time: Baseline, Recovery) x 3 (Group: Task-irrelevant, Task-relevant, Control) mixed analysis of variance (ANOVA) revealed a significant interaction between time and group (see Figure 1D), $F(2, 59)= 5.914$, $p = .005$, $\eta_p^2 = .167$. This interaction was explained by an increase in State Anxiety in the Control, $t(19) = -3.263$, $p = .004$, $d = .72$, and Task-Irrelevant group, $t(20) = -4.462$, $p = .000$, $d = .93$, but not in the Task-Relevant group, $t(20) = .243$, $p = .81$, $d = .05$.

Participants also completed an 11-item questionnaire that assessed their subjective appraisal of their performance and the event itself (i.e. the TSST presentation).

Experimental groups differed significantly from each other in overall task appraisal (see Figure 1F), $F(2, 59) = 7.608$, $p = .001$, $\eta_p^2 = .205$. Pairwise comparisons (Bonferroni corrected) showed that the Task-Relevant group ($M = 43.9$, $SD = 3.5$) appraised the task significantly more positively ($p = .001$) than the Task-Irrelevant group ($M = 63.3$, $SD = 3.5$), and at a trend level ($p = .088$) compared to the Control group ($M = 55.2$, $SD = 3.6$). These effects persisted in the follow-up measurement 24 hours later.

Behavioral Measures

Task-relevant positive future thinking boosts task performance

To assess whether the intervention enhanced task performance, we calculated the number of climate change facts that participants remembered to incorporate in their presentation. We found a significant effect of group $F(2, 59) = 3.481$, $p = .037$, $\eta_p^2 = .11$, that was explained by the task-relevant group ($M = 6.67$, $SD = 1.35$) presenting significantly more facts than the control group ($M = 5.15$, $SD = 2.01$), $t(39) = 2.849$, $p = .007$, $d = .89$. However, contrary to what might be expected based on the subjective data, the task-relevant group did not present more facts than the task-irrelevant group ($M = 6.1$, $SD = 2.11$), $t(39) = -1.041$, $p = .304$, $d = .46$.

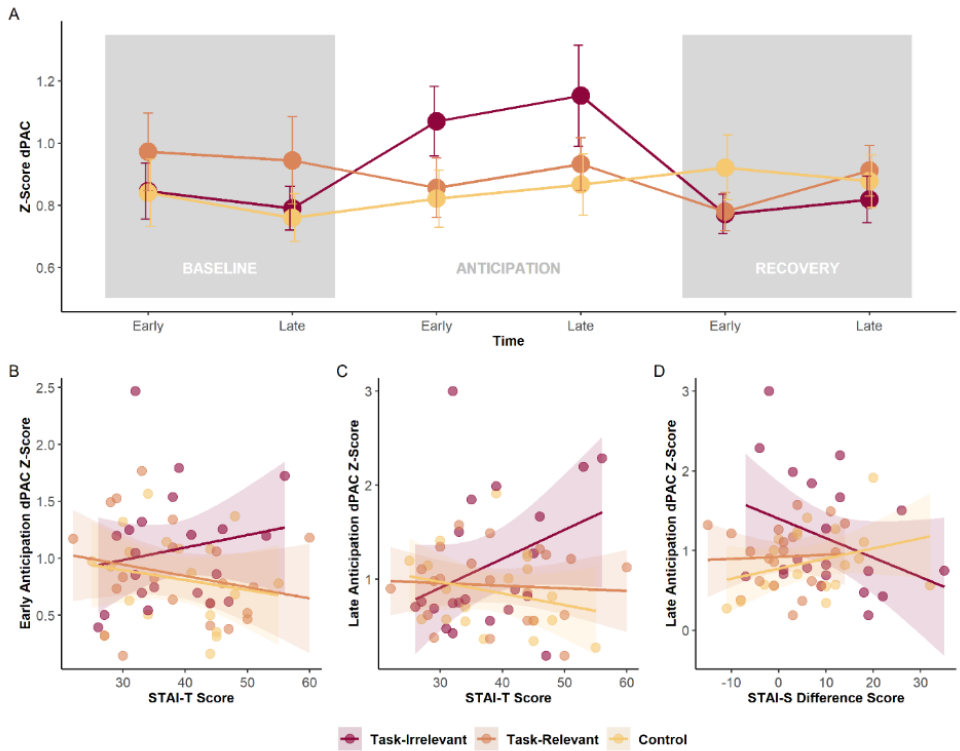

Figure 2. Delta-beta phase amplitude coupling. **A)** Mean and SE of Z-scored delta-beta dPAC (average of electrodes Fz, F3 and F4) per experimental group. Line graph shows the progression of dPAC levels over the three phases of the experiment (Baseline, Anticipation and Recovery). Early and Late reflect an average dPAC level for the first (early) and last (late) 80 seconds of that phase. **B)** Scatter plot showing group differences in the correlation between Early Anticipation dPAC and Trait Anxiety scores. **C)** Correlation between Late Anticipation dPAC and Trait Anxiety scores **D)** Correlation between Late Anticipation dPAC and State Anxiety Difference scores (Recovery – Baseline).

Cross-frequency EEG Measures

Delta-beta dPAC increases as a function of trait anxiety and stress

We expected that levels of frontal delta-beta phase-amplitude coupling (see Supplementary Figure S2) would increase more for the intervention groups (Task-Relevant > Task-Irrelevant) leading up to the TSST compared to the control group, and wind down again during recovery. To assess this, we ran two linear mixed regression models, one for the upward slope (early baseline to late anticipation) and one for the downward slope (late

anticipation to late recovery), using group and time as fixed factors and allowing random slopes per subject. Compared to the control group, delta-beta dPAC levels in the task-irrelevant group increased at trend level from early baseline into late anticipation (β = .11, *p* = .09) and decreased again from late anticipation to late recovery (β = -.17, *p* = .07) (see Figure 2A). This trend was not found for the Task-Relevant group.

Next, to assess the effect of trait vulnerability on emotion regulation and the interaction with the intervention groups, we included Trait Anxiety as a fixed effect in both models. Leading up to late anticipation, we found a significant interaction between group, time and trait anxiety levels, *F*(2, 178.94)= 3.053, *p* = .04 (see Figure 2B and C). Trait anxiety significantly predicted increases in dPAC over time in the Task-Irrelevant group (β = .019, *p* = .014). From late anticipation to late recovery, higher levels of trait anxiety were also associated with a steeper, though not significant, decrease in dPAC in the Task-Irrelevant group (β = -.02, *p* = .07).

To explore whether delta-beta PAC coded for stress reactivity rather than emotion regulation, we used delta-beta dPAC scores during late anticipation as a predictor for changes in State Anxiety levels pre to post TSST (Recovery minus Baseline). The hypothesis here was that if delta-beta PAC reflects emotion regulation it should be negatively related to task-related changes in State Anxiety. Indeed, increased delta-beta coupling in the Task-Irrelevant group was negatively predictive of task-related increases in State Anxiety (β = -12.3, *p* = .06) (see Figure 2D).

Discussion

In this study, we investigated if positive future thinking can be used to attenuate negatively biased perception of a social stressor (TSST). Our data show that task relevance of the intervention, and not positivity alone, determines its benefit. Positivity without task relevance led to more negative task appraisal and a more severe stress reaction in response to the social stressor. This adverse effect of the task-irrelevant positive intervention may have been somewhat counteracted by the engagement of neural stress regulation mechanisms.

Our hypotheses regarding the working mechanism of the interventions were centered on the notion that positive future thinking promotes effective emotion regulation, as a way of planning ahead (i.e. the event will still be stressful but participants feel more in control). Instead, we found that when the intervention is task-relevant, it seemingly prevents the stress reaction that the TSST typically induces. Participants in the task-relevant group reported comparable levels of anticipatory stress to the control group and did not show a task related increase in state anxiety while both the control and task-irrelevant group did. Perhaps anticipatory anxiety in the task-relevant imagery group did not translate into state anxiety increase during the TSST because the participants simulated and planned successful presentations scenarios. Another possible explanation for the discrepancy between task-relevant and irrelevant future thinking in terms of stress response is that the former intervention modulates memory schema activity. Higher-order conceptual knowledge is used as a perceptual filter that facilitates the interpretation of novel information as well as the selection of appropriate actions (3,55). Through future thinking, the task-relevant group may have instantiated contextually appropriate positive schema, which likely caused the interpretation of the new external information to assimilate into the active schema (56,57). In the task-irrelevant group, the instantiated schema did not hold contextually relevant information that could help the individual deal with the stressor. Such incongruency may have prompted the reinstatement of the dominant schema for having to give a presentation in front of a jury (58,59), which is negatively biased for many people. Furthermore, due to this incongruence, these participants may have felt less prepared to deal with the stressor, as suggested by heightened anticipatory stress and stronger engagement of frontal emotion regulation compared to controls. Participants in the control group were also negatively affected by the stressor, but may have felt relatively more prepared during anticipation, because they were not distracted with irrelevant positive information beforehand.

