Using Wearable EEG to Quantify Associations Between Sleep Architecture, Anxiety, and Fear Memory

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Imogen Charlotte Birch

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Thesis Summary

Memories are shaped by our emotional state during learning and the integration of information during sleep. In this thesis I aim to clarify the contributions of rapid eye movement (REM) and non-REM sleep, as well as anxiety, towards emotional memory consolidation. In addition, emergent technologies support the progression of sleep research, but evidence is needed for their accuracy. I therefore also explore the utility of sleep wearables.

I conducted a validation of the EEG-based Dreem Headband wearable against the gold standard of sleep measurement, polysomnography, finding Dreem suitable for the estimation of most overnight sleep when manually scored. I then developed and tested a novel, two-day discriminative fear conditioning experiment in 38 healthy people (28 female, aged 18–30 years), utilising Dreem to measure overnight sleep. I extended this investigation in a subset of participants to longer-term extinction learning and fear reinstatement after one week, with an additional exploration of bad dreams. In contrast to current evidence preferentially linking REM sleep and emotional memory consolidation, I found that slow-wave sleep (SWS) duration – as well as slow oscillation event count and density – was associated with greater fear discrimination maintenance across the post-conditioning night. In a dissociation between the stages, more REM sleep in the same night was associated with lower fear responses to safe stimuli the next day. Additionally, anxiety predicted maladaptive reinstatement of fear while bad dreams were associated with maladaptive responses the next day and after one week.

My results suggest that SWS, particularly the coordinated network activity that generates slow oscillations, supports fear memory consolidation in young, healthy people. Meanwhile, anxiety and bad dreams may indicate interindividual tendencies towards maladaptive fear. Finally, sleep wearables appear to be a viable tool to support these investigations, moving towards a mechanistic understanding of sleep and fear learning.

Contents

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Chapter 1

General Introduction

There is consistent evidence that brain activity during sleep makes vital contributions to memory consolidation, yet emotional memory remains somewhat equivocal. In this general introduction, I discuss the current understanding of sleep and sleep methodology in this field. I concentrate on human literature, which is the focus of this thesis, but draw on the advantages of animal models where appropriate. In particular, there is uncertainty regarding the roles of rapid eye movement (REM) and non-REM sleep stages in emotional memory consolidation. I also evaluate emergent wearable technology for sleep measurement and how it may be used to answer these questions.

In my exploration of emotional memory consolidation, I focus on fear, utilising the conditioning model of learning and memory. This highlights the importance of interindividual differences in the fear response, for example, across the spectrum of trait anxiety in a healthy sample. This research has important implications for understanding maladaptive fear learning and ultimately the destructive patterns of pervasive fear seen in conditions such as Post-Traumatic Stress Disorder (PTSD).

1.1 Sleep

1.1.1 Sleep for Survival

Sleep is essential for our wellbeing and function, but it is not a unique requirement of the human brain; sleep is conserved in some form across a vast array of diverse species, including fruit flies, roundworms, and zebrafish (Cirelli, 2009; Miyazaki et al., 2017; Siegel, 2005). The pervasiveness of sleep despite the high cost – in mammals at least – of rendering the body defenceless for extensive periods suggests it is a fundamental part of life. Indeed, sleep is essential to survival; total forced sleep deprivation of rats led to skin lesions, weight loss, increased stress hormones, reduced body temperature and (after 11–32 days) eventual death (Rechtschaffen et al., 1989).

Sleep is driven by homeostatic pressure – an exponential drive that increases with time spent awake (Borbély et al., 1989; Borbly, 2001), and the circadian cycle – an endogenous rhythm mediated via the anterior hypothalamus which follows the 24-hour light/dark rotation of the earth (Borgs et al., 2009). Circadian rhythms regulate a variety of physiological processes linked to sleep including body temperature, hormone secretion, and cell cycle regulation (Saper et al., 2005; Zee et al., 2013). In particular, melatonin has been strongly tied to these rhythms (Arendt & Skene, 2005; Brzezinski, 1997). Released from the pineal gland, melatonin starts to increase two hours before natural sleep onset, peaking around five hours later (Bartlett et al., 2013). In fact, melatonin supplements have been used as a treatment for insomnia and have even been suggested as a protective agent against neurodegenerative disorders like Alzheimer's Disease (Chen et al., 2020; Low et al., 2020; Miller et al., 2015; Polimeni et al., 2014).

Before scientific advances allowed researchers to quantify brain activity, it was thought that sleep was a passive state resulting from a lack of input (Jha & Jha, 2020). This changed with the development of electroencephalography (EEG): electrodes on the scalp measuring electrical activity, largely derived from the summation of postsynaptic potentials; the resultant complex waveform can be analysed in both the temporal and frequency domain (Harmon-Jones & Amodio, 2012). Such analyses indicated that sleep is a dynamic process characterised by unique patterns of oscillatory neural network activity; this is discussed further in section 1.1.2. Sleep also involves neurochemical alterations such as a gradual reduction in adrenaline and noradrenaline (Lechin et al., 2004). Broadly, these large-scale changes promote network restoration while sleep supports synaptic plasticity at the cellular level via related gene transcription (Abel et al., 2013; Benington & Heller, 1995; Krueger et al., 2013; Miraglia et al., 2021).

Given this, it is unsurprising that sleep causally contributes to many aspects of psychological function. Compromised sleep, for example through night or shift work, has been consistently associated with an array of mental health conditions (Hasler & Pedersen, 2020; Torquati et al., 2019; Montagni et al., 2020). In fact, sleep problems are diagnostic criteria for many disorders including depression and PTSD (Germain, 2013; Nutt et al., 2008; Thase, 2006), while even short-term sleep deprivation leads to impairments in attention, working memory, and reward or aversive stimulus processing (Killgore, 2010; Krause et al., 2017).

1.1.2 Measuring Sleep

1.1.2.1 Polysomnography

Polysomnography (PSG) is the gold standard for the quantification of human sleep. The primary feature of PSG is electroencephalography (EEG) which records electrical activity from the brain, specifically, voltage fluctuations which arise from the ionic current within neurons (Buzsáki et al., 2012; Krishnan et al., 2018). During sleep, the brain generates dynamic and coordinated electrical field potentials across cortical networks (Blinowska & Durka, 2006). The amplitude and frequency of these neural oscillations indicate hallmark features of sleep stages.

Human EEG is generally recorded non-invasively via electrodes placed across the scalp, although intracranial EEG can be obtained from neurosurgery patients (Andrillon et al., 2015; Staresina et al., 2015). Intracranial EEG is the default approach in animal studies (Takahashi et al., 2010; Mirsattari et al., 2007). Scalp EEG typically has poor spatial resolution reflecting the summed electrical activity from large populations of neurons, somewhat distorted through the skull, skin, and hair (Burle et al., 2015). In addition, the EEG signal reflects the electrical difference between two recording points. Normally, scalp positions are referenced to the mastoids: a bony location behind each ear which should yield little electrical activity (see M1 and M2 in **Figure 1.1**). EEG is thus not a direct measure of brain activity. Nevertheless, it offers excellent temporal resolution and has proved practical for sleep, making it the default approach for measuring brain activity overnight (Mantini et al., 2010; McLoughlin et al., 2014).

PSG comprises of EEG with electrooculography (EOG) and electromyography (EMG) which measure eye movement and muscle tone respectively (Rundo & Downey, 2019). An internationally recognised arrangement of EEG electrodes is the 10-20 system (Homan, 1988; Ives-Deliperi & Butler, 2018): channel Cz is centred to the participant's midline, measured halfway between the mastoids (M1, M2), nasion, and inion (Nz, Iz); other electrodes are placed relative to this. For PSG, electrodes around the eyes and chin measure EOG and EMG.

Autonomous wearable devices for measuring sleep, such as the Dreem Headband (discussed in section 1.1.2.3), may not obtain the same coverage (**Figure 1.1**).

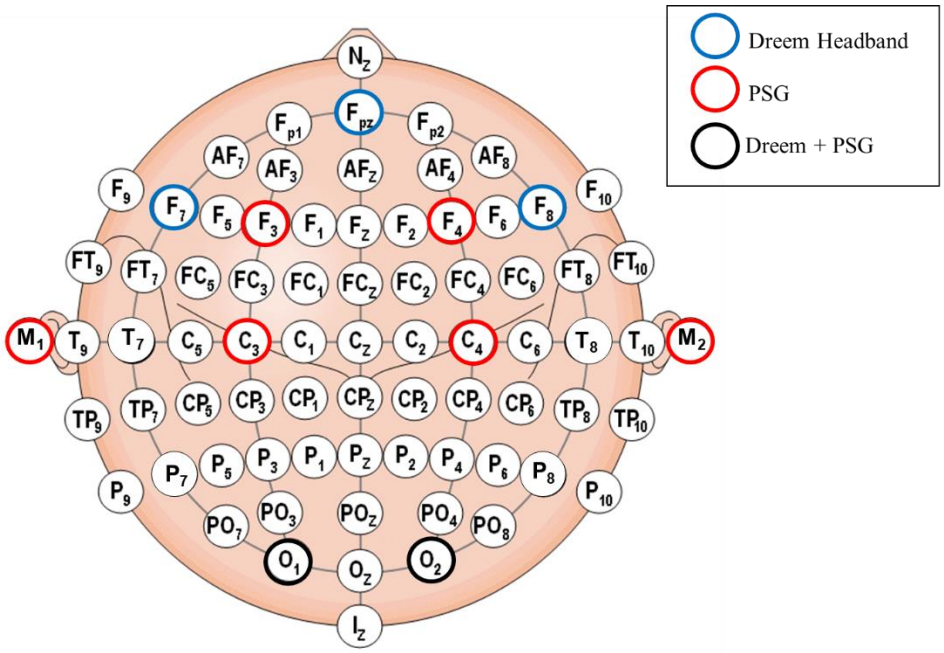


Figure 1.1 The 10-20 System for EEG Electrode Placement

Illustration of the 10-20 system of EEG electrode placement. Primarily, letters refer to brain lobes (F = frontal, C = central P = parietal, O = occipital, T = temporal); odd numbers indicate the left hemisphere and even numbers indicate the right hemisphere. “A” refers to anterior, and “z” refers to “zero” for electrodes placed on the midline and therefore unlikely to reflect cortical activity. For referencing and correct placement, “N” and “I” indicate the nasion and inion respectively, “M” refers to the mastoid process behind each ear.

Not all electrodes are essential. Red circles highlight the electrodes recorded during my PSG measurement (Chapter 2). Blue circles highlight the electrodes recorded by the wearable device, the Dreem Headband (Chapters 2 and 3). Black circles highlight those recorded by both methods.

1.1.2.2 Sleep Stages

In the most basic distinction, human sleep can be divided into REM and non-REM (Miyazaki et al., 2017). While EEG activity in REM is similar to wake, the non-REM stages represent a gradually deepening state of synchronisation across the cortex. This can be seen in the EEG as slow frequency, high amplitude oscillations which are unique to sleep. Non-REM is divided into stages N1, N2, N3, and sometimes N4 (Shrivastava et al., 2014). Rodent sleep follows a

less structured pattern through the stages and is only separated into REM and non-REM (**Figure 1.2**); however, it contains many of the same features as human sleep and is therefore often utilised to study sleep and memory (Genzel et al., 2014; Havekes et al., 2015; Squire et al., 2015).

