How anxiety alters the perception of time: probing the neurocognitive impacts of anxiety using a translational temporal judgement task

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Declaration

I, Ioannis (Yannis) Sarigiannidis, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Anxiety, the state of anticipating that a negative event may occur, can be adaptive by promoting harm-avoidant behaviours, and thus preparing an organism to react to threats. However, it can also spiral out of control, resulting in anxiety disorders, with these being one of the most common mental health issues leading to disability. Despite decades of research, progress on treating anxiety seems to have stalled. This lack of progress has been attributed, at least in part, to the gap between animal and human research. By adopting a cognitive task and anxiety manipulation that are translational, this thesis attempts to bridge the aforementioned gap by investigating the neurocognitive effects of adaptive and pathological anxiety in humans; research that could be in turn translated into animals. Towards that goal, a temporal bisection task and a threat-of-shock manipulation were used.

The first experimental chapter (Chapter 3) showed that induced anxiety can reliably shift time perception, while fear does not, suggesting that anxiety and fear might be distinct entities. The second experimental chapter (Chapter 4) attempted to tease apart the mechanism of the aforementioned effect, by investigating whether a load manipulation shifts time perception similarly to induced anxiety. Load did not shift time perception; hence it is unclear whether anxiety leads to temporal alterations via 'overloading' limited cognitive resources. The third experimental (Chapter 5) chapter explored the neural correlates of the effect of anxiety on time perception using functional magnetic resonance imaging, employing a pilot and a pre-registered study. The findings suggested some overlap between anxiety and task related processing, leaving open the possibility that anxiety impacts cognition via commandeering finite mental resources. The (preliminary) data of the fourth experimental chapter (Chapter 6) suggested that time perception is not impaired in clinically anxious individuals, but

working memory is, highlighting potential dissociations between adaptive and pathological anxiety. In the final chapter the findings are discussed in light of neurocognitive theories of anxiety, alongside a discussion of the overall approach of the thesis and future experiments that could clarify disparate findings.

Impact statement

While anxiety and fear have been hypothesised to be distinct concepts since the time of the Danish existential philosopher Søren Kierkegaard, my studies are the first to provide supporting cognitive task data in line with this: in Chapter 3 I showed that anxiety and fear lead to different impacts on cognitive performance. This is an important finding since accurate conceptualisations of fear and anxiety are essential in order to better understand their relative contribution in mental health disorders. Seen through different lenses, the finding of Chapter 3 that anxiety (defined as the response to unpredictable threat) alters time perception but fear (defined as the response to predictable threat) does not, highlights that uncertain threat more profoundly alters cognition. Moreover, this thesis is the first to comprehensively demonstrate an impact of anxiety on time perception, and therefore opens up a whole new area of cognition important for understanding anxiety.

A major theory regarding how anxiety affects cognition is that it 'overloads' inherently limited neurocognitive resources by prioritising threat-processing, thus leaving little capacity for any other task at hand. The results from Chapters 4 & 5, albeit inconclusive, suggest that the 'overloading' of neurocognitive resources might not the only way via which anxiety alters cognition. More research on the anticipatory/arousal aspect of anxiety and how it affects cognitive performance seems to be needed to clarify which aspects of anxiety interact with cognitive processing. In addition, Chapter 5 replicated previous findings that areas such as the insula and the subgenual cingulate cortex are involved in threat anticipation and that areas such as the pre-SMA and mid-cingulate are involved in time perception.

One possibility is that pathologically anxious individuals are ‘stuck’ in an anxious state, similar to the transient one healthy individuals experience when under actual threat. However, the findings from Chapter 6 did not support this, since time perception in clinical anxiety was not shifted (under no threat) in the same way that it was shifted in healthy individuals (under threat; as found and replicated in Chapter 3). While pathologically anxious individuals performed at the same level in the time perception task, they underperformed in a working memory task. This highlights that individuals suffering from pathological anxiety might face particular difficulties with tasks that require prompt storage and manipulation of information.

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List of abbreviations

2AFC	Two-alternative forced choice
ACC	Anterior Cingulate Cortex
BDI	Beck Depression Inventory
BOLD	Blood oxygenation level-dependent
BP	Bisection Point
CBT	Cognitive Behavioural Therapy
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
FMRI	Functional Magnetic Resonance Imaging
FWE	Family-wise Error
GAD	Generalised Anxiety Disorder
MDD	Major Depressisve Disorder
MINI	Mini International Neuropsychiatric Interview
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
PD	Panic Disorder
PFC	Prefrontal Cortex
PTSD	Post-traumatic Stress Disorder
RDoC	Research Domain Criteria
ROI	Region Of Interest
rTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
STAI	State Trait Anxiety Inventory
WF	Weber's Fraction
WM	Working Memory

Note to examiners

The findings from Chapters 3 and 4 have been published in two peer-reviewed articles:

Sarigiannidis I, Grillon C, Ernst M, Roiser J, Robinson O (2020) Anxiety makes time pass quicker while fear has no effect, Cognition, 197, 104116.

Sarigiannidis I, Kirk PA, Roiser J, Robinson O (2020) Does overloading cognitive resources mimic the impact of anxiety on cognition? J Exp Psychol Learn, 46(10), 1828-1835.

The findings from Chapter 5 have been published as a pre-print

Sarigiannidis, I., Kieslich, K., Grillon, C., Ernst, M., Roiser, J. P., & Robinson, O. J. (2020). Anxiety makes time pass quicker: Neural correlates. BioRxiv, 2020.07.11.198390. https://doi.org/10.1101/2020.07.11.198390

The work reported in this thesis is entirely my own except for the contributions acknowledged below. All chapters have benefited from guidance by my supervisors, Dr Oliver Robinson and Prof Jonathan Roiser. Additionally, Drs Christian Grillon and Monique Ernst provided comments for Chapters 3 and 5.

In Chapter 3, participant screening and recruitment of Experiment 3 was conducted by research assistants of the Grillon lab.

In Chapter 4, the data collection for Experiment 3 was exclusively conducted by Peter Kirk (PhD student at UCL).

In Chapter 5, participant screening and recruitment of Experiment 1 was conducted by research assistants of the Grillon lab. Prof Karl Friston, Prof Joe Devlin and Dr Steve Fleming advised on the design of Experiment 2.

In Chapter 7, Karel Kieslich (research assistant at UCL) and Yumeya Yamamori (research assistant at UCL) assisted with screening clinically anxious individuals.

Chapter 1: General Introduction

1.1 What was and what is anxiety: a cognitive perspective

In the western world, conceptualisations of anxiety have been around since antiquity: for example, in ancient Greece it was personified as the god Deimos (ancient Greek: *Δεῖμος*, meaning dread). Fast-forwarding to the 19th century, the existential philosopher Søren Kierkegaard viewed anxiety as an integral part of the human condition (Kierkegaard, 1957); such views very much resonate with the ubiquity of anxiety in today's world. However, anxiety arguably became a cultural phenomenon after World War II, during the golden age of French existentialism and psychoanalysis, mainly due to Sartre and Freud, whose conceptualisations of anxiety were largely influenced by Kierkegaard (Freeman & Freeman, 2012). Since then, discussions of anxiety have inspired paintings that became household names (The Scream by Edvard Munch), poems (The Age of Anxiety by W.H. Auden) and more recently a plethora of self-help books and relaxation phone apps.

The word anxiety comes from the Latin *anxietas*, which has its root in the ancient Greek *ánkhō* (in Greek alphabet*: ἄγχω*); a word mainly used in ancient Greek writing to indicate physical sensations of choking, but also mental distress (*Henry George Liddell, Robert Scott, A Greek-English Lexicon, Ἄγχω*). Colloquially, anxiety is now often used interchangeably with words such as "stress", "being under pressure", "worry", in order to indicate generic mental distress, interestingly in line with how the ancient Greeks used it.

In scientific communities, terms such as anxiety and stress refer to constructs that were derived from distinct literatures and fields of studies. On the one hand, the concept of

stress was based on seminal studies by Walter Cannon (Cannon, 1915) and Hans Selye (Selye, 1936, 1950) and is often associated with neurophysiological investigations across different species involving the hypothalamic–pituitary–adrenal axis (HPA axis; (Godoy et al., 2018; McEwen & Akil, 2020)). Within this literature, salivary cortisol levels in human studies are frequently used, since they are considered a reliable biomarker of HPA reactivity (Bozovic et al., 2013). One the other hand, anxiety is a concept that was developed by existential philosophers, including Kierkegaard and Heidegger, before it was adopted by psychology and psychiatry.

Contemporary cognitive conceptualisations of anxiety can be traced back to the book 'The Concept of Anxiety' by Kierkegaard (1957). Kierkegaard distinguished between fear and anxiety, suggesting that fear is associated with specific objects, while anxiety is about the future and its object is rather indeterminate.

> "Anxiety differs from fear in that the object of anxiety is usually indeterminate"
> "Anxiety is about tomorrow"
>
> Søren Kierkegaard (1957)

Not far from such conceptualisations, neuroscientists today distinguish fear from anxiety, suggesting that they might play different roles across anxiety disorders (American Psychiatric Association et al., 2013). Specifically, fear is considered an immediate response to a specific threat that is present right now, while anxiety is defined as a prolonged state of anticipating the occurrence of a less identifiable event, with this occurrence also being less predictable (Barlow, 2002).

"Anxiety is often elicited by less specific (…) threats"

"Anxiety is a future-oriented mood state"

Davis et al. (2010)

From an evolutionary perspective, fear is thought to prepare the organism to act in a fight or flight fashion when facing threatening situations, while anxiety is a more complex mental state of anticipating negative events (Barlow, 2002); both of which promote survival. According to the Blanchards, fear induces defensive behaviours due to the (actual) presence of a predator, while anxiety is induced due to the potential presence of a predator (Blanchard et al., 1993; Blanchard et al., 1997). Regarding how fear is conceptualised in humans, there is a specific external threat that is either present or imminent, while in anxiety the threat may be less identifiable and its occurrence less predictable. Anxiety can be more internal, and more of an expectation, rather than a certainty, and can even be an imagined possibility with a very low likelihood of occurring (see also Table 1-1).

Table 1-1: Conceptual differences in fear and anxiety, based on Table 1.2 in LeDoux (2015)

	fear	anxiety
Threat is imminent and specific	yes	no
Can be evoked by cues	yes	no
Is reasonably threatening	yes	no
Has a specific onset and offset	yes	no
Leads to a fight or flight response	yes	no
Leads to sustained vigilance	no	yes

For example, let's think of a thriller in which the hero is trying to escape a haunted house. The hero is anticipating that something terrible will happen, and so they very cautiously walk down the squeaky staircase in half-light, while trying to escape. From a cognitive perspective, the hero of the film is in a state of *anxiety*. When at some point of

the film a scary creature suddenly appears (usually introduced in the scene by some loud/scary noise), the hero is screaming/trying to defend themselves i.e. demonstrating a *fear* response.

1.1.1 Operationalising fear and anxiety

In rodents, fear and anxiety have been operationalised in the Fear/Defense Test Battery (F/DTB) and the Anxiety/Defense Test Battery (A/DTB). The former quantifies defensive behaviours to approaching predators (e.g. a cat), while the later measures reactions to the potential presence of a predator (Blanchard et al., 1993; Blanchard et al., 1997). In the case of fear, the presence of the threat is certain, while in anxiety, its presence uncertain.

The most widely known investigations of fear and anxiety have been conducted using Pavlovian cued and contextual conditioning respectively. Such experiments often utilise rodents confided to a specific chamber, to which footshocks are delivered. The rodents respond to the shocks by engaging in defensive behaviour: freezing. In *Pavlovian cued* conditioning the rodent receives an electrical shock (US) after a cue (CS), such as a light. As soon as the rodent learns the association between CS and US, it exhibits defensive behaviour (freezing) at the presentation of the CS. In other words, the CS elicits a *fear* response to the rodent. In *contextual conditioning* the occurrence of the electrical shock (US) is not predicted by any cue (CS). On this occasion, the context itself becomes the CS and the rodent exhibits defensive behaviours during the whole time it stays in that chamber. In other words, the rodent experiences an *anxiety-like state* of anticipating threat. From another perspective, in cued conditioning the threat is predictable, and in contextual conditioning unpredictable.

Similarly to *cued* and *contextual* conditioning in animals, in humans fear and anxiety are operationalised as *predictable* and *unpredictable* threats respectively (Schmitz & Grillon, 2012). Specifically, fear is evoked when a cue presages a negative event (e.g. an electrical shock), while anxiety is evoked when such an event occurs unexpectedly, without any warning. In adults, electrical shocks are usually used as the negative reinforcer, while in children and adolescents aversive sounds seem effective to some extent (Schmitz et al., 2011). In both animal and human models of fear and anxiety, the concept of uncertainty is key: fear is associated with low uncertainty regarding a negative event occurring, while anxiety is associated with high uncertainty.

While fear and anxiety can be conceptually separated and are a potentially promising scientific framework for explaining anxiety disorders (American Psychiatric Association et al., 2013; Davis et al., 2010), we arguably do not experience them as distinct entities in real life. It seems impossible to experience fear without anxiety; if we are scared of something, we worry (defined as “a chain of thoughts and images” that are “negatively affect laden and relatively uncontrollable”; Borkovec et al., 1983) over potential consequences of that perceived threat. Imagine walking alone late at night in an area where a friend had been recently mugged and suddenly noticing someone speeding up his pace towards you. You would probably perceive them as a threat, triggering a fear response, while at the same time you would worry about what that person might do next. The relationship between fear and anxiety becomes further entangled when considering more abstract, social threats, such as rejection. On many occasions, we experience rejection as if it had already happened. As Roland Barthes notes: “for the lover's anxiety: it is the fear of a mourning which has already occurred, at the very origin of love. Someone would have to be able to tell me: "Don't be anxious

anymore-you've already lost him/ her."". Which echoes Michel de Montaigne: “He who fears he shall suffer, already suffers what he fears.”

However, even if fear and anxiety might seem intertwined in how we experience them, this does not exclude the possibility that they might be distinct entities. In fact, previous neuroimaging studies have shown that they rely on overlapping but distinct neural circuits (Hur et al., 2020; Tovote et al., 2015). Additionally, pharmacological analyses of defensive behaviours in rodents show that anxiety is sensitive to anxiolytic drugs, whereas fear is not (Blanchard et al, 1993), suggesting that fear and anxiety might be distinct in the neurochemical level.

Fear and anxiety are known to alter cognitive processing (i.e. information processing) by shifting attention to threatening stimuli, causing ambiguous information to be interpreted as threatening, and promoting overestimation of the probability and personal cost of negative events (Grupe & Nitschke, 2013a). Understanding how fear and anxiety might differentially impact cognition is an essential step towards treating the disorders that result from an excess of these. However, very little work has investigated this. We currently lack behavioural evidence suggesting that fear and anxiety have separable impacts on cognition, which would further support the hypothesis that they are distinct. This will be addressed in the first experimental chapter, **Chapter 3,** of this thesis.

1.1.2 The spectrum of anxiety: adaptive to maladaptive

> “The cold of anxiety is very real”
>
> Louise Bourgeois

A common theme across the existential, stress and the anxiety literatures is that anxiety can be beneficial to the organism. Kierkegaard (a rather anxious person himself)

considered anxiety essential for a successful life, claiming that "whoever is educated by anxiety is educated by possibility" (Kierkegaard, 1957). In line with this, an inverted U relationship between anxiety and cognitive performance has been proposed: there is a certain level of anxiety that leads to optimum performance, while with too little anxiety one is not motivated, and with high anxiety one's performance is impaired (Yerkes & Dodson, 1908).

Although an adaptive response that promotes harm avoidant behaviour (Blanchard et al., 2011), anxiety can become pathological. Anxiety disorders are among the most prevalent mental health problems, constituting a major public health issue (Stein & Craske, 2017). It has been estimated that one in four individuals are likely to have, or have previously had, an anxiety disorder (Kessler et al., 2005). Not only are they the most common mental health disorders in the United States (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) Europe (Wittchen et al., 2011), and the rest of the world (Steel et al., 2014); but they also are one of the leading causes of chronic disability (Vos et al., 2012). This is attributed to anxiety being highly comorbid with a number of disorders, both 'mental' (e.g. depression and substance abuse disorders; see Grant et al., 2015; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012) and 'physical' (e.g. cardiovascular disorders; Steptoe & Kivimäki, 2012).

Despite the ubiquity of anxiety disorders and the importance of alleviating their burden, their treatment represents a major challenge (Koen & Stein, 2011; LeDoux & Pine, 2016). Although cognitive behavioural therapy (CBT) seems to be effective for a wide range of anxiety disorders, its efficacy is limited to only around 50% (Loerinc et al., 2015). At the same time, pharmacotherapy has suboptimal efficacy, alongside unwanted side effects that often lead patients to discontinue treatment (Koen & Stein, 2011). In fact, progress in developing new drugs has been stagnant in anxiety (and mental health

in general) compared to other fields: this has been attributed to the complexity of the brain as well as inadequate animal models of mental disorders (Agid et al., 2007). This is in contrast to the tremendous progress we have seen in recent years on understanding basic neural mechanisms such as threat detection in animals, which are considered key in anxiety and its disorders (LeDoux & Pine, 2016). Although many drug targets are initially deemed promising in animals, they fail to show clinical efficacy over and above current standardly-prescribed medications. Such continued lack of progress has led a large part of the pharmaceutical industry to terminate or downsize research programmes into mental health disorders (Nutt & Goodwin, 2011). The slow progress in the treatment of anxiety disorders has been attributed to limitations of both animal and human models, stemming from a lack of a truly translational approach. Some possible remedies are discussed below.

1.1.3 Current approaches to studying anxiety disorders

1.1.3.1 Animal models & their limitations

Animal models are used to investigate the development of diseases, based on the assumption that there are some core features of the disease that are similar between animals and humans. At the same time, the usage of animal models comprises one of the first stages of drug development, used to verify safety and provide potential evidence of drug effectiveness (Bueters et al., 2013). Animal models provide an opportunity to investigate in depth the genetic, molecular and neural mechanisms of mental phenomena, given the availability of more invasive experiments. Such research has allowed a better understanding of gene to phenotype relationships, the

characterisation of functional neurocognitive systems, and their underlying neural basis (Kaiser & Feng, 2015; Santos et al., 2015).

However, animal models of mental disorders have been criticized for their construct validity, i.e. whether they are indeed a good analogue of the human pathologic phenomenon they represent: there are obvious differences in the human vs. animal mental experience. To some, it might seem like reducing the rich phenomenology of human mental disorders to the simple non-verbal behaviour in animals. But in fact, many animal models do not aim to model whole diseases but rather specific symptoms/components of the disorder at hand (Koob, 2012). A challenge in this particular field is "to isolate" the symptoms/components that are the most important and thus should be reflected in animal models. This might be particularly difficult in anxiety disorders, considering the wide range of different possible anxiety diagnoses, the heterogenous symptoms within specific diagnoses and the low reliability of diagnoses (Hovenkamp-Hermelink et al., 2019; Lieblich et al., 2015; Zbozinek et al., 2012).

1.1.3.2 The issue of human diagnoses

In contrast to many diseases, the diagnosis of mental disorders relies solely on subjective report rather than objectively quantifiable observations (e.g. blood tests). For example, of the six diagnostic criteria for generalized anxiety disorder (as defined in DSM-5) only one sub-criterion (sleep disturbances) can be assessed by observation; the rest rely on the individual's self-report. Without robust measurable constructs of mental pathology that are shared in animals and humans, the possibilities for true translational research seem limited. Obviously, one cannot ask a rodent to self-report, and even if they could, how would the rodent respond if not in an anthropomorphic way?

1.1.3.3 The Research Domain Criteria (RDoC) approach

Recent approaches in human psychopathology are therefore beginning to move away from symptom-based accounts of mental health and instead aim to identify common neurocognitive mechanisms that are impaired across different mental conditions. Among them, the Research Domain Criteria (RDoC) project seeks to describe mental health and illness in terms of six major domains of human functioning (Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, Arousal/Regulatory Systems, Sensorimotor Systems).

Of particular interest for anxiety are the Negative Valence Systems and the Cognitive Systems, considering that they are often implicated in pathological anxiety (Williams et al., 2016). Specifically regarding the former, anxiety seems to be associated with altered processing of acute threat, potential threat and sustained threat, (Duits et al., 2015; Grupe & Nitschke, 2013a; Robinson et al., 2019). At the same time, anxiety disorders seem to coincide with alterations to Cognitive Systems including attention, cognitive control and working memory (Bar-Haim et al., 2007; Bishop, 2007; Cisler & Koster, 2010; Eysenck et al., 2007; Moran, 2016; Robinson, Vytal, et al., 2013; Shi et al., 2019; Van Bockstaele et al., 2014).

The emphasis of the RDoC approach is on describing aspects of health and disease from multiple perspectives: from low level such as gene, molecule and cell perceptive, to high level such as circuit, physiology, behaviour and self-report (Insel et al., 2010)

1.1.4 Bridging the translational gap: Approach of this thesis

Inspired by the aforementioned framework, the aim of this thesis is to better characterise anxiety and its disorders using human experiments that have translational

potential. Emphasis is put on targeting fundamental cognitive functions that are similar across animals and humans. This would allow one to develop the appropriate treatment targets in humans, the detailed mechanisms of which can be further illuminated with invasive techniques used in animals. With such relevant targets at hand, this approach might be particularly promising for anxiety, given that unlike other psychiatric symptoms, it is theoretically tractable in the laboratory: the neurocognitive mechanisms of defence responses to threat, which are dysregulated in anxiety, seem to be largely preserved across species.

Central to my approach will be the focus on healthy human participants, in an attempt to gain insight into the spectrum of adaptive and maladaptive/ pathological anxiety. The validity of such an approach is consistent with a dimensional view on psychopathology that conceptualises mental illness as a spectrum from health to disease, assuming that the underlying mechanisms follow a similar pattern (Forsyth & Zvolensky, 2001; Insel et al., 2010; Kotov et al., 2017; Vervliet & Raes, 2013).

A key hypothesis of this approach is that anxiety disorders stem from a dysregulation or exaggeration of adaptive, evolutionarily preserved, responses to threat. This is based on studies suggesting that the same neurocognitive system that is activated in pathological anxiety is also activated in healthy individuals, albeit in a milder fashion (Costello, 1994; Garner et al., 2011, 2012; Robinson et al., 2014). Detecting normative neurocognitive mechanisms of anxiety would allow refined hypothesis to be generated regarding pathological mechanisms. A main advantage of this approach is that it attempts to bridge the gap between basic research in animal and clinical research in patients. It might be easier to assess normative neurocognitive mechanisms of anxiety in animals than create pathological animal models.

1.1.4.1 Focus on cognition

Central to this dissertation will be the usage of cognitive tasks to better understand anxiety and its disorders. I define cognition in the broad sense, encompassing any tasks that relies on "information processing". These include sensory perception, attention, decision making and executive functions among many others.

In this dissertation I will make a distinction between *hot* cognition, involving emotionally-valenced information, and *cold* cognition, involving neutral information. Although these categories are probably too simplistic and they are not considered to be dissociable or map into specialised networks of the brain (Barrett & Satpute, 2013; Damasio, 2005; Duncan & Barrett, 2007; Lindquist & Barrett, 2012; Pessoa, 2015), they might be useful as broad frameworks to discuss how anxiety alters different aspects of information processing. Specifically, while alterations in hot cognition have been extensively studied in anxiety, alterations in cold cognition have started to receive more attention in the past decade (Bar-Haim et al., 2007; Bishop, 2007, 2009; Moran, 2016; Robinson, Vytal, et al., 2013; Shi et al., 2019).

The emphasis on cognitive functions comes after a focus of the literature on translational psychophysiological markers of defence mechanisms which seem to lack specificity in humans. In particular, the well-studied fear-potentiated acoustic startle reflex (a physiological marker), although initially a promising target for fear and anxiety disorders, is actually elevated across a range of disorders including panic disorder, drug addiction and depression (Gorka et al., 2016; Gorka et al., 2013, 2015, 2017; Grillon et al., 2009, 2016; Moberg et al., 2017). Moreover, it has not shown evidence of heritability, raising serious concerns regarding its place as an endophenotype of fear and anxiety disorders (Savage et al., 2019). This might not be a problem for cognition, since

cognitive functions seem heritable to some extent. (Spengler et al., 2018; Vogler et al., 2014). It is worth noting that heritability varies greatly across different cognitive measures, although part of this is due to measurement quality.

At the same time, the cognitive aspects of anxiety are clearly important, considering the success of cognitive behavioural therapies for some anxiety disorders (Beck et al., 1961; Hofmann et al., 2012). This literature has suggested that specific mental processes might serve as risk factors in the development of anxiety disorders and has provided elaborate cognitive models (Clark, 1999; Eysenck et al., 2007; Mathews & Mackintosh, 1998). A better understanding of the involvement of such cognitive functions in anxiety might be a promising next step to treat anxiety disorders.

1.1.4.2 How anxiety affects cognition

The effects of anxiety on cognition are broad. Overall, anxiety draws attention to threat-related stimuli (Bar-Haim et al., 2007; Cisler & Koster, 2010) and impairs performance in a range of cognitive tasks, from basic sensory processing to higher cognitive functions, such as executive functions and decision making (Moran, 2016; Robinson et al., 2013; Shi et al., 2019; but see Birk et al., 2011; Robinson, Krimsky, et al., 2013). Additionally, some studies have found that anxiety can also improve cognition (Moran, 2016; Robinson, Krimsky, et al., 2013).

Studies in this literature investigate anxiety both as an acute mental state (state anxiety) and a personality trait (trait anxiety). State anxiety is often manipulated using anxiety induction techniques or measured during naturally occurring stressors. Trait anxiety is measured in individuals that have received a diagnosis of an anxiety disorder, or in healthy individuals with subclinical symptomatology. The State and Trait sub-scales of the State Trait Anxiety Inventory (STAI) is the standard method to measure the

aforementioned kinds of anxiety respectively (Spielberger, 1983), although state anxiety is often measured by questions devised by each experimenter.

The impact of anxiety on hot cognition has been well-studied (Bar-Haim et al., 2007; Cisler & Koster, 2010) and it is believed to be affected similarly by state and trait anxiety (Robinson, Krimsky, et al., 2013). Although anxiety seems to impair cold cognition including working memory (Moran, 2016), attentional control (i.e. the ability to attend to some stimuli and ignore others; Derakshan et al., 2009; Eysenck et al., 2007; Shi et al., 2019) and higher cognitive functions (Robinson, Krimsky, et al., 2013), fewer studies have been conducted on the topic and the differential impacts of state and trait anxiety on cold cognition are not clear (Robinson, Krimsky, et al., 2013). Considering the need for more research on this topic, the focus of this thesis will be on cold cognition. Different anxiety induction techniques that can be used with cold cognition tasks will be briefly reviewed in the following section.

1.1.4.3 How to induce anxiety

Early studies employed the so-called *ego-threat* anxiety induction. In these, difficult cognitive tasks themselves are used as a threat to the participants' self-esteem: individuals are typically informed that they are performing poorly in a task that most participants excel, and/or that performance is related to some aspect of intelligence. Studies employing this technique usually find impairments in task performance (Leary et al., 2009) and measures of working memory (Coy et al., 2011; Hodges & Spielberger, 1969; Moldawsky & Moldawsky, 1952). A widely used anxiety manipulation in this category is the Trier Social Stress Task, which threatens the participants' social-image. In this task, participants provide an impromptu speech while being videotaped in front of an audience of experts, and then complete a complex mental arithmetic task

(Kirschbaum et al., 1993). Classic markers of stress such as increased salivary cortisol levels and heart rate are observed after the manipulation, alongside decreased performance in working memory tasks (Oei et al., 2006; Schoofs et al., 2008). It should be noted that most of the research employing this manipulation has measured mainly physiological outcomes rather than cognitive functions (Allen et al., 2016).

Other studies have employed affective video clips to induce anxiety. In this, participants watch scenes from disturbing films. This method is frequently used because it does not require specialised equipment. However, results are often mixed, possibly due to the lack of a standardised procedure/material (Fales et al., 2010; Gray, 2001; Gray et al., 2002; Qin et al., 2009).

Another anxiety manipulation is the Cold Pressor task, in which the participant has to immerse their hand in cold water until the pain becomes unbearable. This manipulation leads to increased salivary cortisol levels and heart rate. The effect of this manipulation on cognition has not been well studied, presumably due to its short-lived effect. The Cold Pressor task seems to impair free recall and recognition performance (Schwabe & Wolf, 2010a) as well as consistently promoting habitual behaviour in humans (Schwabe & Wolf, 2009, 2010b). However its effects on decision making (Lighthall et al., 2012) and working memory (Duncko et al., 2009; Porcelli et al., 2008) have been mixed.

The threat-of-shock manipulation has been relatively recently employed to induce anxiety. In this paradigm, participants perform a task in a state of anticipating unexpected shocks that are unrelated to the task ("threat" condition), and a baseline state in which they will not receive any shocks ("safe" condition). In the threat condition, participants experience elevated anxiety, as measured by self-report and physiological markers (Davis et al., 2010). This is a translational manipulation

(imported from the animal literature; Davis et al., 2010) that has been successfully combined with a large number of cognitive tasks (for a review see Robinson, Krimsky, et al., 2013). While in the other anxiety inductions participants perform the cognitive task *after* anxiety has been induced, in threat-of-shock participants perform the task *while* anxiety is induced. This is an obvious advantage of threat-of-shock, considering that induced affect can be rather short lived (Garrett & Maddock, 2001; Gross, 1998), possibly leading to inconsistent findings in studies using the other anxiety manipulations. At the same time, it is not clear whether the effects of these other anxiety manipulations reflect anxiety, or the *recovery* from an anxiogenic event (Shackman et al., 2006).

Another advantage of the threat-of-shock manipulation is that it stems from an animal literature, and thus, it can be used as a truly translational tool to investigate anxiety (Davis et al., 2010). An anxiety manipulation that has similar translational advantages to threat-of-shock is the CO_2 challenge (Leibold et al., 2016). In this, participants inhale a low dosage of CO_2, leading to increases in blood pressure and respiration rate and disruption in cognitive processing (Matthew Garner et al., 2011, 2012). However, since it also induces panic-like symptoms, its compatibility with cognitive tasks is questioned.

Overall, the threat-of-shock manipulation seems to be a good candidate to use to investigate the impact of anxiety on cognition (Robinson, Vytal, et al., 2013), and as long as it is paired with an appropriate cognitive task (i.e. one that is translational), it can be used as a truly translational tool to investigate anxiety.

1.2 Rationale for the thesis

Considering the above review of anxiety research, I adopted the following approach, summarized in these steps:

(1) Select translational cognitive tasks that into tap anxiety-relevant components, which can be translated between humans and animals. Regarding cognitive tasks, human tasks tend to be complex and difficult to adapt to animals (e.g. those requiring multiple button presses and/or involving complex instructions). Hence, illuminating as they might be at probing anxious cognition in humans, they do not have strong translational potential. At the same time, a simple task by human standards is often not simple enough for animals: in order for them to perform the easier cognitive task, they can require weeks of persistent reward-based training. Such considerations need to be taken into account when attempting to bridge the translational gap between humans and animals in anxiety research.

At the same time, to ensure fully translational anxiety research, one would need to elicit anxiety in a laboratory setting, in a fashion that is similar between animals and humans. A number of such techniques cannot be implemented in humans for ethical reasons. For example, animal experiments on learned helplessness (Amat et al., 2006; Baratta et al., 2007; Maier & Seligman, 1976; Maier & Watkins, 2005), which have inspired a lot of theoretical and questionnaire-based studies linking uncontrollable stressors to depression/anxiety (Altshuler & Ruble, 1989; Nolen-Hoeksema et al., 1986; Williams, 2007), often put animals in near-death situations and cannot be in any way compared to human studies where participants can walk away at will (we remain grateful to ethics committees for that). At the same time, specific human-oriented concepts of anxiety such as social stress induced by the Trier Social Stress Test have no animal analogue. Translational paradigms such as threat-of-shock are a good candidate for the purpose, as explained in the previous section.

(2) After establishing that a (translational) cognitive task is affected by induced anxiety, the next step will be to try to pinpoint the exact cognitive components that

are affected. For example, a number of cognitive tasks rely on multiple cognitive components such as working memory and attention, both of which are known to be altered in anxiety (Bar-Haim et al., 2007; Cisler & Koster, 2010; Eysenck et al., 2007; Hakamata et al., 2010; Mathews et al., 1997; Moran, 2016). The contributions of attention and working memory to such cognitive tasks (or of any entangled cognitive components of interest) can be tested by either performing latent variable modelling or other kinds of computational modelling, or by specific attention/working memory manipulations.

(3) The next step will be to delineate the neural basis of the specific effect of anxiety on cognition in healthy individuals. This will allow one to further refine and test hypotheses regarding how anxiety impacts cognition from a neural perspective. At the same time, this step will serve as the starting point of work seeking to understand neural differences between adaptive and pathological/clinical anxiety.

(4) The final step will be to compare the identified neurocognitive processes in healthy individuals from the previous steps, to pathologically anxious individuals. This allows one to test hypotheses regarding adaptive and maladaptive anxiety. For example, one possibility is that in pathological anxiety, the mechanism driving adaptive responses to threat is chronically engaged and thus dysregulated, so that it is activated even in the absence of threat.

1.3 Time perception tasks to probe cognition in anxiety

1.3.1 A brief history of psychological time

The perception of time is central to cognition; and human and animal cognition seem to share similarities (Lejeune & Wearden, 2006; Wearden & Lejeune, 2008). Research on

time perception can be traced back to the early days of experimental psychology (James, 1890), and has since been studied for over a century. Contrary to the hopes of early psychophysicists, the brain does not measure time like a device from classical physics: the relationship between external magnitudes and internal representations cannot be described with simple mathematical equations (Laming, 1997). Instead, how external and internal time relate seems complex. There is not a single organ dedicated to measuring time, not even a single pathway carrying temporal information from the periphery to the brain (Vroomen & Keetels, 2010). Multiple brain cells seems to be sensitive to time and the particular mechanisms underlying the perception of time remains unclear (Harvey et al., 2020; Paton & Buonomano, 2018). While earlier psychological theories posited the existence of a single central clock ('internal clock') that accumulates temporal pulses emitted by a pacemaker (Allman et al., 2014), more recent neural theories suggest that there are multiple local clocks that can be manipulated independently (Buhusi & Meck, 2009; Buonomano et al., 2009; Karmarkar & Buonomano, 2007).

Of interest to this thesis' framework is that time perception tasks can be adapted to animals. In fact, major theories about time perception stem from animal research (Gibbon, 1977; Meck, 1983, 1996). Such tasks can be combined with recent optogenetic techniques, resulting in insight into the neurochemical basis of time perception (Soares et al., 2016). At the same time, as will be explained below, time perception is influenced by attention and threat, constructs that are both highly relevant to anxiety.

1.3.2 Factors influencing time perception: attention

Time perception is profoundly affected by attention (see also section 1.4), which is of relevance to the anxiety literature given the relationship between attention and anxiety

(Bar-Haim et al., 2007; Bishop, 2009; Cisler & Koster, 2010; Hakamata et al., 2010; Moran, 2016; Shi et al., 2019). Experiments have shown that drawing attention to a stimulus facilitates its processing and results in prolongment of apparent duration: similarly, directing cognitive resources to a timing task lengthens its perceived duration (Casini & Macar, 1997; Coull et al., 2004; Macar et al., 1994; Matthews & Meck, 2016). Additionally, time perception tasks measuring subjective duration are considered a good index of attention to a stimulus (Matthews & Meck, 2016). They can therefore be used as a probe to explore cold cognition in anxiety.

1.3.3 Factors influencing time perception: threat

Time perception is influenced by a number of cognitive factors (Eagleman, 2008; Matthews & Meck, 2016), rendering it particularly sensitive to different emotional states (Sylvie Droit-Volet & Gil, 2009; Sylvie Droit-Volet & Meck, 2007), which are known to affect non-emotional processing. From an anecdotal perceptive, time perception is implicated in threat processing. For example, individuals that have experienced traumatic or life-threatening events recall that in these moments it felt as if time slowed down (Arstila, 2012; Stetson et al., 2007). Specifically, in both animals and humans, looming stimuli, which induce defensive responses as they signal anticipated collision with an approaching object (Ball & Tronick, 1971; Regan & Beverley, 1978; Schiff et al., 1962; Vagnoni et al., 2012), have been found to lead to temporal distortions. It is noted that looming stimuli in rodents look like shadows of predators (e.g. birds), hence why they are particularly anxiogenic. One study found that humans judged animated looming disks to last longer compared to receding ones (van Wassenhove et al., 2008). Such looming-receding differences were also found in the auditory/audio-visual domain (Grassi & Darwin, 2006; Grassi & Pavan, 2012) in humans. Importantly, such effects seem to be abolished when the object's trajectory

does not imply observer-collision, highlighting that temporal distortions are closely linked to perceived threat (Ono & Kitazawa, 2010).

Many studies have explored temporal distortions due to threatening stimuli. This line of research is exemplified by the work of Droit-Volet et al. (2004), which showed that the duration of threatening (angry) faces was overestimated compared to neutral ones; a finding also replicated in children as young as 3 years old (Gil et al., 2007). This effect has also been replicated with fearful faces (Sylvie Droit-Volet & Gil, 2009; Tipples, 2008, 2011), threatening images above and below conscious awareness (Grommet et al., 2011; Yamada & Kawabe, 2011) sounds (Mella et al., 2011; Noulhiane et al., 2007) and predictable, fear-inducing electrical shocks (Fayolle et al., 2015). Interestingly, such effects cannot be attributed to the physical properties of the pictures (i.e. to low level confounds): similar overestimation effects can be observed when a neutral stimulus is associated with a threatening one (i.e. due to associative learnning; Kliegl et al., 2015), echoing the finding that defence responses can be elicited by conditioned learning. Additionally, temporal distortions seem to depend on the level of perceived threat: Tipples (2011) found that the temporal overestimation of fearful and threatening faces (compared to neutral) depended on individual differences in fearfulness (see also Bar-Haim et al., 2007).

1.3.4 Overview of time perception tasks

Having established the relevance of time perception for anxiety research, the following section will review the main types of time perception tasks. Over the years different time perception estimation methods have been developed. These are primarily divided in two categories: those that require *retrospective* temporal judgments and those that require *prospective* judgments (Block et al., 2010; Grondin, 2019; Zakay, 1993).

In retrospective tasks, participants are not aware that they will be asked to provide temporal estimates of a particular task or activity. These paradigms tend not to be that popular since they are single trial tasks. Conversely, in prospective tasks participants are aware that they have to time the duration of temporal intervals.

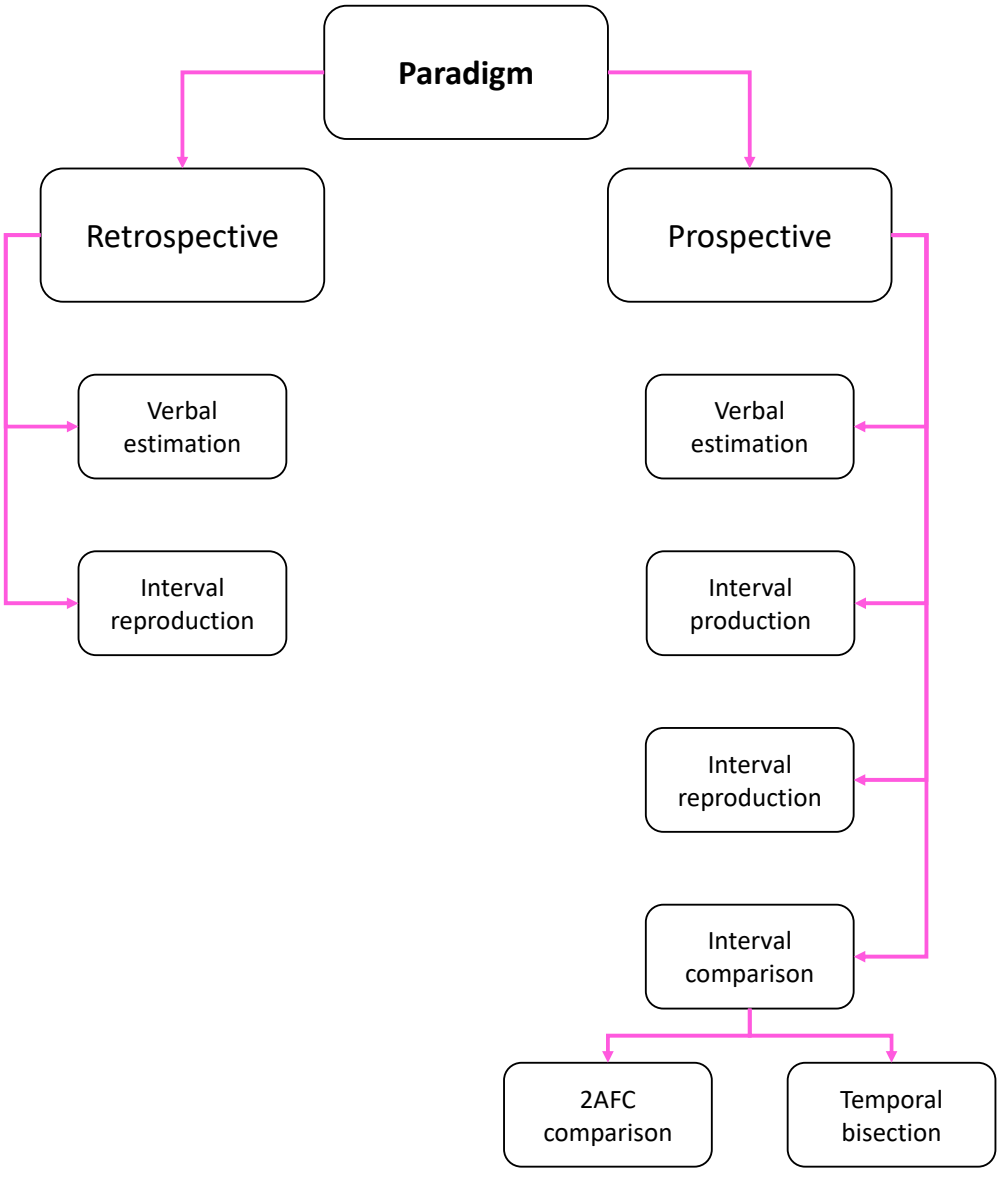


Figure 1-1: Synopsis of different methods used to investigate time perception. See text for the description of each task. (2AFC=Two-alternative forced choice)

Based on the specific method of temporal estimation, tasks are divided into four categories (Grondin, 2019). In *verbal estimation*, participants observe temporal intervals

and then provide an estimate of their duration in chronometric units (seconds or minutes). In *production* tasks, participants have to produce temporal intervals, as indicated by the experimenter, in chronometric units: e.g. participants told to produce 3s are then required to make button presses (usually one to indicate the beginning and one to indicate the end) in order to mark this temporal interval. The difference between *production* and *reproduction* tasks is that, in the latter, participants have to observe the temporal interval they need to reproduce - i.e. they are shown a continuous stimulus or two signals delimiting the beginning and the end of the interval to reproduce. It is noted that *verbal estimation* and *interval reproduction* are the only tasks used with retrospective paradigms, while in prospective paradigms all of these tasks have been used.