This study has important implications and recommendations for psychological interventions that leverage positive imagery or simulation-based learning to reduce anxiety. First, positivity should not be applied indiscriminately. General positivity training may be beneficial in affective disorders like depression (60), where overall positivity tends

to be reduced (61), but it does not help to reduce anticipatory anxiety and (paradoxically) increases it. However, similar to our findings, work on affective forecasting errors has shown that unmet positive expectations can negatively affect well-being (62) and suggests that people may even downward adjust their subsequent future expectations as a result (63). This reality problem is something the positive psychology movement has also been criticized for in the past (64). As data from our task-irrelevant group shows, by replacing negatively biased event anticipation with irrelevant positive information, the individual may feel less equipped to handle the situation. Second, the task-relevant positive future thinking intervention is effective even if it does not specifically address the upcoming stressful situation. That is, our task-relevant group imagined scenarios where they gave a presentation, but the presentations could concern anything from a wedding speech to a job application. This might be helpful in situations where individuals have a difficult time envisioning positive alternatives to a highly feared situation. Finally, due to its positive effects on state anxiety and task performance, task-relevant positive future thinking could be a useful tool to enhance both exposure willingness and efficacy in pathological anxiety (also see 22).

This work extends findings on the transfer of valence through simulation-based learning. A recent study showed that future thinking can serve as a substitute for lived experience in updating pre-existing beliefs or attitudes. By imagining liked (or disliked) people together with a neutral location, participants changed their appraisal of the location towards the valence associated with the person (65). Here, we show that such transfer of valence does not just apply to existing semantic representations, but also immediately affects the interpretation of new experiences that are semantically related. These positive effects on event appraisal remain at 24-hour follow-up. So, while it is unclear whether future thinking can establish long-term changes in pre-existing beliefs, the effects on information learned directly following the intervention are relatively stable.

Our findings also extend earlier work on the relation between stress and frontally mediated delta-beta coupling. Functionally, delta-beta PAC has been positioned as a stress regulation mechanism. This assumption is fueled by previous research (33,36) showing that coupling increases as a function of state nervousness during anticipation (but see 66), which our

results corroborate. However, these earlier studies do not include measures that reflect whether higher PAC is associated with more effective regulation of stress, merely that PAC increases as a response to stress. This study shows that people with higher levels of delta-beta PAC during anticipation tend to have a lower or no increase in state anxiety following the stressor. While replication of these findings is certainly needed given the limited sample size, our data provide preliminary support for the notion that delta-beta PAC is reflective of adaptive stress regulation. However, as noted by others (47,66,67), whether this mechanism is actually engaged seems to depend both on context and trait predisposition.

Elevations in delta-beta PAC during stress anticipation were limited to the task-irrelevant group (i.e. the group with the highest subjective levels of anticipatory stress), and were not statistically robust. The latter may in part be due to variability in trait anxiety within this group, which was positively correlated to levels of delta-beta coupling. So, only participants in the task-irrelevant group with high levels of trait anxiety increased in delta-beta PAC during anticipation. Since only a small percentage of our sample met these specific conditions, these analyses lack power and would require replication to verify the validity of the effect. However, similar moderating effects of trait anxiety have been found for other slow/fast wave EEG patterns, like delta-beta and theta-beta ratio, in relation to stress regulation and threat bias (68–70). This may suggest that some individuals with a trait vulnerability engage this frontal delta-beta PAC system to regulate stress when cognitive resources that help deal with the situation are low. It should be noted that increased activity does not automatically mean that emotion regulation is also effective (71,72), as our data also suggest. Highly anxious individuals may exert more effort to regulate their emotions in response to stress but vary in their level of efficiency in doing so. This was also shown in an IAPS picture viewing task, in which individuals with high trait anxiety showed greater engagement of prefrontal emotion regulation systems to establish similar levels of emotional down-regulation as low-anxiety individuals (73).

Our work complements existing work on frontal emotion regulation using other EEG-derived markers, like frontal alpha asymmetry. In contrast to the current experiment, where emotion regulation efficiency was assessed indirectly as a function of state anxiety changes, work on the up and down-regulation of emotion has shown a correlation to frontal

asymmetry in the alpha frequency band. On a trait level, effective emotion regulation is related to greater left frontal alpha asymmetry (i.e. alpha power decreases from the left to right hemisphere) (74). Furthermore, similar to our results, frontal alpha asymmetry has been related to state dependent (only in high stress conditions) differences in emotion regulation (75). Future work may focus on the independent contributions of these EEG derived markers of emotion regulation. One possibility is that alpha asymmetry, due to its role in the functional association between the frontal lobe and amygdala, is important for regulating emotional experience. Whereas delta-beta coupling may facilitate effective goal-directed behavior needed to manage the situation at hand, as suggested by its involvement in decision making (76) and attentional control (77).

While the use of delta-beta coupling in relation to emotion regulation and social anxiety is not new (33,66), analyses typically focus on the contrast between two groups (e.g. high and low trait anxiety). Leveraging the temporal resolution of EEG, it is possible to track the functional dynamics of cortical-subcortical crosstalk measures, like delta-beta coupling, over time and in relation to specific task contexts (e.g., 67). We opted to average coupling over longer epochs, to ensure comparability to earlier work. However, delta-beta coupling dynamics can even be tracked on a millisecond scale using MEG (78). Furthermore, recent work has shown that emotion (regulation) dynamics can be tracked using EEG microstates (79,80). These efforts present exciting new ways to examine the precise temporal dynamics of EEG/MEG derived correlates of emotion regulation.

A limitation to the current work is the relatively small sample size, in particular for the eye-tracking data where a lot of data was lost due to quality issues. The power analysis for this study was based on the behavioral effect and therefore may not be representative for the eye-tracking and EEG data. Nevertheless, the study was adequately powered for the behavioral data, which show a consistent benefit of task-relevant positive future thinking over task-irrelevant future thinking or no intervention. Another limitation of this study is the absence of affect measures throughout the experiment. In following the TSST protocol (26) we included the Stress Index right before onset of the presentation, and added a second measure of State Anxiety directly following the TSST. To delineate the proposed mechanism behind the paradoxical effect of task-irrelevant positive future thinking, future

research may use affect measures at different stages of the experiment to clarify how and when imagery exercises increase different facets of positive affect.

To summarize, positive future thinking can be an effective tool to induce *a priori* positive reappraisal of aversive situations and enhance task performance and goal-directed behavior. However, the contextual relevance of the imagined future scenarios to the aversive event is a clear boundary condition for this effect: when future thinking is incongruent with the aversive event, it can (paradoxically) increase stress and anxiety. Task-relevant positive future thinking may be used to increase willingness and efficacy of exposure therapy for pathological anxiety and could be an accessible way for people to deal with negative anticipation in daily life. Over time, this could help to update the negative biases surrounding these situations, but this is an empirical question that awaits future research.

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Open Practices Statement

The experiment reported in this article was not preregistered. Requests for raw data and materials can be e-mailed to the corresponding author. Pre-processed data that were used for the main analyses can be found at:

https://osf.io/tj9q5/?view_only=1f28e17503104c3b8b8de42bae9fcac4

Data & Code Availability

Raw data are available from the corresponding author upon request. Materials, code and preprocessed data for all outcome measures generated during and/or analyzed during the current study can be found at:

https://osf.io/tj9q5/?view_only=1f28e17503104c3b8b8de42bae9fcac4 .

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Chapter 6

General Discussion

The aim of this thesis was to increase our understanding of the mechanisms that drive memory generalization and future thinking and their role in anxiety related disorders. In the first section, I examined how the temporal structure of episodic events is represented on a neural level, showed that general knowledge can systematically bias recall and that acute stress may amplify this bias in temporal context memory. In the second section, I examined anxiety related differences in emotional future thinking as well as how positive future thinking can be used as tool to limit the negative cognitive-behavioral impact of stressful situations.