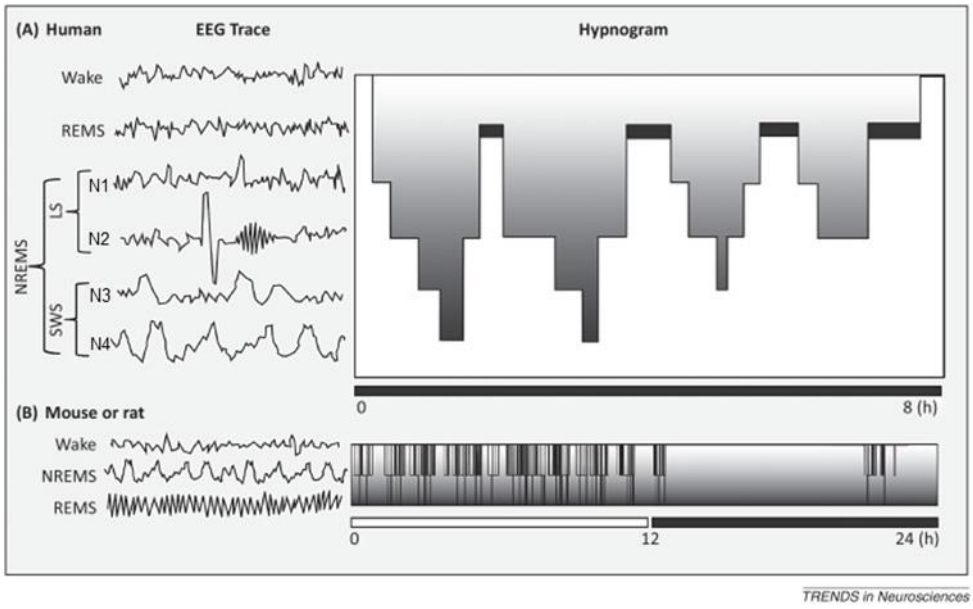


Figure 1.2 Sleep Stages in Humans and Rodents

Human non-REM sleep shows increasing slow oscillations from light sleep (LS) to slow-wave sleep (SWS). In contrast, human REM sleep shows wake-like activity. Rodent sleep shows similar oscillations in non-REM and similar frequencies in REM, although the pattern of sleep across the night (hypnogram) is very different. Image adapted from Genzel et al. (2014).

In light sleep, N1 is characterised by mixed amplitude, low frequency EEG with slow, rolling eye movements. N1 invariably transitions to N2, characterised by K-complexes, a single well-delineated slow oscillation at a slow delta 0.5–2 Hz, and sleep spindles, short bursts of activity in the sigma 9–16 Hz frequency (Ohayon et al., 2017; Silber et al., 2007). The deep sleep stages N3 and N4 are commonly known together as slow-wave sleep (SWS) and in recent years are generally not separated. SWS is characterised by increasing slow oscillations, although sleep spindles also occur less visibly (Maquet et al., 1997). Both slow oscillations and spindles, discussed in more detail in section 1.1.2.3, have been a strong focus of interest in memory consolidation (Fernandez & Lüthi, 2019; Fogel & Smith, 2006; Purcell et al., 2017; Schabus et al., 2004).

REM makes up the final part of healthy overnight sleep. REM sleep has historically been known as paradoxical sleep, as cortical activity lacks the synchrony of non-REM and appears similar to that seen during waking hours. REM is characterised by low amplitude EEG activity in the 4–8 Hz theta frequency alongside rapid eye movements and low muscle tone (Andrillon et al., 2015; Valjakka et al., 1998). REM offers less easily defined EEG signatures than non-REM; however, theta rhythms have been associated with emotional memory consolidation (Boyce et al., 2016; Hutchison & Rathore, 2015; Nishida et al., 2009).

A hypnogram (**Figure 1.2**) shows how human sleep stages are typically represented across the night: on average, people spend approximately 5% in N1, 50% in N2, 20% in SWS and 25% in REM (Shrivastava et al., 2014). Largely, sleep repeats a 90-minute cycle through the stages; however, the amount of REM increases in each subsequent cycle while SWS correspondingly decreases. This means that the first half of the night contains the majority of our deep sleep while the second half contains the majority of REM. This is thought to be regulated by the same interaction between homeostatic and circadian mechanisms which determine sleep onset (Borb & Achermann, 1999).

1.1.2.3 Hallmark Features of Sleep EEG

Most mechanistic details of sleep have been gleaned from the study of non-REM. In particular, the synchronisation of thalamocortical circuits seen across non-REM's hallmark features – slow oscillations and sleep spindles (**Figure 1.3**) – are easily recorded in human scalp EEG and have been widely studied in relation to memory consolidation (Gais et al., 2006; Marshall & Born, 2007).

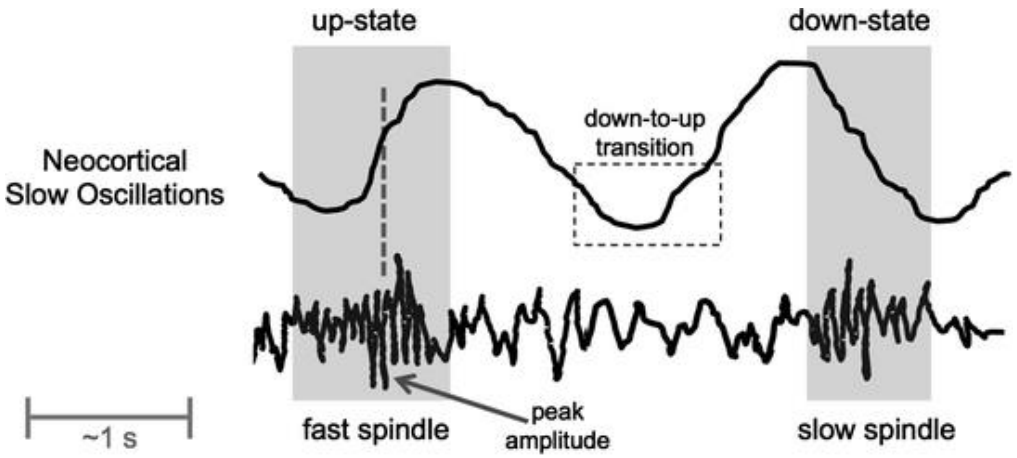


Figure 1.3 Slow Oscillations and Sleep Spindles in Human EEG

Non-REM sleep is characterised by slow oscillations and sleep spindles. Fast sleep spindles tend to occur time-locked to slow oscillation up-states, while slow spindles occur more often within slow oscillation down-states. Image from McDevitt et al. (2017).

1.1.2.3.1 Slow Oscillations

Slow oscillations are generally defined within 0.3–2 Hz frequencies, although specificity within this range is disputed: they have been defined at < 1Hz, < 1.5 Hz, and < 2 Hz (Lockmann et al., 2016; Mölle & Born, 2011; Parrino et al., 2009). These high amplitude oscillations reflect depolarising up-states of increased neuronal activity alternating with hyperpolarising down-states of relative neuronal silence (Mölle & Born, 2011; Sanchez-Vives, 2020). Slow oscillations indicate a striking coordination across the cortex which is generally not seen during waking hours and has been associated with spike timing-dependent plasticity (González-Rueda et al., 2018). The neocortex receives input from the thalamus during slow oscillations (Neske, 2016). However, slow oscillations have also been reported to occur in isolated cortical slices in the absence of driving input, when in vitro slices were maintained in specific ionic concentrations (Sanchez-Vives & McCormick, 2000).

During non-REM sleep, slow oscillations have been reported to start in the prefrontal neocortex and travel, in slow waves, in an antero-posterior direction at approximately 1–7 metres/second in young, healthy people (Massimini et al., 2004). Massimini and colleagues also found consistent slow oscillation origin and propagation across nights in the same individuals, suggesting this non-REM sleep feature is indicative of functional network connectivity. In support of this, aberrant slow oscillation patterns have been associated with

neurodevelopmental disorders such as schizophrenia (Bartsch et al., 2019; Castelnovo et al., 2020; Zhang et al., 2020) and autism (Lehoux et al., 2019).

1.1.2.3.2 Sleep Spindles

Sleep spindles are short (0.5–2 second) bursts of oscillatory activity that occur during non-REM sleep (Fernandez & Lüthi, 2019). Like slow oscillations, the exact frequency definitions vary, but spindles can be divided into fast (approximately 12–15 Hz) and slow (approximately 9–12 Hz) subtypes. The fast spindle may reflect the 'classic' spindle, which originates from thalamic circuits and often occurs locked to a slow oscillation up-state, as seen in **Figure 1.3** (Niethard et al., 2018; Silversmith et al., 2020). Intracranial EEG has suggested that this happens primarily locally, rather than distributed across the cortex (Nir et al., 2011). There is more uncertainty concerning the origin of slow spindles. Generally, slow spindles occur on the down-state of the slow oscillation (Klinzing et al., 2016; McDevitt et al., 2017; Mölle et al., 2011), though this has not been replicated in every study (Gonzalez et al., 2018).

Fast and slow spindles may be generated by different neural mechanisms. In 28 healthy people (10 female, mean age 26 years), either carbamazepine (n=13, targeting a reduction in Na^+ channel activity) or flunarizine (n=15, targeting a reduction in Ca^{2+} channel activity) were administered prior to sleep. Both were compared to a placebo in the same individuals. The results indicated that carbamazepine reduced fast spindles (~14 Hz) but enhanced slow spindles (~10 Hz) during non-REM sleep, while flunarizine had the opposite effect (Ayoub et al., 2013). In support of this, human intracranial EEG has suggested fast and slow spindles originate from separable cortical layers (Hagler et al., 2018). This is reflected in scalp EEG, where slow and fast spindles are seen most clearly from frontal and central regions respectively (Cox et al., 2017; D'Atri et al., 2018; Mölle et al., 2011).

In general, spindles show interindividual differences in spatial and spectral dynamics that are highly heritable (Purcell et al., 2017). Spindle density (often defined by mostly fast spindle frequencies) has been associated with immediate memory consolidation after sleep (Barakat et al., 2011; Nishida & Walker, 2007; Schabus et al., 2004), but also with trait factors such as intelligence (Fang et al., 2017; Fogel et al., 2007; Ujma et al., 2016). In addition, like slow oscillations, aberrant spindles have been associated with various conditions, particularly schizophrenia (Castelnovo et al., 2020; Merikanto et al., 2019; Sasidharan et al., 2017).

1.1.2.4 Moving Beyond PSG: Wearable Technology

PSG is the gold standard for sleep measurement and analysis, yet it is resource heavy. A trained technician or researcher must correctly place each electrode and ensure recording quality: the skin is prepared with a mild abrasive, impedance is lowered with the use of conductive recording gel, and electrodes are temporarily affixed to the scalp. PSG equipment is also expensive and cumbersome, so participants often have their sleep recorded in a sleep laboratory. PSG carried out in the home gives less control, although a familiar environment may promote better sleep quality (Bruyneel et al., 2011; Bruyneel & Ninane, 2014; Fry et al., 1998). However, this imposes a greater demand on the researcher, who has to travel to each participant and set up the equipment in unfamiliar surroundings.

Finally, a trained researcher must visually score every 30-second epoch of the PSG recording for characteristic signatures of the sleep stages. The American Association of Sleep Medicine (AASM) defines guidelines for human sleep stage scoring, providing a standardised approach across sleep research (Danker-Hopfe et al., 2009). To enhance accuracy, two researchers often score the sleep data independently and then compare their classifications. It is generally accepted that 80% agreement across each night is adequate to determine sleep stages, though this is not always achieved between researchers from different research groups (Danker-Hopfe et al., 2009; Magalang et al., 2013; Norman et al., 2000). Scoring accuracy may also vary across sleep stage, with lower agreement reported for N1 and SWS compared to N2 and REM (Rosenberg & Van Hout, 2013). Disagreed epochs may be resolved over discussion if 100% agreement is required. Manual sleep scoring is not only subjective, but also a significant contributor towards the extensive time and resource demands of a PSG-measured sleep study.

Recent advances in software, however, have led to the development of automated scoring algorithms, potentially negating the need for the time consuming and subjective process of visual sleep scoring (Mousavi et al., 2019; Supratak et al., 2017; Tautan et al., 2019). One step further, there are now a variety of sleep wearables – autonomous devices to record and analyse overnight sleep with no expert input. These range from actigraphy watches which record movement and heart rate to more sophisticated devices with EEG electrodes (Garcia-Molina et al., 2018; Lee et al., 2018; Liang & Chapa Martell, 2018; Zambotti et al., 2019). One promising device with a published validation against PSG is the Dreem Headband (Arnal et al., 2020). This device is worn as a flexible band around the head with five embedded dry EEG electrodes measuring from frontal and occipital regions. The EEG signal is automatically sleep scored in real time and Arnal et al. reported 74–85% accuracy against expert scoring of PSG

in stages N2, SWS, REM and wake. The Dreem Headband is described in more detail in Chapter 2.

These wearables provide enormous potential. Unlike PSG, a wearable sleep device aimed at the general public must be easy to use, affordable, and portable. Replacing the expensive and time-consuming PSG recording and analysis with an autonomous device in the home would free up valuable resources. For example, in one study more than 3,000 pregnant women were sent a wearable device to measure breathing overnight (Facco et al., 2015). The device required minimal set up and was sent by post, while the data were securely transferred to the researchers remotely. Wearable sleep trackers used in the same way could allow data collection on an equally large scale.