The fourth category of tasks involve *interval comparisons*. These are particularly interesting since they are closer to some traditional methods used in psychophysics. Tasks that are based on two-alternative forced choice comparisons require participants to make a judgement about the duration of two intervals presented in succession (i.e. which was shorter or longer). There is also another sub-category of tasks, in which comparisons occur with an implicit baseline, usually presented at the beginning of the experiment. In these *temporal bisection tasks*, participants view two anchor durations, a "short" and a "long". Then, they view single stimuli and are asked to identify whether this stimulus was more similar to the "short" or the "long" anchor. Temporal bisection tasks seem to be preferred in recent investigations of timing in animals and humans (Soares et al., 2016; Terhune et al., 2016; Zhang et al., 2016) given their simplicity and the fact that some of their properties are known, at least in humans (Kopec & Brody, 2010). Based on these, the focus on this thesis will be on temporal bisection tasks.

This last category of tasks has been extensively used in animals, rendering them particularly promising for translational research. Such experiments typically involve more invasive methods, including pharmacological agents (Meck, 1983; Santi et al., 2001), lesions (Breukelaar & Dalrymple-Alford, 1999; Meck et al., 1984) and optogenetic manipulations (Soares et al., 2016). It should be noted that interval comparison tasks in animals differ to the human ones in that they have to be paired with a reinforcer (food). However, this is not a limitation specific to this category of tasks, since a very large number of animal tasks implements reinforcers such as food.

1.3.5 Section synopsis and relevance to Chapter 3

Taken together, the evidence discussed above suggests that time perception tasks could serve as a useful probe to better understand cognitive alterations in anxiety. While threatening stimuli might lead to increased attentional engagement and thus prolongment of their perceived duration, it is likely that the uncertain presence of threat might disrupt attentional engagement with the stimuli, leading to the opposite effect. In other words, while some studies can be interpreted to suggest that fear leads to time overestimation, anxiety might lead to the opposite effect. This is a particularly interesting question for the time perception literature and anxiety research: fear and anxiety have not been shown to lead to different effects at the behavioural level, leading to questions on whether they are distinct entities. These questions will be addressed in **Chapter 3**, in which a timing task will be combined with an anxiety (threat-of-shock) and a fear manipulation.

1.4 Which aspect of anxiety is affecting cognition?

Anxiety can affect cognition due to anxious apprehension/worrisome thoughts and due to anticipating/monitoring negative events. Clarifying which process is leading to

cognitive impairments is important in order to remediate its deleterious effects. Similarly, threat-of-shock can affect laboratory tasks of time perception via at least two possible mechanisms: 1) Dual-task effects, since participants will be performing the task while worrying about when the next shock will be delivered; their thoughts occupying cognitive resources as if they were performing another cognitive task 2) Anticipation, since participants will be expecting another event to occur (a shock) while performing the timing task. It is noted that these mechanisms might not be distinct, but they are reviewed separately below since they have been studied by different strands of the time perception literature.

1.4.1 Dual task effects in temporal perception

According to the attentional control theory, the most influential theory of how anxiety impacts cognition, anxiety causes attention to be allocated to monitoring threat and preparing harm-avoidant behaviours, thus reducing attentional focus on the current task (Eysenck et al., 2007). In other words, anxiety can be seen as a kind of secondary task while participants are performing a main cognitive task. Worry (or anxious apprehension) is considered to be the specific component of anxiety that leads to impaired performance, although results are not entirely clear (Moran, 2016). As expected, worry is more often observed in high trait anxiety individuals (Eysenck, 1992). Worrisome thoughts are considered to consume limited attentional resources, thus leaving little available for concurrent task processing. For example, in one study participants were asked to worry about a negative topic while performing a random number generation task. It was found that individuals who tend to worry more performed worse on the task. (Hayes et al., 2008).

While this interference mechanism is central to explaining cognitive impairments under anxiety, few studies have experimentally tested it. One would expect that the amount of time participants spend worrying vs. focusing on a particular task would predict their performance. Studies on task performance and subjective experience have investigated how task-related and unrelated thoughts affect performance. This has been achieved via sampling thought probes, i.e. asking participants to describe what was on their mind during specific moments of the task. In one of these studies, it was found that individuals who reported thoughts akin to worry (appraisals of the self/task) consistently made more errors of commission in a sustained attention task (Smallwood et al., 2004). Similar results were obtained in Grillon et al. (2017), where participants performed a sustained attention task under a threat-of-shock anxiety manipulation. The authors found that the more the threat-related thoughts of the individuals, the worse their performance was (lower no-go accuracy). Although these studies provide evidence that increased worry/anxious appraisal is related to impaired cognitive performance, they have not shown that this is because cognitive resources are taken away from processing. In fact, participants report similar levels of task-related thoughts both under induced anxiety and during the baseline condition (Grillon et al., 2017; Grillon, Robinson, et al., 2016), rendering results inconclusive.

A number of studies have investigated how time perception is altered when attention is divided between a timing task and a secondary task. A seminal study in the field is by Brown (1997), in which participants had to produce 2 or 5 second intervals at a steady rate throughout a 2-minute trial, while also performing a secondary cognitive task. The secondary tasks included visual search and mental calculation paradigms and came in both easy and hard versions. Temporal productions became more variable and longer when they were combined with the secondary tasks, and this effect was more

pronounced when the difficulty of the secondary task increased. The findings of this study have been further replicated with a range of different secondary cognitive tasks (Grondin, 2010).

These results show that when performing a secondary task while keeping track of time, time seems to be *shortening*. This might seem counterintuitive, since under the dual task scenario participants' responses were actually *longer*. This possibly confusing aspect of temporal production tasks will be explained with the following example. Let us assume the situation in which someone has perfect time perception and every 2 seconds exactly they hit a button to indicate the passage of 2 seconds. In line with the aforementioned results, while doing a secondary task, they will hit the button every 3 seconds to indicate the passage of 2 seconds i.e. providing *longer* estimates. This suggests that the participant has lost temporal information, and thus it takes them longer to reach the criterion of what they perceive as 2 seconds. These three seconds, have seemed *shorter* to them, hence we refer to this as the *shortening* of time. This is well-known in the time perception literature, supported by findings that temporal production tasks provide opposite results to temporal reproduction ones (Pouthas & Perbal, 2004; Sgouramani & Vatakis, 2014; Zakay, 1993).

Additionally, a meta-analysis of 117 experiments in which secondary tasks were performed simultaneously to temporal tasks found that higher cognitive load led to temporal judgments that were shorter and more variable (Block et al., 2010). This effect was stronger for temporal production tasks, such as the ones used by Brown (1997), but it also generalized to verbal estimation and temporal reproduction tasks.

Such effects of secondary tasks on time perception are typically explained within an attentional allocation framework. The hypothesis is that individuals direct limited

attentional resources towards either “temporal” or “non-temporal” information: directing attention away from time, results in less temporal information being accumulated, leading to shorter and more variable temporal estimates (Michon, 1972; Thomas & Weaver, 1975). It has been suggested that this allocating of attentional resources can be under voluntary control. Two studies have shown that the percentage of attention participants are asked to devote to either temporal or non-temporal aspects of the task influences temporal judgements parametrically (Coull et al., 2004; Macar et al., 1994). Similarly, in an experiment where participants had to report both the luminance and the duration of a light, they tended to underestimate its duration when asked to focus more on the luminance discrimination task (Casini & Macar, 1997).

1.4.2 Anticipation effects in temporal perception

Other studies have investigated how time perception is affected while another event is occurring at the same time. In one of these, participants viewed to-be-timed stimuli whose luminance increased at different points of its presentation (Casini & Macar, 1997). In this task, participants were then asked to estimate the duration of the stimuli and report the magnitude of the luminance change. When the luminance increase happened later in the presentation, the subjective duration of the to-be-timed stimuli decreased. It has been suggested that this effect occurs because participants are diverting some attentional resources away from the timing task to monitor the luminance change: the later the luminance change occurs, the more cognitive resources participants would have spent monitoring for luminance change and thus the shorter the subjective duration of the to-be-timed-stimuli. This *location* effect has been replicated (Claudette Fortin, 1999; Rousseau et al., 1984). At the same time, there are also some studies suggesting that this effect can be observed even when there are no explicit

requirements to monitor the second co-occurring event, although results are mixed (Champagne & Fortin, 2008; Gaudreault et al., 2010; Macar, 2002).

It has been shown that anticipation can disrupt timing, even when there is not a separate secondary event co-occurring. Such studies simply inserted a break during the stimulus presentation. For example, Fortin & Massé, (2000) found that participants' subjective perception of time was shorter when the break occurred later during the stimuli presentation. Similarly to dual task scenarios, the authors attributed this effect to limited attentional resources: participants are dedicating resources in order to monitor for the stimulus break, and thus the later the break occurs the more temporal information is lost, leading to shortening of subjective time. Further experiments showed that such effects were larger when participants were told that a break would occur but it actually never did. Additionally, signalling to participants that there will not be a break in the following trial decreased the effect, suggesting that when participants are not monitoring for an interruption, they direct their cognitive resources exclusively to monitoring the passing of time. Such break expectancy effects have been widely replicated in humans (Claudette Fortin et al., 2009; Claudette Fortin & Tremblay, 2006; Tremblay & Fortin, 2003) and animals (Buhusi & Meck, 2009).

1.4.3 Section synopsis and relevance to Chapter 4

These studies suggest that a secondary task (either via a dual-task or an anticipation effect) can lead to temporal information being lost, which is manifested as shortening of perceived time. Considering that anxiety can serve as such a secondary task (i.e., processing the anxiety constitutes a 'task'), these studies can be a starting point to better elucidate how anxiety affects cognition: is it the dual-task aspect of anxiety (i.e. anxious apprehension/worry) that alters temporal cognition, or is it the state of

anticipating/monitoring for negative outcomes? This question will be explored in **Chapter 4**.

1.5 Neural aspects of anxiety

Combining neural and behavioural evidence might be particularly powerful in terms of helping us understand how anxiety affects individuals, and understand the phenomenon from a different level of biology. Hence, key neuroimaging studies that are focusing on anxiety will be briefly reviewed below, followed by the aim of this corresponding chapter of this thesis, which is to test neural hypotheses derived from a cognitive theory of anxiety.

1.5.1 Neuroimaging studies of anxious cognition

Early neural models posited that anxiety results from a hyper-responsive threat-detection system with amygdala at its core (Mathews et al., 1997). The importance of prefrontal areas in the allocation of attention was later recognised and influenced neurocognitive conceptualisations of anxiety (Bishop et al., 2004; Ohman, 2005). Recent connectivity studies have revealed the importance of the interplay between prefrontal areas and the amygdala in anxiety: in a series of studies, Robinson and colleagues suggested that the dorsomedial prefrontal cortex/anterior cingulate cortex (dmPFC/ACC) and the amygdala constitute a circuit that is associated with increased threat processing under anxiety (Robinson et al., 2012; Robinson et al., 2013; Vytal et al., 2014). In one of these studies which employed threat-of-shock to induce anxiety in healthy individuals, increased attentional bias to fearful faces was associated with increased functional connectivity between the dmPFC/ACC and amygdala (Robinson et al., 2012). In other words, it was shown that attributing more cognitive resources to threat detection was associated with greater prefrontal-amygdala connectivity. Other

studies that employed a similar anxiety-induction technique also showed that the dorsolateral prefrontal cortex (dlPFC) and frontoparietal areas are associated with the effects of anxiety on cognition (Balderston, Hsiung, et al., 2017a; Balderston, Vytal, et al., 2017; Torrisi et al., 2016a).

The role of the dlPFC in anxiety has been highlighted, by showing that its activity is negatively correlated with self-reported anxiety, and physiological markers of anxiety (Balderston, Liu, et al., 2017). These results can be explained using classical neural models of anxiety: a hyper-active threat-detection circuit dampens down prefrontal inputs, leading to increased anxiety. Consequently, one would expect that increasing prefrontal activity would result in lower anxiety. However, in a further experiment, the authors found the opposite results: repetitive transcranial magnetic stimulation (rTMS) to the dlPFC, which is expected to increase dlPFC activity, led to increased physiological anxiety (Balderston, Beydler, Roberts, et al., 2020). In another study, the same authors showed that inhibitory rTMS to the intraparietal sulcus (IPS) led to decreased physiological anxiety (Balderston, Beydler, Goodwin, et al., 2020). It should be noted however, that no effects were observed on self-reported anxiety. These studies paint a rather complex picture regarding the neural basis of anxiety, suggesting that there are multiple brain areas involved, with different possible roles.

1.5.2 Section synopsis and relevance to Chapter 5

Neuroimaging studies illustrate that while the prefrontal cortex and the amygdalae are important in anxiety, different brain areas and neural circuits are correlated with anxiety-related task impairments, depending on the particular tasks that are being used. This is in line with dual-task studies which show that there is no single dual-task area in the brain that correlates with dual-task interference, but rather, task-dependent brain

areas that complete for limited neurocognitive resources (Maillet et al., 2019; Nijboer et al., 2014; Watanabe & Funahashi, 2018). While task-related and threat-related information are considered to interact to determine task performance under anxiety, the underlying mechanism is not clear. In an attempt to better understand the contribution of task- and anxiety-related processing in determining cognitive performance, an fMRI study using a time perception task under threat-of-shock was conducted (**Chapter 5**).

1.6 How does adaptive and pathological anxiety impact cognition?

So far, only the effect of induced anxiety on neurocognitive functions has been discussed. Whether such an adaptive response to an anxiety induction impacts cognition differently in pathological anxiety disorders is a central question with important implications for the treatment of anxiety disorders and will be reviewed below.

1.6.1 Cognitive impairments in pathological anxiety

Clinically oriented theories posit that pre-existing individual differences in cognitive functioning may constitute risk factors, which in combination with environmental stress, predispose individuals for later anxious symptomatology (Mathews & MacLeod, 2005; Ouimet et al., 2009). Individual differences in working memory (Moran, 2016), attentional control (Eysenck et al., 2007; Shi et al., 2019), and attentional biases (Cisler & Koster, 2010) are often considered causal in the aetiology of anxiety disorders.

However, it has also been suggested that the relationship between anxiety and cognitive impairments is more cyclical that was previously thought. In the case of working memory, individual differences may increase the likelihood of later anxiety, which could then interfere with working memory (Moran, 2016). This is based on the idea that anxious apprehension (worry) and working memory are bidirectionally affecting each

other. There is some experimental evidence suggesting this: specifically, it has been found that engaging in a highly demanding cognitive task under a threat-of-shock anxiety manipulation, leads to decreased physiological anxiety (as measured by startle reflex: Balderston et al., 2016; Balderston, Vytal, et al., 2017), compared to the usual effects of threat-of-shock on physiological anxiety (without engaging in a demanding cognitive task) . Similar proposals have been put forward regarding attentional biases, considering evidence suggesting that the relation between anxiety and attentional bias is bidirectional (Van Bockstaele et al., 2014).

At the same time, there are very few studies directly comparing how adaptive and pathological anxiety affect cognition, rendering it difficult to disentangle risk factors from symptoms. Hence, comparisons between studies on adaptive and pathological studies will be drawn below.

1.6.2 Cognition in pathological vs. adaptive anxiety during threatening/stressful situations

It is generally assumed that cognitive functioning will be more impaired in clinically anxious individuals compared to healthy individuals when both are in threatening/stressful situations. High trait anxiety, which is a hallmark of pathological anxiety, is believed to interact with state anxiety, the situational kind of anxiety, affecting cognitive performance in a nonlinear manner (Easterbrook, 1959; Eysenck, 1992; Eysenck et al., 2007; Yerkes & Dodson, 1908). However, the specific relationship between trait and state anxiety seems to be rather complex, and the scarcity of available studies renders any conclusions tentative.

Older studies have produced mixed results. One found no interaction between trait anxiety and an ego-threat manipulation on a digit span task (Hodges & Durham, 1972),

while another found a significant interaction but only in the control (no threat) condition (Walker & Spence, 1964). Another study suggested that an anxiety induction led to impaired complex span performance only for the high trait anxious group. However, under the control condition, high trait anxious individuals overperformed (Sorg & Whitney, 1992).

A more recent study has investigated how an anxiety induction (threat-of-shock) impacts performance in a working memory task for high and low trait individuals. High trait anxious individuals reported greater overall anxiety during the task, and increased physiological anxiety (measured by startle reflex) when task difficulty was high. However, trait anxiety did not mediate the relationship between induced anxiety and working memory performance (Patel et al., 2017). Additionally, a meta-analysis found that trait anxiety did not interact with the severity of state anxiety in impairing performance on cognitive tasks (Shi et al., 2019).

One possibility for these mixed findings is that additional (sometimes uncontrolled-for) factors interact with state and trait anxiety in determining cognitive performance; for example, age with trait anxiety (Shi et al., 2019). At the same time, high trait and state anxiety on a number of occasions seem to be associated with better performance on cognitive tasks, where some of these effects are mediated by cultural differences, rendering the picture more complex (Moran, 2016).

Focusing on cold cognition, I will briefly review below studies in adaptive and pathological anxiety. The emphasis will be on cognitive tasks that are well-established in the anxiety literature and engage attentional resources, either requiring a storage component (i.e. temporarily storing information in working memory) or not.

1.6.3 Adaptive and pathological anxiety effects on tasks that require a storage component

The link between anxiety and working memory impairments is becoming increasingly well-established (Moran, 2016). Pyke & Agnew (1963) conducted one of the earliest studies using a threat-of-shock manipulation on a digit span task. They found that in the anxiety condition participants performed worse. A more recent study found similar performance impairments under induced anxiety in a spatial 3-back task but not a phonological one (Shackman et al., 2006). Importantly, these results on the spatial task were also obtained in a modified threat-of-shock manipulation, when shocks were not actually delivered, suggesting that the effect was not related to receiving electrical shocks (Lavric et al., 2003). Vytal and collaborators further elaborated on such findings using 1-, 2-, and 3-back task versions. They found impaired performance under threat on all levels of difficulty of the spatial n-back task. Interestingly, they also found impaired performance in the 1- and 2-back but not the 3-back phonological task (Vytal et al., 2012, 2013).

Pathological anxiety is increasingly associated with impairments in working memory in the absence of threat, as evidenced by studies on the topic (Darke, 1988; Moran, 2016; Ouimet et al., 2009). A recent meta-analysis suggested that pathological anxiety impairs performance on a variety working memory tasks (phonological and spatial), and this effect seems to hold for different levels of symptom severity (Moran, 2016).

Taken together, these results suggest that adaptive anxiety (i.e. anxiety induced in healthy individuals under a threat-of-shock manipulation) seems to impair working memory similarly to pathological anxiety, even in the absence of threat.

1.6.4 Adaptive and pathological anxiety effects on tasks that do not require a storage component

Pathologically anxious individuals typically underperform on tasks that rely on attentional process and don't require a storage component. These tasks involve the Stroop task, the go/no-go task and the anti-saccade task, among others (Shi et al., 2019). Adaptive anxiety seems to inconsistently affect performance in such tasks. Depending on the study, combining the Stroop task with a threat-of-shock manipulation has yielded no effects (Tecce & Happ, 1964), impaired performance (Choi et al., 2012; Pallak et al., 1975), or improved performance (Hu et al., 2012). Although some of these inconsistencies could be attributed to experimental differences with regards to older non-computerised studies, (Pallak et al., 1975), even recent studies yielded mixed results. While threat-of-shock impaired performance on incongruent trials of a modified Stroop task (Choi et al., 2012) a study conducted by the same group showed improved performance on the classic Stroop (Hu et al., 2012). Results inconsistent with the pathological anxiety literature were also obtained when combining threat-of-shock manipulations with anti-saccade (Cornwell et al., 2012) and go/no-go tasks, which actually led to improved performance (Robinson, Krimsky, et al., 2013; Torrisi et al., 2016).

As mentioned, pathological anxiety (without induced anxiety) negatively impacts performance in this category of tasks. Regarding the Stroop task, impaired performance has been observed in anxiety disorders (Lagarde et al., 2010; Litz et al., 1996). A number of studies have shown that performance on the anti-saccade task is worse in individuals with increased anxious symptomatology (Derakshan et al., 2009; Garner et al., 2009).

1.6.5 Is pathological anxiety a case of adaptive anxiety that never goes away?

In adaptive anxiety, cognitive impairments are attributed to threat-related processing that is competing for attentional resources. This is believed to have provided evolutionary advantages, in the sense that under actual threat, it is possibly dangerous to maintain high attentional control to specific locations or objects. Instead, the best strategy to detect threat is to allocate attention widely, taking away cognitive resources from any ongoing task.

Similar cognitive impairments are observed in pathological anxiety. In one study, increased anxious symptomatology in healthy individuals was associated with decreased prefrontal engagement over threat-related distractors while performing a cognitive task (Bishop et al., 2004). However, in pathological anxiety, such impairments are often present even when there are no threat-related stimuli present (Eysenck et al., 2007). Following up on their previous work, Bishop and colleagues showed that such impoverished prefrontal control of attention is present in individuals with high anxious symptomatology, even in the absence of threat (Bishop, 2009).

In a series of neuroimaging studies, Robinson and colleagues found that a dmPFC/ACC –amygdala circuit was recruited not only under induced (threat-of-shock) anxiety in healthy individuals, but also in pathological anxiety in the absence of threat (Robinson et al., 2014). In these studies participants performed a simple emotion identification task (fear vs happy faces). The authors further suggested that in pathological anxiety the neural circuit might be "stuck" in an anxious state, similar to the transient kind that is observed in healthy individuals under induced anxiety (Robinson et al., 2014; Robinson et al., 2013).

While this is believed to be true for "hot" cognition (i.e. cognition that involves emotionally-valenced information, including attentional biases to threat; see also Shi et al., 2019), the evidence for "cold" cognition (involving emotionally neutral information) seems mixed (Robinson et al., 2013) and thus will be the focus of **Chapter 6**.

1.6.6 Section synopsis and relevance to Chapter 6

While both adaptive and pathological anxiety seem to impair attentional control tasks that involve a storage component, the picture is less clear for tasks that do not involve a storage component. Time perception tasks are a good candidate to clarify the latter, a question that will be explored in **Chapter 6**.

1.7 Thesis aims and summary of chapters

The aim of this dissertation is to contribute towards an understanding of the neurocognitive processes that are altered in adaptive and pathological anxiety. While there is some consensus regarding hot cognition, cold cognition findings are mixed. The latter might be particularly important to investigate since they might be risk factors in the development of pathological anxiety. From the studies discussed in the introduction, it seems that the threat-of-shock manipulations alongside time perception tasks might be particularly useful in probing such mechanisms.

1.7.1 Chapter 3: The impact of fear and anxiety on temporal cognition

Chapter 3 will investigate how anxiety and fear might differentially affect cold cognition and, specifically, the subjective perception of time. Anxiety and fear manipulations will be combined with a temporal bisection task to elucidate the long-hypothesised dissociation between fear and anxiety. The main findings of Chapter 3 are

replicated two times and across different populations (UK and USA), in line with recent efforts to establish reproducibility in psychological research.

1.7.2 Chapter 4: Does overloading cognitive resources mimic the impact of anxiety on temporal cognition?

Chapter 4 will attempt to elucidate the mechanism(s) by which anxiety affects cold cognition, focusing on time perception. It is possible that when anxious, individuals' cognitive resources are overloaded by worrisome thoughts, impairing their performance on the current tasks they are performing. How induced (threat-of-shock) anxiety impaired cognitive performance in the temporal bisection task of Chapter 3 will be used as a model. If, under threat-of-shock, participants are worrying about the upcoming unpredictable shock, which is (over)loading limited cognitive resources, and thus interfering with their performance on the task, one would expect the same cognitive performance impairments to be observed under cognitive load. Hence, in this chapter I will present experiments in which participants perform the same temporal bisection task under different levels of cognitive load.

1.7.3 Chapter 5: The neural correlates of how anxiety makes time pass quicker

The relative contributions of task-related and anxiety-related neural processing in determining cognitive performance will be explored in Chapter 5. The attentional control theory (Eysenck et al., 2007) posits that anxiety is using attentional resources at the expense of task-processing, a hypothesis that can be further tested with neuroimaging. An adapted version of the temporal bisection task of Chapters 3 and 4 will be used, combined with threat-of-shock. Two fMRI studies will be reported, with the first serving as a pilot in order to determine relevant regions of interest.

1.7.4 Chapter 6: Does pathological anxiety alter cold cognition similarly to induced anxiety in healthy individuals?

Finally, Chapter 6 will investigate the hypothesis of whether in pathological anxiety the cognitive system is "stuck" in a state of anxiety, like in adaptive (threat-of-shock induced) anxiety, and thus leading to similar impairments in cold cognition. Specifically, it will be tested whether the cognitive alterations in time perception produced by threat-of-shock are reproduced in pathologically anxious individuals under no threat.

Chapter 2: Experimental Methods

This chapter will introduce the common methodological approaches that were used in the experimental chapters that follow.

2.1 Self-report mood and anxiety questionnaires

For each study of this thesis participants completed self-report measures of state-trait anxiety (State Trait Anxiety Inventory: STAI; Spielberger, 1983) and depression (Beck Depression Inventory: BDI; (Beck & Steer, 1987). These questionnaires were employed in all chapters, with the exception of Chapter 4, in which no anxiety manipulation was utilised. Additionally, in Chapter 6, the STAI and BDI were used to investigate how individual differences in depression and anxiety might explain performance in cognitive tasks.

The STAI questions are divided into two groups: those measuring state anxiety (how participants are feeling "right now, at this moment") and trait anxiety (participants' propensity to experience anxiety in general) which is considered a stable personality trait. Possible scores in both sections range from 20 (low anxiety) to 80 (high anxiety). Regarding trait anxiety, the healthy population generally scores in the range of 20 and 50 (Knight et al., 1983) while scores above 50 may indicate clinically relevant anxiety (Julian, 2011). The BDI assesses depressive symptoms. Participants respond to 21 questions regarding how they have been feeling over the *past two weeks*, and their scores can range from 0 to 63. Scores above 15 are considered clinically relevant (Sprinkle et al., 2002).

2.2 Shock calibration

In Chapters 3 and 5, participants received electrical shocks to their wrist during cognitive testing. Prior to testing, a shock calibration procedure was followed in order to control for shock tolerance and skin resistance. Single shocks or trains of shocks of different durations (the duration of the calibration shocks was identical to the shocks used in the experimental paradigm) were delivered to the non-dominant wrist via a pair of silver chloride electrodes using a DS5 or DS7 stimulator (Digitimer Ltd, Welwyn Garden City, UK). It is noted that

Participants received shocks sequentially with step increases in amplitude (starting with a low intensity and moving up), which they had to rate using a scale from 1 to 10 (1 meaning "I barely felt it" and 10 meaning "the shock is approaching the maximum level I can tolerate"). As soon as participants rated a shock as 10, the procedure was restarted, using the intensity participants rated as 3. After this, the procedure was repeated one more time (three in total) starting with the intensity participants rated as 3 in the previous run. For each participant I used the intensity they rated as 8 on the final run, throughout the experiment.

2.3 Time perception task

The main cognitive task used in all chapters of this thesis is a visual temporal bisection task (see Chapter 1, section 1.3 for general information regarding this category of temporal cognition tasks). This task has been combined primarily with an anxiety manipulation (threat-of-shock; Chapters 3 & 5) but also with a fear manipulation (Chapter 3), which will be described below. Chapter 2 utilised the same temporal bisection task under cognitive load, while in Chapter 6 clinically anxious and healthy control participants performed the task as is, with no manipulation (see Figure 6-3).

2.3.1 Temporal perception under anxiety

In Chapters 3 & 5, participants completed the visual temporal bisection task under two alternating conditions: “threat-of-shock” (labelled “threat”), during which they could receive shocks at any time and without warning, and “safe” during which they could not receive any shocks (the order was counterbalanced). The task screen was flanked by coloured borders that indicated the condition (safe or threat), taken from a pool of four colours (red, blue, green, magenta), which was counterbalanced across participants.

A short training phase preceded the main task. It consisted of presenting participants with two anchor durations, a “short” duration and a “long” duration, corresponding to the shortest and the longest duration presented in the main task. Each anchor was presented three times, and presentation order was pseudorandomised. In addition, before the beginning of each block (safe or threat) the anchor durations were repeated.

On each trial, the to-be-timed stimuli were emotional facial expressions (happy, fearful and neutral; Tottenham et al., 2009) whose durations varied according to a predetermined range (300–700ms or 1,400–2,600ms depending on the study). Stimulus durations were pseudorandomised, and presented equally often in each threat and safe block to avoid potential biases (Wearden & Ferrara, 1996). On each trial participants were required to make a choice: press “short” if the duration of the stimulus was judged to be similar to the “short” anchor, or press “long” if the duration of the stimulus was judged to be similar to the “long” anchor (left and right buttons for these options were counterbalanced across participants). After the 1.5 sec response limit, there was a variable inter-trial interval (ITI: three possibilities different for each experiment (see below), pseudo-randomised). Following each block, participants rated their anxiety levels using a continuous visual analogue scale.

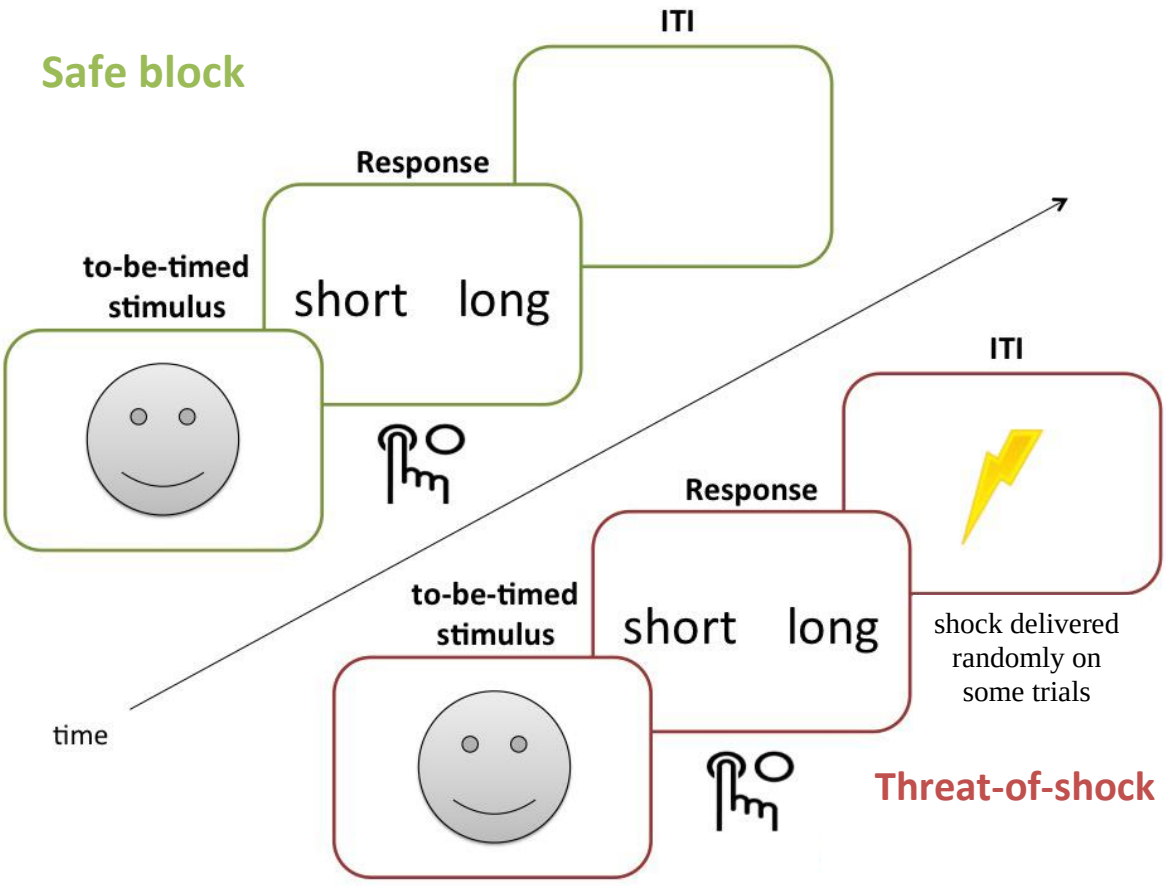


Figure 2-1: Temporal perception under anxiety: task design. Participants made time judgements during safe and threat-of-shock blocks. Note: in the actual experiment participants were presented with images from the NimStim Face Stimulus Set (happy neutral and fearful); smiley faces are presented here to avoid infringement of copyright.

2.3.2 Temporal perception under fear

The same visual temporal bisection task as above, but modified to include a fear manipulation was also used in Chapter 3. Task changes under the fear manipulation are described below.

In this task the colour of to-be-timed stimuli indicated whether participants would receive a shock ("shock" trials) or not ("no shock" trials). During "shock" trials participants always received a shock and during "no shock" trials they never received a shock. The shock was delivered as soon as the stimuli disappeared. The order of the "shock" and "no-shock" trials was counterbalanced on each block. On each trial, the to-

be-timed stimuli were fractals (blue or green) indicating “shock” or “no-shock” trials (colour counterbalanced).

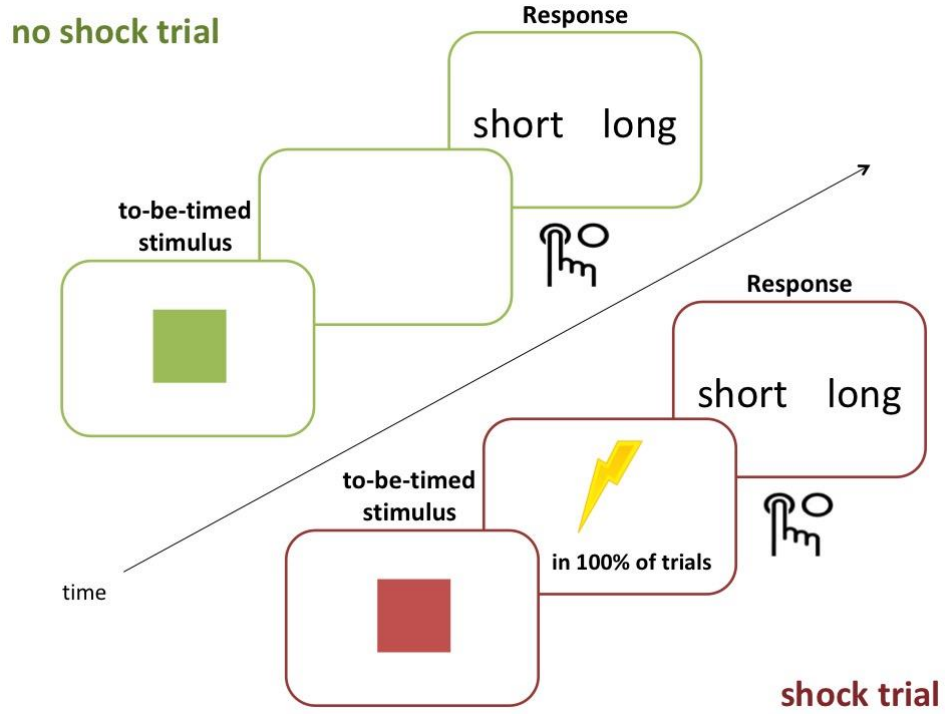


Figure 2-1: Temporal perception under fear: task design. Participants made time judgements while alternating between shock and no shock trials. In the actual experiment participants were presented with blue and green fractal images (counterbalanced) indicating 100% chance of shock or no shock.

2.3.3 Fitting logistic curves

Data from the temporal bisection task were modelled using the following procedure in all chapters: for each participant I fitted psychometric functions to trials separately for each condition (safe, threat, load: depending on the study), and computed the bisection point (BP) and Weber fraction (WF) (Figure 2-3). The BP is the time interval that is perceived to be equidistant between the shortest and longest anchor; i.e. the time interval corresponding to 50% p(Long) (proportion of stimuli classified as long) (Kingdom & Prins, 2010). It provides a measure of the perceived duration of comparison intervals. A rightward shift of the psychophysical curve would lead to a

greater BP, indicating underestimation of time (and vice-versa for a leftward shift). The WF is a measure of the precision of sensory discrimination (Kingdom & Prins, 2010). The more sensitive participants are to the task durations, the more quickly the curve will rise at its steepest point, resulting in a numerically smaller WF. A small WF indicates that small differences between the stimuli are detectable, in other words that sensitivity is higher. Paired samples t-tests were employed to compare BP and WF across the safe and threat conditions in all Chapters.

To obtain these measures, the data was modelled using the Palamedes toolbox in MATLAB (Prins & Kingdom, 2009). The proportion of long responses, p(Long), at each comparison interval, was fitted with logistic functions defined by four parameters: threshold α, slope β, guess rate γ, and lapse rate λ. In line with previous studies, γ was fixed at 0 since the task was 2-alternative forced-choice; λ was fixed at 0.1 to allow for occasional attentional lapses (Terhune et al., 2016). α and β were free parameters and estimated using maximum likelihood estimation. The duration corresponding to the 50% threshold on the psychometric function was defined as the BP. To calculate the WF I calculated the difference between the durations corresponding to the 75% and 25% thresholds, and divided by twice the BP, or (t(pLong=0.75) – t(pLong=0.25))/(2*BP)), where t is the interval duration (x-axis in Figure 2-3) at the respective location on the fitted psychometric function.

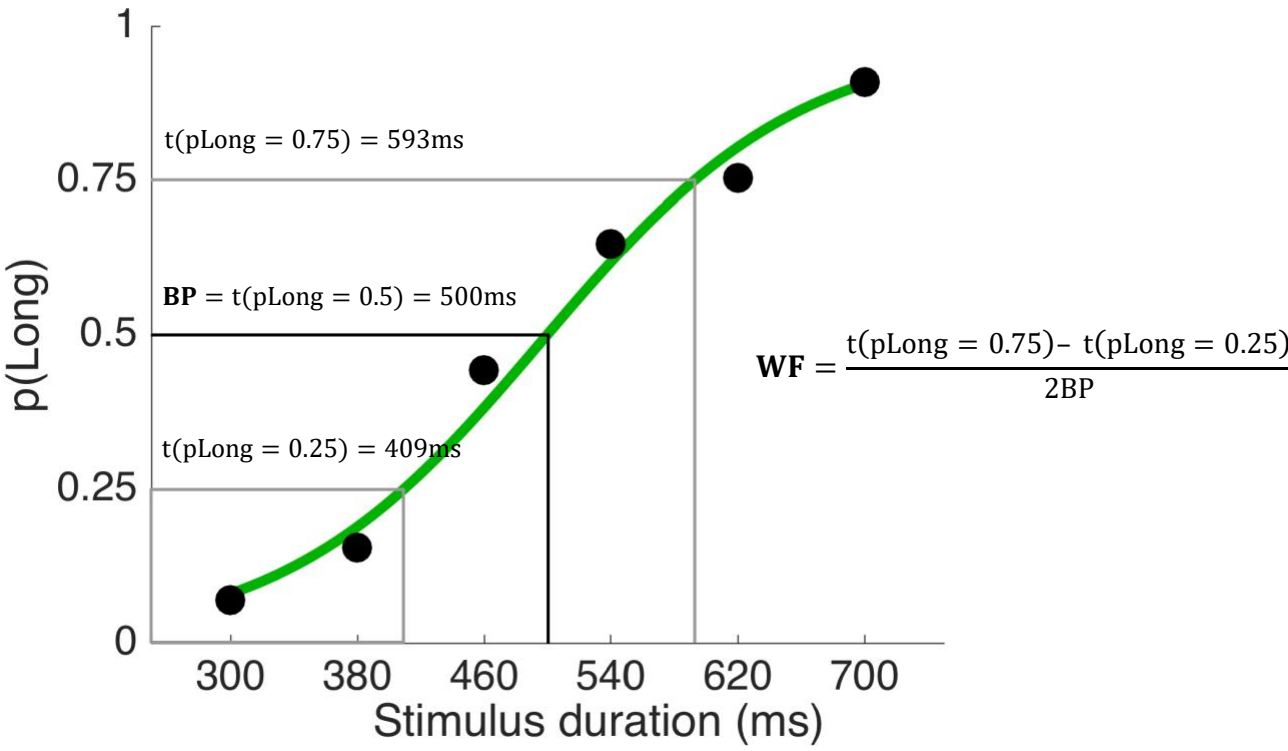


Figure 2-3: Example illustrating the calculation of the bisection point (BP) and Weber fraction (WF) (data from an exemplar participant in the safe condition in Chapter 2, Experiment 1). p(Long)=proportion of stimuli classified as long; ms=milliseconds; t=stimulus duration that corresponds to p(Long) on the psychometric curve.