SECTION I – WHEN TIME IS MEMORY

In section I, we examined how fine-grained temporal relations between episodic events are retained, both under normal conditions and after experiencing stress. The accurate retention of temporal context information serves several important purposes, two of which I want to highlight in the context of this thesis. First, beyond the obvious importance of remembering what and where something happened, time provides a scaffold along which experiences unfold, and gives a sense of the (causal) relationship between episodic events (1). Without temporal context memory, our recollection of events is unlikely to make much sense as events build on each other to create a coherent narrative. For example, in determining why your coffee mug fell over you will need to remember not only which other events led up to the fall, but also which event was closest to it happening such that it might have been the cause. Second, with repeated experience, memory of these temporal relationships allows us to predict how similar events are likely to unfold in the future and plan accordingly (2). For example, if you figure out that the cat knocked your mug over you may be more vigilant in the future to keep the cat away from your coffee. The ability to accurately retain such temporal patterns is especially relevant in stressful situations where wrong predictions can be quite consequential (3).

In **chapter 2**, we examined how the hippocampal-entorhinal cortex is involved in both the representation of specific temporal relations between episodic events and how general knowledge of similar event sequences influences temporal memory. Prior research on this topic had shown that the hippocampal-entorhinal cortex is centrally involved in processing

and remembering event sequences. However, it was unclear if neural patterns in this area might also reflect more fine-grained temporal relations like the time distance between events. To assess this, we developed a novel paradigm in which participants gradually developed a sense of virtual time. We compared neural pattern similarity between events in the same sequence to assess if events that were closer together in time showed more representational overlap.

The results showed that neural pattern similarity in the anterior hippocampus indeed reflected fine-grained temporal distances between events and not just sequence order. Interestingly, the hippocampus used a different representational format to map similarities in temporal structure between similar episodic event sequences. So, this suggests that the hippocampus uses two distinct formats (4,5) to simultaneously map the precise temporal relationship between events within a sequence, and how the temporal structure of this sequence compares to similar event sequences. To put this effect to practice, these two formats respectively allow people to recollect how long after breakfast they left for work this morning and deduce whether this time was earlier or later than they usually leave. The latter format may facilitate generalization of temporal patterns between contextually similar experiences.

Next, in line with accounts that general knowledge can guide recall (6,7), we tested whether knowledge of the general temporal structure of the other events sequences biased recollection of specific event times (figure 1). Indeed, behavioral virtual time estimates were systematically skewed towards the mean virtual time of events in the other sequences (see figure 1). So, if you left for work at 9:15 this morning, but you usually leave at 9am you are more likely to estimate that you left at 9:10 than 9:20 because recall is biased towards what is generally true. Furthermore, this bias was stronger when neural patterns of time distance in the hippocampus were less precise. This suggests that people may use general knowledge to compensate when specific episodic memory is poor, and that this general knowledge can bias recall relatively soon after encoding. Over time such recall biases may become more pronounced as specific episodic details fade and people start to rely more on general knowledge to guide recollection.

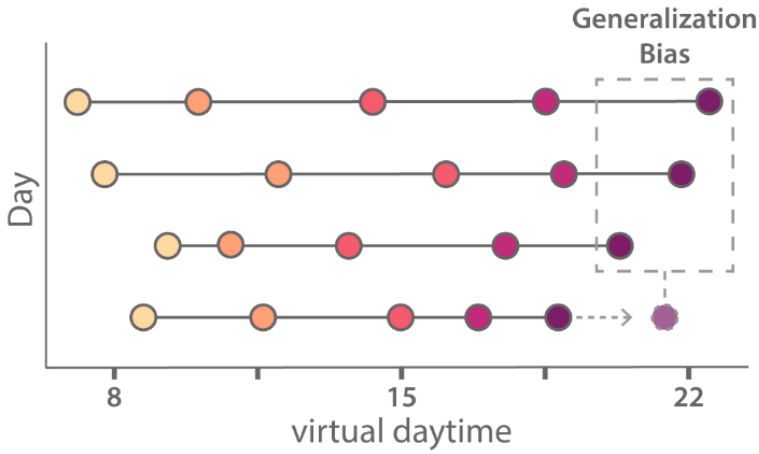

Figure 1. Illustration of how recalled virtual events times are biased towards the mean virtual time of events that occupy the same sequence position in the other event sequences (dashed purple circle). Each line represents one of the four virtual days in the task, and solid colored circles reflect the true virtual time of each event in that day. If the purple events in sequence 2 – 4 occurred relatively later than the purple event in sequence 1 (bottom line), the virtual time of the latter was systematically estimated to be later.

In **chapter 3**, we built on the findings of chapter 2 and examined whether acute stress interferes with the temporal contextualization of episodic events. Stress is known to interfere with hippocampal functioning (8), and contextual binding (9) . As such, acute stress experienced during a negative situation may disrupt encoding of temporal relations between events. To examine the effects of stress on temporal context participants underwent the socially evaluated cold pressor before completing the virtual day learning task (as in **chapter 2**). Contrary to our expectations, acute stress did not reduce accuracy of temporal context memory. Next, we investigated whether the generalization bias reported in chapter 2 could be replicated, and whether stress may increase this bias. Indeed, like chapter 2, virtual time estimates in all experimental groups were biased towards the general mean of the other sequences (figure 1). Interestingly, this bias effect was stronger following acute stress. This may suggest that following stress people rely more heavily on a general knowledge to aid memory for temporal context.

To conclude, across chapter 2 and 3 we show that while temporal context is encoded at a more fine-grained level than previously reported, general knowledge of similar sequence structures may systematically bias memory for time. This generalization bias may be amplified after stress. Thus, for events that directly follow stress, we may rely more heavily on general knowledge and expectations for that specific situation to infer temporal structure. Speculatively, this suggests a role of acute stress in the (temporal) generalization threat-related memories in anxiety.

Thus far, most work on generalization of emotional and threat-related memory has looked at generalization from items to broader perceptual and semantic categories, and not detailed retention of the episodic event sequences themselves (such as in Chapter 2 and 3). For example, fear is known to generalize from a specific exemplar (your neighbors scary dog) toward the semantic category (all dogs) that item belongs to (10). While this work is important to map generalization of fear in memory in terms of content (i.e., the what of an episodic event), it does not inform how threat expectations may generalize across spatio-temporal contexts (where and when). As I touched upon at the start of this section, knowledge of how episodic events unfold over time enables us to make predictions about how similar event sequences will unfold in the future. In the context of anxiety, fear generalization towards similar items may inform broad scope predictions about threat expectancy, e.g., all dogs are dangerous. However, it does not inform predictions about the temporal progression a fear-inducing event which may similarly include maladaptive overgeneralizations. Expanding knowledge about specific patterns of generalization in fine-grained complex episodic memories may be critical in understanding the etiology of anxiety disorders like social anxiety where contextual factors play a larger role.

As suggested in chapter 3, stress can interfere with detailed retention of temporal context and generalize temporal memory towards an average timeline to a higher degree than usual. While we did not assess this, our results that stress interferes with the proper retention of temporal information could include encoding of event boundaries between stressful and neutral events. Event boundaries are thought to have an important function

in separating different contexts (11), and particularly emotional contexts. Indeed, a recent fear conditioning study showed that event boundaries may protect emotional fear memories from competing with similar safety memories (12). Participants learned to associate pictures from one semantic category (e.g., animals) with a shock, while another category (e.g., tools) was not paired with a shock. When fear acquisition and safety learning were separated by a clear event boundary, participants only showed enhanced memory for images from the shocked-paired category that were learned during the acquisition phase. This memory benefit did not transfer to images from the same category that were learned after the event boundary. This suggests that event boundaries that separate emotional from safe contexts may help protect the emotional memories from interference and limit the emotional response to the appropriate context.

However, following high-intensity emotional events competing signals originating from the amygdala may interfere with proper encoding of event boundaries in the hippocampus. This may cause a neutral event to blur into the emotional event (13). Thus, in future work it might be important to consider that emotion can differentially affect memory depending on the intensity of the emotion.