Sleep wearables have the capacity to greatly improve sleep research, allowing greater sample sizes and easier replication. However, the literature is still in its early stages and the requisite quality must be maintained. Consequently, sleep wearables are an exciting avenue to explore, but more validation is needed before they become standard in sleep research.

1.1.3 Sleep-Dependent Memory Consolidation

Memory relies on widespread connections throughout the brain and can be most simply defined as a series of dynamic processes – encoding, consolidation, storage, and retrieval (Bliss et al., 2003). Seminal studies demonstrated that the hippocampus was central to memory processing (Burgess et al., 2002; Eichenbaum, 2000), and there is now consistent evidence that memories are represented in the hippocampus by distinct neuronal firing patterns or 'engrams' (Goode et al., 2020; Hainmueller & Bartos, 2018; Lacagnina et al., 2019). Current understanding posits that while much of the information we process in our short-term memory is immediately forgotten, some experiences are encoded in the hippocampus, consolidated via structural and chemical changes (e.g. a strengthening of synaptic connections between neurons), and integrated into long-term storage in the cortex where they can be retrieved (Nadel et al., 2012; Squire et al., 2015; Gilboa & Marlatte, 2017).

It is well-established that sleep supports memory consolidation (Born & Wilhelm, 2012; Diekelmann & Born, 2010), but both sleep and memory are multifaceted processes. A common distinction in memory is between declarative – explicitly remembered experiences such as a recent holiday, and procedural – implicit learning such as riding a bike. In-depth case studies have greatly supported evidence for the separation between different types of memory. For example, patient S.Z. had severe damage to the medial temporal lobe, yet was able to demonstrate significant improvement over time in his saxophone playing (a procedural

task), despite not consciously recalling his previous practice (Cavaco et al., 2012). It has been suggested that declarative and procedural memories are supported by non-REM and REM sleep respectively (Marshall & Born, 2007). However, while there is evidence for this (Fogel et al., 2007; Rasch et al., 2007; Smith et al., 2004; Tucker et al., 2006), the notion has also been contested with evidence for connections between declarative memory and REM, as well as procedural memory and non-REM (Gais et al., 2000; Goerke et al., 2013; Holz et al., 2012).

In this thesis I focus on declarative memory. Declarative memory relies on cross-cortical connections and plasticity at a systems level, while synaptic consolidation processes involve the underlying cellular changes (Paller et al., 2021). Patients such as S.Z. with damage to the medial temporal lobe display profound impairment in novel declarative learning and memory, termed anterograde amnesia (Markowitsch, 2008; Squire, 2009), and so highlight that this brain region is crucial for this type of memory. In fact, theories of systems consolidation in declarative memory centred around the medial temporal lobe and hippocampus were largely based on the findings of such case studies (Klinzing et al., 2019).

Memory consolidation does not only occur in sleep, but sleep's unique oscillatory patterns of neural network activity have been strongly associated with (compared to an equivalent time spent awake) enhanced declarative memory consolidation (Diekelmann & Born, 2010; Gais et al., 2006). Many theories have drawn a distinction between REM and non-REM sleep, applying a sequential element to memory consolidation mirroring the sequential nature of sleep stages. For example, a cortical-hippocampal-cortical loop has been described which suggests that experiences are first characterised by cortical activity, hippocampal replay – occurring in wake but to a greater extent in non-REM sleep – then plays a vital role in synaptic consolidation mechanisms transferring the information back to storage in the cortex (Paller et al., 2021). This type of sleep-based reactivation has been suggested to explain how some memories are consolidated and others are forgotten.

Other theories suggest that both REM and non-REM are involved in declarative memory consolidation. The "Sequential Hypothesis" suggests that SWS sorts memories and discards those which are irrelevant or interfering, while remaining memory traces are strengthened and integrated into existing networks in subsequent REM (Giuditta, 2014; Giuditta et al., 1995). In contrast, the "Dual Process Hypothesis" suggests that REM supports emotional (and procedural) memories while SWS supports non-emotional declarative memory (Ackermann & Rasch, 2014; Peigneux et al., 2001).

The strongest links between sleep and memory consolidation have focussed on oscillatory patterns in non-REM sleep. A widely held model, the Active Systems Consolidation Theory,

suggests that slow oscillations orchestrate the transfer of newly encoded memories from the hippocampus to a long-term store in the cortex. This occurs via coordination with thalamic sleep spindles and hippocampal sharp-wave ripples (150–250 Hz oscillations), see **Figure 1.4** (Born & Wilhelm, 2012; Klinzing et al., 2019; Mölle & Born, 2011). As discussed in section 1.1.2.3, slow oscillations and spindles are characteristic features of non-REM EEG and have both been associated with declarative memory consolidation (Lustenberger et al., 2015; Miyamoto et al., 2017; Schabus et al., 2004; Varga et al., 2016). Furthermore, hippocampal sharp-wave ripples have been found nested in slow oscillations and spindles in human intracranial EEG (Clemens et al., 2007; Staresina et al., 2015). These ripples have also been associated with memory consolidation (Norman et al., 2019).

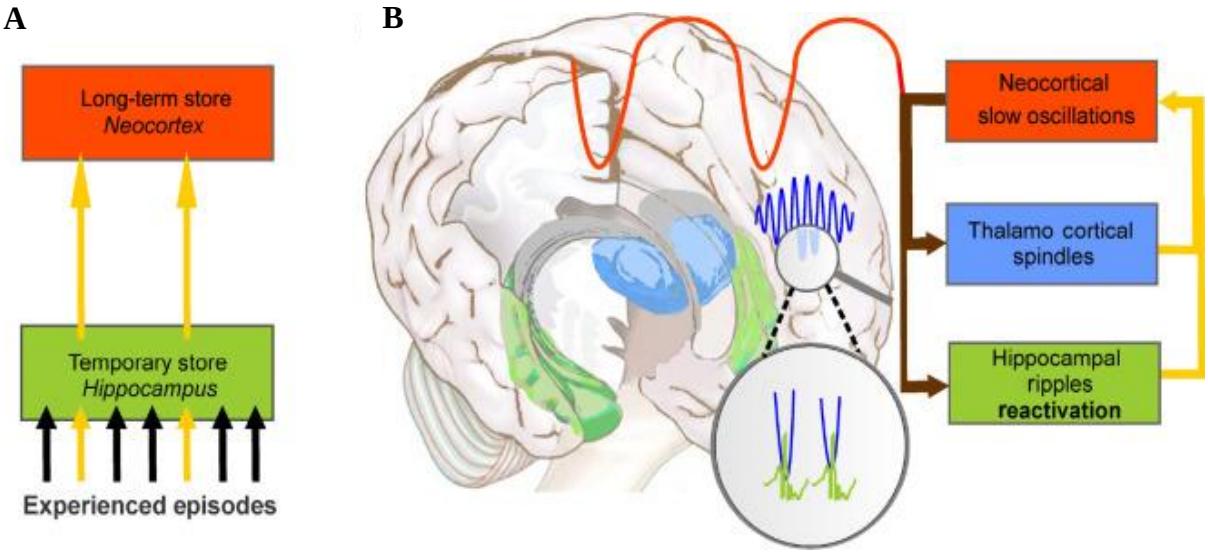


Figure 1.4 The Active Systems Consolidation Theory

The Active Systems Consolidation Theory suggests that some experiences, represented by neuronal firing patterns, travel from a temporary store in the hippocampus, through the thalamus, to long-term storage in the neocortex; in contrast, weakly encoded memories are discarded (**A**). This process is orchestrated via synchronisation between hippocampal sharp-wave ripples, nested in thalamic spindles, nested in cortical slow oscillations (**B**). Image from Mölle & Born (2011).

In animal models, hippocampal engrams encoded during wake reactivate in the same pattern during subsequent non-REM sleep; this has been posited as a mechanism of memory consolidation (Derdikman & Moser, 2010; Ólafsdóttir et al., 2018; Lee & Wilson, 2002). In further support of the Active Systems Theory, this 'replay' has been associated with hippocampal sharp-wave ripples (Fernández-Ruiz et al., 2019; Ji & Wilson, 2007), while ripple

disruption appears to compromise memory consolidation (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). In humans, replay has been suggested by the identification of cortical firing patterns (recorded via intracranial EEG) that were present during learning, repeated in subsequent non-REM sleep (Jiang et al., 2017). Similar results have been suggested using non-invasive magnetoencephalography (Higgins et al., 2021), although these findings do not reflect specific neuronal firing patterns as in rodent data. Nevertheless, there is excellent translational evidence for the Active Systems Theory of non-REM sleep and memory consolidation.

A related theory is also centred around the synchrony of slow oscillations during non-REM sleep. The Synaptic Homeostasis Hypothesis suggests that slow oscillations perform a vital function in synaptic plasticity and our continuing ability to encode and consolidate new memories. Specifically, synaptic strength builds across wake, then slow oscillations during non-REM sleep facilitate synaptic downscaling (a negative feedback response) targeted to specific memories (Bushey et al., 2011; Cirelli & Tononi, 2015; Tononi & Cirelli, 2003, 2006). This is broadly compatible with the Active Systems Theory, as both support a central role of non-REM in memory consolidation, although the Synaptic Homeostasis Hypothesis does not specifically suggest memory reactivation.

Finally, some research has sought causal interventions to demonstrate the importance of slow oscillations. For example, enhancement of slow oscillations via auditory stimulation has been reported to boost memory performance (Marshall et al., 2006; Ngo et al., 2013; Zhang & Gruber, 2019). This provides further evidence for non-REM sleep's role in memory consolidation processes. In addition, novel learning has been demonstrated during SWS (Züst et al., 2019). There is thus evidence for a strong and consistent role for non-REM sleep in memory consolidation. However, the roles of emotion and REM in sleep-dependent memory consolidation remain ambiguous.

1.1.4 Emotional Memory Consolidation During Sleep

Experiences are shaped by our emotional state during learning, consolidation, and retrieval (Hamann, 2001; Smeets et al., 2008; Tyng et al., 2017). Broadly, greater emotional arousal enhances memory across wake and sleep (Dolcos et al., 2017; Fairholme & Manber, 2015), though this may not occur in every situation (Lipinska et al., 2019). As posited by the Dual Process Hypothesis, emotional memory consolidation has been most strongly associated with REM sleep.

A prominent theory of REM-based memory consolidation is the Sleep to Forget, Sleep to Remember Hypothesis. This suggests that REM sleep offers a preferential window for emotional processing through the reactivation of emotional memories, supported by REM's unique electrical and chemical signatures: activity in limbic and paralimbic structures, dominant theta oscillations between cortical and subcortical nodes, and minimal noradrenergic input (Stickgold, 2011). The theory predicts that over time, memory reactivation without the associated emotional arousal should elicit re-learning and an eventual amelioration of the emotional response (van der Helm & Walker, 2009) see **Figure 1.5**. This complements related research into REM sleep and dreams for the reactivation of emotional thoughts and ultimate resolution of experiences (Eichenlaub et al., 2018; van Rijn et al., 2015; Vanderheyden et al., 2015).

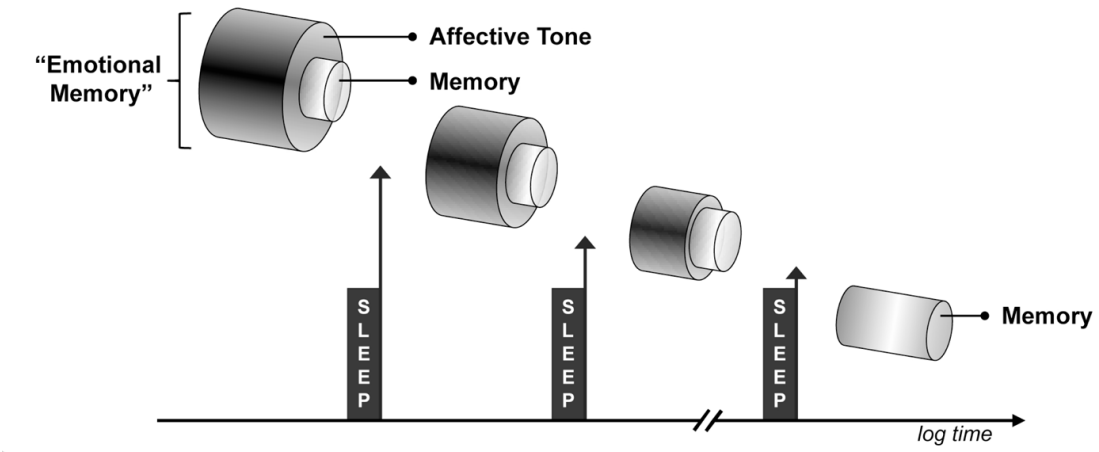


Figure 1.5 The Sleep to Forget, Sleep to Remember Hypothesis

The Sleep to Forget, Sleep to Remember Hypothesis suggests that the declarative content of emotional memories is strengthened over repeated episodes of REM sleep while the affective tone is gradually reduced. Image from Walker and van der Helm (2009).