2.4 Working memory and non-verbal IQ measures

In Chapter 6, the WAIS-III Digit Span (Wechsler, 1997) and Raven's Progressive Matrices (Raven & Raven, 2003) were used in order to match healthy and clinically anxious individuals on working memory and non-verbal IQ respectively. Additionally, in Chapter 4, the WAIS-III Digit Span was utilised as a covariate for a cognitive task, given the high variability in human working memory (e.g. see Fougnie et al., 2012).

The forward and backward digit span were used from the WAIS-III Digit Span (Wechsler, 1997). Participants listened to sequences of digits, and then were asked to repeat the sequence back in either forward or reverse order. Sequences were presented in ascending order of difficulty, from 2 to 9 digits (forwards) and 2 to 8 digits

(backwards). The total number of correctly repeated forward and backward sequences were used as a working memory score, stopping at the point where the participant fail to recall a sequence twice. Raven's Standard Progressive Matrices were used to assess non-verbal IQ. These consist of 12 multiple choice questions in the form of a visual geometric design with a missing piece. The questions are of increasing difficulty, and are considered to measure fluid intelligence.

2.5 Mini International Neuropsychiatric Interview (MINI)

In Chapter 7, clinically anxious participants were screened using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). This is a brief structured diagnostic interview used to assess symptoms of psychiatric disorders, considering both the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-5) and the International Classification of Diseases (ICD) 10th revision.

Healthy individuals were included in the study presented in Chapter 7 only if they did not meet criteria for any of the MINI sections. GAD patients were included in the study if they met the MINI criteria for GAD and did not present with hypomanic episodes (past or current), psychotic disorders, or alcohol or substance abuse (in the last 2 weeks) or dependence. Considering the high levels of comorbidity within anxiety disorders, as well as between anxiety and depression, other anxiety disorders and depression did not constitute exclusion criteria.

Chapter 3: Anxiety makes time pass quicker while fear has no effect

3.1 Abstract

People often say that during unpleasant events, e.g. traumatic incidents such as car accidents, time slows down (i.e. time is overestimated). However, aversive events can elicit at least two dissociable subtypes of reactions: fear (transient and relating to an imminent event) and anxiety (diffuse and relating to an unpredictable event). I hypothesised that anxiety might have an opposite effect on time perception compared to fear. To test this, I combined a robust anxiety manipulation (threat-of-shock) with a widely used timing task in which participants judged whether the duration of a stimulus was long or short. In line with my hypothesis, across three experiments (with varying stimulus timings and shock levels), participants significantly underestimated time under induced anxiety, as indicated by a rightward shift of the psychophysical function (meta-analytic effect size: d=0.68, 95% confidence interval: 0.42-0.94). In two further studies, I was unable to replicate previous findings that fear leads to time overestimation, after adapting my temporal cognition task, which suggests a dissociation between fear and anxiety in how they affect time perception. These results indicate that experimentally inducing anxiety leads to underestimating the duration of temporal intervals, which might be a starting point for explaining different subjective experiences of disorders related to fear (e.g. post-traumatic stress disorder) and anxiety (e.g. generalised anxiety disorder).

3.2 Introduction

The emotional valence of an experience is thought to distort our subjective sense of time (Sylvie Droit-Volet & Meck, 2007). Everyday experience and experimental evidence suggests that "time flies when having fun" (Gable & Poole, 2012; Simen & Matell, 2016), but slows down during unpleasant experiences (Fayolle et al., 2015; Stetson et al., 2007; Tipples, 2008). The latter seems to occur in situations such as car accidents or free falls (Arstila, 2012; Stetson et al., 2007). However, it might not be the case that time slows down during all kinds of aversive events. For example, time also seems to fly when one is in the rather anxiogenic state of having to work to a deadline just hours away.

One explanation for this discrepancy is that in the above examples during which time slows down (car accidents and well-controlled free falls: (Arstila, 2012; Stetson et al., 2007), it is *fear* that is induced (an acute aversive state elicited by immediate and certain threat), which is distinct from *anxiety* (a more prolonged aversive state elicited by an uncertain threat that may occur in the future; for further discussion of the distinction between fear and anxiety see (Davis et al., 2010; Kierkegaard, 1957; Tovote et al., 2015)). The hypothesis that the passage of time slows down during states of fear (i.e. time is overestimated) is supported by studies using fear-provoking pictures (Grommet et al., 2011; Tipples, 2008, 2011), looming stimuli, which are considered intrinsic threat cues, (van Wassenhove et al., 2011), unpleasant noises (Sylvie Droit-Volet et al., 2010) and electrical shocks (Fayolle et al., 2015). An unresolved question, however, is whether the effect of anxiety on our perception of time is distinct from that of fear. One study that used electrical shocks hinted that this might be the case, though given that a probabilistic fear conditioning paradigm was used, it is not clear whether fear or anxiety

was induced in this experiment (Lake, Meck, et al., 2016).

During *fear*-inducing events (e.g. a car crash) attention is focused on timing the present. This could be adaptive: for example, when a car is speeding towards you, keeping track of time is critical, as taking evasive action at the right moment may allow you to avoid the collision. This is supported by experimental evidence which found that looming (inherently fear-inducing), but not receding stimuli, result in time overestimation (van Wassenhove et al., 2011). This increased attention to timing is thought to lead to overestimation (Thomas & Weaver, 1975), and is supported by experiments showing that individuals with greater susceptibility to fear (and thus increased attention to fear-related cues) overestimate the duration of fearful stimuli (Bar-Haim et al., 2010; Tipples, 2008). During *anxiety*, by contrast, attention is divided between what is happening at this moment and anticipating an uncertain aversive event that may happen in the near future. For example, imagine being an undergraduate student who has just started work on an assignment, the deadline for which is just three hours away: time seems to fly as the student is uncertain whether they will make the deadline. Whilst worrying about potentially missing the deadline, one is distracted from what is happening in the present moment (e.g. writing). It is thought that this type of distraction from time could lead to "missing ticks from our mental clock" (Coull et al., 2004; Macar et al., 1994; Thomas & Weaver, 1975). This explanation leads to the hypothesis, as yet untested, that anxiety – as distinct from fear – should result in *underestimating* time.

To test this hypothesis, I combined a commonly used timing task (Kopec & Brody, 2010) with an established anxiety manipulation: threat-of-shock (Robinson, Vytal, et al., 2013; Schmitz & Grillon, 2012). During threat-of-shock, participants anticipate

intermittent and unpredictable painful electrical stimulation to the skin while performing a cognitive task. This procedure reliably increases self-report, physiological and neurobiological indices of anxiety (Robinson, Vytal, et al., 2013; Schmitz & Grillon, 2012). Given the uncertain nature of the threat (which should elicit anxiety rather than fear), I hypothesised that participants would allocate attentional resources away from the timing task at hand and towards anticipating the next shock, which should lead to underestimation of time intervals (see Figure 3-1).

This hypothesis was tested over the course of five separate experiments. In Experiment 1, participants performed a subsecond temporal bisection task under threat-of-shock and safe conditions. I predicted time underestimation due to increased anxiety, which should be evident in a rightward shift to this psychophysical curve (see Figure 3-1). Since different mechanisms are considered to be involved in the estimation of subsecond compared to suprasecond durations (Buhusi & Meck, 2005; Koch et al., 2008), Experiment 2 sought to generalise these findings using suprasecond stimuli durations. Finally, given that in my threat-of-shock manipulation participants actually receive shocks, it is possible that any effects observed are due to the shocks *per se*, rather than the induced anxiety. Therefore Experiment 3 examined time estimation under threat, similar to Experiment 2, but without any shocks being delivered. In Experiment 4 & 5 I sought to replicate a previous study (Fayolle et al., 2015) showing that fear leads to time overestimation, using the same temporal cognition task used in Experiments 1, 2 & 3.

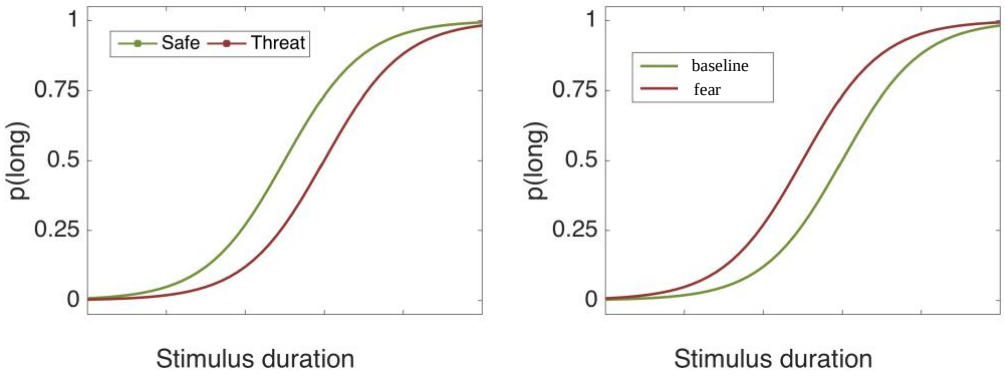


Figure 3-1: Predicted effect of anxiety (threat-of-shock) and fear on the temporal bisection task. The curves represent the proportion of long responses [p(Long)] as a function of stimulus duration. (left) I predict that the anxiety condition (threat) would promote a rightward shift of the curve, compared to the baseline (safe) condition, due to underestimation of time intervals. (right). In the fear condition, I predict a leftward shift of the curve compare to the baseline condition, due to overestimation of time intervals, replicating previous findings (Fayolle et al., 2015).

3.3 Materials and methods

3.3.1 Overview

During a single testing session, following written informed consent, participants initially completed questionnaires assessing their mood and anxiety levels (see Chapter 2.1), followed by a shock calibration procedure to determine an appropriate level of aversive electrical stimulation (see Chapter 2.2; shock calibration). Participants in Experiments 1, 2 & 3 completed the temporal bisection task under an anxiety manipulation (threat-of-shock; see Chapter 2.3.1), while participants in Experiments 4 & 5 completed the temporal bisection task under a fear manipulation (see Chapter 2.3.2). Information relating to participant recruitment and inclusion/exclusion criteria is provided in each of the experiment-specific methods sections below.

3.3.2 Apparatus

All experiment material was presented on Windows computers using Cogent 2000 (www.vislab.ucl.ac.uk/cogent.php; Wellcome Trust Centre for Neuroimaging and Institute of Cognitive Neuroscience, UCL, London), running under MATLAB.

Table 3-1: Experimental parameters.

	Manipulation	**Stimulus duration**	**Shock occurrence**	**Shock type (duration)**	**Task duration**
Experiment 1	anxiety (unpredictable shock)	300-700ms	immediately after response	train of shocks (3 s)	40 min
Experiment 2	anxiety (unpredictable shock)	1,400-2,600ms	during ITI	train of shocks (2 s)	20 min
Experiment 3	anxiety (unpredictable shock)	1,400-2,600ms	no shock delivered	no shock	10 min
Experiment 4	fear (predictable shock)	1,400-2,600ms	after stimulus disappeared	single pulse (0.2 s)	10 min
Experiment 5	fear (predictable shock)	1,400-2,600ms	after stimulus disappeared	train (0.5 s)	20 min

3.3.3 Data analysis

All data was preprocessed in MATLAB (v. R2015b), and statistical testing was carried out in SPSS (v. 23). The fitting of the logistic curves was carried out as described in Chapter 2.3.3. The meta-analysis of the three Experiments in which threat-of-shock was

used was carried out in JASP (Version 0.8.6).

3.3.3.1 Proportion of long responses

Trials on which participants did not make a response were excluded from the analysis. Repeated-measures analyses of variance (ANOVAs) were performed on the proportion of stimuli participants judged to be long (proportion of long responses, p(Long)). The effects of threat (safe or threat-of-shock condition), duration (six stimulus durations), the emotion depicted on the stimulus (fearful, happy or neutral) and block (where relevant) were used as within-subject factors. Experiment 3 consisted of only one safe and one threat block, and hence the ANOVA did not include block as a factor. Greenhouse-Geisser corrections were applied when violations of sphericity occurred.

3.3.4 Experiment specific methods

Demographic information of Experiments 1-5 is provided on the table below.

Table 3-2: Sample demographic information for the five Experiments. Figures represent counts or means (SDs). BDI = Beck depression inventory. STAI = Trait anxiety from the State Trait Anxiety Inventory

	Sample size	**Age**	**Female**	**BDI**	**STAI**
Experiment 1 (anxiety)	25	22.76 (0.67)	16	7.04 (1.92)	40.16 (2.66)
Experiment 2 (anxiety)	25	23.36 (0.83)	13	4.96 (0.96)	36.24 (1.93)
Experiment 3 (anxiety)	20	27.90 (6.42)	14	2.85 (2.30)	32.05 (6.51)
Experiment 4 (fear)	25	24.28 (2.05)	18	6.16 (6.51)	40.08 (10.62)

Experiment 5 (fear)	35	22.42 (2.83)	24	8.91 (8.62)	43.08 (11.91)

3.3.4.1 Experiment 1: Threat-of-shock, subsecond durations

The experiment and all procedures were approved by the UCL Research Ethics Committee (Project ID Number: 1764/001) and were in accordance with the latest version of the Declaration of Helsinki. Participants were recruited from UCL subject databases.

A power calculation (G*power version 3.1.9.2; Faul et al., 2007) determined the sample size based on the only study that fulfilled the following criteria: a) usage of a temporal bisection procedure as a timing task; b) manipulation of temporal cognition by delivering electric shocks: Fayolle et al., (2015). Only the experiment in which the to-be-judged durations were subsecond (from 0.2 to 0.8 seconds) was considered for the power calculation, since it was the closest to the stimulus duration range I used (0.3 to 0.7 seconds). This choice was made after considering that task properties might differ in sub- and supra-second temporal tasks (Buhusi & Meck, 2005; Koch et al., 2008). The effect size (Cohen's d) of the (Fayolle et al., 2015) study was calculated to be d=1.89. This extremely large effect size may have occurred because on half of the trials participants always received a shock *while* timing a stimulus, and thus pattern of results might be due to the delivery of shocks *per se*. By contrast, in my threat-of-shock manipulation, shocks were delivered rather infrequently and occurred during ITIs. Hence, I conservatively decreased the Fayolle et al. (2015) effect size by 70% to d=0.56: with 80% power and an alpha of 0.05 (two-tailed), the required sample size was estimated to be 25 participants.

Participants had normal or corrected to normal vision and no present (or past)

neurological or psychiatric diagnosis. All provided written informed consent and received £10 for their participation in this study, which lasted approximately 1 hour and 20 minutes. Three participants' data were not analysed due to incomplete data acquisition, and thus three extra participants had to be recruited to achieve a final sample of 25.

The session consisted of 18 blocks (nine in the safe and nine in the threat condition), with each block comprising 48 trials. On each trial, participants viewed a picture of an emotional face (happy, fearful or neutral; taken from the standardised NimStim; Tottenham et al., 2009 set) that remained on screen for 300, 380, 460, 540, 620 or 700ms.

Seventy-two pictures were used in this experiment, depicting happy, neutral and fearful facial expressions, taken from 24 actors. During each block, participants viewed an equal number of happy, fearful and neutral facial expressions (16 each), the order of which was pseudorandomised. Similarly, stimulus durations were pseudorandomised within each block, so that all durations were repeated eight times. The ITI (500, 750, 1000ms) was also pseudorandomised.

Participants received a total of 18 trains of shocks during the session, only during threat blocks, in the following combinations: four shocks in two blocks; three shocks in one block; two shocks in three blocks; one shock in one block. No shocks were delivered in two of the threat blocks. The order of the shocks was random for each participant and occurred on different trials, immediately following the participant's response. Each train of shocks consisted of 20 pulses delivered over 2 seconds, and the average shock intensity (based on the shock calibration procedure) was 5.99 mA (SD = 3.22). After each safe and threat block, participants rated how anxious they felt using a continuous

visual analogue scale ranging from “very little” to “very much”.

3.3.4.2 Experiment 2: Threat-of-shock, suprasecond durations

The experiment and all procedures were approved by the UCL Research Ethics Committee (Project ID Number: 1764/001) and were in accordance with the latest version of the Declaration of Helsinki.

Participants were recruited from UCL subject databases. All had normal or corrected to normal vision, had no present or past neurological or psychiatric diagnosis. All provided written informed consent and received £10 for their participation, which lasted approximately 1 hour. The same power calculation was used as for Experiment 1, requiring N=25.

Each session consisted of 8 blocks, 4 safe and 4 threat, with each block comprising 48 trials. Similar to Experiment 1, on each trial participants viewed a picture of an emotional face (happy, fearful or neutral; taken from NimStim; Tottenham et al., 2009), but these remained on screen for 1,400, 1,640, 1,880, 2,120, 2,360 or 2,600ms. All other task aspects were identical to Experiment 1, apart from the number and duration of shocks, as explained below.

Participants received between 5 and 11 shocks in total during the session, only during threat blocks. The shocks were randomly chosen from the following combinations: four shocks in one block, three shocks in one block, two shocks in two blocks, one shock in one block. No shocks were delivered in one of the threat blocks. The order of the shocks was random for each participant and occurred on different trials, at any time during the ITI. Each train of shock consisted of 30 pulses delivered over 3 seconds and the average shock strength was 10.01 mA (SD = 0.65). After each safe and threat block, participants

had to rate how anxious they felt using a continuous visual analogue scale ranging from "very little" to "very much".

3.3.4.3 Experiment 3: Threat without shocks, supra-second durations

The experiment and all procedures were approved by the NIH Institutional Review Board Project (ID Number: 01-M-0254) and were in accordance with the latest version of the Declaration of Helsinki.

Participants were recruited through advertisements (newspaper and public transport) in the Washington, D.C. metropolitan area. Following an initial telephone screen, participants visited the National Institutes of Health (NIH) for comprehensive screening by a clinician, which comprised a physical examination, urine drug screen, and the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition (American Psychiatric Association et al., 2013). Exclusion criteria were: contraindicated medical disorder (i.e. those thought to interfere with brain function and/or behaviour); past or current psychiatric disorders; and use of psychoactive medications or recreational drugs (per urine screen). Twenty participants were tested (reduced from 25 in the first two experiments) which provided 80% power at an alpha of 0.05 (two-tailed) assuming the smallest effect of threat-of-shock detected in the first two experiments (i.e. d=0.68).

All participants provided written informed consent and were reimbursed $140 for their participation. Each single session consisted of two blocks, one safe and one threat (counterbalanced) with each block comprising 48 trials. All other task parameters were identical to Experiment 2. Even though participants underwent the shock-work up (with shocks that lasted 200 ms), they did not receive any shocks during threat blocks. After each safe and threat block, participants had to rate how anxious they felt using a

continuous visual analogue scale ranging from “very little” to “very much”.

3.3.4.4 Experiments 4 & 5: Fear manipulation, supra-second durations

The experiment and all procedures were approved by the UCL Research Ethics Committee (Project ID Number: 1227/001) and were in accordance with the latest version of the Declaration of Helsinki.

A power calculation (G*power version 3.1.9.2; Faul et al., 2007) determined the sample size of Experiment 4 based on the averaged effect size of Experiments 1, 2, & 3. Thus, to achieve an effect size d=0.68 with 90% power and an alpha of 0.05 (two-tailed), the required sample size was estimated to be 25 participants. Given that the results of Experiment 4 were trending towards significance, I ran Experiment 5, in which the expected effect size was d=0.50: to obtain 90% power and an alpha of 0.05 (two-tailed), the required sample size was estimated to be 35 participants.

Participants had normal or corrected to normal vision and no present (or past) neurological or psychiatric diagnosis. All provided written informed consent and received £4 in Experiment 4 and £6 in Experiment 5 for their participation.

The session consisted of 2 blocks in Experiment 4 and 4 blocks in Experiment 5 with each block comprising 48 trials. On each trial, participants viewed a fractal image that remained on screen for 1,400, 1,640, 1,880, 2,120, 2,360 or 2,600ms.

Forty-eight pictures were used in this experiment, depicting twenty-four green and twenty-four blue fractal images, each presented once per block with their order pseudorandomised. The colour of the fractal image indicated whether participants will receive a shock in the specific trial or not, and was counterbalanced. Stimulus durations were pseudorandomised within each block, so that all durations were repeated eight

times. The ITI (2s, 2.5s and 3s) was also pseudorandomised.

Participants received a total of forty-eight shocks during the session, only during shock trials. No shocks were delivered in the no-shock trials. In Experiment 4 the shock consisted of a single pulse and in Experiment 5 of 5 pulses. At the end of each experiment, participants were asked to verbally report how unpleasant and pleasant they found each the shocks using a scale from 1-10, where 1 means “very little” and 10 “very much”.

3.4 Results

3.4.1 Experiment 1: Threat-of-shock, subsecond durations

3.4.1.1 Manipulation check: subjective ratings

Across blocks, participants reported being significantly more anxious in the threat (M=0.74, SD=0.22) compared to the safe (M=0.24, SD=0.20) condition ($F(1, 24)=77.10$, $p<.001$, $\eta_p^2=.763$). The effect of block ($F(4.24, 101.77)=1.59$, $p=.180$, $\eta_p^2=.062$) and the threat-by-block interaction were non-significant ($F(8, 192)=1.51$ $p=.156$, $\eta_p^2=.059$). Hence, self-reported anxiety was elevated during the threat condition, and this effect was stable throughout the experiment (Figure 3-4).

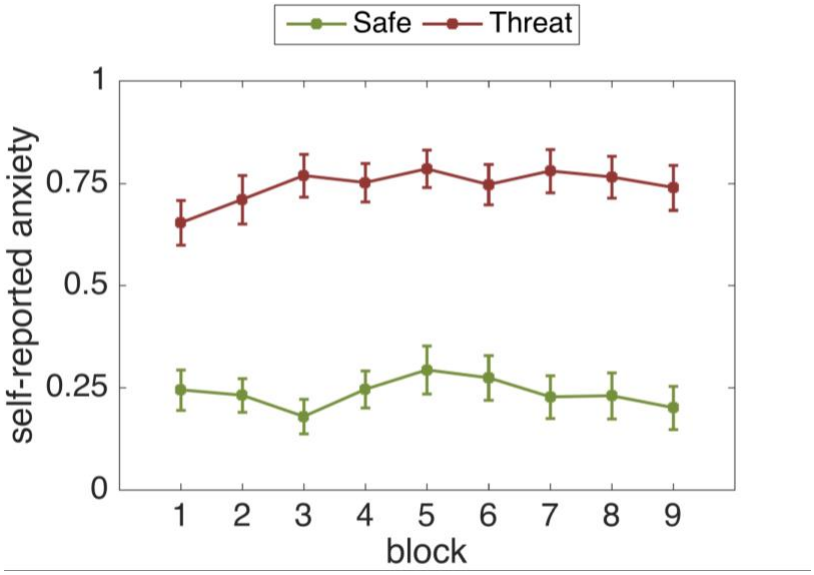


Figure 3-4: Self-reported anxiety levels on each block per threat condition. Greater values reflect higher anxiety. Error bars are standard errors of the mean (SEM).

3.4.1.2 Time estimation: proportion of long responses

For this ANOVA analysis, data from five participants were excluded, as there were missing responses in some conditions, probably due to the long duration and repetitive nature of the task. However, the curve fitting analysis is more robust to missing data (see Bisection Point analysis below), which should therefore be considered with more confidence.

There was a significant main effect of stimulus duration ($F(2.08, 39.58)=222.07$, $p<.001$, $\eta_p^2=.914$). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 3-5). All interactions with stimulus duration were non-significant. There was a significant main effect of threat ($F(1, 19)=6.10$, $p=.023$, $\eta_p^2=.243$) but not of emotion ($F(2, 38)=0.61$, $p=.550$, $\eta_p^2=.031$), and the threat-by-emotion interaction was non-significant ($F(2, 38)=0.07$, $p=.936$, $\eta_p^2=.003$). Participants made significantly more "long" choices as the experiment progressed (main effect of block: $F(8, 152)=6.54$, $p<.001$, $\eta_p^2=.256$) and the threat-by-block interaction was also

significant (F(8, 152)=2.66, p=.009, η_p^2=.123). This suggests that participants' temporal perception and the effect of threat changed over the course of the experiment.

To make the above results easier to interpret, I performed a *post-hoc* analysis binning data into three experimental stages (first six blocks, middle six blocks, final six blocks). The effect of threat was significant for the first six blocks, (F(1, 24)=7.10, p=.014, η_p^2=.228) and, the middle six blocks (F(1, 24)=12.69, p=.002, η_p^2=.346), but not for the final six blocks (F(1, 24)=1.81 p=.191, η_p^2=.070). As shown in Figure 3-5, participants underestimated time under threat-of-shock, but this effect disappeared during the final blocks of the experiment.

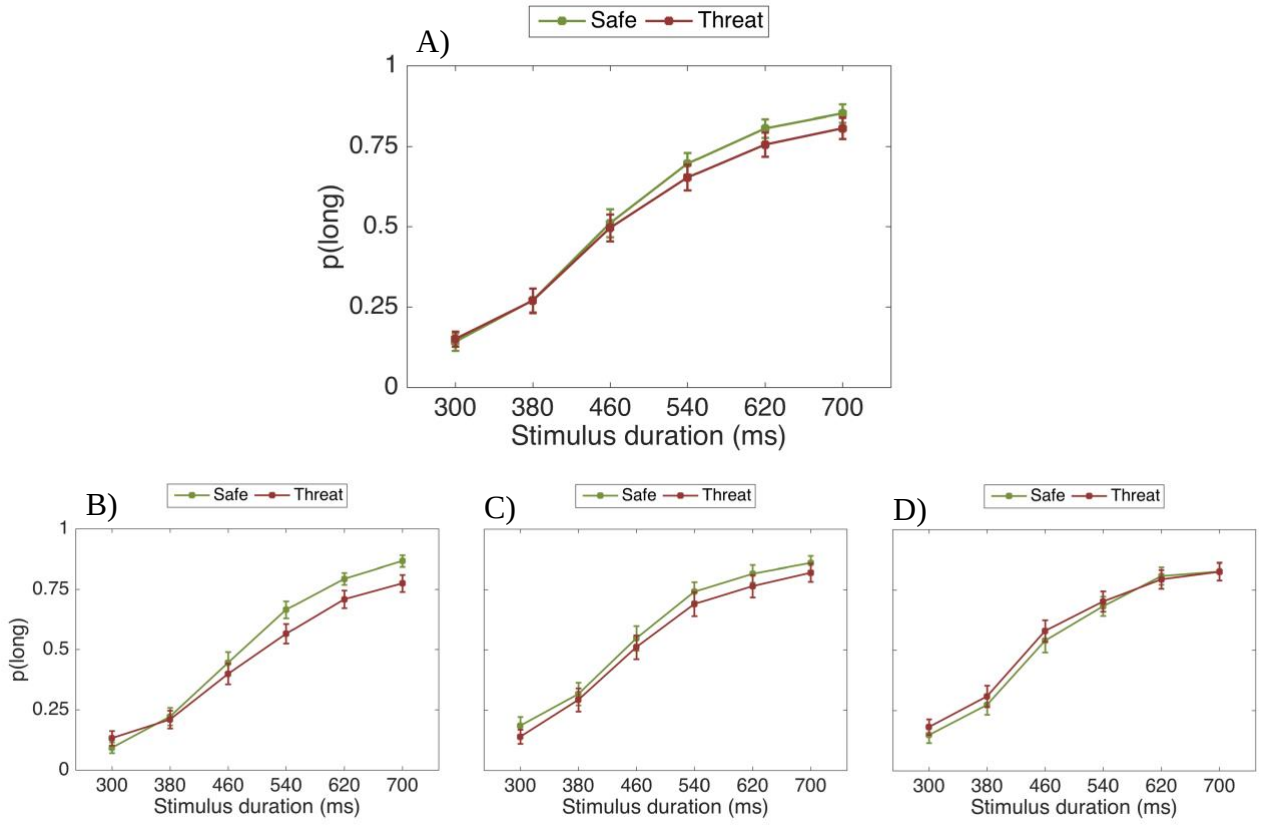


Figure 3-5: Proportion of stimuli rated "long" as a function of the actual presentation length and threat condition. A: All 18 blocks | B: First six blocks | C: Middle six blocks | D: Final six blocks. Error bars are standard errors of the mean (SEM).

3.4.1.3 Psychophysical modelling

Bisection point

Averaged across blocks, the BP was significantly larger during the threat (M=483.83, SD=116.20) compared to the safe (M=456.86, SD=107.20) condition (t(24)=3.79, p=.001, d=0.76). This indicates that in the threat condition the psychometric curve was shifted to the right, and thus time was underestimated.

Weber fraction

Averaged across blocks, WF was not significantly different between the threat (M=0.25, SD=0.02) and safe (M=0.23, SD=0.02) conditions (t(24)=1.26, p=.221, d=0.25). Thus there was no evidence that the sensitivity to time intervals differed between the safe and threat conditions.

3.4.2 Experiment 2: Threat-of-shock, suprasecond durations

3.4.2.1 Manipulation check: anxiety ratings

Across blocks, participants reported being significantly more anxious in the threat (M=0.76, SD=0.17) compared to the safe (M=0.26, SD=0.22) condition (F(1, 24)=97.81, p<.001, η_p^2=.803). The effect of block was non-significant (F(1.99, 47.83)=.458, p=.634, η_p^2=.019), but the threat-by-block interaction was significant (F(3, 72)=3.17, p=.029, η_p^2=.117). Self-reported anxiety was strongly elevated during the threat condition relative to the safe condition, and this effect increased over time (Figure 3-6). This seemed to be because individuals became even less anxious in the safe condition while at the same time becoming slightly more anxious in the threat condition.

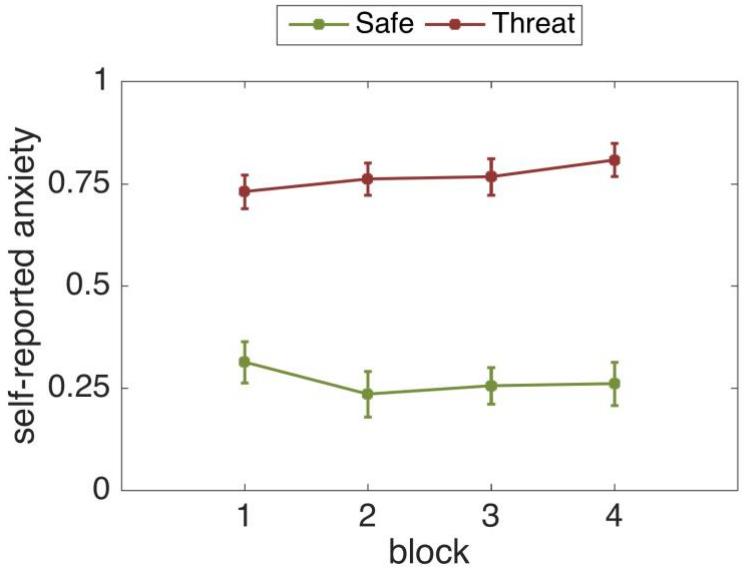


Figure 3-6: Self-reported anxiety levels on each block per threat condition. Greater values reflect higher anxiety. Error bars are standard errors of the mean (SEM).

3.4.2.2 Time estimation: proportion of long responses

For this analysis, data from one participant was excluded, as there were missing responses in some conditions. There was a significant main effect of stimulus duration ($F(2.06, 47.46)=217.33$, $p<.001$, $\eta_p^2=.904$). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 3-7). The threat-by-stimulus duration interaction was significant ($F(3.23, 74.25)=3.57$, $p=.016$, $\eta_p^2=.134$). As shown in Figure 3-7, the threat manipulation mainly affected the longer stimulus durations. Specifically, threat caused longer durations to be experienced as shorter, whereas this effect was reduced for shorter durations. All other interactions with stimulus duration were non-significant.

There was a significant main effect of threat ($F(1, 23)=13.05$, $p=.001$, $\eta_p^2=.362$) but not of emotion ($F(2, 46)=2.09$, $p=.136$, $\eta_p^2=.083$). The threat-by-emotion interaction was non-significant ($F(2, 46)=0.02$, $p=.980$, $\eta_p^2=.001$). Participants made significantly more "long" choices as the experiment progressed (main effect of block: $F(3, 69)=4.70$,

p=.005, η_p^2=.170) but the threat-by-block interaction was not significant (F(3, 69)=1.34, p=.251, η_p^2=.057). This suggests that participants' temporal perception changed over time regardless of threat condition. This differs from Experiment 1, in which the effect of threat decreased over the course of the experiment.

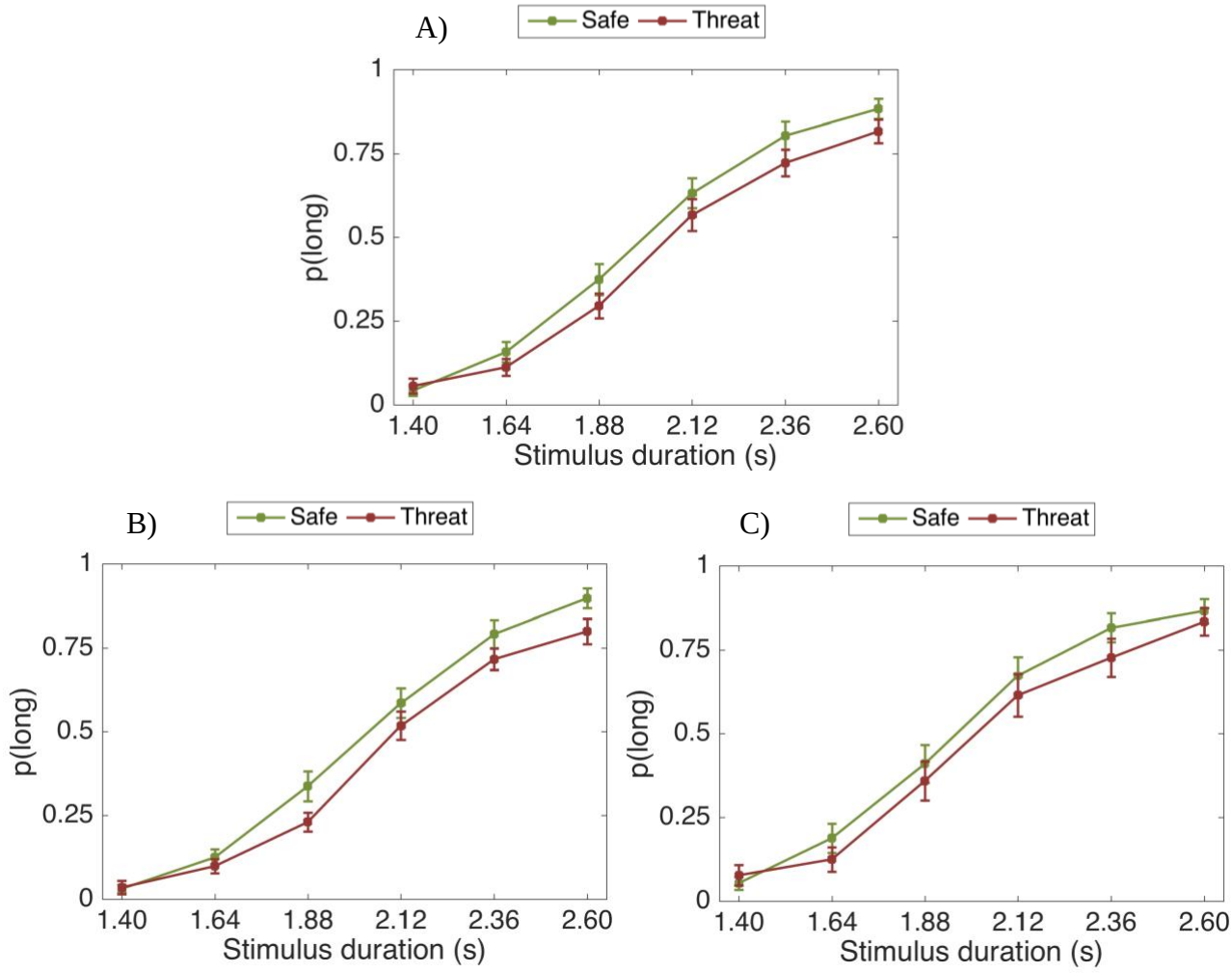


Figure 3-7: Proportion of stimuli rated "long" as a function of the actual presentation length and threat condition. A: All eight blocks | B: First four blocks | C: Final four blocks. Error bars are standard errors of the mean (SEM).

3.4.2.3 Psychophysics modelling

Bisection point

Averaged across blocks, the BP was significantly larger during the threat (M=2,123.74, SD=271.66) compared to the safe (M=2,035.62, SD=276.29) condition (t(24)=3.39,

p=.002, d=0.68). This indicates that under threat, the psychometric curve was shifted to the right and thus time was underestimated.

Weber fraction

Averaged across blocks, the WF was not significantly different between the threat (M=0.13, SD=0.02) and safe (M=0.11, SD=0.01) conditions (t(24)=1.77, p=.088, d=0.35). Thus there was no evidence that the sensitivity to time intervals differed between the safe and threat conditions.

3.4.3 Experiment 3: Threat-without-shocks, supra-second durations

3.4.3.1 Manipulation check: anxiety ratings

Despite the lack of shocks, across blocks, participants reported being more anxious in the threat (M=0.36, SD=0.27) compared to the safe (M=0.11, SD=0.17) condition (t(19)=4.37, p<.001, d=0.98).

3.4.3.2 Proportion of long responses

There was a significant main effect of stimulus duration (F(2.56, 48.75)=116.93 p<.001, η_p^2=.860). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 3-8). All interactions with stimulus duration were non-significant.

There was a significant main effect of threat (F(1, 19)=6.88, p=.017, η_p^2=.266), but not of emotion (F(2, 38)=0.73, p=.487, η_p^2=.037), and the threat-by-emotion interaction was non-significant (F(2, 38)<0.01, p=.997, η_p^2<.001). These results, which are consistent with the first two Experiments, suggest that time was underestimated in a threatening situation (Figure 3-8), even though participants did not actually receive any shocks.

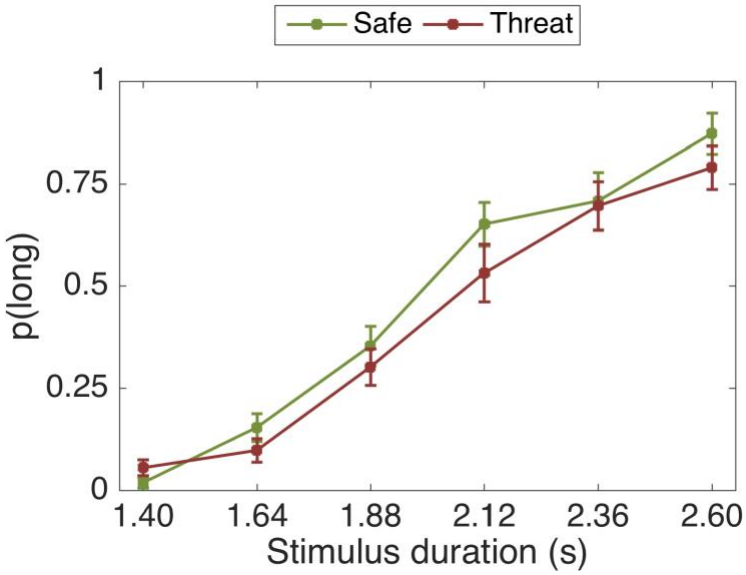


Figure 3-8: Proportion of stimuli rated "long" as a function of the actual presentation length and threat condition (one safe vs. one threat block). Error bars are standard errors of the mean (SEM).

3.4.3.3 Psychophysical modelling

Bisection point analysis

The BP was significantly larger during the threat (M=2,121.34, SD=246.75) compared to the safe (M=2,027.04, SD=186.19) condition (t(19)=2.66, p=.015, d=0.60). This indicates that under threat the psychometric curve was shifted to the right, and thus time was underestimated.

Weber fraction analysis

The WF was not significantly different between the threat (M=0.31, SD=0.21) and safe (M=0.29, SD=0.13) conditions (t(19)=0.48, p=.639, d=0.11). Thus there was no evidence that the sensitivity to time intervals differed between the safe and threat conditions.