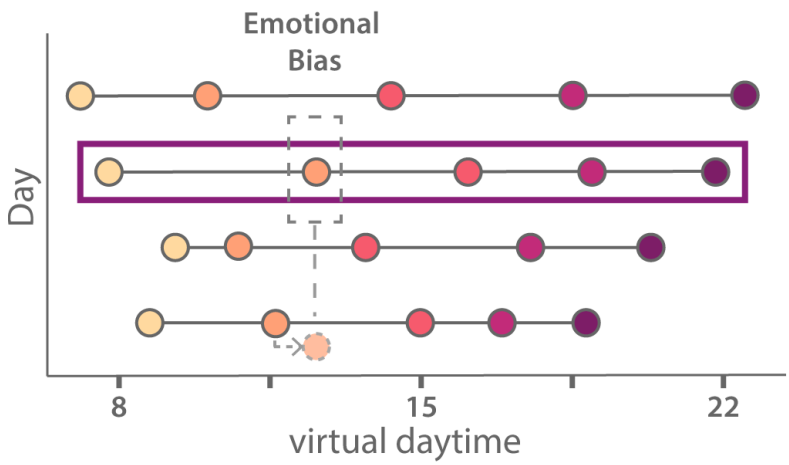

Figure 2. Proposal for potential biasing effect of emotion on memory generalization. Each line represents one of the four virtual days in the task, and solid-colored circles reflect the true virtual time of each event in that day. The sequence highlighted in purple signifies an emotionally arousing event sequence. Due to the prioritized role of emotion in memory, recall of virtual event time (dashed

orange circle) may bias towards the most emotionally salient exemplar sequence rather than to the general mean of all similar sequences.

Finally, an interesting next step using the virtual time paradigm would be to investigate whether highly emotional events bias temporal memory towards the emotional sequence (Figure 2) rather than the general average (Figure 1). This could be investigated by, for example, replacing one of the neutral event sequences, with a sequence consisting of emotionally salient situations (purple highlighted sequence in Figure 2). If this is the case, it would mean that emotional memories are not only more stable (14–17), but also bias memory of competing (neutral) experiences such that they become more structurally similar to the emotional experience. Such generalization of memory towards emotional material has already been demonstrated for memory content (what), spatial context (where) and the neural representation of complex scene images, but not for episodic event sequences (when).

Specifically, work on threat learning using Pavlovian conditioning has shown that items from the same object category (e.g. both utensils) were mistaken for the item that was previously linked to a shock more often than items from a different category (18). In other words, the fear response generalized to safe items within the same object category. For spatial context, weaker hippocampal representations of spatial context predicted higher levels of fear generalization to a safe context. This is reminiscent of to our finding that temporal memory generalization was associated with weaker hippocampal time coding (**chapter 2**). Expanding this line of work to naturalistic episodic material, for example videos or controlled real life experiences (19), might be instrumental in understanding how emotional or fear related experiences may bias recollection of similar neutral experiences across all aspects of memory (what, when and where).

SECTION II – WHEN IT IS TIME FOR MEMORY

In section II, we looked at the effects of emotional memory biases on episodic future thinking and goal directed behavior in the context of anxiety and stress. The biasing effects of schematic knowledge are not limited to recall of the past. Representations of regularity, abstracted from individual experiences, allow us to predict how conceptually similar future

events are likely to unfold. Episodic future thinking builds on prior experience by constructing potential future scenarios using schematic knowledge as a scaffold (6,20). An important function of future thinking is to aid the selection of behaviors that help the individual work towards future goals or avoid unwanted situations by mentally simulating a potential course of events (21). Since these goals are not always in the immediate future, it is important that we are able recall these future thoughts over time. Because episodic future thinking relies on the same constructive system as episodic memory (22,23), memory for future events might be subject to similar patterns of decay and bias as memory of the past.

In **chapter 4**, we examined if emotional memory biases similarly affect the retention of imagined future events. Specifically, we sought to replicate the positive bias that is generally reported for healthy individuals (24,25), and secondly examine whether this bias is reversed for individuals with high levels of anxiety. To study this, we recruited individuals with either low or high levels of trait anxiety from a larger sample of students. Participants were asked to imagine a series of positive, negative and neutral future events based on a cue word trio that they felt could realistically occur within the next 5 years of their lives. After mentally simulating the future event, participants were asked to describe the future event in as much detail as possible. The next day, participants returned to recall each future event. We assessed memory fading in terms of cue recall and episodic specificity of the event descriptions. Contrary to earlier work (24,26), participants with low trait anxiety levels did not show a positive memory bias for imagined future events. Rather we found that emotion in general, not just positive emotions, improved cue recall. Interestingly, the high anxiety group did not show this type of emotional memory enhancement. In addition, high anxiety was associated with a greater decay of episodic specificity. So, while high trait anxious individuals may be more inclined to imagine negative future events (27,28), they do not appear to retain them to a higher degree than neutral or positive future events. However, the faster memory decay for future events in anxious individuals can still be consequential as it hinders goal maintenance.

Initially, we had hypothesized that positive future thinking in and of itself could be used to counteract the negative bias that is associated with anxiety (28,29). By selectively training

people to imagine positive events the underlying schematic bias may neutralize as positive memory associations are rehearsed and become more accessible. However, the results from **chapter 4** show that future events are not retained well in anxious individuals. Therefore, imagining positive future events likely does not result in the type of selective strengthening needed to update maladaptive schema in this population. That being said, we did not find any initial differences in the level of episodic specificity and emotional intensity with which emotional future events could be simulated between the low and high anxiety group. Thus, while positive future thoughts may not be accurately retained over time, perhaps positive future thinking can be leveraged to induce short-term positive biases.

Through its role in goal-directed behavior and decision making, future thinking is used to exert a certain level of control over the situations that will be experienced in the future. In addition, pre-experiencing events can skew the interpretation of these events when they eventually do transpire (30). In **chapter 5**, we investigated if future thinking can be used to induce a temporary positive bias to make a typically stressful event feel less aversive. Participants performed a newly developed positive future thinking induction before being subjected to the Trier social stress task (31). The goal was to use future thinking to induce a (temporary) positive bias to mitigate the stress response that is typically elicited by the TSST. To dissociate the effects of positive mood from goal-directed to non-goal directed imagination, participants received either a task-irrelevant, task-relevant, or no intervention. The task-irrelevant group imagined generally positive events, such as going on vacation. The task-relevant group imagined positive events that related to them giving a presentation, such as receiving a standing ovation after a speech. As this manipulation aims to increase mental availability of positive information that is relevant for the task, we expected a stronger stress-reducing effect of the intervention for the task-relevant group. We included delta-beta phase amplitude coupling as a neural marker for stress reactivity based on earlier work that showed that this EEG metric increased as a function of state nervousness and anxiety (32).

Our data showed that task-relevant future thinking indeed positively biases perception and participants in this group seemed to benefit from the intervention both on a subjective and

behavioral level. Paradoxically, the task-irrelevant group reported more anticipatory stress and evaluated their own performance more negatively than both the control and task-relevant group. This increase in stress reactivity was also evident on a neural level. The task-irrelevant group, in particular those with higher levels of trait anxiety, showed increasing levels of frontal delta-beta phase amplitude coupling in the period leading up to the stressor. Higher levels of delta-beta PAC were predictive of lower task-related state anxiety. This suggests that this neural system is primarily engaged to limit the cognitive emotional damage of an impending stressor, but its efficacy may differ depending on individual differences like trait anxiety.

The results of chapter 4 and 5 provide further insights into the lasting effects of episodic future thinking. Previous research had established that imagined future events are retained over time, and most evidence thus far pointed to the presence of a positivity bias akin to that observed in episodic recollection (24,25,33). In contrast, in chapter 4 we posit that, when allowing for thorough elaboration, future thinking instead was best described as goal directed. The results show that the retention of both positive and negative future events was enhanced, which typically hold more adaptive benefits than neutral events (21). It is possible that, in a healthy population, the reported positivity bias in future event memory (24) is instead reflective of the relative ease of simulation of positive over negative future events and not of a bias in the recollection of future events. The discrepancy in results may stem from differences in task design. Earlier work elicited future thinking in a fast-paced paradigm (15-20 sec simulation time), whereas in our paradigm participants imagined each future event for 3 minutes. Speculatively, people may generally find it easier to come up with positive scenario's, leading to an apparent positive memory bias under time pressure. However, when given enough time have, participants have equal ability to vividly simulate, and thus later remember, negative and neutral scenario's (**chapter 4**). This interpretation is in line with predictions from the theoretical framework of pragmatic prospection, whereby future thinking is initially optimistic followed by reflective realism (34). In daily life, this combined pattern may present as the increased propensity to simulate positive future events, but the preserved ability to equally retain negative future event when they are

simulated. Finally, for anxious individuals, use of a fast-paced paradigm would likely have resulted in a negative future memory bias (35), and have obscured our finding that both positive and negative future events are not retained well over time.