Evidence linking REM sleep with a reduction in emotional arousal provides support for the Sleep to Forget, Sleep to Remember theory. In one study, healthy participants (n=34, 19 female, aged 18–30 years) viewed the same emotional images in a Magnetic Resonance Imaging (MRI) scanner before and after 12 hours of daytime wake or recorded overnight sleep (van der Helm et al., 2011). Participants who had slept showed reduced amygdala activity and increased prefrontal connectivity, compared to those kept awake. These neural changes were associated with overnight reductions in subjective reactivity, and both subjective ratings and

neural changes were associated with reduced gamma activity (30–40 Hz) during REM sleep – a proxy of adrenergic activity. Although the groups differed in testing time of day, an additional test of new stimuli suggested that the results could not be explained by circadian factors. This supports the view that REM promotes a reduction in emotional responses to previously encoded stimuli.

REM sleep has also been linked with emotional disturbances outside a laboratory environment. Increased REM duration has been associated with PTSD (Habukawa et al., 2018; Mellman et al., 2014). In addition, REM alterations (shortened REM latency, increased REM duration and density) have been consistently found to precede the onset of depression and are also found as endophenotypes in the relatives of depression patients (Berger & Riemann, 1993; Palagini et al., 2013; Pesonen et al., 2019). This suggests a causal link between REM sleep and impaired emotional processing.

However, there are mixed findings as to whether REM facilitates emotion reduction. In another study, participants (n=24, all male, aged 18–30 years) had three hours of SWS-dominant sleep in the first half of the night or REM-dominant sleep in the second half of the night. Those who had REM showed enhanced discrimination of new versus old emotional pictures, compared to those who were kept awake or allowed SWS; however, emotional ratings were unaffected (Wagner, 2002). In a similar study where participants (n=16, all male, aged 20–26 years) learned neutral and negative pictures before early or late sleep, memory retention was better for emotional pictures after REM but valence ratings were preserved rather than reduced (Groch et al., 2013). These studies suggest that REM supports emotional memory but not necessarily emotional alleviation.

In more recent evidence though, REM duration has been associated with a short-term increase in emotion but long-term reduction. When participants (n=76, all female, aged 18–32 years) viewed negative images before and after a daytime nap, REM duration was associated with increased aversiveness ratings the same day, but reduced intensity, number, and duration of intrusive memories of the images three days later (Werner et al., 2020). In support of the Sleep to Forget, Sleep to Remember Hypothesis, this study suggests that the timing of REM-based effects may be critical. However, the aversiveness of the stimuli could also affect whether the emotion of the experience can start to be decoupled over just one night.

While there is good evidence for a relationship between emotional disturbance and memory and REM sleep, emotional memory has also been linked with non-REM sleep. For example, healthy participants (n=15, all male, aged 19–28 years) learned emotional and neutral stories before three hours of SWS-rich early sleep (Groch et al., 2011). Clonidine, a drug blocking

noradrenaline release from the locus coeruleus, eliminated the superior memory for emotional items. This suggests that noradrenaline release during SWS supports emotional consolidation. SWS may also interact with other sleep stages. For example, REM duration has been associated with vocabulary learning after memory reactivation via auditory cues presented in SWS (Batterink et al., 2017). This suggests that a dichotomy between REM and non-REM sleep may be a simplification which overlooks potential interaction between the stages.

1.1.5 Summary

Sleep is essential for our function, in fact, for our survival. PSG provides a non-invasive measurement of neural activity and this has driven a mechanistic understanding of sleep, but this method is expensive, slow, and cumbersome. Sleep wearables therefore have enormous potential to expand sleep science with greater data collection, which should improve the reliability of the field. However, validation is required to build confidence in the accuracy and consistency of wearable sleep technology.

Methodology aside, sleep plays a significant role in the optimisation of learning and memory. While various theories of sleep-dependent memory consolidation convergently suggest contributions of non-REM and REM towards non-emotional and emotional memory respectively, these roles are not clear-cut. In particular, there is good evidence for both the mechanisms and outcomes of the Active Systems Theory of non-REM, but there is no reason this would not apply to emotional memory; indeed, non-REM has also been associated with emotional memory consolidation. The Active Systems Theory also does not preclude a role of REM such as that suggested by the Sleep to Forget, Sleep to Remember Hypothesis. Therefore, since evidence exists across REM and non-REM sleep stages, the contributions of both towards the consolidation of emotional memories warrants further investigation.

While there is a lack of evidence for complementary roles of REM and non-REM sleep in emotional memory consolidation – or whether REM (or non-REM) supports an increasing attenuation of emotion over time – these investigations are complicated by the numerous contributing factors in sleep-dependent consolidation including the time lapse between sleep and encoding, interference from other experiences, and previous reactivation of the memory (Kolibius et al., 2021; Mander et al., 2011). This may be compounded by the variety and complexity of emotional responses (Agbo & Ngwu, 2017; Bianchin & Angrilli, 2012; Feldner et al., 2003; Tsai et al., 2006). A simple model of emotional consolidation is therefore preferable.

1.2 Fear

1.2.1 The Fear Response

Emotions are complex states which manifest as physiological, behavioural, and psychological responses. Occurring in response to threat, fear is seen across the animal kingdom (Adolphs, 2013; Steimer, 2002), and can elicit rapid autonomic arousal and attention, avoidance behaviour, and long-term changes to learning and memory (de Quervain et al., 2017; Field & Lawson, 2003; Levenson, 2006; Rachman & Hodgson, 1974; Vuilleumier & Brosch, 2009).

Physiologically, threat detection triggers a cascade of responses in the nervous and endocrine systems. First, activation of the autonomic nervous system recruits the sympathetic pathway; this stimulates the release of adrenaline and noradrenaline which leads to physical reactions such as increased heart rate (Hamill et al., 2012). At the same time, the Hypothalamic-Pituitary-Adrenal (HPA) axis stimulates a series of stress hormones leading to the release of cortisol from the adrenal glands; this aids in increasing blood pressure and circulating glucose in the blood (Novak et al., 2013). This hormonal response happens on a relatively long timescale of minutes, compared to the fast-acting autonomic response in milliseconds (Herman et al., 2016).

The behavioural and psychological correlates of fear are more diverse. While immediate fear often leads to 'fight, flight, or freeze' behaviour (Maack et al., 2015; Thompson et al., 2014), there are complex psychological interactions with individual traits and tendencies. For example, Olive Flounder fish with prior tendencies towards boldness and shyness were significantly more likely to respond to simulated capture with a fight-flight response or freeze-hide response respectively (Rupia et al., 2016). In addition, female rats were more likely to dart in response to an unavoidable footshock whereas male rats were more likely to freeze (Jones & Monfils, 2016). In humans, there is consistent evidence of interindividual differences in response to the same fear stimuli across a range of experimental situations, most commonly associated with measures of trait anxiety (Arnaudova et al., 2013; King et al., 2017; Laing et al., 2019; Ochsner et al., 2006). I discuss this in more detail in section 1.2.4.

Since fear elicits a complex response across the brain and body, it is an oversimplification to wholly attribute specific brain regions. Nevertheless, fear has been most often associated with the limbic system (Forster et al., 2006; Lai, 2019; LeDoux, 2012), centrally comprised of but not necessarily limited to the amygdala, thalamus, and hippocampus (**Figure 1.6**). These structures have been generally associated with emotion, learning, and memory (Grodd et al., 2020; LeDoux, 1993; Morgane et al., 2005; Rajmohan & Mohandas, 2007; Rolls, 2015), but in particular, the amygdala is often considered the fear hub of the brain. Indeed, multiple lines

of evidence have suggested that fear processing is substantially impaired when it is damaged (Adolphs et al., 1995; Feinstein et al., 2013; LeDoux, 2003; Ressler & Maren, 2019).

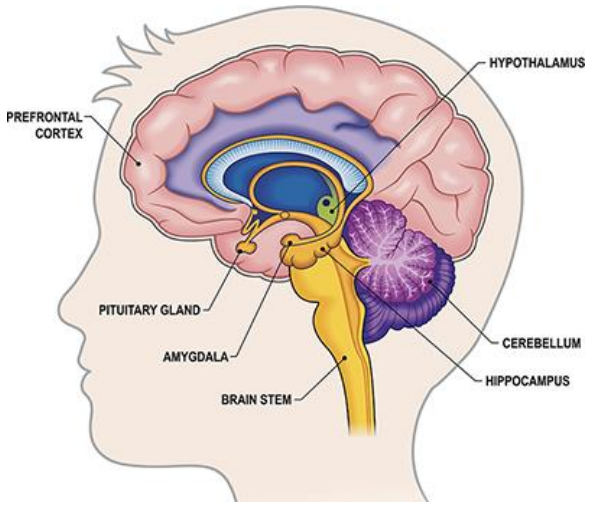


Figure 1.6 Fear Processing in the Brain: The Extended Limbic System

The limbic system is centrally composed of the amygdala, hippocampus, and thalamus (directly above the hypothalamus). These structures contain strong links to the prefrontal cortex (associated with higher reasoning), and cerebellum and brainstem (associated with sensory and motor processing). The hypothalamus and pituitary gland link the nervous and endocrine systems, regulating hormone secretion. Image from Benson (2020).

Historically, theories of emotional correlates in the brain have been constantly changing (Roxo et al., 2011). One prominent theory proposed the limbic structures as an evolutionarily old system reflecting that fear is a primitive survival instinct acquired before higher reasoning capabilities. However, this has now been contested due to its strong links to the prefrontal cortex (LeDoux, 2012). A current model of fear processing posits two distinct fear pathways in the brain. Initially, a fast, subcortical pathway via the thalamus to the amygdala sends limited information on the perceived threat. Then, a slower pathway through the cortex forms the conscious experience of fear (Ledoux, 1998; LeDoux, 2012). In support of this, in human intracranial EEG (11 participants, 5 female, aged 29–59 years), only low frequency fearful images elicited a fast ~70 ms response from the amygdala, while both low and high frequency fearful images elicited a slower ~100 ms response from cortical areas (Méndez-Bértolo et al., 2016). This supports evidence for the amygdala as an alert mechanism for threat.

The human amygdala has been widely studied in relation to fear and fear learning, often in conjunction with the hippocampus. Patient case studies have demonstrated a double dissociation between these regions: patient R.H. had bilateral damage to the amygdala and hippocampus and was unable to acquire declarative facts (sensory details of the stimuli) or conditioned fear; patient W.C. had bilateral damage to the hippocampus but intact amygdalae and was able to acquire a fear response but not recall sensory details of the stimuli; finally, patient S.M. had bilateral damage to the amygdalae but intact hippocampi and was able to recall declarative details but not acquire a fear response (Bechara et al., 1995). This highlights how the amygdala is crucial specifically to fear while the hippocampus is crucial specifically to declarative memory. Consequently, in healthy people, the amygdala plays a significant role in fear learning and memory. One proposed mechanism of this interaction is the action of stress hormones on beta-adrenergic receptors in the basolateral amygdala influencing memory storage (through connections on the vagus nerve to the locus coeruleus stimulating the release of noradrenaline) and thereby modulating memory encoding, storage, and retrieval (McIntyre et al., 2012).

1.2.2 Measuring Fear

1.2.2.1 The Fear Conditioning Model

Conditioning is a simple model of behavioural learning where the response elicited by one stimulus is associated with another, potentially unrelated, stimulus. For example, a dog exhibits excitement at the sight of his lead because he associates it with (because in the past it has often been followed by) an enjoyable outcome – going for a walk. On the other hand, a person who was attacked by an aggressive dog may afterwards exhibit fear at the sight of the dog. Some conditioning occurs gradually over multiple experiences, but just one highly salient experience can cause a strong and lasting conditioned response. These responses are also known to generalise, in the latter scenario for example, to a fear of all dogs, even those that are friendly.