3.4.4 Exploratory combined analysis on the effect of emotion

In contrast to previous studies (Droit-Volet et al., 2004; Tipples, 2008, 2011), I did not detect a significant effect of the facial expression of the to-be-timed stimulus (fearful, happy or neutral) on participants' temporal judgements in Experiments 1-3. One possibility is that my studies were underpowered to detect such differences, given that previous studies used larger sample sizes (the original study by Droit-Volet et al. 2004 used 37 participants, while an indirect replication by Tipples, 2008, used 43). Hence I pooled data together from Experiments 1, 2 and 3 (combined N=70) and performed a repeated-measures ANOVA on p(Long) with threat, emotion and stimuli duration as within subject factors. This analysis revealed a significant effect of threat ($F(1, 69)=28.59$, $p<.001$, $\eta_p^2=.293$) but not of emotion ($F(2, 138)=1.59$, $p=.208$, $\eta_p^2=.023$). Thus, taken together, these Experiments suggest that the emotion depicted on the to-be-timed-stimuli did not affect the perception of time.

3.4.5 Meta-analysis of the effect of anxiety on time perception

A meta-analysis was conducted across these three experiments to quantify more precisely the effect of threat on temporal perception (Figure 3-9). The differences in BP and WF between the threat and safe conditions were used as the dependent variables for this meta-analysis of the effect of the anxiety manipulation on time perception.

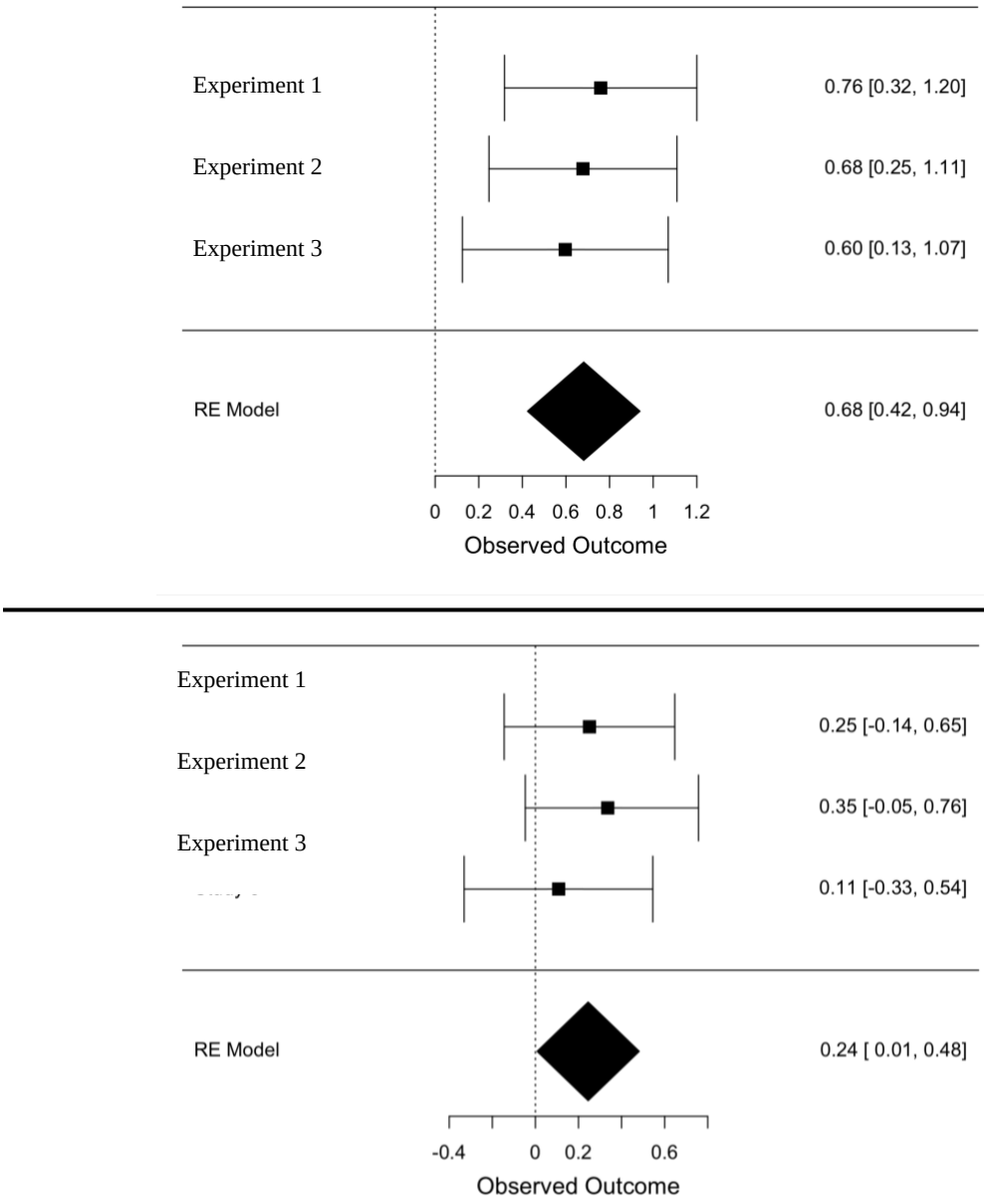


Figure 3-9: Meta-analytic results for the difference in bisection point (top panel) and Weber's Fraction (bottom panel) between threat and safe conditions. The measure of effect size is Cohen's d (standardised mean difference). RE = random effects.

There was a significant effect of threat on the BP ($Z=5.18$, $p<.001$) and WF ($Z=2.02$, $p=0.043$) The meta-analytic effect size for the BP was $d=0.67$ (95% confidence interval: 0.42-0.94) and for WF $d=0.24$ (95% confidence interval: 0.01-0.48).

3.4.6 Experiment 4: Fear, suprasecond durations

3.4.6.1 Manipulation check: shock ratings

After the end of the experiment participants were asked to rate on a scale from 1 to 10 how pleasant and unpleasant they found the shocks, where 1 corresponds to very little and 10 very much. Overall, participants rated the shocks as more unpleasant (M= 6.52, SD=1.92) than pleasant (M=2.64, SD=1.62) and the difference was statistically significant ($t(24)=6.99$, $p<.001$, $d=1.4$).

3.4.6.2 Time estimation: proportion of long responses

There was a significant main effect of stimulus duration ($F(2.13, 51.26)=124.63$, $p<.001$, $\eta_p^2=.839$). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 3-10). The fear-by-stimulus duration interaction was not significant ($F(5, 120)=1.98$, $p=.086$, $\eta_p^2=.076$). As shown in Figure 3-10, the fear manipulation mainly affected the longer stimulus durations. All other interactions with stimulus duration were non-significant.

The main effect of fear ($F(1, 24)=3.78$, $p=.063$, $\eta_p^2=.136$) was not significant, but was approaching significance. Thus, it was not clear whether participants' temporal perception changed due to the fear manipulation. Regardless, the direction of the results are opposite to that of Experiments 1, 2 & 3 in which time was underestimated when anxiety was induced. These results show that, unlike anxiety, the fear manipulation does not seem to make participants underestimate the temporal intervals.

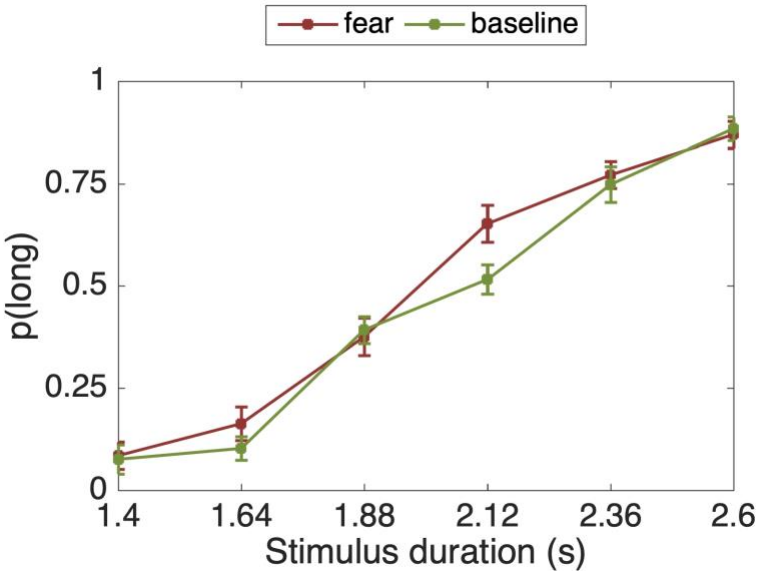


Figure 3-10: Proportion of stimuli rated "long" as a function of the actual presentation length and fear condition. Error bars are standard errors of the mean (SEM).

3.4.6.3 Psychophysics modelling

Bisection point

Averaged across blocks, the BP was numerically smaller during the fear (M=2,004.77, SD=194.98) than the baseline (M=2,083.58, SD=153.06) condition, but the effect was again non-significant (t(24)=1.99, p=.058, d=0.40). There is nevertheless a trend that under fear, the psychometric curve was shifted to the left and thus time was overestimated, while the curve was shifted to the right in Experiments 1, 2 & 3.

Weber fraction

Averaged across blocks, the WF was not significantly different between the fear (M=0.16, SD=0.16) and baseline (M=0.15, SD=0.11) conditions (t(24)=-.38, p=.707, d=0.01). Thus there was no evidence that the sensitivity to time intervals differed between the baseline and fear conditions.

3.4.7 Experiment 5: Fear, suprasecond durations (extension of Experiment 4 with larger sample size, more intense shocks and more trials)

3.4.7.1 Manipulation check: shock ratings

After the end of the experiment participants were asked to rate on a scale of 1 to 10 how pleasant and unpleasant they found the shocks, where 1 corresponds to very little and 10 very much. Overall, participants rated the shocks as more unpleasant (M= 6.72, SD=1.33) than pleasant (M=2.96, SD=1.81) and the difference was statistically significant (t(34)=9.13, p<.001, d=1.54).

3.4.7.2 Time estimation: proportion of long responses

There was a significant main effect of stimulus duration (F(2.49, 84.87)=142.77, p<.001, η_p^2=.808). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 3-11). The fear-by-stimulus duration interaction was not significant (F(5, 170)=0.57, p=.720, η_p^2=.017).

The main effect of fear (F(1, 34)=0.02, p=.888, η_p^2=.001) was not significant.

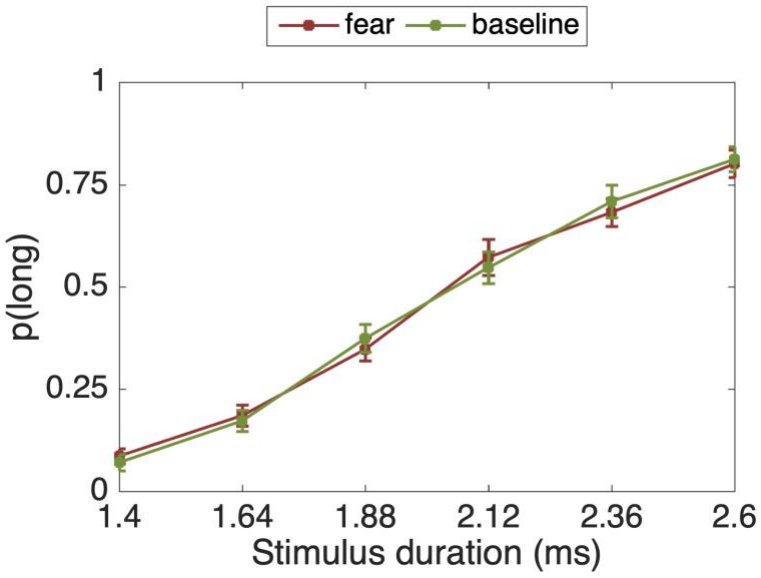


Figure 3-11: Proportion of stimuli rated “long” as a function of the actual presentation length and fear condition. Error bars are standard errors of the mean (SEM).

3.4.7.3 Psychophysics modelling

Bisection point

Averaged across blocks, the BP during the fear (M=2,129.33, SD=316.05) compared to the baseline (M=2,150.82, SD=331.25) condition did not differ statistically (t(34)=0.41, p=.687, d=0.06).

Weber fraction

Averaged across blocks, the WF was not significantly different between the fear (M=0.18, SD=0.10) and baseline (M=0.17, SD=0.13) conditions (t(34)=-.27, p=.791, d=0.04). Thus, there was no evidence that the sensitivity to time intervals differed between the baseline and fear conditions.

3.5 Discussion

These results suggest that experimentally inducing anxiety leads to underestimating the duration of temporal intervals. Hence, although prior studies indicated that time slows down (i.e. time is overestimated) during aversive events (Arstila, 2012; Fayolle et al., 2015; Stetson et al., 2007; Tipples, 2008), one possibility is that this might be true only for events in which there is imminent threat, which induce a fearful (rather than anxious) state (states that are dissociable experimentally; Davis et al., 2010). However, I did not find that fear leads to overestimation of temporal intervals, failing to replicate the findings of a previous study that provided clear evidence for that; thus painting a more complex picture. In any case, my results suggest a dissociation on how fear and anxiety affect time perception.

3.5.1 Effect of anxiety on time perception

In Experiments 1-3, I found that participants underestimated time when anxious (i.e. their psychometric curve shifted to the right), while I did not detect a significant effect on temporal sensitivity (WF did not differ statistically between the threat and safe conditions). This indicates that under the threat-of-shock manipulation, the perception of time was biased, but the sensitivity to the time intervals was not affected *per se*. In other words, anxiety did not impair the ability to discriminate between different time intervals, but only led participants to *perceive* the time intervals as shorter. In the meta-analysis I conducted, pooling together effects from Experiments 1-3, I found a significant effect of anxiety on both BP and WF. The latter effect was, however, relatively small ($d=0.24$) and barely significant ($Z=2.02$, $p=0.043$), thus I cannot conclude with confidence that anxiety shifted WF.

A possible limitation in Experiments 1 & 2 is that participants received shocks in the anxiety condition compared to the baseline, which may have resulted in distraction due to the electrical stimulation, or other confounds relating to movement or pain. This was addressed by Experiment 3, which latter showed that participants still underestimated time even though they did not receive shocks during the anxiety manipulation. This suggests that the effect of threat on time perception cannot be attributed solely to the physical properties of the shocks that participants received. In fact, previous studies showed that pain results in the opposite effect to what was found in these experiments: i.e. temporal overestimation (Rey et al., 2017). Thus, being in the anxiogenic state of anticipating an unpleasant event (without such an event occurring), seems sufficient to bias the perception of time.

There is considerable work suggesting that different mechanisms are responsible for sub

and supra-second duration time perception (Buhusi & Meck, 2005; Koch et al., 2008; Wiener et al., 2010) so the replication in Experiment 2 of the findings for Experiment 1 is an important demonstration of generalizability.

The meta-analytic effect size of the effect of threat-of-shock on BP is d=0.68, and although large for psychology standards, in real-life situations it might actually be even larger as we operate over longer durations/anxiety-inducing situations. For example, during prolonged periods of anxiety e.g. during an exam, time might feel like it flies, in line with my underestimation effect.

3.5.2 Effect of fear on time perception

Taking together the findings from Experiments 4 & 5, the evidence is not strong enough to argue that my fear manipulation shifted time perception and thus one can't reject the null hypothesis that there is no effect of fear on time perception. Although in Experiment 4 participants seemed to be overestimating temporal durations (in line with my hypothesis) the effect was only trending significance. In the follow-up Experiment 5, in which power was increased (by a. increasing the number of participants b. increasing the number of trials c. and by making the manipulation stronger, i.e. the shocks more aversive), there was no evidence of temporal overestimation. At the same time, in none of these Experiments did I detect an effect of fear on temporal sensitivity (WF did not differ statistically between the fear and baseline trials). These results are not in line with a previous study that used a similar design to mine (Fayolle et al., 2015) and found a rather large effect of fear on time perception (d=1.89). A key difference between these studies is that in Fayolle et al., the shock could be received at any point during the presentation of the to-be-timed stimulus, whereas in my study, the shock was delivered only *after* the to-be-timed stimulus disappeared from the screen. Thus, in this

other paradigm (Fayolle et al., 2015), it is not clear whether it is fear or the recovery from an negative event that has just happened that led to overestimating time. In both of these studies, shocks were delivered on 100% of the shock trials, which leaves open the possibility that participants habituated to the shocks early on in the task, and thus raises the question of whether the fear manipulation was successful. Future studies could try replicating my results by decreasing the shock reinforcement to 80%, in line with the current fear conditioning literature. Nevertheless, this null result provides a compelling indication that my anxiety findings are not a 'generic' effect of aversive stimuli, and instead are potentially specific to unpredictable threats (i.e. anxiety).

3.5.3 Hypothesised mechanism behind the effect of fear and anxiety on time perception

These results provide a more refined understanding of how aversive mental states might influence how we perceive time, and are consistent with the notion that anxiety and fear have different effects. The way each of these mental states affect our perception of time can be explained by considering attention-based models of time perception (Thomas & Weaver, 1975), as well as experimental work (Coull et al., 2004; Failing & Theeuwes, 2016; Macar et al., 1994; Thomas & Weaver, 1975; Tse, Intriligator, Rivest, & Cavanagh, 2004; Wearden, O'Rourke, Matchwick, Min, & Maeers, 2010). Specifically, during a fearful event, e.g. a car accident, it is adaptive to focus attention on the threatening object, including its timing. In the example of a car crash, paying close attention to the timing properties of the car driving towards you makes it more likely that you will turn at the right moment to avoid the collision. Thus, it is possible that increased attention paid to timing the threatening object during a fearful state leads to time overestimation (although not found in this study). The same attentional mechanism

might be in place in general for surprising or novel experiences. Experimental studies suggest that surprising events, which automatically capture attention (Horstmann, 2015), lead to a slower perception of the passage of time (i.e. time overestimation). This has been well documented in oddball paradigms, in which repetitive "standard" stimuli are interrupted by a deviant "oddball" stimulus, with the latter automatically attracting attention. In such studies, the oddball stimuli were consistently judged as lasting for longer compared to the standard stimuli (Birngruber et al., 2014; Failing & Theeuwes, 2016; Tse et al., 2004), consistent with the hypothesis that increased attention allocation to the surprising stimulus leads to time overestimation.

While during fearful events attention is focused on the situation occurring at the present moment, in anxiety attention may be shifted away from the task at hand, towards threatening events that could happen in the future (e.g. while trying to finish an essay, worry about potentially missing the looming deadline). In that sense, perceiving time under anxiety could be compared to psychological studies during which participants perform two competing tasks simultaneously. Such tasks have showed that the subjective duration of stimuli is increasingly underestimated the more participants attend to nontemporal stimulus features, such as form, colour (Coull et al., 2004; Hicks et al., 1977) or semantic meaning (Macar et al., 1994). In anxiety, *decreased* attention is directed towards what is happening right now, including timing the present, and towards anticipating the occurrence of a negative event. Given that decreased attention to time has been associated with a feeling that time flies (i.e. time underestimation, Block et al., 2010), this might explain my finding that anxiety leads to time underestimation.

Previous studies suggest an association between interval timing and arousal i.e. that stimuli eliciting an arousal response are typically perceived as being longer in duration

(for a review see Lake, LaBar, et al., 2016). Given my paradigm, it is reasonable to conjecture that my studies' effects are driven partly by arousal, since anxiety leads to increased arousal. However, this study's principal result (i.e. time underestimation) is opposite to what is typically observed for arousing stimuli, and so I conclude that my results are most parsimoniously explained by an attentional mechanism.

These results therefore might help explain different subjective experiences in fear and anxiety disorders. On the one hand, in specific phobias and post-traumatic stress disorder, it might be the fear component of the relevant stimuli/experiences that leads to the feeling that time slows down (Vicario & Felmingham, 2018). On the other hand, in generalised anxiety, given that individuals anticipate that negative events could occur at any moment, and thus their attention is always distracted from what is happening right now, this might leave them with a sense that time flies (Mioni et al., 2016).

3.5.4 Effect of emotional faces on time perception

In contrast with previous studies (Sylvie Droit-Volet & Meck, 2007), I did not find that emotional pictures affected the perception of time. Pooling data from all my Experiments together to increase power also failed to show an effect on emotion, despite a clear impact of induced anxiety. One possible explanation for the surprising pattern of results is that anxiety (including the low levels of anxiety experienced during the safe condition) swamped any impact of the emotional faces. In other words, the emotional impact of viewing happy and fearful faces may have been minimised since participants were in an overall anxiogenic context, anticipating possible painful stimulation. Taking into account the fact that anxiety has been shown to induce an egocentric mindset when inferring other's mental state (Todd et al., 2015) a related possibility is that participants were less likely to be influenced by the facial expressions

they observed, since they were anxious. A final possibility is that the effect of emotional faces on time perception is confounded by perceptual complexity (Folta-Schoofs et al., 2014; Palumbo et al., 2014) and novelty (Cai et al., 2015) and thus might depend on the particular stimuli used. Further experiments investigating the effect of emotional pictures on the perception of time should control for these confounds.

3.5.5 Limitations

For Experiment 2, I used the same power calculation as in Experiment 1, without conducting a new power analysis. My aim was to replicate the findings from Experiment 1 by just changing one parameter, the stimulus durations (suprasecond durations instead of subsecond). Fortunately, if I was to replicate my results, I would need 25 participants assuming a meta-analytic d=0.68, with 90% power and an alpha of 0.05 (two-tailed).

While I found evidence that anxiety leads to underestimating time, the results do not support that fear leads to time overestimation. However, the extant literature contains a number of studies suggesting that fear leads to time overestimation (Sylvie Droit-Volet et al., 2010; Fayolle et al., 2015; Grommet et al., 2011; Tipples, 2011, 2011). Another limitation is that in all these studies I used emotional pictures, and thus it is not clear whether the effect generalises to timing non-emotional events. Even though I did not find an effect of emotion (happy, fearful and neutral expression) on time perception, a future study could attempt to replicate my results using neutral pictures (for example, fractal images) to confirm that this effect is not related to the timing of faces *per se*.

In Experiments 1 & 2 (Figures 3-5 and 3-7), the difference between the two conditions is observed even at the longest durations. This might suggest an effect of anxiety on lapse rate which however was not investigated further as lapse rates do not provide us

information about the underlying sensory mechanism, but rather generic aspects of cognition such as the alertness or motivation of the observer (Kingdom & Prins, 2016). Additionally, the psychometric function model used to estimate the parameters of the curves, fixed the lapse rate to 10% (similarly to a previous study; Terhune et al., 2016) which might have biased the modelling results (Prins, 2012; Wichmann & Hill, 2001). Despite this limitation, the modelling results are in line with the ANOVA analysis and hence reliable to some extent.

It is also worth noting that in this study, consistent with the translational animal literature (Davis et al., 2010), I frame anxiety as response to an unpredictable, but known, aversive outcome. Anxiety may, nevertheless, be exacerbated by unknown aversive outcomes, actual or imagined (e.g. catastrophizing); a hypothesis that may be tested in further research.

It should be noted the anxiety and the fear paradigms are not matched in terms of 1) number of shocks: in the fear experiments participants receive far more shocks compared to the anxiety experiments 2) the timing of the shocks: in the fear experiments the shocks were received as soon as the to-be-timed stimuli disappeared while in anxiety the shocks were received during the ITI. These differences are inherent to the conceptualisation of fear and anxiety, where anxiety is defined as the prolonged state of anticipation of an upredictable negative event (hence less shocks in this paradigm, delivered randomly) while fear is the state associated with a negative event about to happen (hence more shocks in this paradigm, linked to a cue). Additionally, the type of the to-be-timed stimuli differed between the anxiety and fear experiments; emotional faces were used in the former and fractals in the latter. Since the effect of the emotional faces was not significant (either as a main effect or as an interaction) one

would not expect that the different type of the to-be-timed stimuli used in fear and the anxiety experiments might be a confound.

I should note that the present study was designed to better understand the cognitive effects of anxiety (with an ultimate aim to help us better understand a prominent mental health condition) rather than better understand the mechanisms of time-perception. Overall these results are in line with an attention-based account of how anxiety affects time perception. Nevertheless, considerably more work is needed to help us better understand the fundamental mechanisms of time perception.

3.6 Conclusion

In contrast to previous studies suggesting that unpleasant events induce a state during which the passage of time slows down (Bar-Haim et al., 2010; Fayolle et al., 2015; Grommet et al., 2011; Stetson et al., 2007; Tipples, 2008, 2011), this study found that anxiety is associated with temporal underestimation, i.e. that time flies. Grounded in contemporary conceptualisations highlighting the dissociation between fear and anxiety, I suggest that in prior studies in which an aversive event led to temporal overestimation, it was fear that was induced, rather than anxiety. This dissociation between the effects of fear and anxiety on time perception might be explained based on attentional accounts of time perception, and might enable better understanding of the symptoms of fear- vs. anxiety- specific pathological states.

Chapter 4: Does overloading cognitive resources mimic the impact of anxiety on temporal cognition?

4.1 Abstract

Anxiety alters how we perceive the world and can alter aspects of cognitive performance. Prominent theories of anxiety suggest that the effect of anxiety on cognition is due to anxious thoughts 'overloading' limited cognitive resources, competing with other processes. If this is so, then a cognitive load manipulation should impact performance of a task in the same way as induced anxiety. Thus, I examined the impact of a load manipulation on a time perception task that I showed to be reliably impacted by anxiety in Chapter 3. In contrast with my prediction, across three Experiments I found that time perception was insensitive to the load manipulation. These results do not therefore support the idea that anxiety impacts temporal cognition by overloading limited cognitive resources, at least as induced by a commonly-used load manipulation. It is possible, alternatively, that the anticipatory aspect of anxiety (i.e. anticipating that something negative will happen) contributes to cognitive deficits, via an evolutionarily-preserved defence survival system, as suggested by theories of anxiety derived from animal models.

4.2 Introduction

Chapter 3 of this thesis demonstrated that induced anxiety can have profound effects on cognition, in line with previous studies showing that anxiety can be detrimental to performance of real-life and lab-based tasks (Arnsten, 2009; Robinson, Vytal, Cornwell, & Grillon, 2013). Anxious individuals frequently report that their worrisome thoughts are hard to control, to the point where they may be unable to think of anything else, resulting in interference with everyday tasks. One theory posits that the deleterious effect of anxiety on cognition is because components of anxiety, such as worry and self-preoccupation, take up the limited cognitive processing resources necessary to perform the task at hand, thereby impairing performance (Eysenck et al., 2007). An implication of this theory is that the effect of state anxiety on cognition should be similar to that of other manipulations that take up cognitive resources, such as working memory load. Specifically, this account predicts that anxious thoughts should impair performance in a cognitive task the same way that being overloaded by information can impair one's performance (Sweller, 1988).

Support for the idea of mechanistic similarity between anxiety and working memory load comes from experimental evidence suggesting that anxiety and load compete for limited attentional recourses. Specifically, it has been found that anxiety impairs working memory, but also the reverse, that anxiety is affected by working memory load. Regarding the former, threat-of-shock induced anxiety (Schmitz & Grillon, 2012) impaired both spatial and verbal working memory (Lavric et al., 2003; Shackman et al., 2006). Interestingly, this effect was found under low but not high cognitive load, i.e. only when the working memory task was relatively easy (Vytal et al., 2012, 2013). One possibility is that when the working memory task became difficult (i.e. high cognitive

load), attentional resources were shifted towards performing the cognitively demanding task and away from the mildly threatening event (i.e. anticipating a shock during the threat-of-shock condition). If this is the case then one would expect that shifting attention away from threat would lead to decreasing anxiety under this high cognitive load condition. Indeed, this has been shown by a study in which anxiety was measured using a physiological marker: threat-potentiated startle (King & Schaefer, 2011). In another study, when participants were under high cognitive load, their physiological measure of anxiety (startle) also decreased compared to the low cognitive load condition (Balderston et al., 2016). Taken together, these studies indicate that both state anxiety and working memory load can compete for limited attentional resources.

Further support for mechanistic similarities between anxiety and working memory comes from studies examining their effects on physiological measures of arousal. A number of threat-of-shock studies find that threat results in increased physiological markers of arousal including skin conductance and startle reflex (Bradley et al., 2018) as well as pupil dilation (Bitsios et al., 1996). Similarly, working memory load increases pupil dilation, and this effect occurs across a large range of tasks (for a meta-analysis see: van der Wel & van Steenbergen, 2018). In the cognitive domain, it has been reported that cognitive load (Brown, 1997) and clinical anxiety (Bar-Haim et al., 2010) shift time perception in a similar way, although the timing tasks that were used in these studies were not directly comparable.

Overall, this evidence suggests that working memory load influences measures of arousal in a similar way to anxiety and that both load and anxiety compete for similar attentional resources. However, to my knowledge no study has directly assessed whether working memory load and anxiety impact temporal cognition in the same way

on identical cognitive tasks. In this study, I therefore combined a time perception task (Kopec & Brody, 2010) which I have previously shown to be influenced by induced anxiety (see Chapter 3), with a cognitive load manipulation. In this Chapter, I found that anxiety induced by threat-of-shock (Schmitz & Grillon, 2012) led to the underestimation of temporal intervals. I argued that when participants were in the anxious state, worrisome thoughts related to the anticipation of the shocks took up limited attentional resources, which led participants to underestimate temporal intervals. In other words, anxiety-related thoughts distracted participants from the temporal cognition task at hand. Distraction from time could lead to "missing ticks from our mental clock" (Coull et al., 2004; Macar et al., 1994; Thomas & Weaver, 1975). If this is the case, then one would expect that temporal underestimation would also occur when participants are overloaded by cognitive load.

I therefore took a well-established load manipulation – increasing set size on the Sternberg task – and predicted that the higher the cognitive load, the more attentional resources dedicated towards maintaining it in memory, and therefore the greater the temporal underestimation in the timing task would be. In other words, cognitive load should mimic the effects of threat-of-shock on temporal estimation (Figure 4-1).

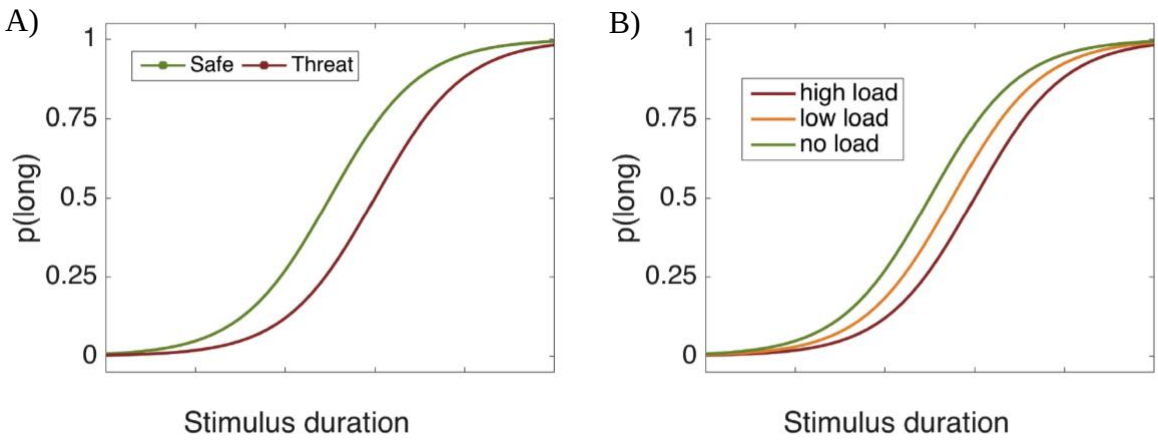


Figure 4-1: A) A model of the results from the threat-of-shock study of Chapter 3. B) Predicted effect of working memory load on the time perception task. The curves represent the proportion of long responses [p(Long)] as a function of stimulus duration and form a characteristic sigmoid shape as stimulus duration increases. I predicted that the cognitive load would promote a rightward shift of the curve, compared to the baseline (no load) condition, due to underestimation of time intervals.

4.3 Materials and Methods

4.3.1 Overview

The study and all procedures were approved by the UCL Research Ethics Committee (Project ID Number: 1764/001) and were in accordance with the latest version of the Declaration of Helsinki. Participants were recruited from UCL subject databases. During a single testing session, following written informed consent, participants completed questionnaires assessing their mood and anxiety levels. Subsequently they completed the WAIS-III Digit Span (see Chapter 2.4) and then the temporal bisection task under different cognitive load conditions. I conducted three Experiments on independent samples (Table 4-1), so I provide an outline of common methods before providing Experiment-specific information.

4.3.2 General methods

4.3.2.1 Participants

A power calculation (G*power version 3.1.9.2; Faul, Erdfelder, Lang, & Buchner, 2007) determined the sample size of Experiment 1 based on a meta-analysis of previous studies I conducted using the same temporal cognition task and an anxiety manipulation. The meta-analytic effect size of induced anxiety on temporal cognition (Cohen's d) was d=0.68. In order to be on the conservative side, I decreased this effect size by ~25% to d=0.49; with 80% power and an alpha of 0.05 (two-tailed), the required sample size was estimated to be 35 participants.

Participants had normal or corrected to normal vision and no present (or past) neurological or psychiatric diagnosis. All provided written informed consent and received compensation for their participation (£7.50 per hour).

Table 4-1: Sample demographic information for the three Experiments. Figures represent counts or means (SDs). BDI = Beck depression inventory. STAI = Trait anxiety from the State Trait Anxiety Inventory. Note: BDI/STAI measures were not collected for Experiment 2 due to time constraints.

	Sample size	**Age**	**Female**	**Digit span**	**BDI**	**STAI**
Experiment 1	35	22.71 (2.56)	22	22.11 (2.9)	7.26 (6.60)	40.77 (11.62)
Experiment 2	66	22.83 (2.66)	46	23.66 (4.3)	N/A	N/A
Experiment 3	67	23.22 (3.27)	45	17.70 (3.5)	6.46 (5.64)	39.42 (10.34)

4.3.2.2 Apparatus

All experiment material was presented on Windows computers using Cogent 2000 (www.vislab.ucl.ac.uk/cogent.php; Wellcome Trust Centre for Neuroimaging and Institute of Cognitive Neuroscience, UCL, London), running under MATLAB.

4.3.2.3 Temporal bisection task under load

Participants completed a visual temporal bisection task similar to the one used in Chapter 3, but without receiving shocks, i.e. there was no threat condition. Instead, they performed the temporal bisection task under cognitive load (Figure 4-2). In the load conditions participants were shown letters to remember while performing the temporal bisection task. In the low load condition there were only two different digits (e.g. SSBBB; Figure 4-2B), while in the high load condition, all five digits were different (e.g. SXBLP; Figure 4-2C). Participants also performed the task also under no load, which was used as a baseline. The order of the conditions was counterbalanced across participants. There were 36 trials in each block, and thus a total of 6 blocks (2 for each condition).

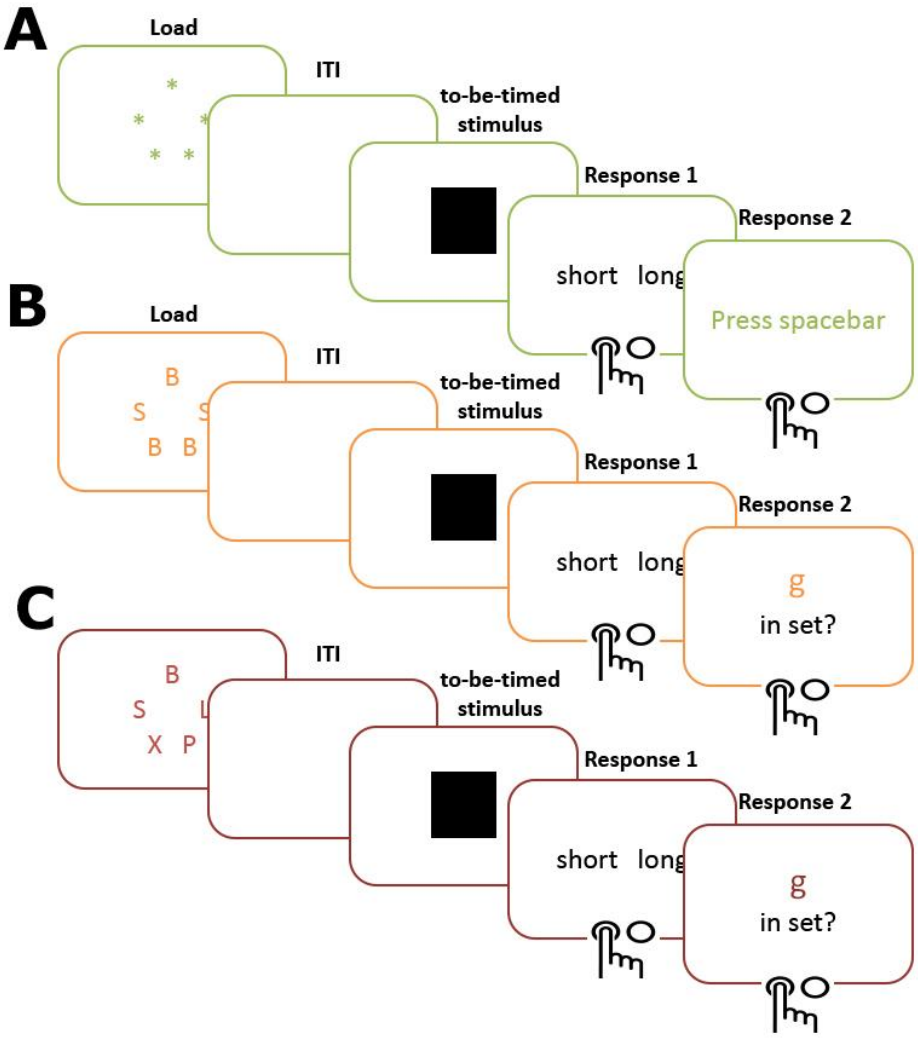


Figure 4-1: Task design. In Experiment 1, the task consisted of: A) no load condition, B) low load condition and C) high load condition. The image colours (green, orange, red) are for illustration purposes and were not used in the actual experiment. Note: in the actual experiment, fractal images were used, which where the to-be-timed stimuli.

A short training phase preceded the temporal bisection task. It consisted of presenting participants with two anchor durations, a "short" duration (1,400ms) and a "long" duration (2,600ms). Each was presented three times, and presentation order was pseudorandomised. In addition, before the beginning of each block (high load, low load, or no load) the anchor durations were repeated.

Each trial started with a set of letters presented for 1.5 seconds, which had to be memorised and repeated out loud throughout the trial. A to-be-timed fractal image was

then presented for one of six durations: 1,400, 1,640, 1,880, 2,120, 2,360, or 2,600ms. On each trial participants were required to make a choice: press “short” if the duration of the stimulus was judged to be similar to the “short” anchor, or press “long” if the duration of the stimulus was judged to be similar to the “long” anchor. After the 2 second response limit, a single letter probe appeared on the screen for 2 seconds. Participants had to indicate with a button press whether that single letter belonged to set shown at the beginning of the trial. For the no load condition, participants had to press spacebar. The feedback participants received on their performance was “Correct”, “Wrong” or “Too slow”, shown for 500 ms. There was a variable inter-trial interval: 1000 ms, 1500 ms or 2000 ms. Following each block, participants rated how difficult they found the memory task using a visual analogue scale.

The fractal images (12 different images) that participants had to time were pseudorandomised, and presented equally often in each condition to avoid potential biases (Wearden & Ferrara, 1996). The load letters that participants were instructed to remember were all capitalised consonants, while the single probe letter was in lowercase, to avoid engaging visual recognition memory. In order to avoid repetition effects, the same letters were not shown in 3 consecutive trials. In the no load condition, participants viewed asterisks instead of a set of letters and were instructed to press a button instead of responding to a probe letter. All other aspects of the no load condition were identical to the load condition. All button presses were counterbalanced across participants.

4.3.3 Data analysis

A similar approach in analysing this data was followed as in Robinson, Bond, & Roiser (2015). All data was pre-processed in MATLAB (v. R2015b). Frequentist significance

tests were run in SPSS (v. 23, IBM Corp, Armonk, NY) while Bayesian analyses were run in JASP (v. 0.9). Frequentist and Bayesian repeated-measures analysis of variance (ANOVA) models were constructed in exactly the same way for all analyses, with frequentist ANOVAs used to generate F-statistics, p-values and effect sizes for interactions of interest, and Bayesian ANOVAs used to generate log Bayes factors ($logBF_{10}$) for models of interest relative to a null model.

The Bayesian approach allows one to compare the relative predictive ability of a specific model. Rather than, for example, stating that the main effect of load, main effect of time, and their interaction are significant, one could conclude (on the basis of a model comparison) that e.g. the interaction is actually the more parsimonious model. I defined the 'winning' model as the model with the highest BF_{10} relative to the null. The relative predictive success of one model over another was computed by dividing the BF_{10} for one model by the other. It is noted that any value greater than one shows that a model is better at predicting the data than the comparison. For brevity and to help interpretations, labels were assigned, ranging from anecdotal (1–3), to substantial (3–10), to strong (10–30), to very strong (30-100), to decisive (>100; Jeffreys, 1998); these labels correspond to in differences of log BF. It is noted that when interactions are reported, the Bayes factors represent a model that includes the interaction plus the main effect of each component of the interaction.

4.3.3.1 Proportion of long responses

Trials on which participants did not make a response were excluded from the analysis. Repeated-measures analyses of variance (ANOVAs) were performed on the proportion of stimuli participants judged to be long (proportion of long responses, p(Long). The effects of load (no load vs. load), duration (six stimulus durations) were used as within-

subject factors. Greenhouse-Geisser corrections were applied when violations of sphericity occurred.

4.3.4 Experiment specific methods

Following Experiment 1, for Experiment 2, I further decreased the initial effect size for the power analysis (d=0.68) by ~50% to d=0.35; with 80% power and an alpha of 0.05 (two-tailed), the subsequent sample size was estimated to be 66 participants. The low load condition was dropped after Experiment 1, as it did not differ significantly from baseline. For Experiment 2, participants repeated letters in their head, because participants were within earshot during testing and I did not want them overhearing each other's voices and thus being distracted. Lastly, the high load condition was increased to eight digits for Experiment 3 (Table 4-2).