However, the preserved ability of detailed positive future thinking in people with high levels of anxiety was cause for optimism. Belief in occurrence of future events depends on the level of autobiographical contextualization (36), and can be modulated through repeated simulation (37). These factors contribute to whether positive future thoughts themselves feel realistic, but does this positivity also translate to how we experience those events once they occur in real life? In chapter 5, we showed initial evidence that task-relevant future thinking can elicit short-term biases over the way we perceive current events. Beyond the clinical relevance of this finding (see Clinical Implications), it also shows how jumbled time can become in constructive memory processes. Imagining a possible (distant) future, based on memory of the past to ultimately change how we perceive the present. It has been proposed that constructive episodic simulation may be intrinsically atemporal, with the attribution of the label past present and future only coming at a later stage of the constructive process (38). While on the surface the difference between the three seems clear cut, the deeper you dive into the many inconsistencies of memory the more blurry the lines become (39,40). Indeed, evidence from neuroimaging has revealed that the neural processes that are engaged during imagination of the both the past and future are strikingly similar, if not identical (41). Source monitoring processes (42) that typically allow us distinguish similar functions based on the underlying cognitive operations may therefore not fully account for how we distinguish between the past and future (43). The allocation of an imagined event to either the personal past or future may therefore be post hoc (38). As demonstrated throughout the chapters of this thesis, episodic experiences inform predictions of the future which in turn can be remembered and impact perception and interaction with the present reality that long precedes the imagined future event. Ultimately, on a neural level episodic information may just be that: information that is reformatted and restructured to fit specific needs, plotted onto different parts of the mental timeline or made more available when deemed important to aid the acquisition of

new information. In the context of anxiety, this lack of temporal distinction may work in our favor, as I will discuss in the clinical implications section.

LIMITATIONS & STRENGTHS

While there is certainly potential for these studies to inform and improve treatment options for anxiety (related) disorders, there also are some limitations to consider. Most prominently, all the work presented in this thesis was performed on healthy young participants, with at most sub-clinical levels of trait anxiety. Work using trait anxiety can provide important contributions without unnecessarily taxing a more vulnerable group, such as people with a clinically diagnosed anxiety disorder. However, while high trait anxious people can approach clinical samples in terms of symptoms, it should not be assumed that therefore future thinking behavior will be the same. As we saw in Chapter 5, even at a sub-clinical level differences in trait anxiety affected emotion regulation efficiency in anticipation of a stressor. On a memory level, patients with anxiety disorders may have more pronounced biases or encountered more formative experiences that bias future thinking more strongly than in sub-clinical populations. Thus, while studies using trait anxiety and stress can provide insights into the mechanistic of emotional (future) memory, it is important to replicate this work in clinical populations.

Second, it is pertinent that future work in this area considers long term effects of future thinking-based interventions. While we were able to show that future thinking can improve negative biases on the short term and at 24-hour follow-up, the real benefit of interventions (like in **chapter 5**) lies in the potential longevity of the memory effects. As we discussed in Chapter 3 and 4, both stress and anxiety can interfere with the long-term retention of (future) memories, the specific dynamics of which may depend on the current context and emotional valence of the event. The transformation of memory over time (months and years) can introduce further biases, that were outside the scope of the current studies but are nonetheless important to consider. Especially in a treatment context.

Tangential to the previous point, the working hypothesis underlying all the studies presented in this thesis is that schematic or generalized knowledge drives biases in constructive memory processes. In the context of anxiety, the goal was to gain

understanding of the emergence (chapter 2 and 3) and propagation (chapter 4) of such biases. While the literature on the functional role of schema in episodic memory is abundant, the manner in which we acquire schematic knowledge is more elusive as schematic representations may only form over the span of months or years rather than days (44). This makes the emergence and influence of stable schema difficult to track experimentally. Novel techniques in neuroimaging may offer a way to reliably track representational change and the utilization of episodic and generalized memories over time. I will discuss these potential avenues of research in the future directions.

Finally, next to these limitations there are several strengths of the presented work that deserve to be mentioned. First, across all four empirical studies a conscious effort was made to make the experimental stimuli and tasks as naturalistic as possible. In chapter 2 and 3 the stimuli were designed using life simulation game The Sims to portray a complex set of scenes that could be mentally construed into a day in the life of the Sim character. In contrast, many studies on sequential memory rely on static images of items (e.g., fruits), or abstract symbols that have no further episodic meaning. In chapter 4 and 5, we leveraged episodic future thinking for scenario's that the participants came up with themselves and felt could realistically occur in their own future. As opposed to imagery work that uses preset narrative vignettes, this type of personal episodic future thinking likely draws on more of the themes that are important to the individual broadening the personal relevance and impact of the mental simulation.

A second strength is the use of multi methods designs that tap into neuro-, cognitive and behavioral processes within the same experiment. In particular chapter 2 and 5 are good examples of this. In both experiments we used a combination of neuroimaging (fMRI and EEG respectively), controlled tasks that tapped into specific cognitive domains and behavioral measures that addressed several aspects of the behavioral response (e.g., using both eye-tracking and self-report to track state anxiety).

Last, while it was previously listed as a limitation, the use of 24-hour follow-up, like we did in chapter 3 – 4, in memory experiments is still somewhat rare. Most experimental designs are completed within the span of a day as this is more practical in terms of time commitment for both the experimenter and the participant. However, assessing recall

accuracy directly after encoding might be more reflective of encoding success than (long-term) recollective strength, which at least requires overnight consolidation of the memory (45). Therefore, while I would still recommend further work on long-term retention, especially in the context of schema formation, the use of 24-hour memory follow up can also be seen as a strength.

THEORETICAL IMPLICATIONS

Throughout the discussion of the chapters I have already highlighted several theoretical implications of the individual studies. Overarchingly, the presented work has implications for the interaction between episodic and semantic/schematic knowledge in the constructive memory processes.

As described in the introductory chapter of this thesis, episodic and semantic memory are more entangled than originally thought. Importantly, episodic experience can lead to the abstraction of general knowledge, and in turn general knowledge is used as a scaffold episodic recollection and related constructive processes like future thinking. Understanding how highly contextualized episodic information and decontextualized general knowledge feed into each other is important due to the wide application of memory in everyday behavior. Especially in the context of mental disorders like anxiety. The first section of this thesis contributes to this by showing that both on a neural and behavioral level the detailed retention of episodic information (like temporal context) and the formation of general knowledge co-occur and interact directly after memory acquisition. Specific memory for temporal context was biased towards the general structure of similar event sequences even when memory accuracy was high (**chapter 2**). This suggests that even when there is no clear need, general knowledge is used to aid recollection. Following stress, this reliance on general knowledge may become amplified as specific episodic information fades or is simply not encoded due to the demand stress places on working memory (**chapter 3**). Relying on general knowledge to furnish episodic construction is not innately maladaptive and may even be preferred in some cases as I will address later. However, these findings do suggest that general knowledge, whether maladaptively biased or not, takes precedence over contextualized episodic detail.

The second section of this thesis, and in particular chapter 5, shows the other side of the coin. Namely that constructive memory processes like future thinking draw upon general knowledge to construct highly specific contextualized mental images. While this scaffolding mechanism is well documented in the constructive memory literature (20,46), less attention has been devoted to what this implies in the case of intentional future thinking. Importantly, if the construction of future events necessitates drawing on general/schematic knowledge it directly implies that intentionally constructing a future thought that counters one's general beliefs requires accessing knowledge of likely alternatives. While we only tapped into this implicitly in chapter 5, accessing positive schematic knowledge about a typically stressful situation was not only viable for participants but also showed new information was interpreted in line with the positive belief. Similarly, in chapter 4, highly anxious individuals were able to construct positive future events when explicitly asked to do so, despite the fact that anxiety is characterized by a distinct negative bias. So, while negatively biased knowledge might be more accessible the positive alternative might be as well when adequately prompted.

CLINICAL IMPLICATIONS

Insights from these chapters carry important implications for the (potential) use of episodic future thinking in the treatment of anxiety disorders. A key challenge in treating anxiety disorders is to get people to engage in the situations that they fear. However, exposure to a feared, but innocuous, situation does not automatically mean that people a) experience it positively, b) remember it positively and c) are more likely to seek out these experiences in the future. As we saw in **chapter 5**, future thinking may offer a solution here. By selectively simulating positive future events related to a feared situation, participants felt less anxious engaging in a typically aversive situation. Importantly, participants also reflected on the experience more positively and this effect persisted over time. By harnessing future thinking in this way anxious individuals can be provided with a tool that helps them engage and stay in situations that would typically avoid, not only in a safe therapy setting but also in daily life where there is more uncertainty. The ultimate goal here is that this enables people to have and retain formative positive experiences that are impactful enough to warrant updating any negatively biased expectations surrounding

feared situations. So, rather than trying to negate maladaptive memory biases using cognitive strategies, we are utilizing the routes and principles by which the memory system acquires and generalizes knowledge to update memory biases. A benefit of using future thinking over for example counterfactual thinking of past events is that subjectively the future is less bound by experienced reality. Patients may experience an alternative past as less realistic than a potential future where a lot of options are still open.