Typically, fear conditioning in a laboratory environment links simple sensory stimuli (e.g. sounds or images) with a naturally aversive stimulus (e.g. a sudden loud sound or mild electric shock). Pairing these items creates a novel and simple acquired fear, the development of which can then be measured or perhaps manipulated across learning, consolidation, and retrieval. Fear conditioning is typically used across animal and human research to study fear learning (acquisition), re-learning the threat no longer exists (extinction), and return of fear (reinstatement).

Learned fear has both declarative and implicit features, for example conscious awareness of shock pairings and an unconscious physical response (e.g. in noradrenaline) to a stimulus. These may have different neural correlates, for example hippocampal activity was reported only for consciously perceived Pavlovian conditioning, whereas amygdala activity was reported for both consciously and unconsciously experienced pairings (Knight et al., 2009). These aspects of fear may also generalise differently; in one study, only explicitly recognised threats were found to generalise to similar stimuli (Manassero et al., 2019). Therefore, conditioning occurs consciously and unconsciously; however, while implicit features should be considered within this, fear conditioning in the laboratory is generally considered a primarily declarative memory (Dunsmoor & Kroes, 2019).

During fear acquisition training in an experimental setting, a conditioned stimulus (CS) is paired with an aversive unconditioned stimulus (US), as illustrated in **Figure 1.7**. Repeated presentation of the unpleasant US after the CS creates a 'danger' stimulus or CS+ and eventually the CS+ alone starts to elicit a fear response (Warthen et al., 2011). The US does not have to occur on every trial; conditioned responses have been reported to be longer-lasting when the pairing has been less predictable (Vansteenwegen et al., 2008).

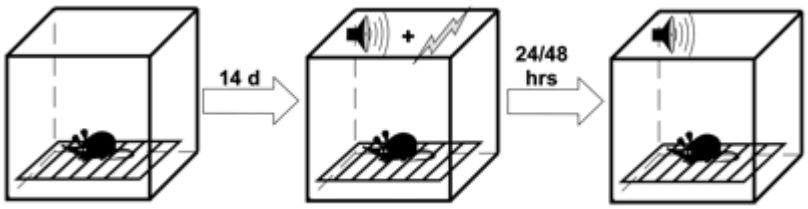


Figure 1.7 A Fear Conditioning Design

In an example of rodent fear conditioning, the mouse is first habituated to its environment. During conditioning, the mouse is exposed to repeated pairings of a specific sound with an unpleasant footshock. After a delay, conditioning memory is tested by measuring the fear response to the sound alone. Image from Warthen et al. (2011).

The CS+ is sometimes compared to a 'safe' stimulus or CS-. In contrast to the CS+ which predicts the unpleasant shock, the CS- predicts a period of relative safety. For example, if a shock often occurs after one distinct tone then the animal exhibits fear at the beginning of the sound because it expects the shock. In contrast, if the animal also repeatedly hears a different tone where a shock never follows, it learns to associate the sound with safety. This safety

learning relies on adequate distinction between the stimuli and has been associated with inhibitory mechanisms (Christianson et al., 2012).

Rodents have been heavily used in fear conditioning research. This is likely to constitute a more immersive experience than human fear conditioning, considering that the rodent does not know the shock is coming and cannot withdraw, but the principle of associative learning is the same. In particular, rodent models have enhanced understanding of the neurobiology underlying the encoding and consolidation of fear conditioned memories (Delgado et al., 2006). Lesion studies have reported impaired fear conditioning after removal of the amygdala (Phillips & LeDoux, 1992). Likewise, activity in the basolateral and central nucleus of the amygdala has been linked to fear acquisition (Rosen, 2004). In another study, lesions of the central nucleus led to reduced fear responses but a maintenance of avoidance behaviour, while in a double dissociation, basolateral lesions led to reduced avoidance behaviour but a maintenance of the fear response (Killcross et al., 1997).

While fear conditioning reflects associative learning processes, fear extinction involves updating learned responses via new learning – repeated presentations of the acquired CS+ without the aversive US. Recognition that the CS+ no longer predicts danger means that the fear response should gradually reduce. A continuation of fear is therefore maladaptive and potentially damaging. Various evidence suggests that continued fear relies on a series of consolidation processes. For example, the L-type voltage-gated calcium channel antagonist nifedipine impaired extinction learning in mice when administered 1 or 3 hours after conditioning, but not immediately (Cain et al., 2005). In another study, a chemical blockade of the metabotropic glutamate receptor in the rat lateral amygdala impaired fear extinction when applied 48 hours after conditioning, but not after 2 hours (Kim et al., 2007). If extinction can be blocked by the artificial prevention of different neural mechanisms at different times it suggests that extinction relies on the state of the encoded memory – which continues to change over at least 48 hours.

Even after extinction, fear responses are susceptible to reinstatement. This can occur after a reminder of the unpleasant US (cued reinstatement) or simply over time (spontaneous reinstatement). This may be possible because extinction learning does not erase the original fear memory but rather overlays a competing trace: in one study, after fear conditioning and extinction, optogenetic stimulation of neurons in the mouse dentate gyrus (part of the hippocampal formation) that were active during fear acquisition caused an increase in fear, while stimulation of neurons active during extinction suppressed fear (Lacagnina et al., 2019). This suggests that the acquisition memory trace persists despite extinction training. Like poor

extinction learning, an unwarranted return of fear is often maladaptive and can lead to anxiety (Hunt et al., 2019; van Meurs et al., 2014).

1.2.2.2 Quantifying Fear Responses

With a controlled experimental model such as fear conditioning, the quantification of the fear response is critical. Since fear can be expressed physiologically, behaviourally, and psychologically, it can be measured across these domains as well. The most appropriate measure is likely to depend on the subject. For example, in animal (primarily rodent) models, fear conditioned responses are commonly measured by behavioural freezing, a well-established indicator of animal fear (Kopec et al., 2007). However, a physiological approach tends to be favoured in human studies.

One physiological measure of the fear response which can be translated from animals to humans, albeit via different methods, is neural activity. This can be measured by MRI or cellular recording from known fear-linked regions such as the amygdala. However, these are not universally applicable methods in the context of fear conditioning. MRI is expensive and lacks temporal resolution, while any index of neural activity may be a simplification of the systemic fear response. That being said, cellular recordings in animal models provide a highly localised measure and are therefore informative in some experimental designs.

A prevalent measure of human fear is the skin conductance response (SCR) derived from electrodermal activity. Electrodes on the skin measure its conductance, which rises with increased sweating (Green et al., 2014). SCRs are usually measured from the high concentration of eccrine sweat glands on the hands or feet, which receive sympathetic innervation via cholinergic fibres (Folk & Semken, 1991; Hodge et al., 2021). The popularity of the SCR may stem from its sensitivity to small changes, relative ease of use, and high participant tolerance (Banks et al., 2012; Christopoulos et al., 2019; Doberenz et al., 2011). Other studies have utilised additional measures of sympathetic activation, namely pupil dilation (pupil constriction in response to threat) and startle response (the magnitude of eyeblink activity) to a startle probe such as a short sound (Leuchs et al., 2019; Kindt & Soeter, 2013; Korn et al., 2017). The startle response may be specific to negative valence (Kuhn et al., 2020), but has in some cases been found to impede safety learning to the CS- (de Haan et al., 2018).

These implicit measures, dependent on the sympathetic nervous system, are indices of arousal; they are likely to reflect fear responses in the context of a fear conditioning experiment, but this may not be a direct relationship. All are susceptible to confounding factors

such as ambient temperature and lighting, as well as interindividual differences in baseline levels (Blumenthal et al., 2005; Braithwaite & Watson, 2015; Phillips et al., 2019). Other measures of human fear do not rely on sympathetic activity. These include freezing behaviours or facial expressions (i.e. measured via muscle activity). However, these are not commonly used in conditioning designs and therefore may be challenging to relate to prior literature.

It is also important to consider measuring both implicit and declarative aspects (Constantinou et al., 2021). Declarative measures, such as asking participants to give shock expectancy ratings or self-reported fearfulness ratings, give an indication of conscious learning. In particular, shock expectancy ratings have shown good diagnostic and construct validity in fear conditioning designs (Boddez et al., 2013). This does not reflect the physiology that is integral to the fear response; therefore, a combination of implicit and declarative measures is required to provide a comprehensive assessment of fear.

1.2.3 Fear Conditioning and Sleep

Given the heterogeneity of emotions and the experimental control of the conditioning model, fear conditioning is an ideal tool with which to study the relationship between fear and sleep. As the broader literature on emotional memory consolidation would suggest, fear conditioned memories are also supported by sleep. For example, in a sleep versus wake design, healthy adults (n=53, 25 female, mean age 23 years) had overnight sleep or a day of wake following conditioning either in the morning or evening (Pace-Schott et al., 2009). Participants saw three coloured lamps, two of which paired with a shock (CS+), one of these was then extinguished (via extinction training) immediately, the other was not. Participants who had overnight sleep showed lower (SCR) fear responses to the unextinguished CS+ the next day, compared to those who had a day of wake and were tested later that evening. Lower responses after sleep to the unextinguished CS+ could suggest that sleep promotes a generalisation of extinction learning (from the extinguished CS). However, sleep could also simply promote extinction regardless of other stimuli. There may also have been confounding circadian effects, since the groups varied in testing time for both learning and recall.

A more recent study supports a connection between sleep and fear generalisation. In the evening, participants (n=40, 32 female, mean age 22 years) were conditioned to two neutral male human faces, one paired with an aversive shock (Zenses et al., 2020). Participants spent the next 12 hours either in unmonitored sleep at home or being kept awake overnight in the laboratory. They were tested the next morning with the CS+, CS-, and a morph of both faces to test generalisation of fear. The sleep group showed lower threat expectancy ratings to the

CS- and greater SCRs to the CS+ and morph stimulus. These results suggest that sleep supports fear consolidation and generalisation. The study also controlled for circadian factors by testing participants at the same time, though the wake group was subjected to the stress of sleep deprivation. However, together, these examples suggest that sleep supports the consolidation and also the generalisation of fearful and extinguished responses. This aligns with previous evidence for sleep as a driver for connecting separate experiences into learning episodes through generalisation (Chatburn et al., 2021; Landmann et al., 2014; Xie et al., 2018).

A link between sleep and fear extinction has been supported by rodent models. These conditioning studies provide greater experimental control and the ability to directly record from the brain. In one study, mice (n=66, all male, 7–9 weeks old) underwent extinction in a novel context either at the beginning of their rest or active phase and the next five hours were controlled as either wake or asleep (Melo & Ehrlich, 2016). Extinction learning was greater at the beginning of the rest phase, compared to the active phase. Meanwhile, extinction recall was greater in the sleep groups compared to the sleep deprivation groups, regardless of rest/active phase. These results, controlling for circadian factors, concur with human findings that post-learning sleep supports consolidation of extinction memory. In another study, rats (n=4, all male, 3 months old) learned the location of an aversive air puff along a running track (Girardeau et al., 2017). Coordinated reactivations of neuronal ensembles in the hippocampus and basolateral amygdala, that were active during learning, peaked during hippocampal sharp-wave ripples in post-learning sleep. These reactivations were stronger for cells active during unsafe track runs (CS+) compared to safe runs (CS-). This suggests that fear memories are reactivated more strongly during subsequent sleep than non-fearful memories encoded at a similar time. This supports the notion of preferential fear memory consolidation, although in this case the reactivations were not related to significant differences in post-sleep behaviour.

Together, these studies suggest that sleep supports the consolidation of fear conditioned memories, extinction memories, and a generalisation of fear. Like the broader field of emotional memory consolidation, there is also mixed evidence for the roles of REM and non-REM sleep. For example, several human studies have related the duration of REM sleep to a strengthening of discrimination between the CS+ and CS- (Menz et al., 2013, 2016; Wassing et al., 2019). However, there is also causal evidence for a role of non-REM. Targeted memory reactivation (TMR) is the presentation of learned stimuli during sleep. Several studies have reported that TMR with either both CS+ and CS- sounds or contextual odour during SWS attenuated fear responses after sleep (Hauner et al., 2013; He et al., 2015; Purple et al., 2017). However, in one rodent model, the CS+ presented during non-REM led to a strengthening of

the memory (Rolls et al., 2013). I discuss this literature in more detail in Chapter 3, but these examples suggest that both REM and non-REM sleep may be involved in fear conditioned consolidation, although greater clarity is required. Ultimately, research into how sleep supports the development of fear memory will develop our understanding of maladaptive fear and how it can lead to persistent fear-related conditions like PTSD.