Table 4-2: Experimental parameters for the Experiments

	Task conditions (digits)	**Load digits**
Experiment 1	no load (0), low load (2), high load (5)	repeated out loud
Experiment 2	no load (0), high load (5)	repeated silently
Experiment 3	no load (0), high load (8)	repeated out loud

4.4 Results

4.4.1.1 Manipulation check: effect of load

There was a significant main effect of load on accuracy for Experiment 1 ($F(2,68)=35.77$, $p<.001$, $\eta_p^2=.513$), Experiment 2 ($F(1,65)=84.43$, $p<.001$, $\eta_p^2=.565$), and Experiment 3 ($F(1,66)=314.75$, $p<.001$, $\eta_p^2=.827$). Participants were less accurate when they had to identify presence of a letter from: five letters compared to two/no

letters (Experiment 1); five letters compared to no letters (Experiment 2); eight letters compared to no letters (Experiment 3; see Figure 4-3). Bayes factor analysis revealed the winning models to be those including a main effect of load for Experiment 1 ($logBF_{10}$=19.69), Experiment 2 ($logBF_{10}$=24.25), and Experiment 3 ($logBF_{10}$=54.40), all of which were decisively (>100 times) better than the null models.

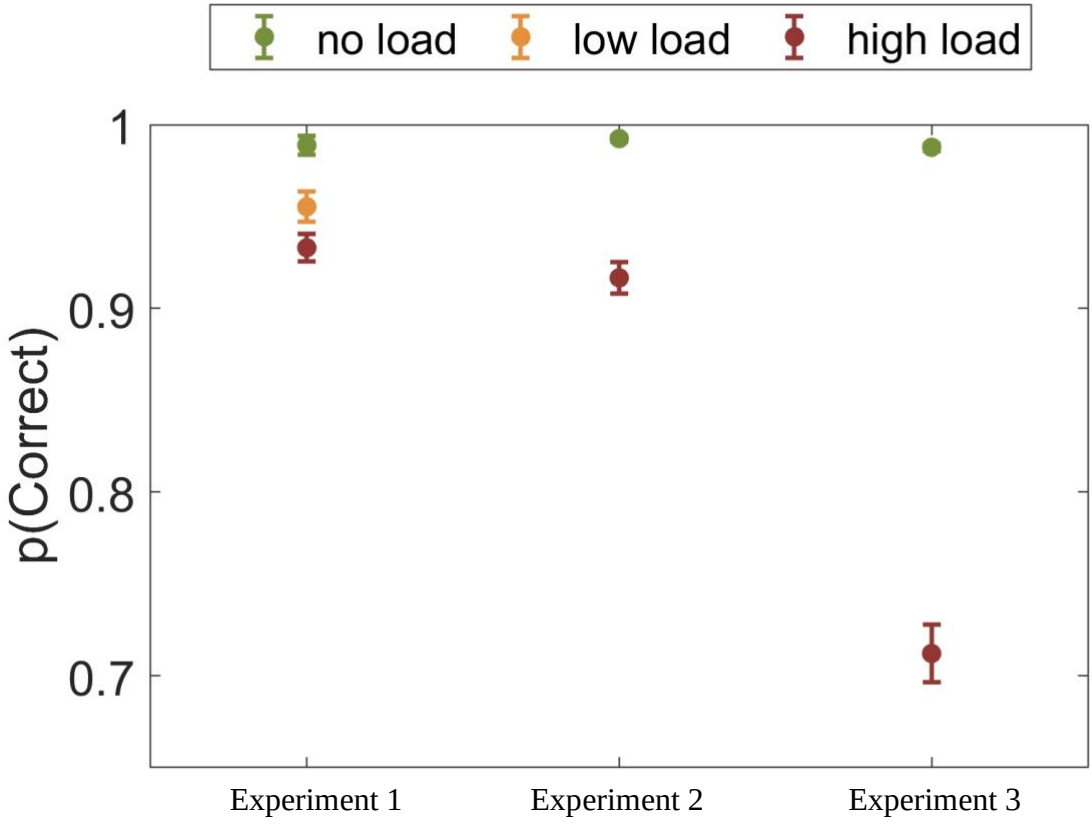


Figure 4-3: Effect of cognitive load on the load task. Greater values reflect higher accuracy. The proportion of correct responses (p(Correct)) decreased across load conditions, showring that the manipulation was effective. Error bars are standard errors of the mean (SEM).

4.4.2 Experiment 1: No load, low load and high load

4.4.2.1 Proportion of long responses

There was a significant main effect of stimulus duration ($F(2.13, 72.50)=164.49$, $p<.001$, $\eta_p^2=.829$). As expected, the longer the stimulus duration, the more likely it was

to be classified as “long” (Figure 4-4). Contrary to my hypothesis, however, load did not significantly affect the proportion of “long” responses ($F(2, 68)=2.46$, $p=.093$, $\eta_p^2=.068$). The stimulus duration by load interaction was non-significant ($F(10, 340)=1.11$, $p=.356$, $\eta_p^2=.032$).

Bayes factor analysis revealed the winning model to be one including only a main effect of duration ($logBF_{10}=334.15$), which was anecdotally (2 times) better than the model including duration and load ($logBF_{10}=333.44$), decisively (391 times) better than the model additionally including a duration by load interaction ($logBF_{10}=328.18$), and decisively (>1000 times) better than the load only model ($logBF_{10}=-2.96$).

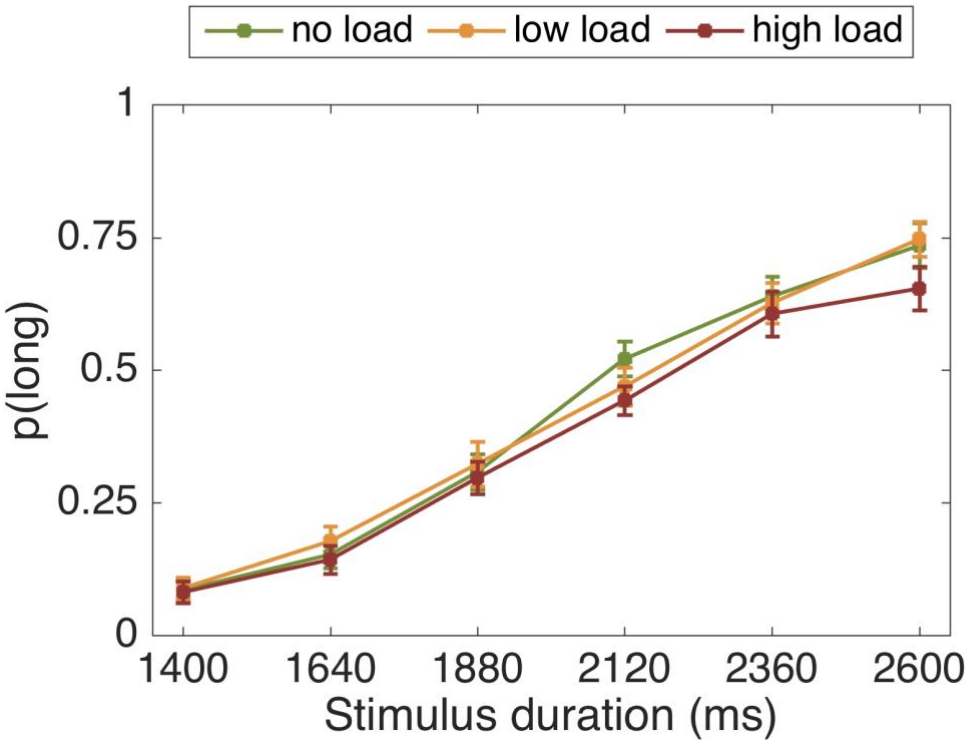


Figure 4-4: Proportion of stimuli rated “long” as a function of the actual presentation length and load condition. Error bars are standard errors of the mean (SEM).

4.4.2.2 Psychophysical modelling

Data from one participant was excluded from this analysis since it was impossible to fit

an accurate sigmoid curve to their data.

Bisection point

The BP was not significantly different between the conditions ($F(1.52, 50.22)=0.44$, $p=.592$, $\eta_p^2=.013$). Thus there was no shift in the psychometric curve, and the perception of temporal intervals did not differ under load.

Bayes factor analysis favoured the null model, which was substantially better (4 times) than the model including load ($logBF_{10}=-1.5$).

Weber fraction

WF was not significantly different between the conditions as revealed with a repeated-measures analyses of variance ($F(2, 66)=0.27$, $p=.763$, $\eta_p^2=.008$). Thus there was no evidence that the sensitivity to time intervals differed under load.

Bayes factor analysis favoured the null model, which was substantially better (4 times) than the model including load ($logBF_{10}=-1.48$).

4.4.3 Experiment 2: No load and high load

4.4.3.1 Proportion of long responses

There was a significant main effect of stimulus duration ($F(2.55, 166.01)=406.60$, $p<.001$, $\eta_p^2=.862$). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 4-5). Similarly to Experiment 1, load did not affect participants' proportion of "long" responses ($F(1, 65)=0.54$, $p=.466$, $\eta_p^2=.008$). The stimulus duration by load interaction was non-significant ($F(4.21, 274.14)=0.95$, $p=.440$, $\eta_p^2=.014$).

Bayes factor analysis revealed the winning model to be one including only a main effect of duration ($logBF_{10}$=521.73), which was substantially (7 times) better than a model including duration and load ($logBF_{10}$=519.75), decisively (884 times) better than the model additionally including a duration × load interaction ($logBF_{10}$=514.99), and decisively better (>1000) than the load only model ($logBF_{10}$=-2.43).

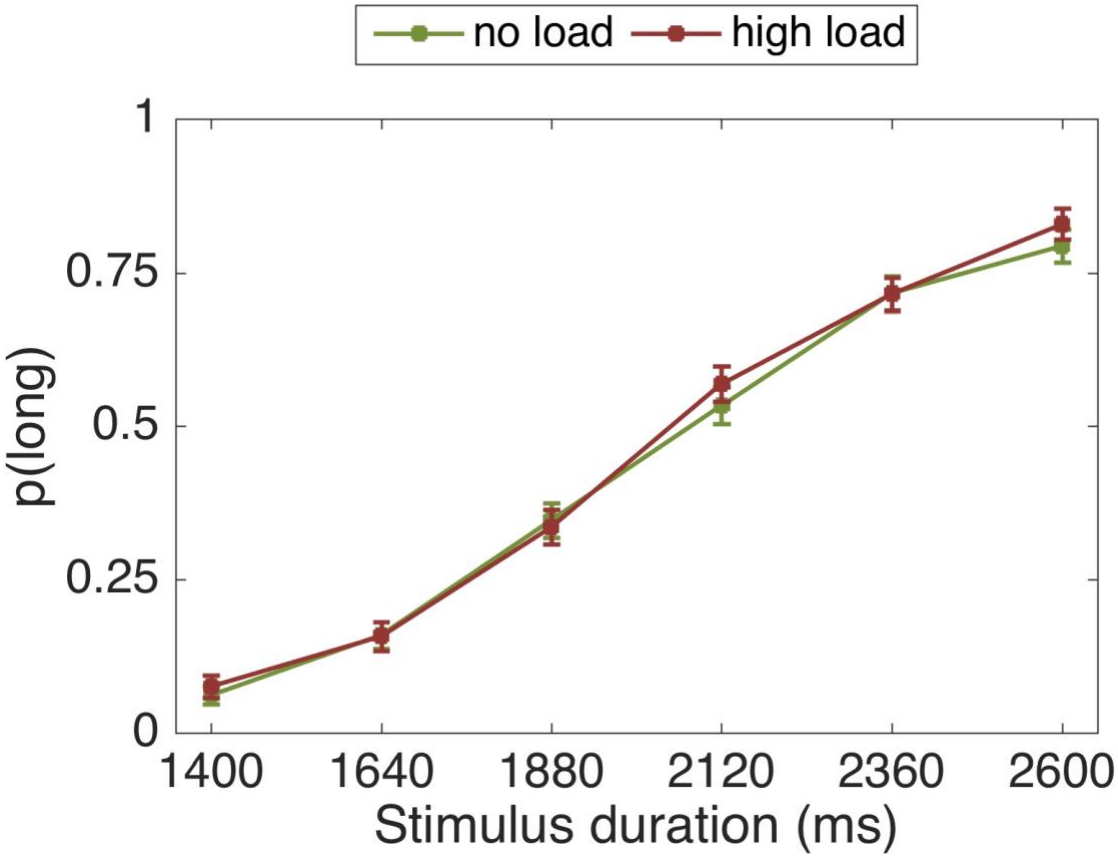


Figure 4-5: Proportion of stimuli rated "long" as a function of the actual presentation length and load condition. Error bars are standard errors of the mean (SEM).

4.4.3.2 Psychophysics modelling

Data from two participants was excluded from this analysis since it was impossible to fit an accurate sigmoid curve to their data. This suggests that participants were not performing the task as instructed.

Bisection point

The BP was not significantly different during the high load (M=2,104.58, SD=262.85) compared to the no load (M=2,147.30, SD=264.83) condition (t(63)=1.40, p=.165, d=0.18). Thus there was no shift in the psychometric curve, and hence we can conclude that the perception of temporal intervals did not differ under load.

Bayes factor analysis favoured the null model, which was substantially better (3.5 times) than the model including load ($logBF_{10}$=-1.29).

Weber fraction

The WF was not significantly different in the high load (M=0.13, SD=0.08) compared to the no load (M=0.13, SD=0.07) condition (t(63)=0.69, p=.494, d=0.08). Thus there was no evidence that the sensitivity to time intervals differed across load.

Bayes factor analysis favoured the null model, which was substantially better (6 times) than the model including load ($logBF_{10}$=-1.91).

4.4.4 Experiment 3: No load and high load

4.4.4.1 Proportion of long responses

There was a significant main effect of stimulus duration (F(2.948,194.582)=266.62, p<.001, η_p^2=.802). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 4-6). There was no main effect of load on proportion of "long" responses (F(1, 66)=1.523, p=.222, η_p^2=.023). The stimulus duration by load interaction was significant (F(5, 330)=3.43, p=.005, η_p^2=.049), however all post-hoc paired-samples t tests for the duration by load interaction were non-significant (p > .05), except the longest duration (t(66) = 2.693, p = .009) which did not survive Bonferroni

correction (corrected alpha = .0083).

Bayes factor analysis revealed the winning model to be one including only a main effect of duration ($logBF_{10}$=408.06), which was anecdotally (2 times) better than a model including duration and load ($logBF_{10}$=407.14), strongly (20 times) better than the model additionally including a duration × load interaction ($logBF_{10}$=405.12), and decisively better (>1000 times) than the load only model ($logBF_{10}$=-2.03).

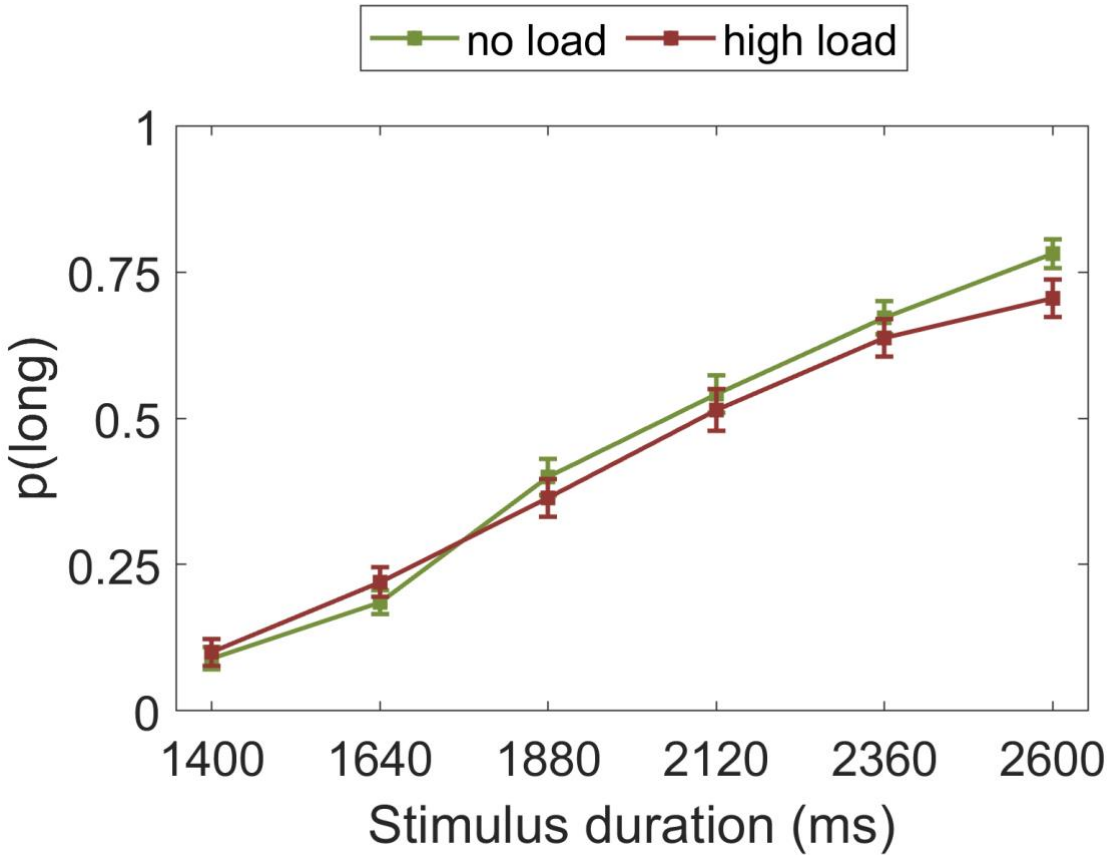


Figure 4-6: Proportion of stimuli rated "long" as a function of the actual presentation length and load condition. Error bars are standard errors of the mean (SEM).

4.4.4.2 Psychophysics modelling

Bisection point

The BP was not significantly different during the high load (M = 2,172.84, SD = 657.12) vs no load (M = 2,101.07, SD = 479.93) condition (t(66) = -1.196, p = .236). There was no shift in the psychometric curve, and hence the perception of temporal intervals did not seem to differ under load.

Bayes factor analysis favoured the null model, which was substantially better (4 times) than the model including load ($logBF_{10}$=-1.33).

Weber fraction

The WF was not significantly different during the high load (M = 0.13, SD = 0.19) compared to the no load (M = .03, SD = .90) condition (t(66) = 1.036, p = .304). Thus, there was no evidence that the sensitivity to time intervals differed across load.

Bayes factor analysis favoured the null model, which was substantially better (4 times) than the model including load ($logBF_{10}$=-1.50).

4.5 Discussion

These results provide no evidence supporting the hypothesis that cognitive load impacts time perception in the same way as induced anxiety. Specifically, participants did not underestimate time under high cognitive load (5 or 8-letter load), while in Chapter 3 participants did underestimate time under induced anxiety. Using psychophysical modelling, I did not detect a significant effect of cognitive load in the task: neither on the perception of time (BP), nor the sensitivity to the time intervals (WF). In other words, cognitive load did not lead participants to perceive the time intervals as shorter

and did not impair their ability to discriminate between different time intervals. Moreover, Bayesian analyses provided evidence favouring the null hypothesis: that the load manipulation had no impact on time perception.

This study does not support the hypothesis that anxiety impacts temporal cognition by overloading limited cognitive resources. Specially, three experiments failed to find that a commonly used manipulation of cognitive load mimics the effect of induced anxiety on a time perception task. Therefore, although cognitive theories of anxiety suggest that anxious thoughts overload limited attentional resources thus leading to cognitive deficits, it might be the case that anxiety impairs temporal cognition in a different way compared to other processes. Here, I am not suggesting that anxiety does not occupy cognitive resources, but that depletion of cognitive resources (at least as induced by this load manipulation) is not the mechanism by which anxiety influences time estimation.

Fear and anxiety animal models posit that threat activates both a cognitive circuit which relies on working memory, as well as an evolutionary conserved subcortical defence survival system which monitors threats, altering behaviour and physiology to promote harm avoidance (LeDoux & Pine, 2016; Moran, 2016). While the threat-of-shock manipulation is likely to activate both systems, it does not seem theoretically possible that the latter system was considerably activated by my load manipulation: although a load manipulation, like any difficult cognitive task, can be mildly anxiogenic, it seems unrealistic to assume that it would constitute an important threat and thus strongly promote the activation of harm-avoidance pathways. Notably, whilst there is an anxiety induction that uses a cognitive task, the Trier Social Stress Test (which uses a mental arithmetic to induce anxiety), this requires a specific and carefully orchestrated set-up in order to elicit strong feelings of anxiety in humans. Taking this into account, the

subcortical defence survival system (activating automatic harm avoidant behaviours due to anticipating harm) might thus be responsible for the unique effect of anxiety on my time perception task.

In order to test this behaviourally, a future study could combine my cognitive task with CO_2 inhalation (Bailey, Argyropoulos, Kendrick, & Nutt, 2005), a manipulation that strongly induces physiological symptoms of anxiety, thus potentially activating the defence survival system but not cognitive load. If this manipulation were to mimic the effect of induced anxiety (as in Chapter 3), it would suggest that anxiety affects temporal cognition via an evolutionarily preserved defence survival system, rather than competing for limited attentional resources.

Whilst the focus of the present Chapter is on cognitive load, my hypotheses were motivated by the notion that anxiety induces worrying thoughts, taking up working memory resources (Eysenck et al., 2007) necessary for time perception. Whether or not physiological sensations of anxiety vs worry may have differential impacts on temporal cognition is an interesting question, but I have not attempted to dissociate these two facets of anxiety in my design. Future studies utilizing a cognitive neuroscience approach would be highly suitable for distinguishing these aspects of anxiety. If it is via purely physiological sensations, would this be reflected by the aforementioned subcortical projections? If worry is driving the effect, but not via working memory, what are the cognitive and neural pathways by which it is interfering with time perception processes?

Alternatively, it is possible that anxiety impacts temporal cognition by overloading limited cognitive resources but my load manipulation was not sufficiently taxing to mimic the effect of induced anxiety on the time perception task. In other words, the load

task might not have been difficult enough and thus performing it did not result in pronounced competition with the temporal cognition task for attentional resources. In both Experiment 1 & 2 participants' performance on the high load task was close to ceiling (around 90%). However, the findings from Experiment 3 suggest that this alternative interpretation is not correct. In this experiment, participants performed at ~70% in the high-load (8 character) condition, which is closer to chance (50%) than it is full accuracy, and yet I found no evidence for a shifted bisection point or main effect of load comparable to the main effect of threat (like in Chapter 3), as predicted a priori (Figure 4-1B). Nevertheless, I did find some weak evidence for a load by duration interaction in the Frequentist analysis, suggesting that perhaps load does have an effect at longer durations. This effect warrants replication, as it does not survive correction for multiple comparisons, and neither the Bayesian analysis nor the psychophysiological modelling support it.

A further possibility is that there was not a sufficient number of trials to capture effects of load. However, Experiment 3 of Chapter 3 made use of just 48 trials per condition (threat-without-shock vs safe) with 25 participants, and was able to detect an effect, whereas the current study utilizes 72 trials per condition, with larger sample sizes (35, 66, 67). Therefore, the trial number and sample size have been shown to be sufficient for capturing the effect of anxiety on temporal perception, so the effect of cognitive load, if it exists, would have to be substantially smaller. Lastly, it could be that cognitive load is not a unitary construct and that different cognitive load manipulations (e.g. mental arithmetic) might have effects closer to threat-of-shock. Future work might seek to test this explicitly.

4.6 Summary

This Chapter's results suggest that a commonly used cognitive load manipulation does not affect a time perception task, unlike my finding in the previous Chapter that induced anxiety results in underestimation of time. Thus, these data do not support the proposition that anxiety impacts cognition by overloading limited cognitive resources, since overloading cognition via a load manipulation did not produce the same pattern of results. Instead, my findings are in line with theories of fear and anxiety derived from the animal literature, suggesting that anxiety might affect behaviour and cognition via activating a defence survival system that monitors threat in order to promote harm avoidance.

Chapter 5: Anxiety makes time pass quicker: neural correlates

5.1 Abstract

Anxiety is a process that promotes harm avoidance. It is accompanied by shifts in neurocognitive processing, but the precise nature of these changes are not fully understood. One possibility is that anxiety impairs concurrent (non-harm related) cognitive processing by commandeering finite neurocognitive resources in order to prioritise threat-related processes and harm avoidance. Chapter 3 showed that anxiety reliably 'speeds up time', promoting temporal underestimation, possibly due to loss of temporal information. Chapter 4 suggested that the effect is not driven by working memory load, however, this does not exclude other forms of neural overlap, which can be investigated by fMRI. Investigating this further, I aimed to examine whether anxiety and time processing overlap. Across two experiments (an exploratory Experiment 1, N=13, followed by a pre-registered Experiment 2, N=29) I combined a well-established anxiety manipulation (threat-of-shock) with a temporal bisection task while participants were scanned using functional magnetic resonance imaging. Consistent with Chapter 3, time was perceived to pass more quickly under induced anxiety. Anxiety induction led to widespread activation in the cingulate cortex, while the perception of longer intervals was associated with more circumscribed activation in a mid-cingulate area. Conjunction analysis identified convergence between anxiety and time processing in the insula and mid-cingulate cortex. These results provide tentative support for the hypothesis that anxiety impacts cognitive processing by overloading already-in-use neural resources. In particular, overloading mid-cingulate cortex capacity may drive emotion-related

changes in temporal perception, consistent with the hypothesised role of this region in mediating cognitive, affective, and behavioural responses to anxiety.

5.2 Introduction

While previous behavioural and neuroimaging work has mainly focused on how anxiety influences the processing of emotional information (i.e. hot cognition) (Bar-Haim et al., 2007; Carlisi & Robinson, 2018; Cisler & Koster, 2010; Mathews et al., 1997), less research has been conducted on how anxiety influences how we process non-emotional information (i.e. cold cognition), with mixed results (Robinson et al., 2013). To this end, I demonstrated in Chapter 3 that anxiety (induced in healthy individuals using threat of unpredictable shock) reliably leads to alterations in non-emotional perception, namely temporal perception. I found clear evidence that anxiety leads to underestimation of time, i.e. that time speeds up under threat of unpredictable electric shock, possibly due to the loss of temporal information. In the present study I extend this work to probe the neural correlates of the influence of anxiety on temporal processing, using a similar bisection task.

Previous functional magnetic resonance imaging (fMRI) studies employing a similar anxiety manipulation to mine (Kirlic et al., 2017, 2017; McMenamin et al., 2014a) have consistently found activation in the anterior insula while participants passively anticipate unpredictable shocks (see also: Robinson et al., 2019). Other brain areas that have been shown to be activated during sustained threat include the anterior and posterior cingulate gyrus, thalamus, caudate and cerebellum (Mechias et al., 2010; Robinson et al., 2019). These brain areas have also been associated with processing and anticipating painful stimuli (Koyama et al., 2005; Wager et al., 2013), supporting the hypothesis that they may play a general role in anticipating negative events over

prolonged periods of time. Consequently, I would expected to replicate these activations in the present study when individuals undergo an anxiety induction (threat-of-shock).

A broad network of brain regions has been reported to be recruited during time perception. A recent study suggested that, similarly to sensory cortical maps, topographic timing maps exist; where different brain areas respond to specific ranges of temporal intervals, and whose selectivity changes gradually (Harvey et al., 2020). For supra-second intervals (the focus of the current work), cortical brain regions are more heavily involved (Nani et al., 2019; Wiener et al., 2010), including the cingulate and frontal cortex, as well as the pre-supplementary motor area (pre-SMA), whose role in the processing of supra-second intervals is considered central (Schwartze et al., 2012).

There have been no studies exploring the interaction between anxiety and time perception at the neural level. However, more broadly, previous studies have highlighted the involvement of frontal areas in the interaction between anxiety and tasks tapping into cold cognition (Bishop, 2007, 2009; Carlisi & Robinson, 2018; Robinson et al., 2019). Consistent with this, two prior threat-of-shock studies found that anxiety increased activation in frontal areas (including the superior frontal gyrus), and these activations were also associated with anxiety-related changes in cognition (Balderston, Hsiung, et al., 2017b; Torrisi et al., 2016b). However, assuming that the effect of anxiety on cognitive function can be likened to classic multitasking interference (where two tasks compete for limited cognitive and neural resources, and hence interfere with one another: Eysenck et al., 2007; Watanabe & Funahashi, 2018), I would not necessarily anticipated that there exists a specific brain region underlying interference between anxiety and cognition. Instead, the precise region(s) implicated may depend on the particular cognitive task used to probe anxiety, since multitasking interference is a result of overlapping resources (Maillet et al., 2019; Nijboer et al., 2014; Watanabe &

Funahashi, 2018). In Chapters 3 and 4 I have previously argued that the impact of anxiety on time perception is driven by demands on attention, a cognitive resource both of these processes might be utilising. It is possible that the impact of induced anxiety on temporal perception is driven by overlap between time- and anxiety-related neural processing. A candidate brain area for such overlap is the pre-SMA, considering that it receives input from threat-related processing and regulatory processing, given its role in cognitive regulation of emotion (Kohn et al., 2014). Additionally, time-perception related activations in the pre-SMA have been reported to vary parametrically with the amount of attention allocated to timing a stimulus (Coull et al., 2004). At the same time, the pre-SMA, although not a main area activated during threat, seems activated by threat-of-shock (as revealed by a meta-analysis: Chavanne-Arod & Robinson, 2020) and seems important for different anxiety disorders and OCD (Harlé et al., 2020; Wagner et al., 2019); thus rendering it a candidate area for where time- and anxiety-related neural processing might overlap.

To test my hypothesis, I initially conducted a small exploratory Experiment (Experiment 1), which was used to refine my design and generate pre-registered (Sarigiannidis, 2019) predictions for the second Experiment (Experiment 2). Importantly, for Experiment 2, I calibrated the temporal cognition task to each participant to exclude the possibility that any neural differences observed were due to the properties of the different temporal intervals of the task. The specific predictions for Experiment 2 were the following:

1) Induced anxiety would lead to temporal underestimation, replicating my previous finding (Chapter 3). Specifically, I predicted that participants would perceive the temporal intervals as shorter when under threat-of-shock.

2) Anxiety would elicit activation in the anterior cingulate cortex and the caudate (in Experiment 2), as identified by my pilot Experiment (Experiment 1).

3) Time perception would elicit activation in the pre-SMA and right inferior frontal gyrus, as identified in a previous meta-analysis (Wiener et al. (2010).

4) Time-related and anxiety-related neural processing would interact in the pre-SMA.

5) Threat-induced activation changes (neural changes) during temporal processing would correlate with the threat-induced changes in time estimation (behavioural index).

5.3 Materials and Methods

5.3.1 Overview

All Experiments consisted of a single testing session. Following written informed consent, as approved by local ethical procedures (see below for specifics), and the completion of questionnaires (BDI and STAI; see Chapter 2.1), a shock calibration procedure (see Chapter 2.2), was completed by the participant in the scanning room to determine an appropriate level of aversive electrical stimulation. Participants then completed the temporal bisection task under threat of unpredictable shock and safe conditions (see Chapter 2.3) inside the scanner. During each one-hour scan, anatomical and functional images were acquired, with each of the two functional runs lasting approximately 15 minutes. During the task, participants chose between two responses (short and long) in a two-alternative forced choice manner inside the scanner, via an MRI-compatible button box. Information relating to participant recruitment and inclusion/exclusion criteria is provided in each of the experiment-specific methods sections below.

Experiment 1 was completed at the National Institutes of Health, Bethesda, MD, USA, while Experiment 2 was completed at University College London (UCL), UK.

5.3.2 Apparatus

In Experiment 1, experimental material was presented on Windows computers using E-prime 2 (Psychology Software Tools, Pittsburgh, PA), while Experiment 2 was run in Cogent 2000 (www.vislab.ucl.ac.uk/cogent.php; Wellcome Trust Centre for Neuroimaging and Institute of Cognitive Neuroscience, UCL, London), under MATLAB.

5.3.3 Shock calibration

A shock calibration procedure was performed prior to testing in order to control for shock tolerance and skin resistance (see Chapter 2.2). Single pulse shocks (Experiment 1) or trains of shocks (Experiment 2) were delivered to the non-dominant wrist via a pair of silver chloride electrodes using a DS7 (Experiment 1) or a DS5 (Experiment 2) stimulator (Digitimer Ltd, Welwyn Garden City, UK).

5.3.4 Experiment specific methods

A summary of the experiments carried out, highlighting their differences, can be seen on the table below. It is noted that a main difference between Experiments 1 & 2 is the different frequency with which the different duration stimuli were presented. While in Experiment 1 participants observed six different durations equally often, in Experiment 2 they were shown only three different durations; with one being presented far more often (78% of the trials) than the other two (22% of the trials).

Table 5-1: Summary of experiments conducted. Note that the experiments were completed at different sites in different countries.

	Sample size	Stimulus duration	Shock type	BDI	STAI
Experiment 1: NIH	13	1.4-2.6s (1.4, 1.64, 1.88, 2.12, 2.36, 2.6s)	single pulse	n/a	n/a
Experiment 2: UCL	29	• BP (this was determined per participant; 78% trials of interest), • 1.4s & 2.6s (22% catch trials)	train of shocks (0.5s)	5.06 (5.53)	35.72 (12.48)

5.3.4.1 Experiment 1: Temporal bisection task under threat-of-shock

The fMRI Experiment and all procedures were approved by the NIH Institutional Review Board Project (ID Number: 02-M-0321) and were conducted in accordance with the Declaration of Helsinki. The aim of Experiment 1 was to identify regions of interest (ROIs); 13 individuals were scanned.

Participants were recruited through advertisements (newspaper and public transport) in the Washington, D.C. metropolitan area. Following an initial telephone screen, individuals visited the NIH for comprehensive screening by a clinician, which comprised a physical examination, urine drug screen, and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association et al., 2013). Exclusion criteria were: contraindicated medical disorder (i.e. those thought to interfere with brain function and/or behaviour); past or current psychiatric disorders; and use of psychoactive medications or recreational drugs (per urine screen). Additional MRI specific exclusion criteria were: brain abnormalities on MRI (assessed by a radiologist), MRI contraindication, and excessive head motion during the functional scans.

All participants provided written informed consent and were reimbursed for their participation.

In Experiment 1, the duration of the to-be-timed stimuli varied between 1.4-2.6s (six possible durations: 1.4, 1.64, 1.88, 2.12, 2.36, 2.6s). The session consisted of two runs, each comprising of four blocks, two in the safe and two in the threat condition (counterbalanced) with 36 trials per block.

Seventy-two pictures were used in this experiment, depicting happy, neutral and fearful facial expressions, taken from 24 actors (Tottenham et al., 2009). During each block, participants viewed an equal number of happy, fearful and neutral facial expressions, the order of which was pseudorandomised. Similarly, stimulus durations were pseudorandomised within each block, so that all durations were repeated six times. Faces were used for this experiment, consistent with previous studies (see Chapter 3).

Participants received between 0-3 shocks during each threat block, and received no shocks during safe blocks. The order of the shocks was random for each participant and occurred on different trials, following the participants' response. This was done in order to potential confounds due to delivering the same frequency of shocks and timing of shocks to participants.

Scanning was performed on a 3T Siemens Magnetom Skyra using a 32-channel head coil. Each volume consisted of 34 slices and was acquired with TR=2s. Other parameters of the functional EPI were the following: voxel size of 3mm × 3mm (slice thickness of 2.5mm, 0.5mm slice separation), field of view of 216mm × 216mm, echo time of 30ms; flip angle of 70°. Anatomical scan were acquired as per NIH regulations, however after my departure from the NIH it was impossible to have access to them and thus they were not used for the analysis.

5.3.4.2 Experiment 2: Modified temporal bisection task under threat-of-shock

The Experiments and all procedures were approved by the UCL Research Ethics Committee (Project ID Number: 1227/001) and were conducted in accordance with the Declaration of Helsinki. Prior to the fMRI Experiment I completed a behavioural pilot to ensure that the properties of the modified task were as expected. I pre-registered this Experiment (Sarigiannidis, 2019).

Participants were recruited from UCL databases. A telephone interview was conducted to screen for past neurological or psychiatric diagnosis and to determine MRI safety. Exclusion criteria were: contraindicated medical disorder, past or current psychiatric disorders. Additional MRI specific exclusion criteria were: brain abnormalities on MRI (assessed by a radiologist), MRI contraindication, and excessive head motion (see below) during the functional scans.

On the day of testing participants completed self-report measures of depression (Beck Depression Inventory: BDI; Beck & Steer, 1987) and trait anxiety (State Trait Anxiety Inventory: STAI; Spielberger, 1983) to ensure they fell within the non-clinical range. Participants provided written informed consent and received £20 for the fMRI Experiment (which lasted approximately two hours: one hour for task explanation and questionnaires, and one hour for scanning).

A power calculation (G*power version 3.1.9.2 (Faul et al., 2007)) determined the sample size based on the meta-analytic effect of threat (d=0.68) from my previous behavioural temporal bisection Experiments (Chapter 3) . Given that the MRI scanner may be an anxiogenic environment, which could raise anxiety levels during the safe condition and therefore reduce condition differences, I decreased the expected effect size by ~30% (d=0.47). In order to achieve d=0.47 with 80% power and an alpha of

0.05 (two-tailed), the required sample size required was 30 participants. In the fMRI Experiment, one participant was excluded from analysis as they pressed the same button on every trial, leaving us with a final sample size of 29.

Before the main task, participants performed the calibration task, which had a structure identical to that of the task used in Experiment 1 (i.e. it included six durations, but consisted only of a single safe block of 72 trials. This data was analysed immediately after completion of the calibration task in order to calculate the BP for each participant (i.e. the duration for which participants responded "short" or "long" equally often). This was set as the main stimulus duration for the fMRI experiment, in order to remove a potential confound of in Experiment 1: in that design, it was not clear whether the stimuli duration contrast indicated the neural correlates of how participants *perceived* time differently, or whether the neural effect was driven by the *actual presentation differences* between the stimuli. In order to minimize scanning time, participants performed this calibration task while anatomical brain images were acquired.

During the main task, each of the two runs consisted of six blocks (three safe and three threat blocks per run). Each block comprised 18 trials: the stimulus duration of 14 trials was set to the BP of each participant (calculated from the calibration task), the stimulus duration of two trials was 1.4s (the short "anchor" duration) and the stimulus duration of two trials was 2.6s (the long "anchor" duration). Thus, although in Experiment 1 and in the calibration task participants viewed six different durations (1.4, 1.64, 1.88, 2.12, 2.36, 2.6s; as in the Experiments of Chapters 3 & 4), in the main task for Experiment 2 they viewed just three (1.4s, BP, 2.6s). Participants were informed that in the main task the stimuli durations would be more difficult to tell apart compared to the calibration task. At the end of each block of the main task, a 20s rest period followed during which the screen went blank and participants were instructed to rest while the scan finished.

Participants received between zero and three shocks per block during the threat condition, according to a pre-determined schedule that resulted in participants receiving between 2-14 shocks in total, following a Gaussian distribution. The order of the shocks was random for each participant and occurred on different trials, during the ITI. Each train of shocks consisted of 10 pulses delivered over 0.5 seconds.

Scanning was performed on a 3T Siemens Magnetom Prisma using a 64-channel head coil. The 1mm isotropic anatomical scan was a T1-weighted MPRAGE with the following parameters: TR=2.53s, TE=3.34ms, acquisition matrix=256 x 256, slice thickness 1mm, flip angle 7°. Functional (echo planar imaging: EPI) scans were acquired with a 2D sequence. Each volume consisted of 42 slices and was acquired in TR=2.94s, with ascending slice order. The angulation of the slice (T>C-30°), the phase-encoding direction, and the compensating gradients (z-shimming) were optimized to minimize the dropout in regions near the orbito-frontal cortex and amygdalae (Weiskopf et al., 2006). Other parameters of the EPI were: voxel size 3mm × 3mm in-plane (slice thickness 2.5mm, 0.5mm slice separation); field of view 192mm×192mm; 12% over-sampling in the phase-encoded direction; bandwidth 2298 Hz/px; echo spacing 0.5ms, echo time 30ms; flip angle 90°. Fat saturation with an excitation of 130° was used prior to each excitation. At the end of each session, I acquired one fieldmap with identical parameters to the EPI scans. Heart rate and breathing were monitored using Spike2 software (http://ced.co.uk/products/spkovin).

5.3.5 Behavioural data analysis

All data was processed in MATLAB (v. R2015b), and statistical analysis was carried out in SPSS (v. 23).

5.3.5.1 Experiment 1

Trials on which participants did not make a response were excluded from the analysis. Repeated-measures analyses of variance (ANOVAs) were performed on the proportion of stimuli participants judged to be long (p(Long)). The effects of threat (safe or threat-of-shock condition) and duration (six stimulus durations) were used as within-subject factors. Greenhouse-Geisser corrections were applied when violations of sphericity occurred. The BP was calculated for safe and threat conditions separately for each participant, and the effect of threat was assessed using a paired-samples t-test.