More generally, in terms of future thinking in psychopathology, there has been a heavy focus on the quality of future thoughts and how this may differ in various populations (47). Quality tends to be operationalized as the level of episodic specificity, as in **chapter 4**. I attribute this trend to early findings that episodic memory detail was lacking in combat veterans with PTSD symptoms, and that low episodic memory specificity before trauma exposure could even be a risk factor for the subsequent development of PTSD (48,49). While the ability to produce and recall future thoughts with a sufficient amount of detail is ultimately a highly adaptive trait (see **chapter 4**), it should be noted that highly detailed future thinking is not always necessary or can even be counterproductive. The future, like the past, can be envisioned at varying degrees of granularity. You can think broadly about what you hope to achieve in your career, or zoom in on a specific situation like how your friend will react to the birthday gift you are planning for them. Depending on what you are trying to achieve with the future thought, different levels of granularity can be appropriate. Envisioning everything with extreme episodic detail will give you a high score on the Autobiographical Interview but can take up a lot of time and energy in daily life especially when trying to achieve goals that do not require it. If anything, it may impede flexibility when something unanticipated unavoidably happens. For example, you can plan a vacation down to the minute, but a delayed flight or lost luggage can derail the entire plan leaving your planning efforts rather void. These types of overthinking are not uncommon in mental disorders and especially anxiety-related disorders. Thus, in understanding and treating future thinking related problems I believe it may not always come down to achieving high levels of episodic specificity, but rather to selecting the right level of specificity for the job. Finally, the results from chapter 4 show that people with (clinically) high levels of trait anxiety are not able to retain emotional future thoughts to the same degree as people with

low levels of anxiety. This has important implications for how well anxious individuals may be able to act and follow through on goals they set for the future, whether positive or negative. To illustrate why this is an issue, in a therapy setting someone may be asked to set specific positive goals for the distant future, e.g. 'I will plan a 3-week vacation to Seoul in the fall of 2024 and try hotteok for the first time'. To achieve this goal, I will need to set specific steps that will likely require me to revisit what I want to do exactly. If such future simulations are not retained well over time, instead of a specific achievable goal, the goal may start to look more like 'I want to visit Seoul'. Similar, to how in chapter 5 generally positive future thinking led to worse stress reactions, such vague goals may feel unachievable and can be disheartening (50,51). Beyond this causing problems in daily life, it is good to be aware of this future memory deficit when using future thinking, especially for distant events, in treatment.

FUTURE DIRECTIONS

As discussed, the work in this thesis has presented several advances. However, there are still several areas in the realm of constructive memory and future thinking that require further investigation, which may be aided by methodological advances.

As I highlighted previously, to use of naturalistic designs was a focal point in the development of the studies in this thesis. Nonetheless, with the immense complexity of memory you often have to sacrifice naturalism in order to examine isolated functions, such as temporal context. In stress research especially, memories are rarely examined in the same amount of complexity as one might experience in real life. Studies may focus on the effects of fear and stress on the what, where or when separately instead (11). Simultaneously, stress effects on memory are known differ vastly depending on factors like timing of the stressor and the presence of emotional and/or neutral material (52,53). Studying aspects of what, where and when in isolation might similarly misconstrue the effect stress has on complex naturalistic memories that combine all elements. Relatedly, episodic events do not occur in isolation either. They are part of longer sequences that combine into a narratives that can bridge across both space and time under and overarching theme (e.g. a romantic relationship)(54). Considering memory in all its

complexity, while laborious, will be instrumental both in understanding episodic memory as a cognitive function and in relation to stress and emotion.

Like the use of EEG fMRI measures in chapters 2 and 5, novel advances in neuroimaging techniques may help elucidate differences in processing that are not apparent from behavior alone, as well as uncover aberrant patterns in cognitive functioning related to psychopathology (55). An emerging line of research that closely connects to future thinking examines neural replay of event sequences (56,57). Systematic activation, or replay, of learned event sequences is thought to be important for consolidation and decision making as information is mentally rehearsed through reactivation (56,57). High resolution neuroimaging allows us to specifically track which events are replayed. In the context of anxiety, neural replay could for example reveal if fear-related events are replayed to a higher degree to inform decisions for the future, or the systematic reactivation of negative schema during narrative interpretation. Recent work on the role of replay in relation episodic memory and decision making has already produced some striking results related to these potential uses. For instance, in line with previous suggestions (58), humans were shown to reactivate context-specific past memories at event boundaries to help make sense of the ongoing event narrative (59). Furthermore, in decision making, replay was boosted for aversive paths when participants decided to approach this risky environment, and this effect was more pronounced in participants with high trait anxiety (60). Last, differences in behavioral flexibility of individual participants corresponded to differential use of replay to support decision strategies (61). While neural replay is still an actively developing field, these early advances show that replay is a powerful tool that can enable detailed tracking of the fate and use of memories over time and is sensitive enough to map individual differences in replay strategies based on traits like anxiety.

Finally, the adaptive value and efficacy of future thinking hinges on whether the individual actually performs the behaviors needed to achieve future goals. Envisioning something with the appropriate level of specificity is only half the job. As we saw in chapter 5, task-relevant future thinking can definitely benefit goal-directed behavior. Furthermore, work on decision making has established that future thinking consistently reduces delay discounting, meaning that a distant future reward is not devalued when engaging in future

thinking (62–64). Similarly, future thinking can be used to increase anticipated pleasure (65). These studies give an indication that future thinking might benefit behavioral activation, but research into the propensity to put future thoughts (both positive and negative) into action is still severely lacking. In the context of anxiety disorders this might be even more pertinent. As we experimentally demonstrated in chapter 5, imagining yourself having a nice time at a dreaded social event might help lower the threshold of actually going and even positively bias your perception of the event once you do. However, based on chapter 4, a lasting impact of positive future thinking is likely only truly achieved by going to the party and experiencing that it might not be as bad as you feared.

CONCLUSION

This dissertation aimed to increase our understanding of the mechanisms that drive memory generalization and future thinking and their role in anxiety related disorders. The current findings emphasize the entanglement between episodic memory and general knowledge and their mutual influence in biasing cognition and behavior, especially in the context of stress and anxiety. The insights presented throughout this thesis further provide novel angles by which constructive memory processes can be leveraged to understand and adjust maladaptive biases in memory, such as those present in anxiety disorder. Future work should build on these insights by combining naturalistic memory tasks with high-resolution imaging techniques to come to an integrative understanding of individual and pathology-related differences in constructive memory.

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EPILOGUE

As I mentioned at the start, I prefer to read books by opening them at a random page. As a reader, you have now made it through this thesis, from start to finish, in sequence, with maybe a few sneaky peaks ahead. I hope that throughout you have started to feel the freedom to also open the pages at random, read a sentence or two and let your mind wander. Knowing that the original stories will be there regardless, while allowing future stories to sprout from them.

For me, I take solace in the idea that even somewhat chaotic creative minds like mine are driven by predictable patterns. Patterns that can be untangled and traced back to their origin. So that the ghosts of futures' past are not here to haunt me, but rather guide me through the chapters that are still to come. With sneaky peaks ahead, from past to future to present and onwards again.

Dutch Summary

Nederlandse samenvatting

Angst wordt gekenmerkt door de verhoogde anticipatie van toekomstige dreiging. De anticipatie van toekomstig gevaar kan erg adaptief zijn. Het stelt ons in staat adequate voor te bereiden om mogelijke gevaren te vermijden. Echter in angststoornissen verhoudt het geanticipeerde gevaar zich disproportioneel tot de daadwerkelijke dreiging. In het dagelijks leven zorgt dit ervoor dat mensen met een angststoornis de gevreesde situaties buitensporig proberen te vermijden. Een verder probleem is dat de angst vaak generaliseert naar andere situaties. Iemand kan bijvoorbeeld in eerste instantie angst ontwikkelen voor drukke sociale situaties, zoals een feestje met veel mensen, maar uiteindelijk ook angst ervaren bij het idee van een kopje koffiedrinken met een vriendin of, in extreme gevallen, niet meer het huis durven verlaten. Deze problematiek bij angst wordt nu veelal geïnterpreteerd vanuit hedendaagse leertheorie, welke focust op de aangeleerde associatie tussen neutrale stimuli en een aversieve uitkomst. Onderzoek naar episodisch geheugen en toekomst gericht denken in angst kan een belangrijke aanvulling bieden op bestaande modellen voor angst generalisatie en de anticipatie van gevaar.