1.2.4 Variation in Emotional Reponses

Emotion – fear particularly – affects how we understand and learn from our experiences and environment. For example, in a case of complete bilateral amygdala destruction, patient S.M. does not experience fear, is unable to recognise dangerous situations and has subsequently been the victim of repeated violent crimes (Amaral & Adolphs, 2016). While this is not the case for most people, interindividual variation in the fear response has been posited as a driving force behind poor mental health (Dibbets et al., 2015; Feldner et al., 2003; Hunt et al., 2019; King et al., 2017).

While fear has been related to a variety of psychopathologies, PTSD in particular may be driven by an abnormal continuation of the fear response experienced at the time of the trauma. While unpleasant symptoms usually pass, people with PTSD show an extended timeline of fear/anxiety-related symptoms such as hyperarousal and distorted cognitive beliefs (Cox et al., 2014). However, not everyone who experiences a traumatic event shows maladaptive responses such as those that characterise PTSD, our traits and tendencies play some role. While these may be numerous, anxiety and dreams in particular have been linked to trauma/PTSD and also vary in healthy (non-clinical) samples (Larsson et al., 2008; Taylor, 2003; Mellman et al., 2007; Moraczewski & McCall, 2019).

Lifetime prevalence of PTSD in the general population has been reported at 7–9% (Breslau et al., 1998; Vries & Olff, 2009), while current treatment options show only mixed efficacy (Reisman, 2016; Watkins et al., 2018). Consequently, research exploring factors such as trait anxiety and dreams in relation to the fear response and how it translates into long-term fear memory will help progress understanding of the susceptibility and maintenance of PTSD and related conditions, ultimately assisting in their treatment and prevention.

1.2.4.1 Trait Anxiety

While fear is an emotional response to threat, anxiety may be a more graded response characterised by apprehension, worry, and subsequent avoidance behaviour (Sylvers et al.,

2011). Physiologically, anxiety recruits many of the same endocrine and autonomic responses as fear, though mediated by greater top-down influences such as executive function (Affrunti & Woodruff-Borden, 2015; Hamm, 2020; Zainal & Newman, 2018). Stress is also related (Duval et al., 2015; Shin & Liberzon, 2010); however, in particular, greater trait anxiety across healthy samples has been associated with greater functional MRI activity (Blood Oxygen Level Dependent [BOLD]) in the amygdala in response to fearful faces (Etkin et al., 2004), as well as greater attentional bias towards mildly threatening images (Koster et al., 2005). This suggests that trait anxiety predisposes people towards stronger or more maladaptive fear responses.

Trait anxiety has been associated with fear conditioned responses. A comprehensive overview of inter-individual differences in healthy people's fear conditioned responses suggested that Intolerance of Uncertainty questionnaire score and activation of the amygdala/anterior insula were associated with maladaptive fear acquisition, extinction, and return of fear (Lonsdorf & Merz, 2017). Lonsdorf and Merz highlight that inter-individual results in this literature such as those pertaining to anxiety scores are often ignored or difficult to understand given differences in study design, so future studies should aim to clarify this dimension, particularly in regard to fear generalisation, as it has strong links to understanding clinical fear pathologies. In support of this, a meta-analysis of anxiety patients and healthy controls suggested that the patient group showed increased fear responses to the CS- during extinction and increased fear responses to the CS+ during extinction (Duits et al., 2015).

In healthy participants (n=23, 13 female, mean age 25 years), subjects underwent both cued (human faces) and contextual (coloured background rooms) fear conditioning and extinction in the MRI scanner; one face (CS+) was paired with an aversive loud scream (Indovina et al., 2011). Trait anxiety was positively correlated with amygdala activation and negatively correlated with ventromedial prefrontal cortex activation (BOLD) to CS discrimination (the difference between responses to the CS+ and CS-). This suggests that trait anxiety is associated with a lack of appropriate fear discrimination learning across a healthy population, although it is not clear whether these results are limited to neural activity. A similar design reported that anxiety in healthy participants (n=32, 20 female, mean age 24 years) was positively correlated with increased amygdala activation and reduced anterior cingulate cortex activation during fear extinction of neutral male faces (Sehlmeyer et al., 2011). Both the ventromedial prefrontal cortex and anterior cingulate cortex have been associated with inhibitory mechanisms (Albert et al., 2012; Gonzalez & Fanselow, 2020); therefore, together these studies suggest that anxiety is associated with impaired discriminatory learning, extended fear, and reduced inhibition.

Trait anxiety has also been linked to fear generalisation. In one study, healthy participants (n=50, 26 female, mean age 31 years) were divided into low and high trait anxiety groups and conditioned to two neutral female faces, one paired with an aversive scream (CS+) which also changed to a fearful expression (Haddad et al., 2012). The other face (CS-) was designed to test fear generalisation. These were compared to a blank oval shape, designed to test fear sensitisation. Participants with high trait anxiety showed increased fear to the generalisation CS- face in startle response, but not SCR or self-reported fear ratings. There was no effect of fear sensitisation. This suggests a link between anxiety and fear generalisation. However, the use of faces means the results may specifically reflect social anxiety.

In a study of abstract fear generalisation, 126 healthy participants were selected for low, medium, or high trait anxiety (State Trait Anxiety Inventory [STAI]) from a wider screening of 992 people (Torrents-Rodas et al., 2013). A generalisation task presented 10 rings of varying sizes where either the smallest or largest was paired with a shock (CS+), the opposite was then the CS-. Participants were conditioned with these two stimuli before being presented with the intermediate rings to test generalisation. In startle responses, SCRs, and risk ratings, there was a gradual generalisation effect (increasing fear from stimuli close in size to the CS- to stimuli close in size to the CS+), but no differences between anxiety groups in acquisition or generalisation.

Fear generalisation may also be influenced by semantic knowledge. Healthy participants (n=37, 26 female, mean age 23 years) were conditioned to three CS+ images from one category (birds or mammals) and three CS- images from the other category (Dunsmoor & Murphy, 2014). This study did not measure trait anxiety, but generalisation was tested with new images from both categories, both typical and atypical. The results indicated that conditioned fear (SCRs and shock expectancy ratings) generalised to new category items, especially from typical to atypical examples. This suggests that generalisation does not require perceptual similarity, rather, relying on a conceptual understanding of the stimuli and how they relate to each other. Although, this study did not test the effects of anxiety.

In clinical groups, anxiety has been consistently linked to greater responses to the CS-. For example, in a meta-analysis of 44 studies including 963 patients with various anxiety disorders and 1,222 healthy controls, patients showed increased fear responses to the CS- during acquisition and extinction learning (Duits et al., 2015). No type of fear measure significantly accounted for these results, suggesting it was robust across the fear response.

In summary, trait anxiety may predict greater fear conditioned responses and reduced inhibition in neural activity, but it is less clear how this relates to behavioural and autonomic

responses. Outside MRI experiments, fear is susceptible to generalisation and anxiety has been linked with fear generalisation in clinical groups, but evidence across the normal spectrum of anxiety is mixed. Given the importance of anxiety and fear generalisation in psychopathologies such as PTSD, trait anxiety's link to fear conditioned responses warrants further investigation.

1.2.4.2 Dreams

Dreams have been associated with both anxiety and emotional dysregulation. One prominent theory suggests that normal dreaming facilitates the resolution of emotional experiences while nightmares reflect a failure of emotional resolution (Levin & Nielsen, 2009, 2007). This theory describes bad dreams and nightmares as similar constructs under the term 'disturbed dreaming'. This refers to the content of dreams rather than the frequency with which dreams are recalled. There is some evidence linking dream recall to personality traits, but greater evidence that daytime experiences affect dream content (Blagrove & Pace-Schott, 2010). In this thesis I therefore focus on negative dreams. Disturbed dreaming has been associated with psychological issues such as increased stress, as well as psychopathologies such as PTSD (Miller et al., 2017; El-Solh, 2018).

There is supporting evidence for dreams as a function of emotional replay in healthy adults. In one study, self-reported frequent dream recallers (n=44, 24 female, mean age 21 years) kept a daily log of life events for 10 days, then had recorded overnight sleep either at home (Nightcap sleep wearable) or in the sleep laboratory (PSG) with multiple awakenings for prompted dream reports (van Rijn et al., 2015). At home, participants were woken during REM sleep an average 81 times. In the lab, they were woken during both REM and SWS an average of 87 times. All participants then kept a dream diary for a further 10 days. The results indicated that emotional life events were incorporated into REM dreams both 1–2 and 5–7 nights later. This 'dream lag' effect was also demonstrated for the emotional experience of sleeping in the laboratory, but only for those participants who had expressed apprehension about doing so. This suggests that emotional experiences may be reactivated during REM sleep over a time-course of at least a week.

In another study, participants (n=20, 10 female, mean age 21 years) were woken from PSG-recorded overnight sleep (REM and SWS) in the laboratory and again asked for immediate dream reports. The frequency of references to recent waking events in REM dreams was significantly associated with REM theta activity (Eichenlaub et al., 2018). Theta rhythms have been previously associated with emotional memory consolidation (Hutchison & Rathore,

2015); therefore, these results also suggest that recent events are replayed and consolidated during REM sleep. These studies support the Sleep to Forget, Sleep to Remember Hypothesis, though they do not suggest whether such consolidation relates to a subsequent amelioration of emotion.

In summary, dreams during REM sleep have been related to recent emotional events. This supports evidence that REM promotes the processing of emotional memories. Given that bad dreams have also been associated with anxiety and fear-related conditions such as PTSD, dreams are an additional feature of emotional processing within sleep-dependent emotional memory consolidation that warrants further investigation, in particular, whether dreams are related to the simple fear responses of a conditioning model, i.e. fear learning rather than highly emotive experiences.

1.2.5 Summary

Fear is a persistent emotion which, like sleep, is both essential for survival and conserved across the animal kingdom. Conditioning provides a controlled and established method to study the relationship between sleep and fear memory. However, like broader sleep-dependent emotional memory consolidation, greater clarity is required as to how REM and non-REM sleep support the consolidation of these experiences and how this affects subsequent responses. Further to this, individual differences across the fear response according to factors such as trait anxiety and disturbed dreaming may also contribute to the understanding of fear memory, but it is unclear how variation across a healthy population affects fear generalisation and extinction and so these also warrant further exploration.

1.3 This Thesis

Current literature suggests that sleep is critical for memory consolidation, but ambiguity remains about the roles of REM and non-REM sleep, especially for emotional memory. Fear is a pervasive emotion with clear neural and physiological correlates while the conditioning model provides high experimental control; fear conditioning is therefore a useful model with which to study emotional sleep-dependent memory consolidation. However, previous research demonstrates that fear responses vary across people, as influenced by factors such as trait anxiety and disturbed dreaming. A better understanding of these influences will help explain how learning can become maladaptive and destructive. Ultimately, further exploration

of interindividual differences in sleep and anxiety as they relate to the fear response across various stages of learning will further understanding of debilitating conditions like PTSD.

In this thesis I aim to investigate sleep-dependent learning and consolidation in the context of a fear conditioning experiment, with a view to better understand the contributions of REM and non-REM sleep. I also aim to investigate how trait anxiety and bad dreams in a healthy population relate to interindividual differences in the development and maintenance of the fear response. To do this, I develop a novel fear conditioning design for the exploration of fear acquisition, extinction, and reinstatement in young, healthy people.

At the same time, the methodology of sleep research is changing. In recent years, a growing literature on sleep wearables has indicated potential for the advancement of sleep quantification, currently a lengthy process which limits sleep study sample sizes. However, validation of these devices must be stringent if the quality of PSG is to be preserved. I aim to provide evidence for the utility of this emergent technology by replicating and extending the validation of a promising device – the Dreem Headband – against the gold standard of sleep measurement, PSG. This will indicate the extent to which Dreem is suitable for future sleep studies and perhaps encourage the use of these new tools for the advancement of this discipline.