5.3.5.2 Experiment 2

Trials on which participants did not make a response were excluded from the analysis. A paired-samples t-test was used to test the effect of threat on the proportion of long responses made at each participant's BP (N=84 trials per condition). I did not analyse catch trials, i.e. the few trials (N=4 per block) whose durations were equal to the "short" (1.4s) and "long" (2.6s) anchors. However, I did use them to exclude one participant who pressed the same button on all trials, including both anchors, indicating that they did not understand/comply with the instructions. In contrast to Experiment 1, where there were six durations of interest, and thus an ANOVA was used, in Experiment 2 there was only one duration of interest, and hence t-tests were used.

5.3.6 Functional neuroimaging data analysis

Experiment 1 was a pilot Experiment which I used to generate ROIs for Experiment 2, and hence the data analysis for Experiment 1 was exploratory. In both Experiments, EPI data were analysed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, www.fil.ion.uck.ac.uk/spm) software in MATLAB

R2015b. After removing the first five volumes from each time series to allow for T1 equilibration, the remaining volumes were realigned to the sixth volume, normalized into standardized space (Montreal Neurological Institute (MNI) template), and smoothed using an 8 mm full width at half maximum Gaussian kernel. Following the realignment stage, all image sequences were checked for translations and rotations greater than 1.5 mm/1 degree – corrupted images were removed and replaced using interpolation. Following normalisation, images were manually checked for artefacts. Brain areas reported were defined using the Atlas of the Human Brain (Mai, 2016).

5.3.6.1 Experiment 1

Trials were modelled as events of zero duration. The regressors of interest were the onsets of the to-be-timed stimuli of all six durations (1.4, 1.64, 1.88, 2.12, 2.36, 2.6s) during safe and threat blocks (i.e. 12 regressors of interest). Regressors of no interest were the training stimuli indicating the anchor durations (presented before the beginning of each block), shocks, as well as the start screens of each block (indicating whether in that block participants were safe or under threat-of-shock). All these regressors were convolved with the SPM 12 canonical hemodynamic response function, time-locked to the onset of the corresponding event. I also included six movement regressors of no interest for all participants.

Using the general linear model, parameter estimate images were created for each regressor, and combined to create the primary contrasts at the subject level.

Second-level analyses were conducted using the standard summary statistics approach to random effects analysis. In this exploratory pilot Experiment, I applied a lenient cluster-forming threshold of $p<0.05$ (uncorrected) cluster size>150, but did not use this to make inference. Instead I used the resulting clusters as ROIs in Experiment 2.

The fMRI contrasts were: 1) the effect of the threat compared to the safe condition; 2) the effect of stimulus duration, which was a linear contrast across the six stimulus durations (from short to long), collapsed across the safe and threat conditions; 3) the interaction of duration and threat.

5.3.6.2 Experiment 2

Due to changes in the experimental design I modelled the entire trial including stimulus presentation, stimulus response and ITI. The four regressors of interest were threat trials (BP trials during the threat condition) and safe trials (BP trials during the safe condition), which were categorised as either "perceived long" (BP trials on which the participant responded with "long") or "perceived short" (BP trials on which the participant responded with "short"). Regressors of no interest were the catch trials (i.e. trials whose duration was 1.4s and 2.6s) as well as missed trials (i.e. trials on which participant did not make a response), which were modelled separately for safe or threat blocks. Other regressors of no interest were training stimuli indicating the anchor durations (presented before the beginning of each block), shocks, as well as the start screens of each block (indicating whether participants will be safe or under threat-of-shock). All these regressors were convolved with the SPM 12 canonical hemodynamic response function, time-locked to the onset of the corresponding event, and taking into account its duration (which varied slightly across participants due to variation in BPs).

I also included six movement regressors of no interest in all participants, alongside 12 regressors extracted from the pulse and respiratory rate, corresponding to a set of sine and cosine Fourier series components extending to the third harmonic (Glover et al., 2000) based on the Spike traces. There were also two regressors to model the variation

in respiratory volume (Birn et al., 2006, 2008) and heart rate (Chang et al., 2009), also based on the Spike traces.

Using the general linear model, parameter estimate images were created for each regressor, and combined to create the primary contrasts at the subject level.

Second-level analyses were conducted using the standard summary statistics approach to random effects analysis. I applied a cluster-forming threshold of $p<0.005$ (uncorrected) and report small-volume corrected p-values for responses in my ROIs as defined in my pre-registration document (Sarigiannidis, 2019). Cluster-level inferences are appropriate for whole brain exploratory analyses and hence are implemented for the exploratory aspects of the sections: neural effect of threat (see 5.4.2.2), neural effect of perceived duration (see 5.4.2.3) and neural effect of threat × perceived duration (see 5.4.2.4). However, when applying ROIs, cluster-based inference tends to be less sensitive as some voxels in a cluster may be cut off by the edge of the mask. Therefore for inferences concerning ROIs, a voxel-wise approach is more appropriate and hence it was implemented for ROI analysis of the following sections: neural effect of threat (see 5.4.2.2), neural effect of perceived duration (see 5.4.2.3) and overlap analysis (5.4.2.5).

The fMRI contrasts were: 1) the effect of threat, i.e. all the BP trials under the threat-of-shock condition, compared to the BP trials in the safe condition; 2) perceived duration ("long" vs "short", though the actual duration was identical), including all the BP trials, collapsed across the threat and safe conditions; 3) the interaction between perceived duration and threat. I additionally examined the overlap between (1) and (2) using a conjunction analysis.

5.3.6.3 Regions of Interest

In Experiment 1 I detected significant threat-induced activation in the anterior cingulate cortex, and since this area was also activated during threat-of-shock conditions in my group's previous studies (Robinson et al., 2014), I used it as a pre-registered ROI for the overlap between anxiety and time-related processing. However, due to a mix-up the co-ordinates identified as the anterior cingulate cortex in the pre-registration document actually refer to the left caudate, because both peaks fell within the same large cluster. In the interests of full transparency, I therefore used both ROIs for the threat contrast using a (standard) 10-mm sphere for both the caudate (MNI coordinates [x=-18, y=11, z=26]) and the anterior cingulate cortex (MNI coordinates [x=0, y=-4, z=50]; prediction 2).

Previous meta-analysis on time perception studies reported strong activation in the pre-SMA (Wiener et al., 2010), and thus for contrast (1) I defined an additional ROI defined as a 10-mm sphere ROI on that area (again this was pre-registered: Talairach coordinates [x=0, y=0, z=56], taken from Wiener et al. (2010), converted to MNI coordinates [x=-1, y=-4, z=62]; prediction 3).

5.4 Results

5.4.1 Experiment 1

5.4.1.1 Behavioural results inside the scanner

Across blocks, participants reported being significantly more anxious in the threat compared to the safe condition ($t(12)=5.40$, $p<0.001$, $d=1.56$). There was a significant effect of stimulus duration ($F(2.46, 29.58)=211.51$, $p<0.001$, $\eta_p^2=.946$; see Figure 5-1). As expected, the longer the stimulus duration, the more likely it was to be classified as

"long". The effect of threat was non-significant ($F(1, 12)=2.57$, $p=0.135$, $\eta_p^2=.177$) and neither was the threat-by-duration interaction ($F(5, 60)=0.27$, $p=0.926$, $\eta_p^2=.022$). The BP was not significantly different between the threat and safe conditions ($t(12)=1.36$, $p=0.194$, $d=0.37$), although the direction of the effect was consistent with my previous studies (a rightward shift in the psychometric function, consistent with temporal underestimation during threat). This non-significant result was expected since the experiment is underpowered, and this was not the purpose of the study.

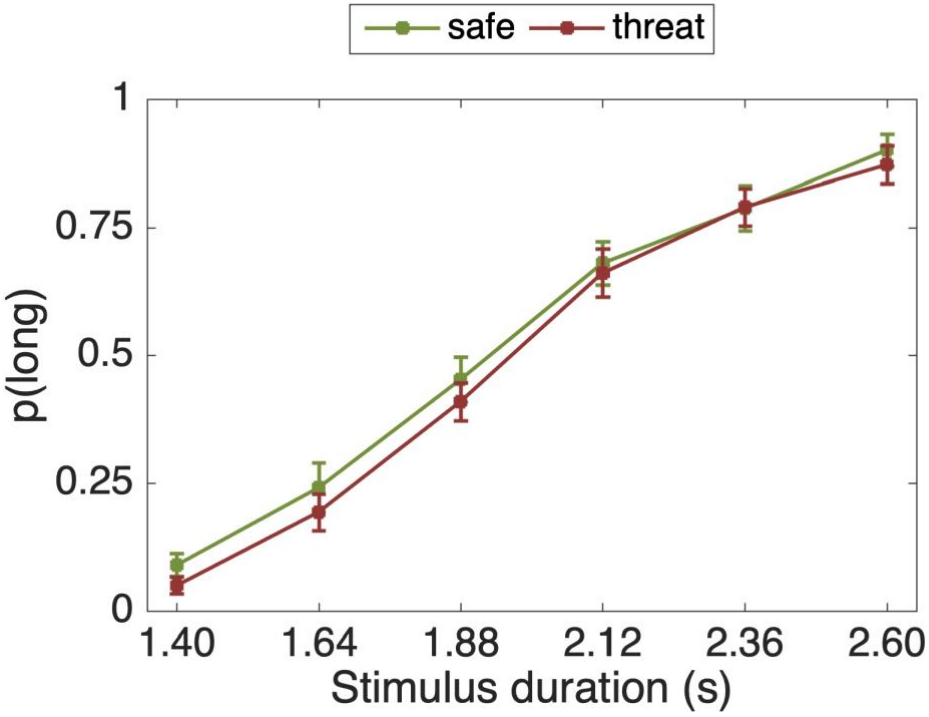


Figure 5-1: Proportion of stimuli rated "long" as a function of the actual presentation length and threat condition. Error bars are standard errors of the mean (SEM).

5.4.1.2 Neural effect of threat

No voxels survived correction for multiple comparisons in the threat contrast, the duration contrast or the interaction. Therefore, the below analyses were conducted using an exploratory threshold of $P<0.05$ (uncorrected), and used to generate hypotheses for Experiment 2. Only large clusters ($k>150$) are reported (see Table 5-2)

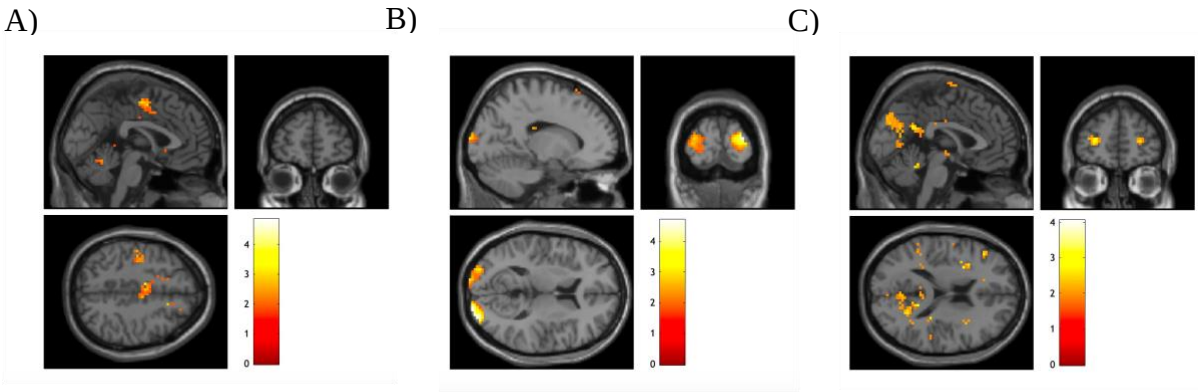


Figure 5-2: Uncorrected, exploratory BOLD activation for each contrast in Experiment 1: A) threat>safe; B) linear effect of lengthening temporal interval; C) positive interaction of A and B. A threshold of P<0.05 (uncorrected) was used, colour bars indicate t-values.

Table 5-2: Activations for the Experiment 1 contrasts, exploratory cluster forming threshold p<0.05 (uncorrected)

			MNI coordinates					cluster	peak
contrast	region	hemisphere	x	y	z	#voxels	Zvalue	p(FWE-corr)	p(FWE-corr)
threat>safe	white matter	n/a	0	27	-7	390	3.51	0.136	1
	caudate	left	-18	11	26	240	3.26	0.626	1
	anterior cingulate	n/a	0	-4	50	"	2.51	"	1
safe>threat	supramarginal gyrus	right	36	-43	35	272	3.77	0.471	0.997
long>short	occipital gyri	right	24	-100	8	247	3.47	0.989	0.992
short>long	superior cerebellar peduncle	left	-3	-25	-13	24626	4.56	<0.001	0.154
interaction	precuneus	left	-9	-67	44	446	2.63	0.491	1
	frontomarginal gyrus	left	-24	46	2	66	3.15	1	1
interaction (inverse)	precentral gyrus	right	59	-2	-23	182	2.88	0.997	1

<u>Threat>safe</u>

This analysis examined the effect of the threat-of-shock vs the safe condition and revealed activations in two large clusters. One cluster was in the parietal cortex,

consisting mainly of white matter, and therefore was not considered further. The peak activation in the other cluster was in the left caudate ([x=-18, y=11, z=26) while in the same cluster, there was also a sub-peak in anterior cingulate cortex ([x=0, y=-4, z=50]); see Figure 5-2A. Both of these areas were used as ROIs for the threat contrast of Experiment 2.

Safe>threat

This analysis examined the effect of the safe vs the threat-of-shock condition and revealed activations in one large cluster, with a peak in the right supramarginal gyrus.

5.4.1.3 Neural effect of stimulus duration

Long>short

This analysis examined the effect of stimulus duration implementing a linear contrast (-2.5, -1.5, -0.5, 0.5, 1.5, 2,5 for the six stimulus durations: 1.4, 1.64, 1.88, 2.12, 2.36, 2.6s) and revealed activation in one large cluster, with a peak activation in the visual cortex (right superior occipital gyrus; see Figure 5-2B).

Short>long

This analysis examined the effect of stimulus duration implementing the inverse of the above contrast which revealed activation in one large cluster, with a peak activation in the left superior cerebellar peduncle.

5.4.1.4 Neural effect of threat × stimulus duration interaction

This analysis examined the interaction of the above effects, revealing activation in one large cluster, with peak activation in the precuneus. There was also activation in the frontal areas, specifically in the left middle frontal gyrus (see Figure 5-2C). The inverse

contrast revealed activation in one large cluster, with a peak activation in the precentral gyrus.

5.4.2 Experiment 2

5.4.2.1 Behavioural results inside the scanner

Participants reported being significantly more anxious in the threat compared to the safe condition ($t(28)=11.28$, $p<0.001$, $d=2.09$). As hypothesised, on BP trials participants responded "short" significantly more often in the threat compared to the safe condition ($t(28)=2.39$, $p=0.024$, $d=0.44$; Figure 5-3).

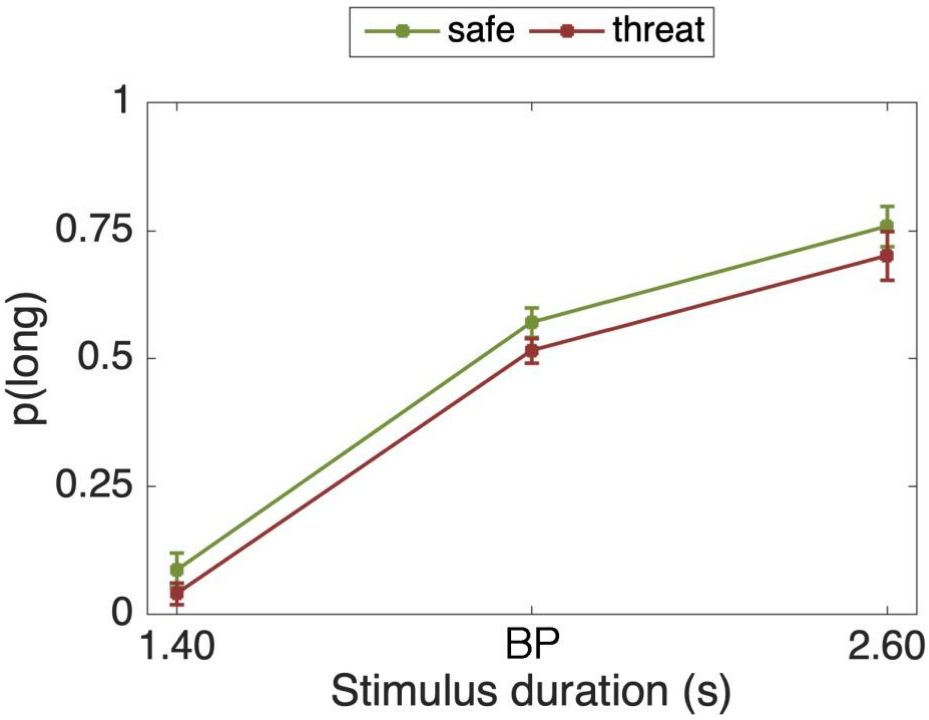


Figure 5-3: Proportion of p(Long) responses was significantly lower in the threat condition for the individually tailored bisection point (BP) duration, suggesting temporal underestimation during anxiety. Error bars are standard errors of the mean (SEM). The 1.4 and 2.6s durations were not used in any analyses and are only plotted here for completeness.

5.4.2.2 Neural effect of threat

Threat>safe

This analysis examined the effect of the threat-of-shock vs the safe condition. There was significant (whole-brain voxel-level FWE corrected) activation in a large cluster (see Figure 5-4 and Table 5-3), including peaks in the subgenual anterior cingulate cortex (bilateral), thalamus (bilateral), claustrum (left only), caudate (left only) and anterior insula (bilateral). Other peaks in this cluster that did not survive voxel-level correction were an insula/orbitofrontal cortex area (right only), the lateral septal area (right only) and the putamen (right only). Three more significant clusters that survived FWE correction revealed activations in the left cerebellum and the parietal operculum (left and right).

In my pre-registration document, I defined the caudate and the anterior cingulate cortex as ROIs, since they were both activated under threat-of-shock in Experiment 1. When small volume correction was applied using a (standard) 10-mm sphere ROI around the peak of the caudate cluster identified in Experiment 1 (MNI coordinates [x=-18, y=11, z=26]), a peak survived FWE voxel-level correction for multiple comparisons ([x=-15, y=20, z=23], Z=3.21, k=37, $p<0.05$). The ROI around the peak of the anterior cingulate cortex cluster from Experiment 1(MNI coordinates [x=0, y=-4, z=50]), also revealed a peak surviving FWE voxel-level correction for multiple comparisons ([x=3, y=-4, z=41], Z=2.90, k=11, $p<0.05$).

Additionally, to explore brain-behaviour correlations, I performed an exploratory analysis in which the effect of threat on behavioural responses ($p(Long)_{threat}$-$p(Long)_{safe}$) was entered as a covariate into the [threat>safe] contrast. I expected that the neural effect of threat>safe would be larger in participants who showed greater temporal

underestimation during threat. However, no activations survived correction for multiple comparisons. Equally, no activations survived correction in the inverse contrast.

Safe>threat

This analysis examined the effect of the safe vs the threat-of-shock condition. There was significant (whole-brain voxel-level FWE corrected) activation in two clusters with bilateral peaks in the inferior temporal gyrus, in the left medial orbital gyrus (see Figure 5-4 and Table 5-3), and in a right parahippocampal area (subiculum). Both clusters extended into the amygdalae, although the peaks there did not survive voxel-level correction.

5.4.2.3 Neural effect of perceived duration

Perceived long> perceived short trials

This analysis examined the effect of the perceived long vs. short trials, i.e. trials in which participants judged the to-be-timed stimulus (which was actually always the same duration at their own BP) as "long" compared to "short". There was significant activation in a single cluster with bilateral peaks in mid-cingulate cortex (see Figure 5-4 and Table 5-3).

In my pre-registration document I defined the supplementary motor area as an ROI since it has been reliably implicated in time perception studies. When small volume correction was applied using a (standard) 10-mm sphere ROI around the meta-analytic peak identified by Wiener et al (2010: MNI coordinates [x=-1, y=-4, z=62]) I identified a peak which survived FWE voxel-level correction for multiple comparisons ([x=0, y=-4, z=53], Z=3.14, k=11, $p<0.05$).

Additionally, in an exploratory analysis, I investigated whether activation in the mid-cingulate cortex peak voxel was associated with the degree of temporal underestimation during threat, but the correlation was non-significant (r(29)=-.28, p=.884).

Perceived short> perceived long trials

This analysis examined the effect of the perceived short vs. long trials, i.e. trials in which participants judged the to-be-timed stimuli as "short", compared to when they judged them as "long". No clusters survived correction at either the peak or voxel level (Table 5-3).

5.4.2.4 Neural effect of threat × perceived duration

This analysis examined the interaction between the effect of threat and that of perceived duration. No clusters survived correction in either this or the inverse contrast.

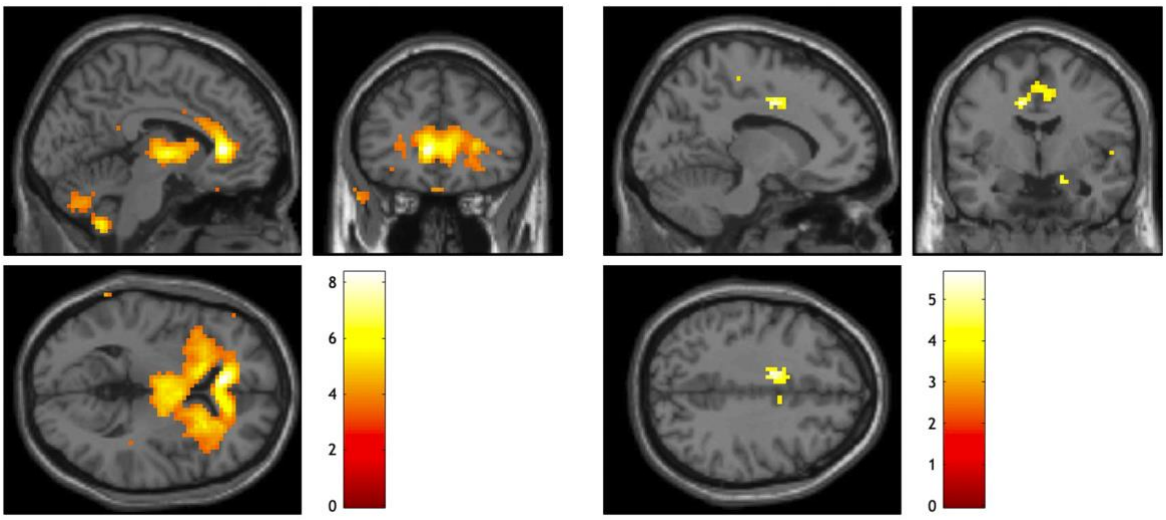


Figure 5-4: Activation for the threat>safe contrast (left) and the perceived long> perceived short trials (right). Cluster forming threshold p<0.005 (uncorrected). The colour bar represents t-values.

Table 5-3: fMRI activations for [threat>safe,] [safe>threat], [perceived long>perceived short], and [perceived short> perceived long] contrasts (cluster forming threshold: p<0.005, uncorrected).

threat>safe

		MNI coordinates					cluster	peak
region	hemisphere	x	y	z	#voxels	Z-value	p(FWE-corr)	p(FWE-corr)
Subgenual anterior cingulate cortex	left	-6	32	5	4951	5.87	<0.001	0
thalamus (inferior thalamic peduncle)	left	-6	-7	2	“	5.2	“	0.004
claustrum	left	-24	20	-1	“	4.95	“	0.012
Subgenual anterior cingulate cortex (BA33)	right	9	32	5	“	4.92	“	0.013
white matter (inferior longitudinal fasciculus)	right	33	2	-10	“	4.86	“	0.017
thalamus (posterior hypothalamic area)	right	3	-10	2	“	4.86	“	0.017
caudate	left	-15	17	8	“	4.74	“	0.027
anterior insula	right	30	14	-10	“	4.66	“	0.038
anterior insula	left	-30	14	-7	“	4.58	“	0.051
insula/orbitofrontal cortex (area orbitoinsularis)	right	27	20	5	“	4.52	“	0.064
lateral septal	right	3	2	5	“	4.49	“	0.071
putamen	right	15	8	-1	“	4.35	“	0.118
putamen	right	18	14	2	“	4.31	“	0.137
white matter	right	24	26	-4	“	4.3	“	0.14
putamen	right	18	20	2	“	4.25	“	0.165
white matter	right	27	32	8	“	4.25	“	0.165
cerebellum	left	-9	-55	-52	1914	4.97	<0.001	0.01
parietal operculum	left	-69	-25	26	278	4.06	0.042	0.295
parietal operculum	right	45	-46	29	364	3.82	0.013	0.528

safe>threat

		MNI coordinates					cluster	peak
region	hemisphere	x	y	z	#voxels	Zvalue	p(FWE-corr)	p(FWE-corr)
inferior temporal gyrus	left	-36	5	-40	266	5.4	0.05	0.002
inferior temporal gyrus	left	-33	17	-37	“	5	“	0.009
inferior temporal gyrus	left	-30	14	-34	“	4.82	“	0.02
medial orbital gyrus	left	-21	32	-19	“	4.56	“	0.055

medial orbital gyrus	left	-24	20	-22	“	4.37	“	0.108
medial orbital gyrus	left	-18	29	-16	“	4.23	“	0.173
amygdala (lateral amygdaloid)	left	-24	-1	-28	“	3.7	“	0.662
amygdala (basolateral amygdaloid)	left	-21	-4	-25	“	3.54	“	0.818
presubiculum	left	-18	-13	-25	“	3.5	“	0.857
parahippocampal (subiculum)	right	18	-10	-25	262	4.42	0.053	0.093
inferior temporal gyrus	right	30	14	-34	“	4.34	“	0.121
inferior temporal gyrus	right	36	8	-40	“	4.15	“	0.225
inferior temporal gyrus	right	42	17	-43	“	4.1	“	0.259
white matter	right	33	-1	-34	“	4.01	“	0.335
white matter	right	27	2	-31	“	3.82	“	0.532
amygdala (lateral amygdaloid)	right	24	-1	-28	“	3.66	“	0.7

long>short

		MNI coordinates					cluster	peak
region	hemisphere	x	y	z	#voxels	Zvalue	p(FWE-corr)	p(FWE-corr)
white matter	left	-12	-4	38	93	4.58	0.016	0.077
mid cingulate	right	6	-1	44	“	3.79	“	0.72
mid cingulate	left	0	-4	50	“	3.46	“	0.963

short>long

		MNI coordinates					cluster	peak
region	hemisphere	x	y	z	#voxels	Zvalue	p(FWE-corr)	p(FWE-corr)
cerebellum	right	27	-73	-46	303	4.33	0.148	0.184
inferior temporal gyrus	left	-51	-46	-10	107	4.15	0.187	0.321
cerebellum	left	-18	-40	-46	38	4.14	0.276	0.331

5.4.2.5 Overlap analyses

The results of Experiment 2 suggest a degree of overlap in the activations identified in the [threat>safe] and [perceived long>perceived short] contrasts, though there was no significant interaction effect. I formally tested this overlap by creating a mask for each contrast (thresholded at t>1.7, corresponding to p<0.05 uncorrected), and using this to perform small volume correction on the other contrast (see Figure 5-5), using a cluster-forming threshold of p<0.005 (uncorrected).

Applying the [perceived long>perceived short] mask to the [threat>safe] contrast revealed significant overlap surviving FWE voxel-level correction for multiple comparisons in right insula ([x=30, y=2, z=-7], Z=4.35, k=57, p<0.05) and left putamen ([x=-27, y=8, z=-7], Z=4.03, k=12, p<0.05).

Applying the [threat>safe] mask to the [perceived long>perceived short] contrast revealed overlap in a mid-cingulate cortex area which narrowly missed FWE voxel-level correction for multiple comparisons ([x=-12, y=2, z=38], Z=4.29, k=15, p=0.068).

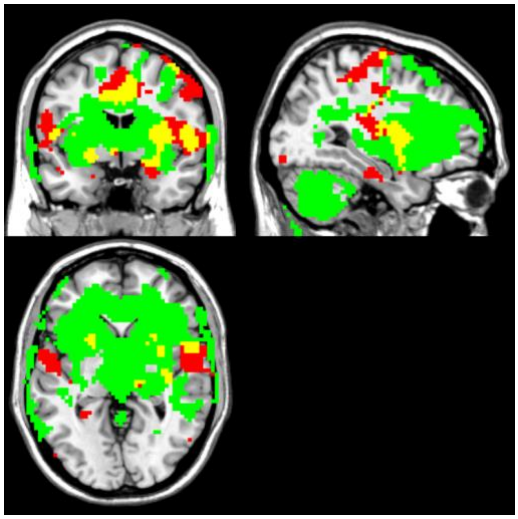
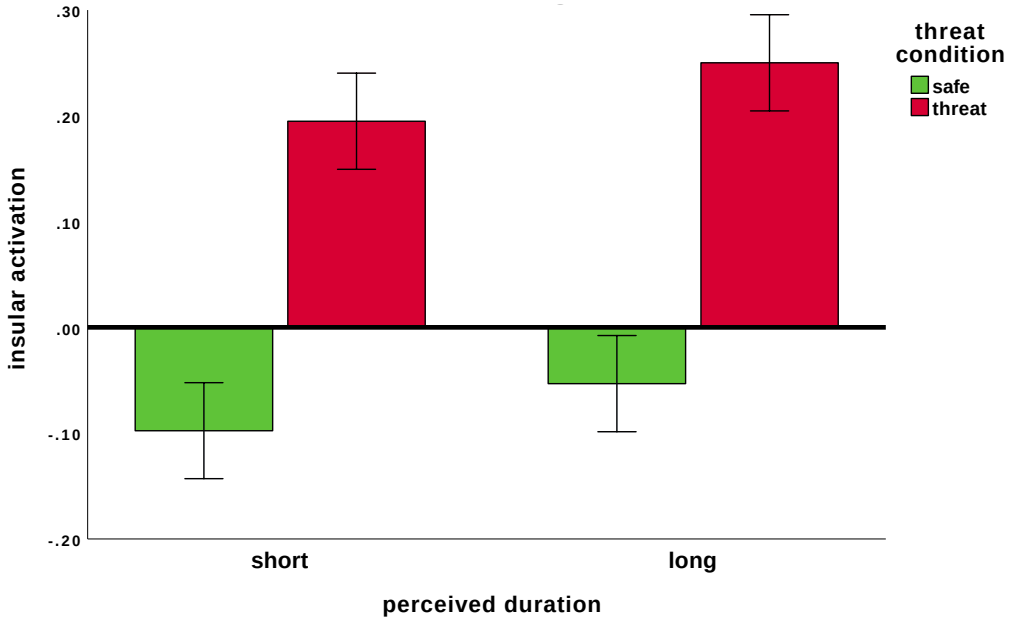


Figure 5-5: Overlapping activations of [threat>safe] (in green) and [perceived long>perceived short] contrasts (in red). Overlapping regions (in yellow) include the insula ([x=-27, y=8, z=-7]), putamen ([x=30, y=2, z=-7]) and mid-cingulate ([x=-12, y=2, z=38]). Figure generated by creating masks from the [threat>short and [perceived long>perceived short] contrasts, both

thresholded at p<0.05 (uncorrected) for display purposes Note: activation of other brain areas has been omitted for clarity.

To test my hypothesis that anxiety may "overload" regions processing time perception, I performed a 2-by-2 (threat-by-perceived duration) ANOVA on average activation across the above ROIs (Figure 5-6). However, there was no significant interaction between threat and perceived duration for either the insula ($F(1,28)=.049$, $p=.827$) or the mid-cingulate ($F(1,28)=.075$, $p=.786$). I report only these interactions here, and not the main effects, to avoid circularity in the analysis. The main effects of threat and perceived durations have already been reported in previous sections.



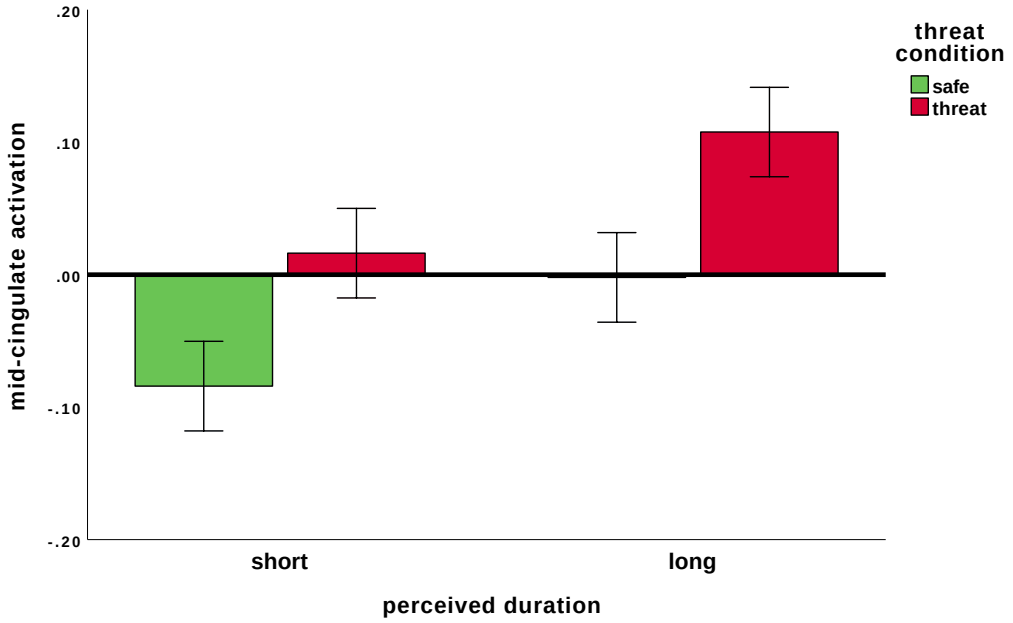


Figure 5-6: Averaged activation across the ROI for each condition in the right insula (top panel) and the mid-cingulate (bottom panel). Errors bars are standard errors.

One possibility is that individuals whose task responses were affected by anxiety (i.e. underestimated time), would show an interaction between the insula and the mid-cingulate, due to neural overloading. At the same time, I would not expect an interaction for individuals who did not underestimate time under threat. Hence, I extracted the activation of the insula and mid-cingulate areas from the interaction contrast, and correlated it with the degree of temporal underestimation during threat. No significant correlations were observed, either between the effect of threat on p(Long) and the right insula from the interaction contrast ($r(29)=.16$, $p=.51$), or between the effect of threat on p(Long) and the mid-cingulate from the interaction contrast ($r(29)=.07$, $p=.72$).

5.5 Discussion

This Chapter explored the neural correlates of how anxiety alters time perception by combining a threat-of-shock manipulation with a temporal bisection task, whilst participants underwent MRI scanning. I replicated and extended my previous behavioural findings (Chapter 3) in the scanner, showing that participants

underestimated the duration of a single temporal interval (corresponding to their BP) when anxious (prediction 1). I further found that induced anxiety activates the anterior cingulate cortex and caudate (prediction 2), as well as the insula, consistent with previous studies (Balderston et al., 2017; McMenamin et al., 2014; Meyer et al., 2019; Robinson et al., 2014, 2019; Torrisi et al., 2016, 2018). Additionally, although the perception of longer temporal intervals was associated with activation in the pre-SMA (prediction 3) consistent with previous studies (Schwartze et al., 2012; Wiener et al., 2010), this ROI analysis did not survive in the whole brain analysis. Instead, a mid-cingulate area was more robustly activated when participants perceived the temporal intervals as long. Finally, in-line with an "overloading" hypothesis, activations in the threat and perceived duration contrasts overlapped in the insula and mid-cingulate area (but not in the pre-SMA; prediction 4).

5.5.1 Neural correlates of anxiety induced by threat-of-shock

The pattern of anxiety-specific neural activations (threat>safe) was largely consistent with previous studies. Specifically, the whole brain analysis in Experiment 2 revealed a large cluster of activation in the ACC, with a peak in the sgACC. This widespread anxiety-related activation included the caudate and an ACC area, both of which were identified as regions of interest in Experiment 1. I confirmed this finding using small-volume correction, supporting prediction 2.

Since participants in this study received more electrical shocks than in previous threat-of-shock studies (e.g. Balderston et al., 2017; Robinson et al., 2014; Torrisi et al., 2016), it is possible that the sgACC activation is due to processing painful stimuli (for a review see Palomero-Gallagher et al., 2015). However, I did regress out the effect of shocks (by modelling shock events as regressors of no interest), hence activation in this

region is most likely due to shock anticipation. This is consistent with sgACC activation being considered central in sustained anticipatory responses in both primates and humans (Robinson et al., 2014; Rudebeck et al., 2014; Wallis et al., 2017).

At the same time, the right insula and the right caudate were activated across Experiments 1 and 2 in response to the threat-of-shock condition. These areas have previously been implicated in induced anxiety (insula: Balderston et al., 2017; McMenamin et al., 2014; Meyer, Padmala, & Pessoa, 2019; caudate: McMenamin et al., 2014; Torrisi et al., 2016). The insula is often co-activated with the ACC (Palomero-Gallagher et al., 2015) and is considered to be part of a putative "anxious anticipation" network (McMenamin et al., 2014a). Although the caudate is less consistently implicated in threat-of-shock studies, a previous study has similarly found activation in the right caudate (Torrisi et al., 2016b). Considering that the caudate is thought to be a key area in pathological anxiety, constituting a target for deep brain stimulation in disorders involving anxiety (i.e. obsessive compulsive disorder; Alonso et al; 2015) future studies could further explore how it relates to anticipatory anxiety. Taken together, these results highlight important roles for the sgACC, the insula and the caudate in anticipatory anxiety.

5.5.2 Neural correlates of temporal perception

These results suggest that a mid-cingulate area was more active when participants perceived a stimulus as "long", than when they perceived the exact same stimulus as "short". It is possible that this mid-cingulate area is involved in monitoring stimulus duration, where increased activation reflects more efficient processing (i.e. fewer temporal pulses were lost). The cingulate cortex has previously been implicated in time perception (for a recent meta-analysis see Nani et al., 2019), but less consistently than

other brain areas such as the pre-SMA. This apparent discrepancy might be attributed to the different experimental tasks used. Specifically, previous fMRI studies on perceptual timing have mainly employed comparative temporal discrimination tasks, in which participants judge which of the two consecutively presented temporal intervals was longer. Thus, in these studies the neural signal may represent general perceptual timing, including processes such as keeping track of different temporal intervals and working memory; since durations have to be kept in mind to allow comparisons on each trial. In my task, participants viewed the exact same temporal interval which they compared with temporal durations they had consolidated (i.e. the anchor durations); hence the neural signal reflects differences in perception, free of working memory confounds or any other confounds related to stimulus duration.

Nevertheless, the pre-SMA has been implicated across different temporal cognition tasks and is considered a key area in timing (Nani et al., 2019; Schwartze et al., 2012; Wiener et al., 2010). In this study, my pre-registered ROI analysis did confirm activation in the pre-SMA (prediction 3). However, it did not survive correction in the whole-brain analysis, which suggests that other regions may be more important in my study. This raises questions about precisely what role the pre-SMA plays in keeping track of time. It is also possible that the pre-SMA participates in some general aspect of temporal processing, such as using strategies to count interval durations, which might explain why it is so ubiquitously activated across so many different temporal cognition tasks (Nani et al., 2019).

Finally, I found overlapping mid-cingulate cortex activation in the threat and perceived duration contrasts. This convergence raises the possibility that mid-cingulate cortex might be implicated in emotion-related alterations in temporal perception, in-line with

the hypothesised role of this region in mediating cognitive affective and behavioural responses to anxiety (Grupe & Nitschke, 2013b).

5.5.3 Neurocognitive mechanisms of temporal underestimation under anxiety

In Chapters 3 & 4 I hypothesised that the effect of anxiety on temporal cognition was due to dual task interference: anxiety may occupy limited neurocognitive resources, thus altering performance in the temporal estimation task. Specifically, in this study I considered the threat-of-shock condition to represent a dual-task scenario, since participants are performing the temporal task whilst also "processing" anxiety, and the safe condition to be single-task, since participants are only performing the time perception task.

I found preliminary evidence that insula and a mid-cingulate area were activated during both the threat and temporal contrasts. It is thus possible that anxiety-related insula activity (Baur et al., 2013; Bijsterbosch et al., 2015; Simmons et al., 2006) interfered with the mid-cingulate cortex (an area associated with time perception, Nani et al., 2019), leading it to less efficiently accumulate temporal information (e.g. losing temporal pulses) and thus resulting in the observed temporal underestimation. However, this hypothesis is not completely supported by my data, considering that I did not find a significant threat-by-perceived duration interaction either at the whole-brain level, or when specifically examining the insula or mid-cingulate. In fact, one might expect no interaction between the insula and mid-cingulate activation in the interaction contrast in participants without threat-induced time underestimation; but an interaction (due to overloading) in those who did underestimate time under threat. However, my data did not support this either: I did not detect any correlation across participants between the underestimation of time during threat and either insula or mid-cingulate activation in the

interaction contrast. Interestingly, this is consistent with Chapter 4, in which we presented experiments suggesting that load does not interact with anxiety. While taken together these evidence suggest that the effect of anxiety on cognition is not due to overloading, one needs to bear in mind the study was probably underpowered to detect such effects (see also the limitations section, below).

Future work could explore this hypothesis by including more participants, to provide adequate power to detect individual differences and by employing a similar task with a fully factorial design, additionally incorporating a control/passive task. This might provide a more complete picture of how anxiety and cognition interact at the neural level.