Episodisch geheugen omvat herinneringen aan het persoonlijk ervaren verleden. Denk bijvoorbeeld aan de eerste dag op je nieuwe werk, of een bezoek aan een mooi museum wat je erg bij is gebleven. Episodische herinneringen zijn verbonden aan een specifieke tijd, zo was die eerste werkdag bijvoorbeeld op 3 Januari 2023. Episodisch geheugen gaat echter verder dan enkel het herinneren van het verleden. Het stelt ons tevens in staat om gedetailleerde beelden te vormen van de toekomst, ofwel episodisch toekomstig denken. In de context van angst kan iemand zich bijvoorbeeld inbeelden dat ze een sociale blunder begaan op het feestje waarna iedereen hen belachelijk maakt. Hoe we onze persoonlijke toekomst voor ons zien wordt voor een groot deel bepaald door verwachtingen die we hebben op basis van voorgaande ervaringen. Unieke episodische ervaringen leren ons wat de verwachte structuur is van gebeurtenissen (A komt altijd voor B), deze geleerde structuur kunnen we vervolgens projecteren op gelijksoortige gebeurtenissen in de toekomst. Meestal werkt dit mechanisme adaptief, echter kunnen er ook genaamde biases ontstaan in het geheugen, bijvoorbeeld als herinneringen niet accuraat worden opgeslagen. Biases kunnen ervoor zorgen dat verwachtingen voor de toekomst

disproportioneel naar een bepaalde uitkomst leunen. Bijvoorbeeld zoals in het angstvoorbeeld dat mensen je altijd uit zullen lachen.

In de hoofdstukken van dit proefschrift heb ik allereerst gekeken hoe mensen in staat zijn de tijdsstructuur van episodische gebeurtenissen te onthouden. Vervolgens heb ik gekeken hoe deze vorm van geheugen mogelijk negatief beïnvloed wordt door het ervaren van stress, zoals in beangstigende situaties.

Sectie I – Wanneer tijd geheugen is

In deze sectie hebben we gekeken naar geheugen voor temporele context, en hoe stress hier mogelijk mee interfereert. In **hoofdstuk 2** hebben we allereerst bekeken hoe tijd wordt waargenomen in het brein. Een belangrijke openstaande vraag was hier of mensen tijd herinneren op basis van de volgorde van gebeurtenissen (A gebeurde voor B), of dat de tijdsafstand tussen gebeurtenissen ook wordt opgeslagen (A gebeurde 30 minuten voor B). Het onthouden van de specifieke tijdscontext kan belangrijk zijn voor het accuraat voorspellen van de toekomst. We hebben dit getest door mensen een computer taak te laten doen waarin ze de volgorde en tijdsafstand moesten onthouden tussen plaatjes die samen de gebeurtenissen binnen een dag representeerden. Deze taak voltooiden mensen in een fMRI scanner welke hun hersenactiviteit mat tijdens het bekijken van de individuele plaatjes voor en nadat ze de tijdstructuur hadden geleerd. Hierdoor konden we kijken hoe de geleerde kennis van de tijdsstructuur het patroon van hersenactiviteit beïnvloedde. We vonden dat tijdafstand, en niet alleen volgorde, werd gerepresenteerd in het hersensignaal en dus dat mensen in staat zijn tot het onthouden van hele specifieke tijdsrelaties tussen episodische gebeurtenissen. Om te onderzoeken hoe deze perceptie van tijd mogelijk beïnvloed wordt door algemene verwachtingen hebben we hierna gekeken of geheugen ‘gebiased’ werd richting de gemiddelde tijdsstructuur van alle dagen in de tijd. Dit bleek inderdaad het geval. Zelfs als geheugen voor tijd zeer accuraat werd vonden we deze generalisatie bias, maar hij was sterker wanneer geheugen minder accuraat was. Hieruit concludeerden we dat geheugen voor tijd beïnvloed wordt door algemene verwachtingen, maar vooral als geheugen minder goed is.

In **hoofdstuk 3** hebben we vervolgens gekeken hoe stress het geheugen voor tijd negatief beïnvloedt, en of het mogelijk deze generalisatie bias versterkt. Hiervoor hebben we dezelfde taak gebruikt als in **hoofdstuk 2**, echter onderging een deel van de participanten een stress taak voordat ze begonnen met leren. De verwachting was dat stress geheugen minder nauwkeurig maakt. De resultaten lieten echter zien dat stress groep niet verschilde van de controlegroep, die geen stress taak was ondergaan, wat betreft het onthouden van de volgorde van de plaatjes en het onthouden van het specifieke tijdstip waarop het plaatje plaatsvond. Echter toen we beter keken naar het type fouten die de verschillende groepen maakte in hun tijdsinschattingen bleek dat de inschattingen van de stress groep sterker 'gebiased' waren richting de gemiddelde tijdsstructuur. Dus de generalisatie bias was sterker wanneer participanten tijd leerden na het ervaren van stress. Dit kan betekenen dat na het ervaren van stress het geheugen meer wordt beïnvloed door algemene verwachtingen. Omdat individuele episodische gebeurtenissen dan dus minder goed worden onthouden heeft dit mogelijk ook gevolgen voor de verwachten die opgemaakt worden uit deze ervaringen. Zo zou stress dus kunnen lijden tot vertekende verwachtingen voor de toekomst.

In de volgende sectie hebben we gekeken naar hoe vertekende verwachtingen invloed hebben op het inbeelden van de toekomst, en hoe dit anders is bij mensen met verhoogde angst. Daarbij hebben we keken hoe het inbeelden van de toekomst mogelijk gebruikt kan worden om negatieve verwachtingen bij te sturen.

Sectie II – Wanneer het tijd is voor geheugen

Eerder onderzoek naar episodisch toekomst denken wees uit dan mensen over het algemeen de toekomst positief inschatten, en deze positieve toekomstbeelden ook beter onthouden. Door de negatieve anticipatie van de toekomst die kenmerkend is voor angststoornissen, is dit mogelijk omgedraaid in deze groep. In **hoofdstuk 4** hebben we daarom onderzocht hoe goed mensen met hoge en lage angst toekomstige beelden konden vormen die positief, negatief of neutraal waren, en daarbij hoe goed ze deze beelden konden onthouden. Onze resultaten lieten zien dat in tegenstelling tot eerdere bevindingen laag angstige mensen zowel positieve als negatieve toekomstbeelden beter onthielden dan

neutrale. Voor hoog angstige mensen gold dit niet, zij lieten deze verbetering van geheugen voor emotionele toekomstbeelden niet zien. Dit kan mogelijk gevolgen hebben voor hoe goed angstige mensen in staat zijn ingebeelde toekomstige gebeurtenissen na te leven.

In **hoofdstuk 5** hebben we vervolgens gekeken of positief toekomst denken negatieve verwachtingen konden bijstellen, en of de inhoud van deze positieve beelden hiervoor relevant was. Hiervoor lieten we mensen een reeks aan positieve gebeurtenissen inbeelden alvorens ze werken blootgesteld aan een stressvolle taak. Voor de stressvolle taak moesten mensen een presentatie geven voor een niet reagerend publiek zonder veel voorbereidingstijd. De positieve beelden waren ofwel algemeen positief, bijvoorbeeld op vakantie gaan, of gerelateerd aan de stressvolle taak, bijvoorbeeld een thesis verdediging die erg goed gaat. De resultaten lieten zien dat taakgerichte positieve toekomstbeelden hielpen om de stressvolle taak als minder vervelend te ervaren. Tevens verbeterde het de prestatie tijdens het presenteren. In tegenstelling daartoe leidde het inbeelden van algemeen positieve toekomstbeelden ertoe dat mensen juist meer angst ervaarden. Deze bevinden hebben belangrijke implicaties voor het gebruik van toekomst gericht denken in therapieën voor angst.

Conclusies

Samen geven de bevindingen uit deze hoofdstukken aan dat processen uit episodisch geheugen in combinatie met stress en angst bijdragen aan het vormen van negatieve verwachtingen voor de toekomst. Hoewel deze bevindingen wellicht een negatief beeld schetsen voor de rol van episodisch geheugen in angst maar kunnen ook worden ingezet om angst te verminderen.