In Chapter 2, I consider the efficacy of the Dreem Headband for sleep staging. I first investigate its full functionality in agreement with PSG, that is, to record and analyse sleep. I then explore a middle ground where Dreem is used to record sleep, but the data are still analysed by eye. I use these findings to inform use of the headband across my fear conditioning design.

In Chapter 3, I present a novel fear conditioning experiment where participants have overnight sleep recorded between fear acquisition on day 1 and extinction and reinstatement on day 2. I investigate the role of both non-REM and REM sleep across fear response outcomes and utilise the Dreem Headband following the results of Chapter 2. I also investigate responses after one week to explore longer-term changes and how these relate to post-conditioning overnight sleep.

In Chapter 4, I present analyses of the sleep EEG data which expand upon the themes of Chapters 2 and 3. First, I explore how the Dreem Headband can be utilised in EEG-based analyses. I use the validation data of Chapter 2 to explore spectral analyses and event detection of slow oscillations and sleep spindles between Dreem and PSG. I then apply these methods to the post-conditioning sleep data, investigating slow oscillations and sleep spindles in relation to fear conditioned responses.

In Chapter 5, I investigate the role of self-reported anxiety on fear learning. I explore several facets of anxiety – state, trait, and intolerance of uncertainty – across this healthy sample. I also explore bad dreams as a predictor of maladaptive fear responses, expanding upon the understanding of individual differences associated with fear learning and consolidation.

Chapter 2

The Dreem Headband: A Validation Study

In this chapter I present novel analyses of a wearable sleep device, the Dreem Headband, validating it against the gold standard of sleep quantification, PSG. Dreem performed moderately in automatic sleep scoring, though did not meet the standards previously reported in a validation study by the manufacturers. However, I also investigated manual sleep scoring of Dreem-recorded raw data, finding significantly greater agreement against PSG. In particular, Dreem was suitable to estimate SWS and REM sleep duration when manually scored. Therefore, future sleep studies should consider utilising the flexibility and convenience of this wearable technology.

2.1 Introduction

Technology is now a universal aspect of daily life. Through developments in computing, internet, and mobile technology, many people have unlimited access to information. Meanwhile, there are more than 300,000 health-related mobile apps (Gordon et al., 2020), some of which are recommended as part of healthcare infrastructures (Li & Chang, 2020; *NHS Apps Library - NHS*, 2020). However, the future of health-related technology is not just in immediate information, but the ability to measure and analyse biological metrics in wearable technology: devices worn on the body offering the user real-time feedback and monitoring over time.

Sleep is an ideal target for the wearable technology sector. The majority of people get up to two hours less sleep per night than they would have 100 years ago (Roenneberg, 2013). People are also aware of the negative implications of poor sleep such as obesity, mental health concerns, and cognitive decline (Anderson & Horne, 2008; Freeman et al., 2017; Khader et al., 2021; Ogilvie & Patel, 2017; Scullin & Gao, 2018; Trahan et al., 2018).

In research and clinical settings, polysomnography (PSG) is the industry standard for measuring sleep. PSG is described in detail in Chapter 1. Briefly, electrodes on the scalp record electrical activity from the brain via electroencephalography (EEG). This activity is classified as stage 1, stage 2, slow wave, and rapid eye movement sleep (N1, N2, SWS, REM). To assist in sleep stage classification, PSG also records muscle activity from the eyes (EOG) and chin (EMG). Finally, every 30-second epoch must be evaluated by a trained sleep scorer to visually identify the correct sleep stage. Time spent in each sleep stage is a commonly used quantification of sleep, although EEG event and spectral analyses are valuable as more specific indicators of neural activity (Fogel & Smith, 2006; Nishida et al., 2009; Purcell et al., 2017).

PSG is expensive, slow, and cumbersome. It is therefore unsuitable for independent use. However, there are now various wearable devices to record, classify, and summarise sleep at home. While some are simplified versions of PSG that utilise EEG electrodes to measure neural signatures, other devices estimate sleep by just movement and heart rate. Such wearable sleep trackers could allow for quicker, easier, and more efficient data collection, but validation is needed to determine whether they are suitable replacements for PSG in sleep research. On entering the public domain, these devices should have undergone testing specific to the advertised claims. However, the demands of the consumer are likely to be lighter than those of a sleep scientist. If wearable sleep devices are to revolutionise sleep research, a strict set of standards needs to be imposed.

While sleep science requires an accurate representation of sleep stages over time, this is difficult due to the individual differences inherent in sleep-dependent neural signatures. Even in the gold standard PSG, it is generally accepted that two experienced scorers will only achieve 80% agreement with each other across a night's sleep (Danker-Hopfe et al., 2009). It is also often unclear what constitutes an experienced scorer and scoring may vary even more between research groups (Collop, 2002). In contrast, wearable sleep trackers use algorithms to sleep score in real time. This should provide a more consistent measure across multiple recordings compared to human visual analysis, but they must be correct. Sleep wearables should therefore first pass an initial level of testing against human scoring of PSG, aiming to reach the 80% agreement that would put them at the same standard as a human scorer.

In this chapter, I test the Dreem Headband against PSG. I also explore manual sleep scoring of Dreem raw data and whether this offers a more accurate way to utilise some of the advantages of this wearable technology even if it cannot fully replace PSG at this time.

2.1.1 Previous Validations of Wearable Sleep Devices

A variety of wearables claim to measure sleep. Broadly, these can be divided into the classification of sleep through primarily movement (actigraphy; though pulse is also measured), or electrical activity from the brain (EEG). I show a range of wearable sleep device images at the end of this section (**Table 2.1**).

2.1.1.1 Actigraphy-Based Sleep Devices

Actigraphy is the study of activity, commonly measured via an embedded triaxial accelerometer. This measure of movement and heart rate has been applied to sleep quantification. However, since sleep scoring relies heavily on neural signatures, actigraphy may not be able to accurately capture all the stages. For example, a characteristic feature of REM sleep is low muscle tone, but this can also occur in non-REM sleep (Tinguely et al., 2006). Furthermore, while reduced heart rate can signal sleep (Ataie, 2020), SWS has been identified by heart rate with only moderate accuracy, $\kappa = 56\%$ (Yoon et al., 2018). Actigraphy devices may also have a poorer signal quality than an electrocardiogram.

These issues have been reflected in the literature. A recent study evaluated sleep measurement in five smart watches by testing them against a research-grade actigraph (ActiGraph GT9X Link) which had been previously validated against PSG (Lee et al., 2018). Participants (n=78, 42 female, mean age 28 years) slept at home for three consecutive nights yielding 92–195 recordings of overnight sleep for each device. In an estimation of time spent asleep, only the Jawbone UP and FitBit Charge fell within 10% of the actigraph. For smart watches to equate with PSG, validation should include sleep staging and ideally be compared against PSG itself. However, these results suggest that most smart watches are inaccurate in the most basic measures of sleep.

In a study comparing the Jawbone UP against PSG in an adolescent sample (n=65, 28 female, mean age 16 years), there was reasonable agreement in basic sleep statistics, with an average 10 minutes less total sleep time and 11 minutes more wake after sleep onset, although these differences were statistically significant (de Zambotti et al., 2015). Limited sleep stage evaluation also indicated that PSG's N2, REM, and arousal index predicted 35%

of the variance in the Jawbone's 'sound sleep', while N2, SWS, arousal index, and awakening index predicted 30% of the variance in 'light sleep'. This study had a good sample size but since sleep changes through adolescence (Tarokh et al., 2016), these modest results may not be generalisable to the majority of the population.

In a similar study (n=32, 15 female, mean age 17 years), the FitBit Charge also showed good agreement with PSG in basic sleep parameters: an average total sleep time 8 minutes more than PSG and 6 minutes less wake after sleep onset, though these differences were also statistically significant (de Zambotti et al., 2016). While FitBit achieved 97% sensitivity and 93% predictive value in detecting sleep, again this was from an adolescent sample and there was no analysis of sleep stage. More recently, FitBit was evaluated across all sleep stages, although this was not against PSG, but the single channel medical EEG device, SleepScope (Liang & Chapa Martell, 2018). In overnight sleep (n=25, 10 female, mean age 25 years), FitBit significantly overestimated the percentage of wake, light sleep, and REM by 5–14%, and underestimated deep sleep by 10%. Without an epoch-by-epoch analysis, it cannot be evaluated whether FitBit reaches the standards of PSG; however, differences in the time spent in each sleep stage suggest significant errors.

Moving away from smart watches, Nightcap was an early autonomous device specifically for sleep measurement which recorded eyelid and body movements. Agreement against PSG in 10 healthy people (3 female, aged 19–42 years) who each recorded three nights of sleep data was reported at 93% for non-REM sleep and 80% for REM (Ajilore et al., 1995). Although, this was based on 1-minute epochs. Further to this, Nightcap achieved 93% agreement with PSG across 10 healthy people (5 female, aged 20–25 years) who each recorded four separate naps (Cantero et al., 2002). Although, this later study only measured the reliability of sleep onset latency and not sleep stages. Overall, this device had promising indications for the separation of REM and non-REM sleep, but it is now no longer commercially available (Jarno et al., 2019).

Finally, the Oura ring estimates sleep through pulse, temperature, and movement. Participants (n=41, 13 female, mean age 17 years) had overnight sleep recorded simultaneously by Oura and PSG in a sleep laboratory (Zambotti et al., 2019). There were no significant differences in sleep onset latency, wake after sleep onset, or total sleep time, with Oura showing 96% sensitivity to detect sleep. In an analysis of sleep stages, agreement for light (N1+N2), deep (SWS) and REM sleep was moderate at 65%, 51%, and 61% respectively, with Oura significantly underestimating deep sleep and overestimating REM. While these results are only moderate, this study does report epoch-by-epoch agreement (the variable of interest between two expert scorers of PSG). In addition, although the sample consisted of

adolescents as well as young adults, there was no significant effect of age in any PSG-Oura discrepancy.

Overall, the accuracy of actigraphy-based sleep wearables appears to be poor. However, the literature is limited by the lack of validation against PSG in adult samples. Additionally, in most cases, the lack of an epoch-by-epoch analysis of all sleep stages means that comparison against the 80% agreement benchmark expected in PSG is impossible. That being said, while many devices are still inaccurate in the broader measures reported, actigraphy devices are popular and affordable and could therefore be suited to large studies investigating basic sleep parameters such as total sleep time. While Nightcap may have been a promising device for sleep stage classification, it is no longer available. Currently, Oura shows some promise to deliver accurate sleep stage classification, but agreement is still too poor for it to be considered as a replacement for PSG.

2.1.1.2 EEG-Based Sleep Devices

Considering that PSG classifies sleep stages principally from EEG signatures, wearables utilising EEG may be more likely to capture sleep stages with greater accuracy than actigraphy. Traditional EEG uses wet electrodes where conductive gel aids alignment with the scalp. However, since this would be impractical in a home device, EEG-based sleep trackers incorporate dry EEG electrodes into a mask or headband. This means that the electrodes are embedded in the device, and no action is required except to pull it onto the head. This is more convenient but could cause additional noise in the EEG signal.

Unlike actigraphy, EEG-based sleep trackers are often designed for sleep measurement. These wearables therefore tend to make more specific claims about sleep classification and so should have undergone appropriate validation. They can be split into single-channel and multi-channel devices.

2.1.1.2.1 Single-Channel EEG Wearables

One early device for sleep, the Zeo system, recorded a single EEG channel. A validation from researchers at the Zeo Sleep Research Centre (n=26, 13 female, mean age 38 years) measured overnight sleep simultaneously with Zeo and PSG (Shambroom et al., 2012). With classification agreement by sleep stage between two expert scorers (independently scoring PSG) and Zeo (scored via its automatic algorithm), Zeo achieved good agreement in REM

sleep at 79–85% and light sleep at 80–82%, but only moderate agreement for wake at 56–62% and deep sleep at 60–67%.

In a further validation of Zeo, 21 recordings from 10 adults (aged 23–45 years) were used to compare Zeo to overnight PSG scored by a sleep expert (Griessenberger et al., 2013). Gender was not reported and seven of the participants had been diagnosed with insomnia disorder, though the average sleep time was 7.25 hours. Across the whole night, Zeo showed moderate agreement with expert scoring of PSG at $\kappa = 56\%$. This was slightly better at 71%, 79%, and 69% for REM, light, and deep sleep, but poor for the detection of wake at 40%. These results were not derived from healthy sleepers and so may not be generalisable. Also, the Zeo algorithm removed frequencies below 2 Hz because of excessive noise from the dry electrodes. Considering that recognition of deep sleep relies on slow oscillations within 0.5–2 Hz (Benoit et al., 2000), this may have omitted a key signature in the detection of deep sleep and could be one reason Zeo is no longer available.