Previous studies have suggested that the dorsolateral prefrontal cortex is implicated in the cognitive alterations due to trait (Bishop, 2009) and induced anxiety (Balderston, Hsiung, et al., 2017b; Torrisi et al., 2016b). However, I did not find such activation here. This discrepancy can be explained by considering that the tasks utilised in the aforementioned studies involved cognitively demanding, fast-paced tasks which were more likely to activate prefrontal areas (Höller-Wallscheid et al., 2017) than my simple task. Taken together my results tentatively support the idea of anxiety altering cognition similarly to dual-task situations, but there was no evidence that this was mediated by dorsolateral prefrontal activation.

5.5.4 Limitations

It should be noted that Study 2 was powered to detect the effect of threat on behaviour. Hence, this is expected to be the largest effect that would be tested for within this study, since behavioural effects are usually larger. That said, it is possible that this study is

underpowered to detect all but very large neural effects. This could explain why many effects tested were not found, and in particular why interactions were not significant.

Experiment 1 was a pilot Experiment with a different design to Experiment 2. In Experiment 1 participants had to judge the duration of six different temporal intervals. This version of the task confounded duration and time perception, such that effects might simply be driven by the duration of the stimuli. In other worlds, it is not clear whether the stimulus duration contrast indicates the neural correlates of how participants *perceived* time differently, or whether the neural effect was driven by the longer presentation times. There is evidence consistent with the latter explanation, since in the contrast of increasing stimulus duration in Experiment 1 I identified activation in the visual cortex, which could be explained by a purely sensory account.

This confound was eliminated in Experiment 2 where participants had to judge the duration of a fixed duration stimulus. This was a stimulus duration that tailored to participants responding equally frequently to "short" or "long" (calculated from a calibration task similar to Experiment 1) and thus any neural differences found in this contrast corresponds to how participants *perceived* time, free of any confounds of the *actual* duration of the stimuli (which was identical throughout). In Experiment 2 I did not identify any visual cortex activation, consistent with the above explanation.

I also failed to find any correlations between a) the behavioural effect of threat on time perception and the neural effect of threat>safe and b) the behavioural effect of threat on time perception and neural activation in the mid-cingulate area that was active during both the threat>safe and the perceived long>perceived short contrasts (exploratory analyses). This may be due to low statistical power, as my study was not optimised to examine individual differences. Indeed, in order to detect a correlation of .30 with 0.80

power I would need 82 participants, which was beyond the scope of the current within-subjects design.

It should also be noted that my fMRI paradigm does not allow one to dissociate between perception of the stimulus and the response, thus all interpretations should be made with this in mind. A future study could further delineate this by introducing a jittered delay between stimuli perception and task response in the design of the task. This (longer) design would enable the investigation of how anxiety affects time perception at the stage of perception and/or decision, and which neural circuits are involved at each stage.

Finally, I tested healthy individuals under an anxiety manipulation. Whether my results would generalise to pathological anxiety remains an open question.

5.5.5 Conclusion

I replicated previous findings of temporal underestimation in anxiety, and found activation in brain areas previously associated with threat-of-shock-induced anxiety (sgACC, insula, caudate) and time perception (mid-cingulate cortex). Despite previous studies suggesting a key role of pre-SMA in temporal perception, the mid-cingulate cortex was more robustly activated in my study. There was some overlap between activations elicited by time perception and anxiety (insula and mid-cingulate cortex), which is partially consistent with the hypothesis that anxiety may influence cognition by further loading already-in-use resources. It is likely that the mid-cingulate cortex might have a role in mediating emotion-related alterations in anxious cognition, although further studies are needed to support such claims.

Chapter 6: Unaltered time perception but impaired working memory in unmedicated pathologically anxious individuals

6.1 Abstract

Anxiety is a debilitating condition in clinically anxious individuals, and an adaptive response in healthy individuals. Some theories posit that the key difference between pathological and adaptive anxiety lies in cognitive functioning. In particular it has been proposed that some cognitive differences are risk factors for the development of anxiety disorders, while others suggest that these cognitive changes are common to both pathological and adaptive anxiety. However, very few experimental studies have utilised the exact same tasks to directly compare cognitive functioning in pathological and adaptive anxiety. In order to remedy this, here I present a preliminary study (N=30) probing pathologically anxious individuals with a temporal bisection task, which I have shown in Chapters 3 & 5 to be reliably shifted in healthy individuals during induced anxiety. In contrast to my prediction, I found no evidence that time perception is altered in pathological anxiety, despite evidence of poorer performance on a verbal working memory task in the same sample. Taken together my results tentatively suggest that temporal perception may only be altered in adaptive state anxiety and not pathological anxiety. Or, at the very least, that the effect of pathological anxiety on temporal perception is not as large as the effect of pathological anxiety on working memory.

6.2 Introduction

Anxiety disorders are some of the most prevalent mental health conditions, constituting a major global health burden (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). They are characterised by a constellation of symptoms (e.g., persistent worry and physical hyperarousal; Nitschke et al., 2001) that have been associated with cognitive changes (Bishop, 2009; Moran, 2016; Robinson et al., 2013; Shi et al., 2019) in laboratory tasks. Whether these cognitive impairments constitute causal (risk) factors in the development of anxiety disorders, or whether they represent common mechanisms in pathological and adaptive anxiety (i.e. anxiety experienced by everyone in response to environmental threats) is part of an ongoing debate (Eysenck et al., 2007; Mathews & MacLeod, 2005; Ouimet et al., 2009; Robinson et al., 2013; Yoon et al., 2018) which has important implications for the prevention and treatment of pathological anxiety (Hakamata et al., 2010). One way to investigate this is to directly compare cognitive functioning on the same cognitive tasks in pathological and adaptive anxiety. Somewhat surprisingly, such direct comparisons are not commonly performed (Robinson et al., 2013).

Previous reviews have yielded mixed results regarding the nature of cognitive impairments in adaptive and pathological anxiety (Robinson et al., 2013). Given that few studies have directly compared the same cognitive tasks across both adaptive and pathological anxiety (Robinson et al., 2015), conclusions have inevitably been drawn from comparisons across studies that utilize tasks that theoretically tap into the same cognitive construct (e.g. working memory), but are not identical. This is particularly problematic considering that even slight changes to cognitive tasks can change the mental functions they rely on, and can thus yield different results (Moran, 2016). For

example, working memory tasks have been shown to be affected differently by anxiety depending on whether they are considered simple complex or running spans, and whether they tap into the visual, phonological or spatial domain (Moran, 2016; Shipstead et al., 2014).

Therefore, in this Chapter I used the exact same task to explore whether cognitive performance in pathologically anxious individuals is shifted in the same way as I have previously shown in healthy individuals during induced anxiety (Chapter 3 & 5). Specifically, across multiple replications I have shown that under threat-of-shock induced anxiety, healthy individuals underestimate the duration of temporal intervals. As such, in line with the possibility that threat-of-shock-induced anxiety might be a model of pathological anxiety (Robinson et al., 2013), as well as one prior study exploring the impact of pathological anxiety on a different temporal perception task (Mioni et al., 2016), I predicted the same pattern of responses (temporal underestimation) in pathologically anxious individuals without anxiety induction. This would support the idea of common cognitive mechanisms in pathological and adaptive anxiety, rather than cognitive impairments constituting risk factors for the development of anxiety disorders.

Time perception is of particular interest in anxiety because it has been shown to rely on cognitive functions such as attentional control and working memory (Droit-Volet et al., 2015; Droit-Volet & Zélanti, 2013; Gu et al., 2015; Lake et al., 2016; Zélanti & Droit-Volet, 2012), which are heavily implicated in anxiety (Moran, 2016; Shi et al., 2019). Specifically, it has been suggested that visual and verbal (but not spatial) working memory impairments are central to pathological anxiety (Moran, 2016), and further that similar changes are observed during induced anxiety (Patel et al., 2016; Shackman et al., 2006; Vytal et al., 2012, 2013). Hence, since temporal bisection relies on working

memory, and working memory impairments are commonly observed in anxiety, it is likely that any effect I observe might be mediated by working memory. In order to investigate this possibility, the pathologically anxious participants also performed a working memory task in addition to the temporal bisection. As the working memory task is a replication, it also has the benefit of potentially acting as a positive control for the novel time perception task.

I hypothesised that:

1) Pathologically anxious individuals would underestimate time in a similar fashion to healthy individuals during induced anxiety in previous Chapters (Chapters 3 & 5; see also Figure 6-1).

2) The effect in the temporal bisection task would be explained by performance differences in working memory between the pathologically anxious and control groups, given the proposed relationship between temporal bisection and working memory (Droit-Volet et al., 2015; Droit-Volet & Zélanti, 2013; Gu et al., 2015; Lake et al., 2016; Zélanti & Droit-Volet, 2012). As such, performance in the temporal bisection task should correlate with performance in the working memory task.

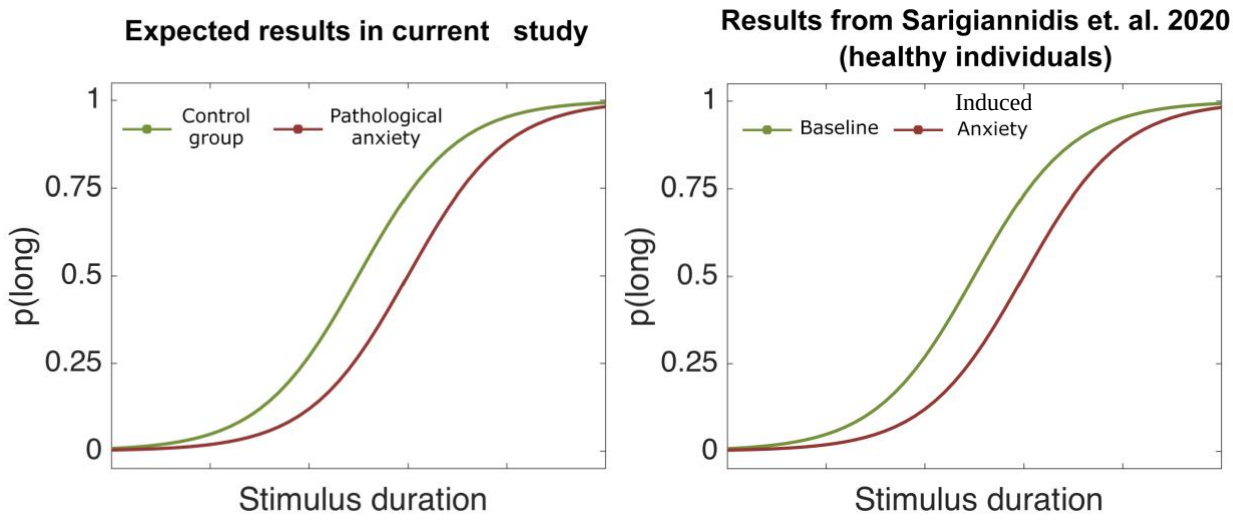


Figure 6-1: Expected results in the current study (left panel) based on my previous findings (right panel). Specifically, I predict that clinically anxious individuals would underestimate temporal intervals compared to healthy controls, similarly to healthy individuals under induced anxiety.

6.3 Materials and Methods

6.3.1 Participants

Unmedicated individuals meeting criteria for generalised anxiety disorder (n = 15) and healthy volunteers with no past or present mental illness (n = 15) were tested (see Table 6.1). All provided written informed consent and were paid £7.50 per hour for their participation. The study was approved by the University College London Research Ethics Committee (Project ID Number: 1227/001).

Table 6.1: Demographics, Questionnaire Scores, and Participants′ Characteristics. BDI = Beck depression inventory. STAI = State Trait Anxiety Inventory. MDD = Major Depressive Disorder, PD = Panic Disorder, PTSD = Post Traumatic Stress Disorder

	Healthy Controls (n=15)	**Pathologically Anxious (n=15)**
Female:Male	13:2	13:2
Age, Mean (SD)	23.86 (3.04)	24.13 (4.05)
Raven's Progressive Matrices, Mean (SD)	9.2 (2.83)	9.7 (1.64)

Digit-span, Mean (SD)	19.4 (3.3)	19.06 (3.5)
STAI Trait Anxiety Score, Mean (SD)	35.53 (9.13)	59.26 (9.97)
STAI State Anxiety Score, Mean (SD)	33.07 (10.36)	53.73 (11.89)
BDI Score, Mean (SD)	4.86 (5.08)	26.13 (12.28)
Comorbid MDD/ PD/ PTSD (%)	n/a	53.33% / 13.33% / 13.33 %

Pathologically anxious individuals were recruited from our laboratory database. These individuals had previously met DSM-5 criteria for Generalised Anxiety Disorder (GAD) assessed using the Mini-International Neuropsychiatric Interview (MINI; see Chapter 2.5) (Sheehan et al., 1998). In cases where the interview was conducted more than eight weeks prior to the intended time of cognitive testing, the MINI was repeated in order to confirm eligibility. The sample size for this study was constrained by recruitment rates prior to the end of my PhD funding. As such the study was only powered to detected large effect sizes of d>1 with 0.8 power. This a large effect, but one that would indicate a major cognitive impairment in pathological anxiety, constituting a relevant target for intervention. The groups were matched on age, biological sex and measures of non-verbal IQ (WAIS-III Digit Span; see Chapter 2.4; Wechsler, 1997) and Raven's Progressive Matrices (Raven & Raven, 2003). As expected, STAI and BDI scores were significantly higher (Table 1) in anxious participants (trait anxiety [$t(28) = 6.19$, $p < .001$], state anxiety [$t(28) = 5.07$, $p < .001$], Beck Depression Inventory [$t(28) = 6.79$, $p < .001$]).

6.3.2 Procedure

All participants performed a verbal working memory task and the temporal bisection task in counterbalanced order on Windows computers using Cogent 2000 (www.vislab.ucl.ac.uk/cogent.php; Wellcome Trust Centre for Neuroimaging and

Institute of Cognitive Neuroscience, UCL, London), running under MATLAB (v. R2015b).

6.3.2.1 Verbal working memory task

Participants viewed sets of letters on the screen and were then asked to respond 'yes' or 'no' for whether a single-letter probe belonged to the set they had just viewed, by pressing the corresponding buttons on a keyboard. Following their response, they received feedback: "Correct", "Wrong" or "Too slow". The task was of increasing difficulty: it started with a training set of 2 letters that was not scored, and increased to 4, 6, 8 and 10 letters in the main task. Each block of 4, 6, 8 and 10 letters consisted of 12 trials (see Figure 6-2 for details regarding trial timings).

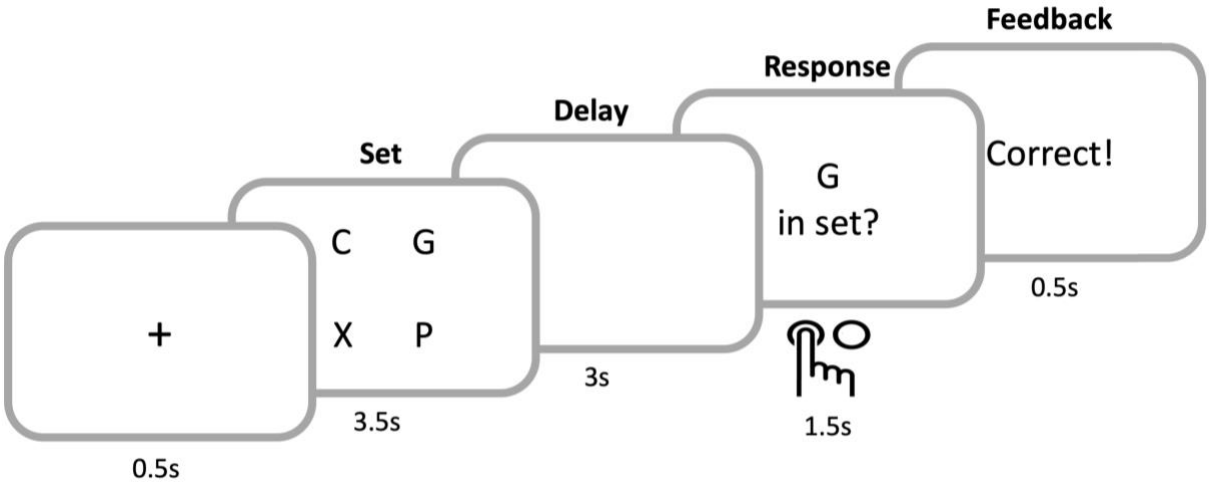


Figure 6-2: Trial structure of the Verbal Working Memory task. The main task was of progressive difficulty and the set of letters increased from 4 to 10 in steps of 2.

6.3.2.2 Temporal bisection task

The temporal bisection task (see Figure 6-3) was identical to the one used in previous chapters of this thesis in order to allow comparisons across studies (see Chapter 3), with the exception that the within-subject threat-of-shock manipulation was removed (therefore halving the number of trials per individual).

The session consisted of 4 blocks with each block comprising 48 trials. Following each block, participants rated their anxiety levels using a continuous visual analogue scale.

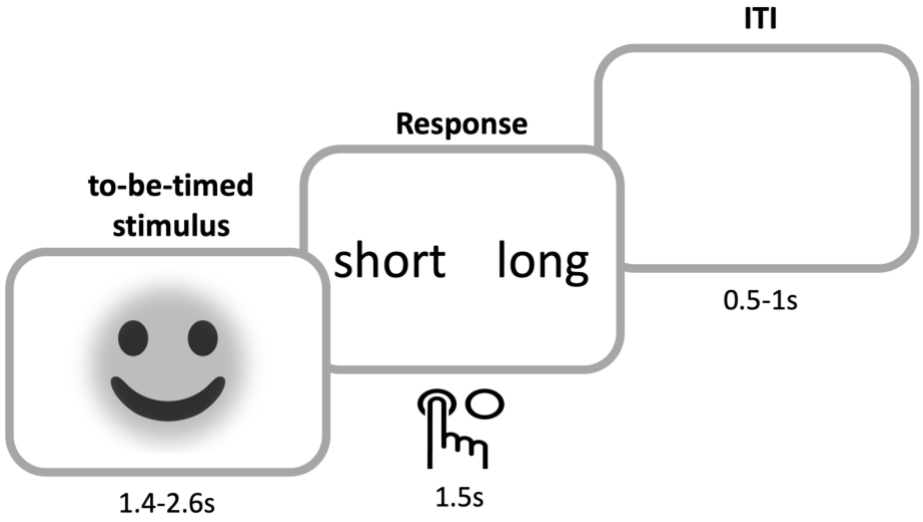


Figure 6-3: Trial structure of the temporal bisection task. Note: in the actual experiment participants were presented with images from the Totenham et al. (2009) Face Stimulus Set (happy, neutral and fearful); a smiley face is presented here for illustration purposes.

6.3.3 Data analysis

Data was processed in MATLAB (v. R2015b), and statistical testing was carried out in SPSS (v. 23). Cohen's d for between-subject effects was calculated using the following formula: t/SQRT(N per group/2).

6.3.3.1 Verbal working memory task

Missed trials were excluded from the analysis. Repeated-measures analysis of variance (ANOVAs) was performed on the proportion of correct trials. The effect of task difficulty (4, 6, 8 & 10 letter conditions), was used as the within-subject factor and the effect of group (healthy or pathologically anxious), as the between subject factor. Only responses from the 4, 6, 8 & 10 letter conditions were recorded and analysed, as the 2 letter condition was used exclusively to train participants on how to perform the task. Greenhouse-Geisser corrections were applied when violations of sphericity occurred.

6.3.3.2 Temporal bisection task: Proportion of long responses

Trials on which participants did not make a response were excluded from the analysis. Repeated-measures analysis of variance (ANOVAs) was performed on the proportion of stimuli participants judged to be long (proportion of long responses, p(Long). The effect of duration (six stimulus durations), was used as the within-subject factor and the effect of group (healthy or pathologically anxious), as the between subject factor. Greenhouse-Geisser corrections were applied when violations of sphericity occurred.

6.4 Results

6.4.1 Verbal working memory

6.4.1.1 Percentage Correct trials

The more letters participants had to keep in mind, the less correct responses they made, as revealed by a repeated measures ANOVA on the percentage of correct responses ($F(3, 84) = 33.73$, $p < .001$, $\eta_p^2 = .546$; Figure 6-4). Anxious individuals performed significantly worse overall on the working memory task compared to healthy individuals ($F(1, 28) = 5.17$, $p = .031$, $\eta_p^2 = .156$), which did not depend on task difficulty (non-significant group by difficulty interaction ($F(3, 84) = 0.129$, $p < .943$, $\eta_p^2 = .005$; Figure 6-4).

6.4.1.2 Percentage Missed trials

Participants did not miss more trials the more letters they had to keep in mind, as revealed by a repeated measures ANOVA on the percentage of missed trials ($F(3, 84) = .948$, $p = .421$, $\eta_p^2 = .033$). Additionally, there was no difference in the proportion of missed trials between the healthy and anxious groups ($F(1, 28) = .136$, $p = .253$, $\eta_p^2 =$

.046). The interaction between task difficulty and group on missed trials was non-significant ($F(3, 84) = 1.23$, $p = .301$, $\eta_p^2 = .042$; see also Figure 6-4).

6.4.1.3 Reaction times

Participants' reaction time was not affected by task difficulty, as revealed by a repeated measures ANOVA ($F(2.24, 62.75) = .173$, $p = .864$, $\eta_p^2 = .006$). There was no difference in the reaction time between healthy and anxious groups ($F(1, 28) = 1.55$, $p = .223$, $\eta_p^2 = .053$). The interaction between task difficulty and group was non-significant ($F(2.24, 62.75) = 2.11$, $p = .123$, $\eta_p^2 = .070$; see also Figure 6-4).

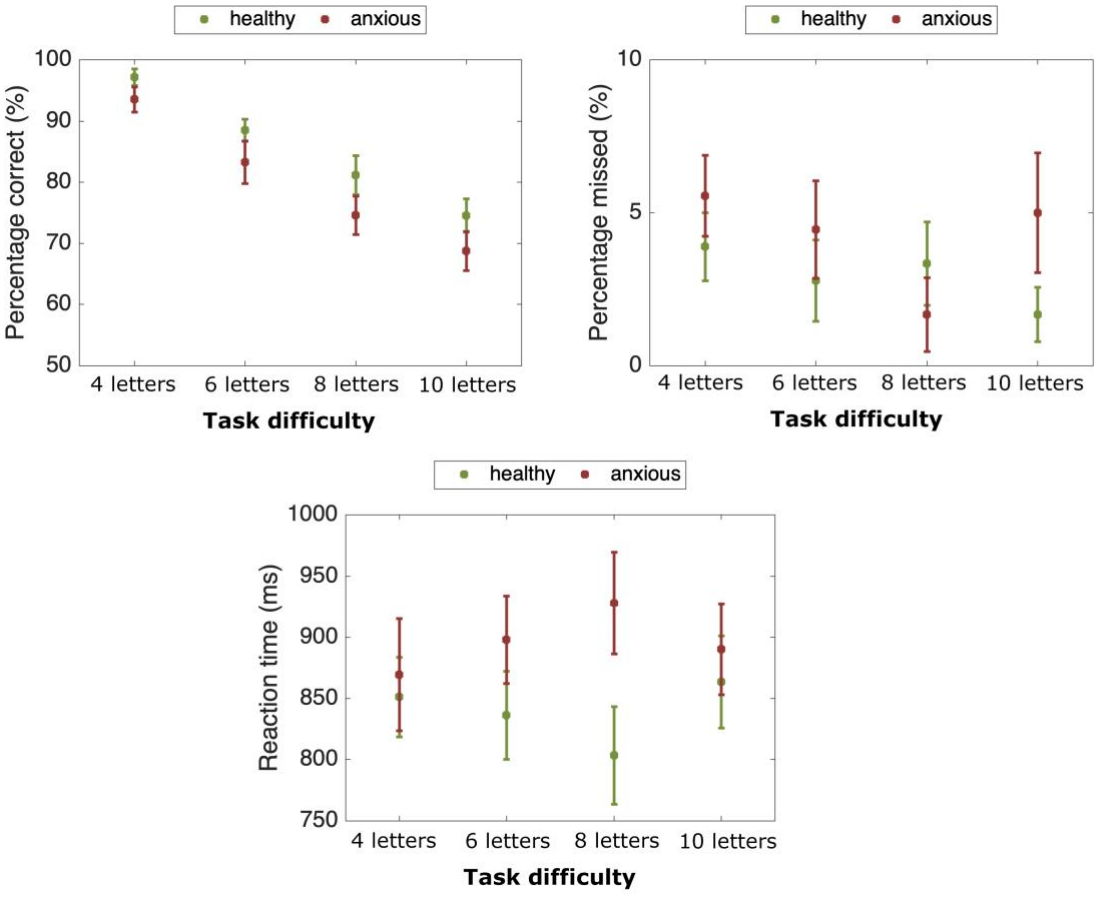


Figure 6-4: Verbal Working memory task performance for each difficulty level and group. Top left: percentage correct responses; greater values reflect higher accuracy. Top right: percentage missed trials; greater values reflect more missed trials. Bottom: reaction times; greater values indicates slower responses. Error bars are standard errors of the mean (SEM).

6.4.2 Temporal bisection

6.4.2.1 Subjective anxiety ratings

Across blocks, individuals in the pathological anxiety group reported being significantly more anxious compared to the control group ($t(28) = 6.273$, $p < .001$, Cohen's $d = 2.30$; see also Figure 6-5).

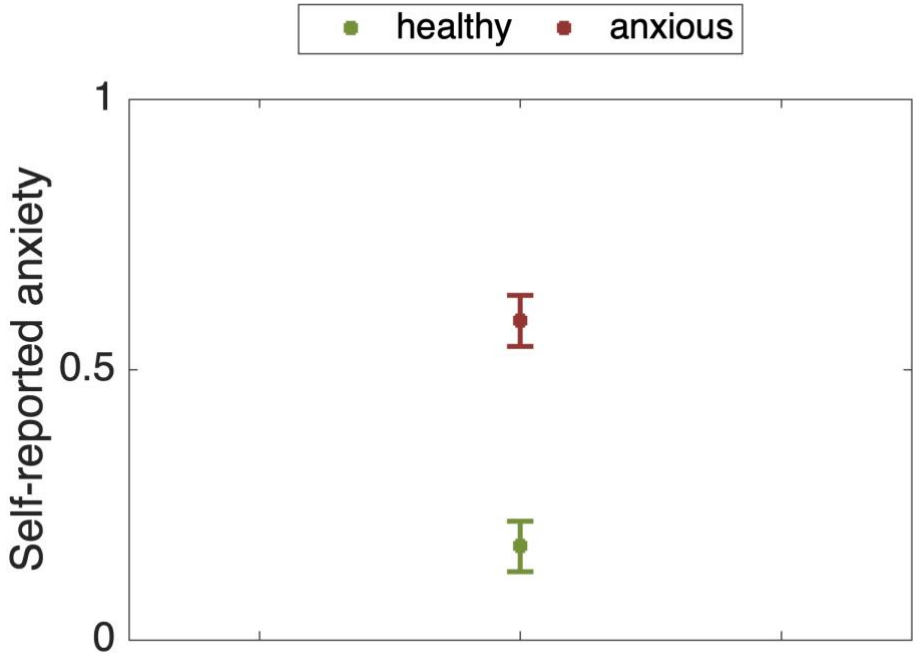


Figure 6-5: Mean self-reported anxiety levels for each group: healthy controls and pathologically anxious. Greater values reflect higher anxiety. Error bars are standard errors of the mean (SEM).

6.4.2.2 Time estimation: proportion of long responses

There was a significant main effect of stimulus duration ($F(2.15, 60.29) = 211.90$, $p < .001$, $\eta_p^2 = .883$). As expected, the longer the stimulus duration, the more likely it was to be classified as "long" (Figure 6-6). The group-by-stimulus duration interaction was non-significant ($F(5, 140) = 0.99$, $p = .424$, $\eta_p^2 = .034$). As shown in Figure 6-6, the two

groups responded quite similarly in the temporal bisection task. Thus, there was no evidence suggesting that pathological anxiety shifts temporal perception.

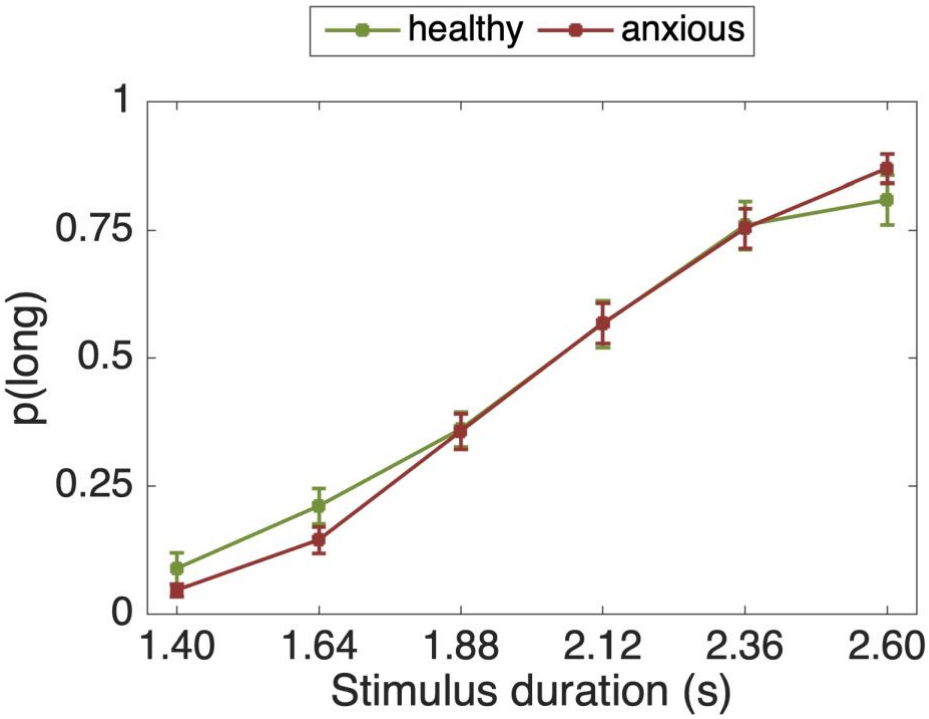


Figure 6-6: Proportion of stimuli rated "long" as a function of the actual presentation length per group. Error bars are standard errors of the mean (SEM).

6.4.2.3 Time estimation: reaction times

Participants' reaction times were affected by the stimuli duration: the longer the duration of the stimuli, the quicker participants responded, as revealed by a repeated measures ANOVA ($F(3.33, 93.23) = 42.47$, $p < .001$, $\eta_p^2 = .603$). There were no reaction time differences between healthy and anxious groups ($F(1, 28) = .137$, $p = .714$, $\eta_p^2 = .005$). The interaction between stimuli duration and group was non-significant ($F(3.33, 93.23) = .55$, $p = .668$, $\eta_p^2 = .019$; see also Figure 6-7).

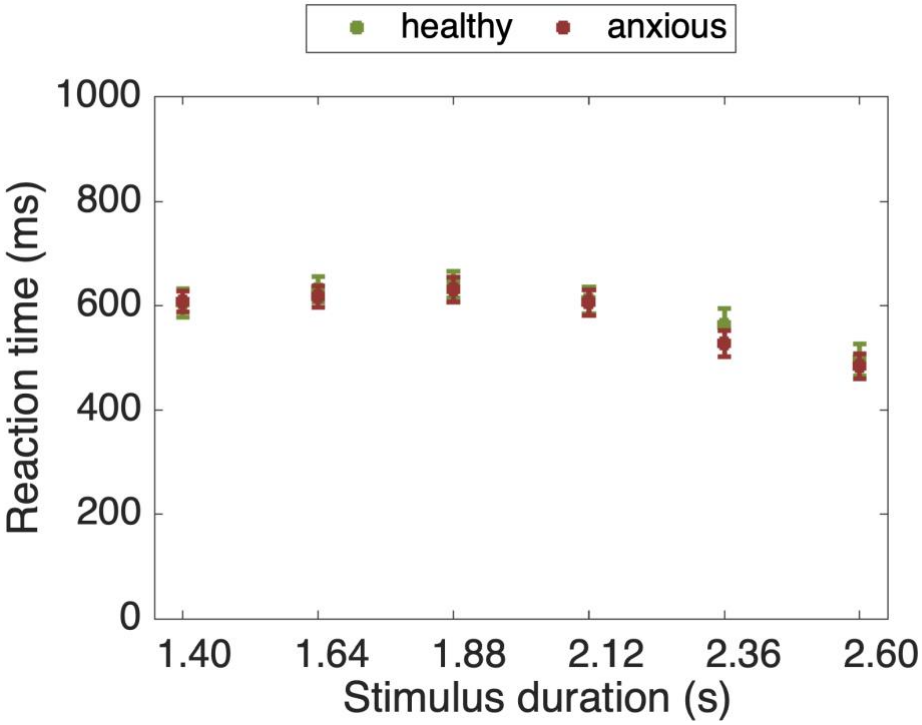


Figure 6-7: Reaction times as a function of the actual presentation length of the stimuli per group. Error bars are standard errors of the mean (SEM).

6.4.2.4 Psychophysical modelling

Data from one healthy participant was excluded from the analysis since their BP and Weber fraction values could not be estimated.

Bisection point

The BP did not differ between the pathological anxiety (M = 2,072.86 SD = 158.10) and the healthy group (M = 2,072.01, SD = 185.04; (t(27) = .012, p = .990, d < .01). Thus there was no evidence suggesting that pathological anxiety shifts temporal perception.

Weber fraction

The WF did not differ between the anxiety (M = 0.127, SD = .032) and the healthy group (M = .165, SD = .136; (t(14.36) = 1.025, p = .322, d = .38). Hence there was no evidence that the sensitivity to time intervals differed between the groups.

6.4.3 Correlations across measures

In order to better understand the relationship between trait anxiety (STAI), depression symptoms (BDI) and performance in the working memory and temporal bisection tasks, I performed correlations in which I collapsed data across groups.

Table 6.2: Correlations across trait anxiety, depressive symptoms and performance in the cognitive tasks

	1. BDI Score	2. STAI Trait	3. Digit Span	4. WM % correct	5. BP	6. WF
1. BDI Score	—					
2. STAI Trait	.75***	—				
3. Digit Span	.72	-.13	—			
4. WM % correct	-.33	-.44*	.52**	—		
5. BP	-.17	.032	-.07	-.30	—	
6. WF	-.16	-.16	.07	-.08	.51***	—

*** Correlation is significant at the 0.0033 level (Bonferroni adjustment for multiple comparisons)

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

As expected, trait anxiety (STAI) and BDI measures were positively correlated $r(30) = .75$, $p < .001$, suggesting that individuals who reported higher anxiety symptoms also reported higher depressive symptoms, a common finding considering the high comorbidity in depressive and anxious symptomatology. Similarly, the BP and WF were positively correlated $r(30) = .51$, $p < .001$. These comparisons survived Bonferroni correction with an adjusted alpha level of 0.0033 per test (0.05/15).

The positive correction between digit span and the percentage of correct responses in the working memory task was marginally significant after Bonferroni correction $r(30) = .52$, $p = .0035$.

There was a negative correlation between trait anxiety and the percentage of correct responses in the working memory task ($r(30) = -.44$, $p = .014$) although this did not

survive correction for multiple comparisons. In other words, the higher the trait anxiety, the worse participants performed on the working memory task. This echoes the finding from the between-group analysis of a significant difference in accuracy on the WM task between the pathologically anxious and control participants.

There were no significant correlations between performance in the working memory task and the temporal bisection task (either BP: $r(29) = -.30$, $p = .118$ or WF: $r(29) = -.07$, $p = .706$).

6.5 Discussion

6.5.1 Main hypothesis

Contrary to my predictions, I did not observe similar time perception shifts in pathological anxiety to those I have previously found in adaptive anxiety (Chapters 3 & 5). Importantly, this discrepancy cannot be attributed to differences in state anxiety since the pathological anxiety group reported elevated state anxiety during the task (as seen in Figure 6.5). This effect cannot be fully attributed to poorly defined or powered groups, as I was able to replicate a significant impact of pathological anxiety on working memory.

These results failed to confirm my hypothesis that adaptive and pathological anxiety shift time perception similarly. Specifically, despite having shown in Chapters 3 & 5 that threat of unpredictable shock in healthy individuals leads to temporal underestimation, in the current study pathological anxiety did not alter temporal perception. Moreover, given that I also found higher state anxiety in pathologically anxious individuals (current study; Figure 6.5) and higher state anxiety in healthy individuals under the anxiety manipulation (Chapter 3) this cannot be attributed to

current anxiety levels. As such, my results suggest a difference in cognitive functioning between pathological anxiety and anxiety in healthy individuals, indicating that these different types of anxiety may have distinct impacts on at least some aspects of cognition. Such a distinction should be emphasised in future studies that discuss cognitive functioning. It seems important for researchers to avoid the umbrella term "anxiety", and instead distinguish between pathological anxiety and anxiety induced in healthy individuals.

Nevertheless, an obvious alternative explanation is that the groups were poorly specified and/or the study was underpowered to detect group differences. Whilst this possibility cannot be fully discounted, it needs to be taken alongside clear group differences in state anxiety and the observation that pathological anxiety *was* associated with decreased performance in a Verbal Working Memory Task in the present study. Specifically, performance decreased as anxiety symptoms increased, supporting claims that working memory impairments are central to clinical anxiety (Moran, 2016), contradicting opposite claims (Shi et al., 2019). Crucially it acts as a positive control for my null effect of time perception by demonstrating that I recruited a sample with enough sensitivity to detect (at least some) large differences in cognitive functioning. Of course, the temporal perception effect may have a smaller effect size, but with the given sample size one can reliably detect group differences of Cohen's $d>1$ with 0.8 power. Overall, I can conclude that performance in a working memory task is likely a better cognitive marker of pathological anxiety compared to performance in a temporal bisection task.

6.5.2 Working memory impairments

Interestingly, I found such a working memory impairment even though the groups were matched on digit span, a task that also relies on working memory. As Table 6.2 shows, performance on the working memory task and the digit span was highly correlated. The aforementioned discrepancy can be explained by considering that the digit span is a measure of simple working memory, which has been shown to be inconsistently affected by anxiety disorders (Moran, 2016). In contrast, my verbal working memory task is considered a complex working memory task, which has been shown to be reliably affected by anxiety disorders (Moran, 2016). A key difference between simple and complex working memory tasks is that the latter requires some manipulation of the memory content, which was indeed the case for my working memory task: participants had to actively search in their mental representation for a particular letter, rather than merely recall information.

6.5.3 Implications for time perception literature

These results have some preliminary implications for the time perception literature, and in particular, the debate concerning which cognitive functions the perception of time relies upon. This Chapter shows large working memory but not large time perception alterations in clinical anxiety. At the same time, no significant correlations were found between performance in the working memory and temporal bisection tasks, suggesting that the temporal bisection task does not heavily rely on working memory. This is further supported by Chapter 4, in which increasing working memory load did not alter performance in a temporal bisection task. Of course, it is possible that the relationship between time perception and working memory exists but is smaller than the within subject correlation effect sizes ($d<1$) this study was powered to detect. It should also be

noted that even if true, this finding, i.e. that my temporal bisection task is independent of working memory, might not generalise across other kinds of time perception tasks (such as temporal reproduction), since different temporal tasks tap onto different cognitive components. The wide range of time perception tasks that are available measure different aspects of how we perceive time, in line with time perception being a complex process that may be altered depending on the context (Lake, LaBar, et al., 2016; Matthews & Meck, 2016).

This diversity of time perception tasks could explain why a previous study, utilising different temporal cognition tasks, *did* find time perception alterations in clinical anxiety (Mioni et al., 2016). In that study participants were shown a temporal duration and were then immediately asked to reproduce it by holding a button down: this poses a significant strain on working memory. Indeed, it could be argued that the time perception task used by Mioni et al. (2016) is more related to a working memory task during which information (in this case temporal information rather than words, objects, or spatial locations) is presented and then individuals are asked to recall it. Since I *do* show that pathological anxiety is associated with working memory impairment, this explanation may resolve the apparent discrepancy between the studies. In my temporal cognition task, by contrast, individuals were asked to judge the temporal durations based on anchor durations they were exposed to several times, with repeated reminders on each block, thus reducing working memory load. Hence my task explores whether clinical anxiety is associated with alterations in the *perception* of temporal durations. In other words, I can reconcile my findings with those of Mioni et 2016 by suggesting that clinically anxious individuals might have difficulty *remembering* temporal durations, but not *perceiving* them as different. Future work could assess this explicitly by asking

patients and controls to both reproduce and judge temporal durations within the same battery of tasks.

6.5.4 Implications for theories of anxiety

According to the attentional control theory (Eysenck et al., 2007), cognitive impairment in anxiety is mainly manifested as differences in reaction time (called attentional control efficiency) rather than performance (called attentional control accuracy). In both my working memory and temporal bisection task, I did not find any differences in reaction time. Instead the main effect was the decreased performance in the working memory task. Hence my results are not wholly consistent with attentional control theory. It is possible that the attentional control theory applies specifically to tasks that tap into the shifting and inhibiting components of attentional control but not updating (with the latter being what working memory tasks are hypothesised to measure).

6.5.5 Limitations

The primary limitation of this study is the small sample size (15 participants in each group), which means that it was only powered to detect effects of Cohen's $d<1$ with 80% power. However, I was able to detect a significant difference between these groups, namely that pathologically anxious individuals performed worse in the working memory task, and I also demonstrated significant state anxiety differences between groups during the temporal perception task. This pattern of responses is typically observed in pathological and clinical anxiety (Moran, 2016), suggesting that my participants are likely to be representative of the condition. Consequently, I can be more confident that my findings regarding the time perception task are somewhat representative. At the very least, I can say that the effects of pathological anxiety on time perception are smaller than the effects on state anxiety and working memory.