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Elze – I must admit it was a bit of a hassle making my way through all the harry potter books, but ultimately very worth the effort to become your friend. I couldn't have wished for a better person to have alongside me for the entire ride that was this PhD, even up until the Wednesday-evening-plan that I totally didn't stick to but we got there in the end I guess. Your immaculate organization skills, my utter chaos, it just works. All the inside jokes, cheese and wine nights with Mand, trips to Heeze, Brummen, Ghent and of course the Efteling, random sleepovers, walks in nature, and the many many drinks made the ride so much more enjoyable. Thank you for being there for me through everything.

Mand – Thank you for daring to be yourself and giving me the courage to do the same. We did not exactly hit it off at first, something about too many walls being in the way and me resenting you for having the audacity to take Arne's desk. But it turns out that we are, in many respects, the same person. Sometimes all you need is someone to hate the same things as you, to make you feel less weird. I can always count on you to supply me with sad boi content, to call in the middle of the night as you cycle home, to send me some deranged voice message or just exist in the same space and finally catch a Giraffe stag after many (many!) laps around the island and broken nets (such a metaphor honestly). There is always a spot on the dog bed ready for you. You're amazing, you tend to forget that so I thought I would remind you again.

Franca – I love that our conversations somehow have depth while still being a never-ending stream of memes. You would think that is a difficult thing to achieve, but it's actually super easy barely an inconvenience. I remember when you came back to Utrecht to finish your PhD here, and how awkward I felt for not keeping in touch the past few years. But how happy am I that the universe in all its weirdness decided that it was time for us to be in the same city again. I love it when the universe forces us to drink cocktails and eat tasty food together. And not once, but twice! Thank you for being a constant light and bringer of fun and happiness despite all the shit that is going on in the world. I am so excited to be in the same city again, and I am looking forward to more wine fueled adventures!

Naomi – You are incredible. Thank you for listening to my rants about the academic system and constantly reminding me that I don't owe them my sanity. I loved attending my first conference with you and spending our evenings watching trash tv. MCGAUGH * bird noises intensify *. To a glittery future filled with drag, poolside photoshoots, good food, drinks and other shenanigans.

Samy – From colleagues, to roommates, to colleagues again. Having lived together I think we both saw a more fragile side of each other. I'm really grateful to have had you on the other side of the hall, to chat or rant or just drink wine and make summer rolls. I guess not much has changed in that regard except your office/room is so much livelier now.

Efraim – It's wild that it has been 14 years already since the inception of our revolutionary dystopian commentary on being an outcast in the workplace. Honestly, we were way ahead of our time on that one. I'm glad we continued our whisky/beer nights over the years. Thank you for all the honest conversations, accidental karaoke nights, and musical holiday/birthday wishes to look forward to each year.

Vanessa – You were truly the student I had hoped for. Our collaboration felt effortless, without hierarchy and with mutual respect and trust. We met when I was in a bit of a vulnerable state, and I want to thank you again for taking my vulnerability as a strength rather than a weakness. You will do great things, and I am proud to have been a small part of your journey. I love that we became friends after your adventure in Utrecht was over,

and can still chat about Downton Abbey, how to not have a capibara sink into a cake and other ridiculousness.

Evi-Anne – How you always manage to make things work out no matter how disorganized it appears is still a mystery to me. Thank you for your eternal optimism and kindness. I loved being paranymph with you and living out all our deranged harry potter fantasies and almost setting the university library on fire in the process (for legal reasons this is a joke). Special shout out to Markus, keep rocking those sunglasses buddy.

Arne & Gaëtan – I'm just going to combine you two, because you kind of belong together in my mind. You were both like the disgruntled older sibling I needed to ground me as a fresh-faced PhD student. Thank you for all the advice on how to science, and not let science science you. Also, the memes, the memes were great (Gaëtan my muse!). Though I could maybe have done without going through life as Monique. Anyway, I digress, I look forward to some beers or whisky in the future.

To all the (ex-) EPP'ers (Angelos, Bart, Elske, Ilse, Katharina, Kevin, Lynn, Mallissa, Marthe, Mitzy, Mathilde, Katharina, Suzanne, Sophie, Thomas, Vera) thank you for making the lab a cozier place. Special shout out everyone who at one point found themselves in the loser kamer.

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Jorge, my love, I had to rewrite my acknowledgements to you because they didn't do you justice. I don't think I would have made it through this without you. Thank you for your constant encouragement and being calm and grounded when I couldn't. You're the most thoughtful person I know, thank you for making me feel so loved.

Pap & Mam – Vroeger was mijn bijnaam altijd vogeltje, bedankt dat jullie me de ruimte hebben gegeven om ook echt te vliegen. Het was niet altijd makkelijk voor jullie om bij te benen waar ik ook alweer mee bezig was, ben ik nou een neuropsycholoog of een neurowetenschapper of toch een klinisch psycholoog, niet te volgen allemaal. Uiteindelijk is dat ook maar bijzaak, wat belangrijker is wie we zijn als persoon buiten dat alles. De kleine tradities en gebruiken van ons gezin die ik denk ik meer ben gaan waarderen nu ik helemaal buiten de context leef waar ik opgroeide. Bedankt voor alle steun tijdens dit proces al was dat soms in de vorm van afstand nemen. Na deze lange school dag hoop ik net als vroeger thuis te komen uitkijkend naar een (metaforisch) met liefde verstopt snoepje onder het kussen op de bank.

Lieve Oma, gedurende de afgelopen jaren waarin ik druk was met het bestuderen van geheugen, heb ik met pijn in mijn hele bestaan moeten toezien hoe jouw herinneringen je langzaam verlieten. Hoe instrumenteel was jij voor mij als persoon, ik weet niet of ik ooit de woorden zal vinden om je daar genoeg voor te bedanken. De kans om die over te brengen is helaas ook al gepasseerd. Ik begon dit boek met hoe geheugen en identiteit met elkaar verweven zijn, maar daar ontbreekt nog een belangrijk punt. Herinneringen zijn ook essentieel voor gedeelde identiteit. Met elke herinnering die jij niet meer herkende, voelde het alsof ik een stukje van mezelf verloor. Zo graag zou ik ze nog een keer doorspelen met jou, geen detail te klein, elk moment een juweel. De tijd die we hadden was prachtig, de tijd die nog gaat komen verlicht door de glans van de herinneringen met jou.

ABOUT THE AUTHOR

Nicole Desirée Montijn was born on June 20th, 1991, in Utrecht, the Netherlands. Nicole completed their bachelor's degree (with honors) in Psychology at Utrecht University (2009-2012) with a major in Clinical Neuropsychology and a minor in Cognitive Neuroscience. During this time Nicole also enrolled in the Von Humboldt Honors College, through which they had the opportunity to do a short research internship at de Hoogstraat rehabilitation center into learning ability after traumatic brain injury.

Based on these early research experiences, Nicole decided to shift their focus from Neuropsychology to Neuroscience and started the research master Neuroscience & Cognition at Utrecht University. Here, they completed two research internships as well as literature thesis. First, Nicole joined the lab of prof. Chris Dijkerman to study problems in body ownership and interoception following surgical resection of the right Insula. Next, Nicole decided to write their literature thesis on Mental Time Travel under the supervision of prof. Albert Postma. Not knowing at the time that this humble literature thesis would morph into a PhD thesis several years later. Finally, after having grown increasingly interested in episodic memory, Nicole joined the lab of prof. Christian Doeller at the Donders Institute in Nijmegen. Here, they conducted an fMRI study to investigate how temporal distance between episodic events is encoded.

After a brief stint as a data scientist at the Erasmus Medical Centre in Rotterdam, Nicole returned to Utrecht to pursue a PhD at the lab of prof. Iris Engelhard with initially dr. Dieuwke Sevenster as co-supervisor, and later dr. Lotte Gerritsen. During this time, Nicole also supervised several bachelor and master students with their thesis. Furthermore, Nicole set up a research visit at the lab of prof. Muireann Irish at the university of Sydney to investigate which qualitative features of an imagined event led to the greatest updating of semantic schema. Unfortunately, the visit got cancelled due to the pandemic. To compensate, Nicole was able to digitally present their work at several top-ranking labs in the field. This included the Schacter memory lab at Harvard, who inspired Nicole to study future thinking as a Master student.

Nicole currently works as an associate editor at Nature Communications, where they are able to apply their love for groundbreaking science and compelling academic writing to help other scientists give their work the platform it deserves.