Another limitation is that my study is based on a community sample, and thus it is not clear if my results generalise to severe anxiety. The pathologically anxious individuals tested in this study were recruited from a community sample, and thus their level of dysfunction is probably lower in comparison with, for example, individuals recruited from a hospital service. A recent meta-analysis showed that cognitive impairments in anxiety correlate with symptom severity (Moran, 2016). If anything, this would suggest that clinically anxious individuals might experience more pronounced working memory impairments than those observed here. Whether individuals with severe clinical cases of anxiety may experience temporal perception alterations needs to be addressed in a future study.

It should be noted that although anxious patients were recruited, a high proportion of participants had also comorbid MDD (about 53%). In case the sample collected were larger, I would have been able to explore how such comorbidity might have affected time perception. For example a previous study showed that anxious patients tended to underestimate temporal intervals and depressed patients overestimated such intervals (Mioni et al., 2016).

6.5.6 Conclusion

In this small preliminary study, I found no evidence that pathological anxiety shifts time perception similarly to threat-of-shock induced anxiety in healthy individuals (Chapters 3 & 5). Although no impairments in time perception were found in the pathologically anxious individuals of this study, working memory impairments were found. These results highlight important differences in cognitive functioning between pathological and adaptive anxiety, supporting the view that working memory impairments are core in pathological anxiety.

Chapter 7: General Discussion

The discussion will first summarise the findings and limitations of each chapter individually. Chapters 3 & 4 will be discussed together, suggesting a model of how different aspects of anxiety might be differentially affecting cognition. Given the inconclusive results of Chapter 5 & 6, these will be discussed in light of future studies that could be conducted to better address the questions put forward. Limitations of the overall approach of the thesis will be discussed, emphasising the potential difficulties in teasing apart adaptive from pathological anxiety, which need to be addressed in order to clarify how this line of research could improve treatments for and understanding of anxiety. The importance of environmental factors in anxiety, which are often overlooked by cognitive and neuroimaging studies, will also be highlighted.

7.1 Chapters 3 & 4

7.1.1 Chapter 3: Summary

The aim of Chapters 3 & 4 was to tease apart the cognitive components that lead to performance alterations in anxiety, with a focus on cold cognition: for that reason, a temporal bisection task was used. This was performed under an anxiety manipulation (threat-of-shock, Chapter 3), a fear manipulation (fear conditioning, Chapter 3) and (in a further chapter; Chapter 4) a cognitive load-manipulation.

In the threat-of-shock paradigm, participants performed the task while anticipating unpredictable electrical shocks to their wrist, a manipulation that induces subjective feelings of anxiety (Schmitz & Grillon, 2012). Compared to the baseline condition, I expected that under the anxiety induction participants would divide their (inherently limited) attentional resources between performing the task and the anxiety

manipulation, leading them to lose temporal information and thus underestimate temporal intervals (Casini & Macar, 1997; Coull et al., 2004; Macar et al., 1994). This was indeed the case, as was manifested in a series of experiments; even in situations where participants were told they would receive shocks but in fact did not. The latter suggests that the effect is not a confound due to receiving electrical shocks, but can be observed when these are merely anticipated.

In the fear manipulation, participants timed stimuli of different durations, whose disappearance from the screen coincided with a threatening event (the delivery of an electrical shock, 100% reinforced). I expected that attentional resources would be directed primarily towards monitoring such stimuli because they cued a threatening event, and thus participants would overestimate their duration. This would have been in line with a number of studies showing that the duration of threatening events and stimuli is overestimated[1] (Sylvie Droit-Volet et al., 2010; Fayolle et al., 2015; Grommet et al., 2011; Tipples, 2008, 2011; van Wassenhove et al., 2011).

However, contrary to my prediction, participants did not overestimate to-be-timed stimuli associated with shocks; in fact, time estimations did not differ between threatening and non-threatening trials (Chapter 3). One possibility is that fear and anxiety are different constructs and in this particular aspect, only anxiety alters time perception, while fear does not. Another possibility is that the shock trials in the fear experiments of Chapter 3 were not salient enough to be preferentially processed, since

[1] Such overestimation effects can be explained as follows: Under normal circumstances, visual stimuli tend to be underestimated; visual stimuli that last e.g. 1.2s are on average verbally estimated to last 1s (Wearden et al., 1998). Hence, since attentional resources are prioritised towards salient stimuli (e.g. those that signal threat), this might result in less underestimation compared to neutral stimuli, leading threatening events to be overestimated compared to neutral ones.

they were reinforced at 100%. In other words, employing full reinforcement (shocks occurring on 100% of the trials), as I did, might be the reason why the hypothesised effect was not observed. In fact, it is established that fear learning is more robust under partial reinforcement compared to full reinforcement (Hochman & Erev, 2013). This has been attributed to prediction errors generated due to partial reinforcement, which render partial reinforcement more salient (Tronson, 2019; Walker et al., 2020). Whether participants would overestimate temporal intervals under partial shock reinforcement (e.g. 80%) as one might predict, remains an open question. Thus, the Chapter 3 results do not exclude the possibility that fear leads to time overestimation, a result that has been well-replicated in the field (Sylvie Droit-Volet et al., 2010; Fayolle et al., 2015; Grommet et al., 2011; Tipples, 2008, 2011; van Wassenhove et al., 2011).

Fear and anxiety are considered distinct concepts. Fear is defined as the response to immediate threat, which in the lab is modelled by predictable threatening events; e.g. whenever the light turns red, you will get a shock. Anxiety is a more vague response to distant threat, which in the lab is modelled by unpredictable threats; e.g. while this song is playing, you are at risk of receiving shocks, but you don't know when or how many. One might argue that an experiment in which shocks are partially reinforced, i.e. rendering them more unpredictable, would blur the lines between fear and anxiety. While this might sound true, one should keep in mind that fear and anxiety are not discrete categories but are thought to fall on a continuum. In the case of partially reinforced shocks, the shocks are still predictable in the sense that participants are aware of when they *could* occur; in contrast to the threat-of-shock anxiety manipulation, in which the shocks are completely random. At the same time, partially reinforced shocks might be more likely to induce fear that fully reinforced shocks, considering that reinforcing a negative event at 100% can lead to habituation (Lloyd et al., 2014;

Mcsweeney & Roll, 1998). In fact, presenting individuals with multiple consecutive instances of a negative event is a technique used in cognitive behavioural therapy to treat specific phobias (see flooding; Schumacher et al., 2015; Wolitzky-Taylor et al., 2008). Hence, a future fear experiment in which shocks are partially reinforced might be particularly illuminating on how fear affects time perception.

7.1.2 Chapter 3: Discussion

Ultimately, I believe that fear and anxiety are different sides of the same coin regarding their effects on cognition, since both draw attention to salient events. For example, imagine that while you are biking to work, a car is moving towards you. The possibility of a collision will induce a fear response and thus any information regarding the position of the car over time will be preferentially processed, as this is relevant to avoiding an accident. This prioritising of information might lead to the impression that time froze during this event (i.e. time was overestimated; Arstila, 2012; Stetson et al., 2007). Fortunate to have avoided the collision, for the rest of the day it might be difficult to concentrate on work, since you might be worrying about the possibility of a future bike accident (and/or whether it is safe at all to use a bike in London). Deep in such anxious thoughts, all of a sudden you realise it is already time to head back home, leaving you wondering how time flew by. This can be explained due to anxiety directing attentional resources away from the task at hand (i.e. work), to worrying about the future, resulting in time being underestimated.

The aforementioned examples illustrate how both fear and anxiety, by prioritising threat information in different contexts, can lead to different cognitive effects. Studies usually explore how fear prioritises attentional resources to feared stimuli, and how anxiety distracts from the main task at hand. For example, on the one hand, using the dot probe

task, it has been found that individuals tend to respond quicker to feared stimuli (Bar-Haim et al., 2007; Mathews et al., 1997; Van Bockstaele et al., 2014). On the other hand, increased state anxiety is usually studied in terms of how it negatively impacts performance on ongoing tasks, due to drawing limited attentional resources towards the worry rather than the task at hand (Eysenck et al., 2007; Moran, 2016; Robinson et al., 2013; Shi et al., 2019).

Overall, the results of Chapter 3 suggest that unpredictable negative events (e.g. unpredictable compared to fully predictable shocks) are more likely to disrupt concurrent task processing. In the threat-of-shock experiments of Chapter 3, participants' performance might be disrupted by thoughts regarding how many shocks they will receive, when will these occur, or how they going to react to them; thoughts they are not likely to have had during the fear experiments of Chapter 3, in which they could predict exactly when they would receive a shock. In other words, individuals in the threat-of-shock condition are in a high state of uncertainty, while in the fear condition there is almost no uncertainty. It is possible that the effect of induced (threat-of-shock) anxiety on the time perception task is driven by a tendency to reduce uncertainty regarding salient events (e.g. shocks), by allocating limited attentional resources to monitoring threatening events. In fact, the idea that cognitive systems strive to reduce uncertainty by utilising mental resources seems to be well-accepted in the biological (Peters et al., 2017) and the social sciences (Berger & Calabrese, 1975). Additionally, negative events seem to be perceived as more threatening when they are uncertain (Grupe & Nitschke, 2013a), leading to more profound cognitive alterations. Studies show that uncertainty is inherently anxiogenic, with individuals who have difficulty processing uncertainty being more prone to worry and anxiety disorders (Buhr & Dugas, 2006; Carleton et al., 2007; Freeston et al., 1994; Holaway et al., 2006). The

finding that unpredictable events disrupt cognition more profoundly than predictable events (Chapter 3) alongside evidence suggesting that anxious individuals are more intolerant of uncertainty (Buhr & Dugas, 2006; Charpentier et al., 2017; Holaway et al., 2006), needs to be considered when treating clinically anxious individuals. Minimizing anxious patients' uncertainty throughout each step of psychological therapy might lead to better treatment outcomes, since it could allow them to free up cognitive resources, focusing more on the therapeutic process.

7.1.3 Chapter 4: Summary

After showing in Chapter 3 that anxiety robustly alters time perception (leading to temporal underestimation), the goal of Chapter 4 was to elucidate the underlying mechanism. Both the *cognitive load* and *anticipation* aspects of anxiety might have led to this effect, considering that each of these could result in temporal underestimation (Matthews & Meck, 2016). Specifically, worrisome thoughts might have overloaded limited attentional resources (Eysenck et al., 2007), leading temporal information to be lost, manifested as temporal underestimation (*cognitive load* hypothesis). At the same time, anticipating the occurrence of a threatening event might have led to enhanced arousal, threat monitoring and activation of defence mechanisms (LeDoux & Pine, 2016), shifting cognitive resources away from the task, similarly leading to temporal underestimation (*anticipation* hypothesis).

In a preliminary attempt to distinguish between these two possibilities, I employed a commonly used 'cognitive load' manipulation, in order to overload cognitive resources without the presence of threat anticipation. In each trial of this task, participants had to keep in mind a set of letters while timing a stimulus. After responding to the timing task

(which was similar to that in Chapter 3), they had to make a choice indicating whether a probe letter belonged to the set of letters they had in mind.

Against my prediction, cognitive load (both high & low) did not significantly alter the perception of time in a series of three experiments. This finding is inconsistent with previous studies suggesting that cognitive load leads to time underestimation (for a meta-analysis see Block et al., 2010). It is possible that the load manipulation was not taxing enough to cause interference with the timing task. One might argue that this is unlikely, considering that in the final experiment, we increased the cognitive load to eight items, and the average performance on this load task fell to around 70%. However, it is possible that given the framing of the experiments, participants considered the timing task to be the priority, and the load task secondary, thus focusing more on the former: participants performed the time perception task both with and without the load manipulation, which might have given such impression. In other words, it is possible that participants primarily allocated cognitive resources to the timing task, and thus concurrent load processing did not result in temporal underestimation. This remains a possibility, especially when considering that participants were not given specific instructions on which task to prioritise. A future experiment could explore this by implementing conditions in which participants are explicitly instructed to a) prioritise their attention to the timing task b) divide their attention between the timing task and the load task, c) prioritise their attention to the load task. Participants could also perform the load task independently of the time perception task, which would enable us to quantify the extent of interference between the load and the temporal bisection task, as it would be possible to observe how performance on both of these tasks is affected when they are performed together.

7.1.4 Chapter 3 & 4: Discussion

Overall, Chapter 4 is not consistent with the idea that anxiety affects time perception via overloading cognitive resources. In other words, these results do not support the proposition that overloading of cognitive resources is the mechanism behind anxiety affecting time perception. It is therefore possible that it is the *anticipation* aspect of anxiety, which was not present in the load manipulation, that is responsible for impairments in cognitive functioning. This includes threat monitoring and promoting harm avoidant behaviours, processes that consume (our limited) cognitive processing capacity.

My *cognitive load* vs *anticipation* hypotheses roughly correspond to worry/anxious apprehension vs arousal aspects of anxiety. Anxious arousal describes physiological changes in heart-rate variability, sweating responses, increased vigilance, and priming of sensory-dependent defensive mechanisms. Anxious apprehension describes awareness of such physiological changes, alongside worry, and rumination (Grupe & Nitschke, 2013b; Heller et al., 1997).

Studies often dissociate between the worry/anxious apprehension and the arousal aspects of anxiety, but the unique contribution of each component to cognition is rarely studied. Specifically, while many studies find that worry predicts performance in cognitive tasks, they do not go as far as exploring whether this is a unique contribution of worry over and above (or instead of) arousal (Moran, 2016). One study showed that worry (as measured by self-report) and working memory mediate the association between trait anxiety and academic performance (Owens et al., 2014). However, when a similar study also considered arousal symptoms (as measured by self-report), they found that both worry and arousal independently predicted academic performance in

adolescents (Putwain et al., 2010). Taken together, the results of Chapter 3 & 4 highlight the need for more research on the anticipatory/arousal aspects of anxiety and how it might affect cognitive performance.

At the neural level, the worry/anxious apprehension and arousal aspects of anxiety might be mediated by two separate circuits (LeDoux & Pine, 2016): 1) a cognitive one, which leads to conscious awareness of anxious states 2) and a defensive survival circuit, which activates automatic harm-avoidant behaviours, accompanying physiological changes in the brain and body. Such conceptualisations are also supported by the finding that self-report and cognitive measures of anxiety often don't correlate (LeDoux & Pine, 2016). The latter was further evidenced by the Experiments 1 & 2 of Chapter 3 (see Table 7-1), in which no associations were found between temporal underestimation under threat and self-reported anxiety while performing the task.

Table 7-1: Participant data collapsed across Experiments 1 & 2 of Chapter 3 (n=50)

	1. Delta BP (behavioural effect of threat)	**2. BDI**	**3. STAI, State Anxiety Score**	**4. STAI, Trait Anxiety Score**	**5. Self-reported anxiety**
1. Delta BP (behavioural effect of threat)	1				
2. BDI	-0.243	1			
3. STAI, State Anxiety Score	-0.164	.685**	1		
4. STAI, Trait Anxiety Score	-0.238	.737**	.827**	1	
5. Self-reported anxiety (within-task VAS ratings)	-0.078	-0.11	0.037	-0.02	1

**. Correlation is significant at the 0.005 level (Bonferroni corrected).

Extending this model, it is possible that both of these circuits alter neurocognitive function by shifting limited neurocognitive resources towards threat processing (Figure 7-1) at the expense of other processes: the first circuit via worry-related processing and the second via monitoring for threat and preparing harm-avoidance-related behaviours. The first system is suggested to involve cortical areas linked to meta-cognition, and the second, subcortical areas such as the amygdala, or other intermediate areas.

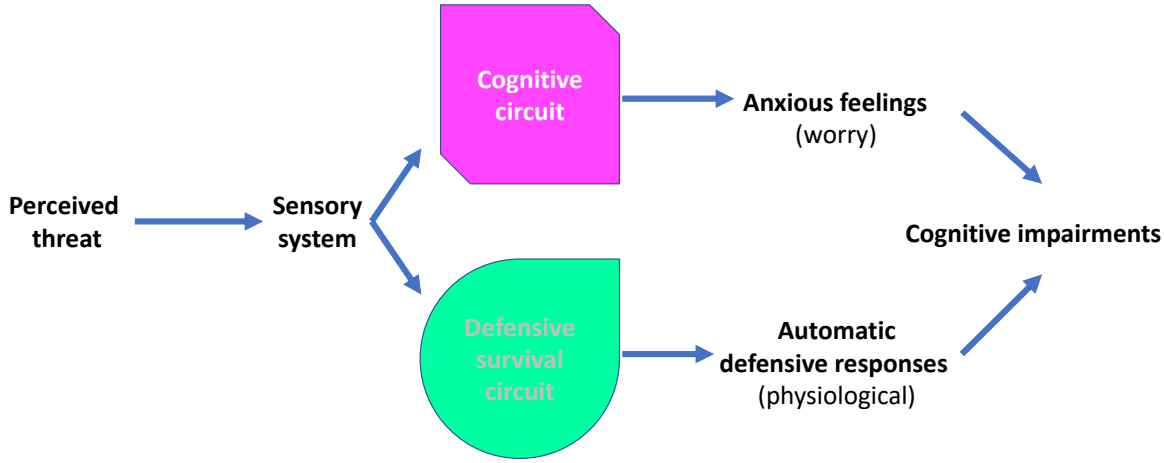


Figure 7-1: In this model, the processing of perceived threat leads to the activation of a cognitive circuit, which leads to conscious feelings of anxiety, including worry. At the same time, a defensive survival circuit that operates unconsciously activates harm-avoidant behaviours, such as threat monitoring. Both of these circuits might impair cognitive functioning, by shifting limited neurocognitive resources to threat-processing, at the expense of concurrent tasks. Adapted from LeDoux & Pine (2016). In the context of threat-of-shock, perceived bodily threat activates both the cognitive and the defensive survival circuits, but it might be the latter which is primarily responsible for altered time perception (see text).

It is possible that each system might be disproportionately impacting specific aspects of cognition. The cognitive circuit might be interfering mainly with phonological information, since worry typically involves inner verbal activity (Rapee, 1993). The defensive survival system centred in the amygdala, being implicated in threat detection, might interfere primarily with spatial and temporal information, which are essential in order to locate threat (Ellena et al., 2020; Peck & Salzman, 2014). Cognitive studies

conducted with threat-of-shock, which might be primarily activating the defensive survival system, support this theory. Threat-of-shock involves threat of bodily harm, hence participants undergoing it, might be monitoring over time the particular areas of their body where electrodes are placed, in anticipation of the shock. In that sense, the kind of anxiety threat-of-shock is generating might be rather different to that induced by ego-threat (e.g. the Trier social stress test), in which participants are not expecting possible bodily harm but social threat; hence threat-of-shock might not be engaging heavily the cognitive system/worry. In fact, threat-of-shock seems to disrupt processes related to temporal and spatial information, but not phonological: Chapter 3 provides strong evidence of threat-of-shock impairing timing, while previous studies have shown that it impairs mainly spatial but not phonological working memory tasks (Hansen et al., 2009; Kalisch et al., 2006; Shackman et al., 2006; Vytal et al., 2012, 2013). At the same time, previous studies did not find an association between threat-of-shock induced thoughts and cognitive performance (Grillon, Robinson, et al., 2016).

This theory could be further tested by comparing the cognitive effects of anxiety manipulations that are more likely to activate the defensive survival circuit (such as threat-of-shock manipulations) versus others that might be more likely to activate the cognitive circuit (such as ego-threat manipulations).

7.2 Chapter 5

7.2.1 Chapter 5: Summary

The overarching theory regarding the effect of anxiety on cognition in Chapters 3 & 4 is that anxiety overloads limited attentional resources, leaving few available for concurrent task processing, hence resulting in cognitive impairments (Eysenck et al., 2007). The aim of Chapter 5 was to further test this theory at the neural level. Hence, participants

performed an adapted version of the temporal bisection task used in Chapter 3 inside an MRI scanner, under threat and safe conditions. Strong support for this theory would be if both anxiety- and task-related neural activation interacted, predicting behavioral performance. No such interaction was found. At the same time, neither activation from anxiety related-areas nor task-related areas correlated with behavioural performance. It is likely that there was not enough statistical power to observe such correlations: in fact, in order to detect a correlation of .30 with 0.80 power I would need 82 participants (rather than the 30 that were included in this study).

Nonetheless, I did find that the insula (part of a putative "anxiety circuit" McMenamin et al. (2014b)) and mid-cingulate areas (part a putative "time perception circuit" (Nani et al., 2019; Wiener et al., 2010)) were activated during both anxiety and task contrasts, leaving open the possibility that anxiety-related and task-related activations interact to determine behavioural performance. However, these analyses provided only weak evidence for such overlap between anxiety- and task-related neural activation. In light of Chapter 4, in which cognitive load did not mimic the effect of anxiety on time perception, one might argue that the 'load' aspect of threat is not overloading cognitive resources, leading to altered behavioural performance, and this is why the interactions were not significant. The fMRI study of Chapter 5 might be underpowered to detect such interactions (it was powered for a relatively large behavioural effect). Hence the evidence, albeit weak, cannot reject the overloading hypothesis.

Overall the results of Chapter 5 are in line with previous studies implicating areas such as the insula and the subgenual cingulate cortex in threat anticipation (McMenamin et al., 2014; Robinson et al., 2014), and areas such as the pre-SMA and mid-cingulate in time perception. (Nani et al., 2019; Schwartze et al., 2012; Wiener et al., 2010).

7.2.2 Chapter 5: Discussion

Given that the results of Chapter 5 are inconclusive, since I did not find particularly strong evidence supporting an overlap between anxiety-related and threat-related neural processing, further studies are needed.

Inspired by previous neuroimaging work that explored brain connectivity under threat-of-shock during early, intermediate and late processing stages, (McMenamin et al., 2014b), a future study could investigate in more detail how anxiety-related and task-related neural circuits interact to determine cognitive performance. In their study, McMenamin et al. (2014) defined a priori three networks: 1) a salience network, consisting of areas that respond to movitationally salient stimuli (Menon & Uddin, 2010), such as the insula and thalamus, which are also part of the threat-processing/anxiety circuit, 2) a default mode network, consisting of areas such as the medial PFC and posterior cingulate cortex, which are engaged during self-referential processing (i.e. when attention is directed internally) and might be associated with worry (Coutinho et al., 2016; Hamilton et al., 2015), and 3) an executive control network, comprising frontoparietal areas that are activated when cognitively demanding tasks require attentional resources (Seeley et al., 2007).

McMenamin et al. (2014) found increased connectivity within the salience network during early stages of threat processing (i.e. as soon as a shock block started), coinciding with decreased connectivity in the executive control network: which seems to be in line with the idea that threat drives cognitive resources away from any ongoing task. In general, the relationship between the executive control network and the default mode network was antagonistic, in line with previous studies (Fox et al., 2005). It might be particularly illuminating to investigate how these neural systems interact to

determine cognitive performance under anxiety. In order to study this, a fully factorial design could be employed using the task of Chapter 5, with task (rest or task) and threat (safe or threat) as within-subject factors. In this way, it would be possible to isolate the neural connectivity of anxiety-related and task-related processing, and how they interact over time, determining cognitive performance.

A further study, employing the aforementioned design, could delinate how these neural circuits are altered in pathological anxiety. Bishop (2009) found that individuals with increased vulnerability to anxiety disorders fail to recuit prefrontal areas in the absence of threat (see also Price et al., 2011). Whether prefrontal underrecruitment in the absence and presence of threat is a characteristic of pathological anxiety could be investigated by comparing functional connectivity within the executive control network across conditions. How the executive control network and the default brain network are affected by worry could also be explored. Although a previous study found that worry does not affect brain areas that fall within the executive control network, only trait worry rather than online worry was measured (Forster et al., 2013) i.e. by online thought probes asking participants to rate on a scale how much they worry right now; hence the neural impact of worry remains unclear. It would be also interesting to explore the properties of the salience system in pathological anxiety. Is it more active during threat processing, in line with hyperactivity theories (Taylor & Whalen, 2015) - i.e are different anxiety phenotypes the result of hyperactive bottom-up processes or hypoactive top-down processes? Or is the salience network turned on irrespectively during threat and safe, in line with threat overgeneralisation theories (Lissek et al., 2014), such that anxiety contaminates even non-threatening encounters.

7.3 Chapter 6

7.3.1 Chapter 6: Summary

Despite anxiety being an adaptive response, it can become pathological, i.e. difficult to control and resulting in impairments to functioning in daily life. The aim of Chapter 6 was to explore the cognitive differences between induced anxiety (investigated in Chapters 3 & 5) and pathological anxiety, by studying individuals with anxious symptomatology. The adaptive vs. pathological question is central, with some studies suggesting that cognitive impairments are risk factors for the development of pathological anxiety, while others claim that such cognitive alterations are common to both pathological and adaptive anxiety. Studies in support of the latter find that adaptive and pathological anxiety impair performance on cognitive tasks, and in particular these relying heavily on working memory (Moran, 2016; Shackman et al., 2006; Vytal et al., 2012, 2013). Somewhat surprisingly, such studies often do not directly compare cognitive functioning using the same cognitive tasks in pathological and induced anxiety (Robinson et al., 2013). To remedy this, I used the same temporal bisection task from Chapters 3 & 5 (in which anxiety was induced to healthy participants) and tested pathologically anxious individuals. I predicted that the performance of pathologically anxious individuals under no threat would be similar to healthy individuals under threat-of-shock. Specifically, I expected that clinically anxious individuals, without being in a 'threat' condition, would underestimate temporal intervals compared to controls, similarly to the finding of temporal underestimation as a result of the 'threat' condition in healthy individuals (Chapter 3). This relationship might be mediated by working memory impairments that are found in clinically anxious individuals (Moran, 2016). In order to account for this possibility, I also included a working memory task.

Contrary to my predictions, I found that time perception (in the absence of threat) was not altered in pathological anxiety. Hence, while induced anxiety alters time perception (Chapters 3 & 5), pathological anxiety might not. These findings cannot be explained due to differences in state anxiety, since pathologically anxious individuals reported being more anxious compared to healthy ones while performing the timing task. At the same time, individuals with pathological anxiety performed worse in the working memory task. A further analysis showed weak evidence that working memory performance correlated with anxious symptoms (trait STAI score).

These findings are not in line with the idea that pathologically anxious individuals are "stuck" in an anxious state, comparable with the anxiety healthy individuals experience under threat. Instead, this study highlights that adaptive and pathological anxiety might have distinct effects on cognition: while working memory deficits characterise both adaptive and pathological anxiety (Moran, 2016; Shackman et al., 2006; Vytal et al., 2012, 2013), time perception seems to be shifted only in adaptive anxiety[2]. However, given the small sample size of the study in pathological anxiety (fifteen individuals per group) it is difficult to interpret the null effect, as it may simply be that the effect of pathological anxiety on time perception is weaker than the effect on working memory.

7.3.2 Chapter 6: Discussion

Chapter 6 found no evidence for altered time perception in pathological anxiety, although a previous study has (Mioni et al., 2016). However, in their experiment, Mioni and colleagues implemented a temporal perception task that possibly taps into working

[2] It should be noted that by 'adaptive anxiety' here, I mean threat-of-shock induced anxiety in healthy individuals. Whether threat-of-shock would lead to similar shifts in time perception across healthy and pathologically anxious individuals remains an open question.

memory, (while the one I implemented might not); hence their findings might actually reflect working memory impairments. In my study pathological anxiety affected the working memory task, but not the time perception task, suggesting that the temporal bisection task I used might not rely heavily on working memory. This is supported by the findings of Chapter 4, in which I showed that varying cognitive load did not alter performance on the temporal bisection task.

My results support the idea that pathological anxiety is associated with decreased working memory performance, while no evidence was found for attentional impairments independent of working memory: pathologically anxious individuals did not underestimate the duration of temporal intervals. While Chapter 6 did not find evidence that attentional deficits independent of working memory are central to anxiety, previous studies have (Bishop, 2009; Derakshan et al., 2009; Eysenck et al., 2007; Shi et al., 2019). However, such conclusions are based mainly on reaction time differences rather than task performance. Chapter 6 found no differences in reaction times in either of the tasks. Importantly, reaction time differences are in general difficult to interpret, and require one to be particularly mindful of the specific experimental design used (Sternberg, 2004.). It is not unlikely that such reaction time differences might be related to different strategies employed by pathologically anxious individuals. For example, a number of anxiety disorders are associated with perfectionism, and hence such individuals might be disproportionally concerned with performing well on laboratory tasks (Handley et al., 2014), which might explain why they might take longer to respond in cognitive tasks. This raises further questions regarding the relationship between pathological anxiety and attentional control deficits.

While I found that pathological anxiety might not be associated with time perception alterations under ordinary circumstances, is this also the case when pathologically

anxious individuals are under induced anxiety, fear or high cognitive load? Future studies could explore how time perception might be altered in clinically anxious individuals under these situations, in an attempt to better understand cognitive alterations in clinical anxiety.

Taken together, Chapter 6 suggests that individuals suffering from pathological anxiety might face particular difficulties with tasks that require prompt storage and manipulation of information (i.e. those that rely on working memory), while the circumstances under which their perception of time might be altered needs to be further investigated.

7.4 Discussion of the approach of this dissertation

This dissertation aimed to elucidate neurocognitive alterations in adaptive and pathological anxiety. The focus was on using human paradigms that are translational, so that in the future they could be adapted to animals in order to investigate the underlying mechanisms in more detail.

7.4.1 The potential of threat-of-shock for probing cold cognition

The anxiety manipulation employed in this dissertation, threat-of-shock, seems to reliably alter 'cold' cognition. In addition to previous studies showing that it can impair working memory (Shackman et al., 2006; Vytal et al., 2012, 2013), Chapters 3 & 5 further suggest that it can also shift performance in a time perception task; a task that does not have an obvious storage and manipulation component (Chapters 4 & 6). Hence, threat-of-shock might be particularly useful in elucidating the negative effect of anxiety on a range of 'cold' cognition tasks, in both human and animals.

However, more studies are required in order to pinpoint the precise components of anxiety that threat-of-shock is affecting. Chapters 4 & 5 provided mixed results regarding whether threat-of-shock impairs cognition via overloading limited attentional resources. As discussed previously, it is possible that different anxiety manipulations affect cognition differently, which needs to be considered. Since threat-of-shock involves threat of bodily harm, it is possibly activating defence mechanisms during threat detection, interfering mainly with spatial and temporal information, but not phonological information (Moran, 2016; Shackman et al., 2006; Vytal et al., 2013, 2013). At the same time, anxiety manipulations such as the Trier Social Stress Test might induce anxiety-related thoughts regarding one's self-image, thus interfering with phonological processes. Whether manipulations such as threat-of-shock and the cold pressor test impair tasks that involve mainly spatial and temporal information, compared with the Trier social stress test which might mainly impair tasks that involve phonological information, remains to be tested by future, large scale studies.

A general concern across all anxiety manipulations, including threat-of-shock, is the kind of anxiety they are inducing, in terms of where they stand on the adaptive—maladaptive spectrum. In this thesis, adaptive anxiety was defined as that one induced under threat-of-shock in healthy individuals. According to my experience of using shocks to induce anxiety in over 400 individuals, on the one extreme there were those who were particularly scared of receiving shocks and withdrew from the study, and on the other extreme, those who did not mind any shock intensity, with some even claiming that they found the shocks pleasant. Which of these responses are adaptive? Is it possible that the most reluctant participants are suffering from some kind of sub-clinical phobia of electrical shocks? And that those who enjoyed the sensation of the shocks can be characterised as sensation seekers (Norbury et al., 2016)? Interestingly,

the neural correlates of specific phobia and threat-of-shock overlap: specific phobia is associated with activity in areas such as the anterior cingulate cortex, thalamus, and insula (Del Casale et al., 2012; Ipser et al., 2013), areas that were also activated under threat-of-shock (Chapter 5). Similarly, for the well-studied Trier social stress test: are the individuals who are mostly affected by it suffering from mild social anxiety, or is it adaptive to be terrified when a panel of stone-faced experts are silently judging you while you are giving an impromptu speech?

At the same time, threat-of-shock seems to differentially affect time perception compared to pathological anxiety, as suggested in Chapter 6. While threat-of-shock leads to temporal underestimation (Chapter 3), pathological anxiety does not (Chapter 6), at least, not to the same extent. Additionally, while verbal working memory is weakly affected by threat-of-shock (Hansen et al., 2009; Kalisch et al., 2006; Shackman et al., 2006; Vytal et al., 2012, 2013), it is clearly impaired by pathological anxiety (Chapter 6 and Moran, 2016).

Pooling together the data from Experiments 1 & 2 of Chapter 3 (see Table 7-1) revealed no significant associations between the behavioural effect of threat on cognition and trait anxiety. Investigations with physiological markets of anxiety under threat-of-shock have yielded similar results (Savage et al., 2019). There might be more important factors determine each participant's response to the threat-of-shock manipulation. For example, prior experiences with shocks, beliefs regarding shock experiments, and cultural differences in emotion expression might be a key factor in determining the effect of threat-of-shock on cognition. While emotional perception and expression seem highly dependent on such factors including cultural differences (Elfenbein & Ambady, 2002; Hareli et al., 2015; Hofmann & Hinton, 2014; Lim, 2016), further studies need to be conducted regarding the threat-of-shock manipulation. With all these in mind, threat-

of-shock does not seem a strong candidate to investigate individual differences of susceptibility to threat.

Although threat-of-shock is believed to be rather robust compared to other anxiety manipulations, (Moran, 2016; Robinson, Vytal, et al., 2013) its properties still remain understudied. For example, the effect of threat on cognition is larger at the beginning on the session as suggested by Figure 3-5 **(**Chapter 5): temporal underestimation under threat seemed larger at the beginning of the session and almost diminished towards the end. Is this because participants are likely to have progressively learned about the task structure and/or habituated to the shocks? Anecdotal analyses suggest that individuals who have been tested multiple times tend to mainly show cognitive differences between threat and safe on their first session, and not on subsequent ones (analyses conducted at the NIH). However, one study found that threat-of-shock has robust test-retest reliability regarding its effect on self-reported anxiety and its effect on a cognitive task (Aylward & Robinson, 2017). It should be noted though, that in this study, threat-of-shock had a rather rare *beneficial* effect on performance: its properties might differ on tasks that are negatively impacted by threat. The latter is particularly important if threat-of-shock is to be used as a human model of adaptive anxiety, in order to bridge animal studies and clinical trials (Grillon et al., 2019). An interesting study investigating how threat related and threat un-related thoughts occurring during threat-of-shock affect cognitive performance was conducted by Grillon, Robinson, et al., (2016). They showed that under threat, participants had more threat-related than threat & task unrelated thoughts. In a follow-up study, they found a significant negative correlation between cognitive performance in a go/no-go task (nogo accuracy) and threat-related/task-unrelated thoughts (Grillon et al., 2017). More research is needed in order to better understand

how aspects of induced anxiety affect cognitive performance. Overall, this paragraph highlights the need for further investigation of the properties of threat-of-shock.

Taken together, although threat-of-shock is a promising manipulation, further studies are required in order to clarify its place in future investigations of anxiety and its disorders. Nevertheless, used in conjunction with other anxiety inductions, it might be helpful in understanding different aspects of anxiety at the neurocognitive level.

7.4.2 Can we treat maladaptive anxiety, sparing the adaptive aspect?

One key goal of this approach is to elucidate neurocognitive circuits that could be then targeted pharmacologically to treat anxiety disorders (Grillon et al., 2019). This is particularly important since anxiety is highly prevalent, and seems to be a common denominator across a number of mental health and neurological conditions (Vos et al., 2012; Wittchen et al., 2011). However, since anxiety is an evolutionarily preserved, adaptive response to threat, it is unclear how such treatments might impact only the maladaptive and not the beneficial aspects of anxiety.

As mentioned in the introduction, philosophers and neuroscientists agree that some degree of anxiety seems essential to human life. Laboratory studies suggest that anxiety can improve performance on cognitive tasks (Aylward & Robinson, 2017; Duncko et al., 2007; Grillon et al., 2017; Grillon, Robinson, et al., 2016; Robinson, Krimsky, et al., 2013; Torrisi et al., 2016b). Considering that adaptive and pathological anxiety share similarities in their effects on cognition (Robinson, Vytal, et al., 2013), and physiology, (Grillon et al., 2019), and may rely on similar neural circuits (Robinson et al., 2014), one might question whether targeting pathological anxiety without impacting on adaptive anxiety is even possible. In fact, after all these years of clinical anxiety

research, it has been impossible to even specifically target anxious feelings, with anxiolytics leading to general emotional and cognitive blunting (LeDoux & Pine, 2016).

7.4.3 We don't know if anxiety is leading to distress, or if distress is causing anxiety

Anxiety is associated with distress and decreased quality of life (Olatunji et al., 2007). In order to alleviate mental distress, one needs to understand its causes and intervene appropriately. Although the current thesis focused primarily on adaptive aspects of anxiety and anxiety disorders, anxiety also characterises a large number of conditions, including chronic pain (Woo, 2010) and cancer (Ng et al., 2017) just to name a few (Vos et al., 2012). Importantly, anxious distress seems to be heavily influenced by environmental factors: it is associated with low socioeconomic status, with the latter being a risk factor for generalised anxiety disorder (Ansseau et al., 2008; Hittner et al., 2019; Mwinyi et al., 2017).

Such studies have provided evidence that socioeconomic disadvantage is associated with higher prevalence of mental health disorders, including depression and pathological anxiety (Richardson et al., 2015). One possible pathway is that higher rates of deprivation expose individuals to multiple stressors, resulting in high prevalence of depression and anxiety (Galea et al., 2007; Ross, 2000). Such stressors include local crime (Astell-Burt et al., 2015), childhood trauma (Heim et al., 2008; Lupien et al., 2009) and job insecurity (Meltzer et al., 2010). At the same time, school status seems to explain variation in depressive symptoms better than neighbourhood deprivation (Dunn et al., 2015), in line with the idea that the effect of one's neighbourhood might be more or less relevant to an individual depending on the stage of their life (Ellen & Turner, 1997). Another factor may be that neighbourhood disadvantage is associated with fewer resources to help individuals with mental health needs and weaker social support

networks, exacerbating depressive and anxious symptomatology (Blair et al., 2015; Cutrona et al., 2005). Additionally, increased exposure of residents from disadvantaged neighbourhoods to drug activity has been linked to increased drug use and associated mental health problems (Galea et al., 2004). Consistent with this, some evidence indicates that moving away from highly deprived areas is associated with mental health benefits (Leventhal & Brooks-Gunn, 2003; Osypuk et al., 2012), supporting a causal relationship between low socioeconomic status and mental distress.

The modern capitalist workplace seems tightly linked with job uncertainty and insecurity (Gordon, 1987; Kalleberg, 2018), with the latter being associated with increased mental health problems including anxiety and depression (Meltzer et al., 2010). Job uncertainty and insecurity seem to an inherent part of the system that allegedly thrives due to inequality (Winship, 2015). In the 30 years following 1977, 60% of the increase in US national income went to just the top 1% of earners (Piketty, 2013), while volatility of incomes at the bottom of the payscale has grown (Hardy & Ziliak, 2014). At the same time two in five hourly-paid workers aged between 26 and 32 in the States, know their schedules less than a week in advance, affecting their quality of life (Lambert et al., 2019).

Although the aforementioned study found that workers without a college degree appear to be at highest risk for precarious scheduling practices, this does not mean that highly educated individuals are not affected by the contemporary anxiogenic workplace. PhD students and early career researchers seem to be disproportionally affected by anxiety ("The Mental Health of PhD Researchers Demands Urgent Attention," 2019). Precipitating factors might include academic capitalism (Jessop, 2018), the winner-takes-all ethos of academia alongside the glorification of overwork, and the mere fact that the short PhD and postdoctoral contracts can allow employers and supervisors to

look the other way when it comes to a duty of care ("Being a PhD Student Shouldn't Be Bad for Your Health," 2019).

Interestingly, the relationship between socioeconomic status and mental distress doesn't seem to be linear. It has been found that individuals in the middle of the organisational hierarchy (such as managers, supervisors, or other contradictory class locations) tend to suffer higher rates of anxiety than those above or below them (Prins et al., 2015). These results are important, since they highlight that social status, independently of economic status, can affect one's mental health.

Moreover, anxiety and anxiety disorders are disproportionately observed in ethnic minorities (Paradies et al., 2015; Williams et al., 2003), LGBT and gender non-conforming individuals (Chodzen et al., 2019; M. King et al., 2008; Pascoe & Smart Richman, 2009; Liadh Timmins et al., 2017; Liam Timmins et al., 2018): groups that have been repressed and marginalized. More than anything, societal dynamics seem to be important in anxiety disorders.

How is it possible that years of poverty, job uncertainty, accumulated repression, and trauma can be undone by short-term pharmacological and/or psychological interventions? Future cognitive neuroscience research needs to focus more on the societal contributions of anxiety disorders. Despite environmental factors being tightly related to anxiety, these are rarely investigated within cognitive and neuroimaging studies. At the same time, although societal contributions to mental health problems (including anxiety) have been extensively studied in epidemiological research, they rarely go beyond mere associations. One suggestion is to include mechanistically relevant measures, including cognitive and neural markers in large population-based longitudinal studies, where socio-economic disadvantage can be assessed

contemporaneously. In fact, this has finally started to happen, for example in the Millennium Cohort Study.

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