A similar current sleep wearable is the Neuroon eye mask, which records a single EEG channel, EOG, a pulse oximeter, triaxial accelerometer, and temperature. Neuroon claims to accurately measure sleep over time, as well as present light and vibrations to improve waking up and encourage lucid dreaming. Neuroon has been validated against the medical EEG device SleepScope and simultaneously compared to FitBit. When 32–35 nights were analysed for sleep stage agreement from two (1 male, 1 female, age not reported) adult participants (Liang & Nishimura, 2017), Neuroon showed an average 158 minutes less total sleep than PSG and correspondingly 222 minutes more wake after sleep onset. This contrasted with FitBit, which showed significant but much smaller differences of 30 and 8 minutes. This study is limited in only recording from two participants and there is a lack of epoch-by-epoch analysis. However, the results suggest Neuroon is highly inaccurate in broad sleep measurements.

In a further validation of Neuroon, adult participants (n=25, 10 female, mean age 25 years) used Neuroon, FitBit, and SleepScope for three consecutive nights (Liang & Chapa Martell, 2018). Again, Neuroon showed large errors in total sleep time and wake after sleep onset of 156 and 173 minutes. Unsurprisingly, in a breakdown of sleep stage there were similar disparities, with Neuroon indicating 165 minutes less light sleep and 20 minutes more deep sleep, although there was no significant difference in REM.

Finally, the Phillips SmartSleep Deep Sleep Headband utilises one frontal EEG channel and one reference channel at the right mastoid. In a validation against manual scoring of the device's raw data by a trained sleep scorer, participants (n=28, 18 female, mean age 37 years)

used the headband for 10 nights, eight at home and two in a sleep laboratory (Garcia-Molina et al., 2018). Accurate identification of 'light' (in this case, N1, N2 and REM) and deep sleep was reported over the whole sample at 75% and 74% respectively. Though, this was greater in deep sleep for the younger participants (< 40 years old) at 79% compared to 67%. The older participants had less deep sleep, but this does not explain why detection was worse; therefore, deep sleep identification may be affected by age. This study also advocates manual scoring of wearable raw data as an alternative measure of validation.

Overall, these studies suggest that single channel EEG, like actigraphy, is largely unsuitable for use in research. In fact, these devices may in some cases perform significantly worse than actigraphy. While the SmartSleep Headband reported good detection of SWS when the raw data were scored by a trained researcher, this was not validated against the same sleep recorded by PSG. Therefore, it is unclear how the hardware of the headband affected sleep scoring, i.e. the EEG signal from the headband is unlikely to be analogous to the coverage of PSG, given the use of one dry EEG electrode.

2.1.1.2.2 Multi-Channel EEG Wearables

Multi-channel EEG sleep trackers offer the closest facsimile to PSG. A significant advantage of multiple channels is the ability to simultaneously record from different areas, considering that many neural signatures exhibit clearer EEG signals in specific brain regions. For example, alpha waves seen in relaxed wake originate in the occipital region (da Silva, 2010), slow oscillations characteristic of SWS arise in the frontal region (Borbly, 2001), and sleep spindles indicating N2 are best seen in the central region (Hagler et al., 2018). While single channel EEG devices tend to record from a frontal electrode, multiple channels should also detect signals from other regions.

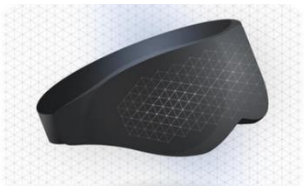
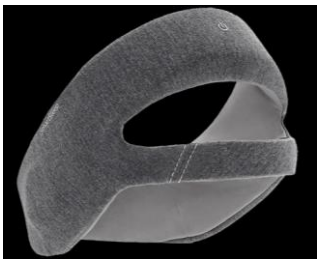
One sleep wearable, the Dreem Headband, utilises multi-channel EEG and has shown promise in a published validation. Dreem started in 2014 and have since released three versions of this device. In 2016, a beta headband only available to 500 customers utilised frontal (Fpz, Fp1, Fp2) electrodes referenced to both mastoids and a 3-D accelerometer. In 2017, the official Dreem Headband (now known as 'Dreem 1') carried a new design of frontal (Fpz, F7, F8) and occipital (O1, O2) electrodes, 3-D accelerometer, and pulse oximeter, without reference to the mastoids. Finally in 2019, an updated headband was released, 'Dreem 2', which keeps the same broad design but claims greater comfort and accuracy (*Dreem 2*, 2019).

Initial use of Dreem in a scientific setting was for closed-loop auditory stimulation (Debellemaniere et al., 2018). This technique has been reported to boost the slow oscillations that occur during sleep via short bursts of sound (Besedovsky et al., 2017; Navarrete et al., 2020; Tononi et al., 2010). This may lead to subsequent improvement in memory performance (Ngo et al., 2013), although null effects have also been reported (Henin et al., 2019).

The Dreem Headband (Dreem 1) has also been validated against PSG for sleep stage classification by the Dreem science team: participants (n=25, 6 female, mean age 35 years) had their sleep measured by the Dreem Headband and PSG overnight (Arnal et al., 2020). Correlations between Dreem and PSG frontal electrodes were moderate to strong in alpha (.71), beta (.71), delta (.76), and theta (.61) frequencies, compared to correlations between two PSG electrodes at .82–.91. Considering the differences in hardware and coverage, this suggests that the Dreem Headband shows a good capability to record the necessary frequencies seen across sleep. For sleep stage classification, the headband's algorithm was tested against PSG scored by a consensus of five expert sleep scorers. Agreement between the five scorers was high at 86%, and a consensus for each epoch was reached through the four experts who showed most agreement with each other. When the algorithm was tested against this consensus, agreement was promising for wake, REM, N2, and SWS at 74%, 85%, 83% and 83%, though poor for N1 at 48%. These results suggest that the Dreem Headband, surpassing the 80% agreement target, could be a suitable replacement for PSG in sleep stages N2, SWS and REM.

In summary, the Dreem Headband presents a convincing alternative to PSG via the previous validation. However, this finding must be replicated. It is also unclear whether the variance between PSG and the Dreem Headband originates from the difference between manual and automatic scoring or the difference in recording quality. Consequently, scoring of the raw data would provide further evidence for Dreem's effectiveness.

Table 2.1 Wearable Sleep Devices

Jawbone Up	 (Swider, 2014)	Neuroon Eye Mask	 (*Neuroon Open*, n.d.)
FitBit Charge	 (*Fitbit Charge 2 Specifications, Features and Price*, n.d.)	Smart Sleep Deep Sleep Headband	 (*SmartSleep Deep Sleep Headband*, n.d.)
Oura Ring	 (*Oura Ring CEO on the Future of Illness Detection and Self-Isolation*, 2020)	Dreem Headband Beta (2016)	
Zeo	 (*Zeo Sleep Manager Goes Right to the Phone*, 2011)	Dreem 1 (2017)	 (*Dreem - Helping the World Being Better at Sleep*, n.d.)

2.1.2 Aims

Previous literature suggests that many sleep wearables are inaccurate in broad sleep measurements. However, the Dreem Headband has shown some promising results. In this study I aimed to validate the Dreem Headband against PSG, field-testing results of the previous validation study (Arnal et al., 2020). Specifically, I aimed to replicate greater than 80% agreement in N2, SWS, and REM between expert scoring of PSG and automatic scoring of the headband to provide additional evidence for or against Dreem's use in sleep science.

Manual sleep scoring of the Phillips SmartSleep Deep Sleep Headband indicated that raw data from a wearable sleep device could be sleep scored by a trained technician and compared to algorithmic scoring of the same data (Garcia-Molina et al., 2018). However, it was unclear how this would relate to PSG. Consequently, I also aimed to explore manual scoring of Dreem raw data when PSG is recorded simultaneously. This additional comparison addresses the extent to which variance when tested against PSG can be explained by a lack of accuracy in the sleep scoring algorithm, when such automatic scoring software is yet to replace expert scoring in typical PSG studies.

2.1.3 Hypotheses

1. Dreem's algorithm will achieve at least 80% agreement in N2, SWS and REM scoring, when tested against manual scoring of PSG.
2. Manual scoring of the Dreem Headband will achieve significantly greater agreement, when tested against manual scoring of PSG, than Dreem's algorithm against PSG.

2.2 Methods

This chapter presents data previously collected and obtained with permission from Dr Ullrich Bartsch and Professor Matt Jones. Data collection was conducted by Dr Ullrich Bartsch, Dr Ross Purple, Amber Roguski and Callum Young. However, I have independently conducted all data processing and analyses for the purposes of this validation study. These analyses are novel, and these data have not featured in any prior publication.

2.2.1 Participants

I obtained sleep data from 10 participants (8 female, 2 male; aged 20–37 years, mean = 25.33) who all contributed two consecutive nights of sleep recorded simultaneously by Dreem and PSG. The original study design recruited 20 participants via advertisements placed around the University of Bristol, UK. Participants completed an online 'Big 5' personality questionnaire which measured neuroticism, extraversion, openness, agreeableness, and conscientiousness, with a free, open-source test (*Free Open-Source BigFive Personality Traits Test*, 2019). Only the participants scoring in the top 25% and bottom 25% in neuroticism were invited to have their sleep recorded. These data were therefore recorded from participants in the top or bottom quartile of trait neuroticism, albeit from a very small sample.

When I obtained these data, four nights were missing (three recorded by PSG, one by Dreem). I discarded an additional Dreem recording due to a loss of readable signal before sleep onset. Since direct comparison relies on intact data from both PSG and Dreem, the final sample consisted of two nights from six participants (n=12) and one night from a further three participants (n=3), a total of 15 nights. I disregarded neuroticism classification in all analyses of PSG and Dreem sleep recordings, following no significant differences between participants in the low and high neuroticism groups in sleep stage classification, p = .934. These results are presented in Appendix D.

2.2.2 Materials

Ambulatory wireless PSG (Embla Titanium) recorded six EEG channels (F3, F4, C3, C4, O1, O2), mastoids (M1, M2), EOG (E1, E2) and EMG (ChinL, ChinR). All channels were referenced to Cz and sampled at 256 Hz.

The Dreem Headband 'Dreem 1' (the same version used in the previous validation study) recorded five dry EEG electrodes (Fpz, F7, F8, O1, O2) sampled at 250 Hz, referenced to

each other yielding seven derivations (Fpz-O1, Fpz-O2, Fpz-F7, F8-F7, F7-O1, F8-O2, Fpz-F8). In addition, a 3D accelerometer measured movement, position, and breathing, while a red-infrared pulse oximeter measured heart rate, sampled at 50 Hz. EEG data were automatically processed internally by Dreem with a Butterworth (order 2) bandpass 0.4–18 Hz filter and (order 3) 50 Hz, 60 Hz and 62.5 Hz notches.

The Dreem Headband automatically scores sleep in real time. Like a human scorer, the algorithm takes previous epochs into account, basing its decision on features from the last 30 (30-second) epochs, as well as power frequency in the delta, alpha, theta and beta bands, and detection of characteristic signals such as spindles, K-complexes, and slow oscillations (Arnal et al., 2020; Debellemaniere et al., 2018). Dreem scores 'S0', 'S1', 'S2', 'S3', 'REM' and 'MT', as wake, N1, N2, SWS, REM, and movement time (analogous to artefacts), respectively. While the headband can deliver closed-loop auditory stimulation, this was deactivated.

2.2.3 Procedure

On responding to the study advertisement, participants were invited to complete the online personality test. Selected participants then attended *Sphere House*: a two-bedroomed house in Bristol, UK, designed to accommodate participants for research purposes. Participants gave informed consent, indicated they were in good physical and mental health, and understood the aims of the study.

On two consecutive nights, participants arrived in the early evening and were 'wired up' to the ambulatory wireless PSG system several hours before sleep onset; the Dreem Headband was worn on top. Participants slept overnight in individual bedrooms, sleeping at their normal time. In the morning, PSG electrodes and Dreem Headband were removed, and participants were free to go about their day as normal. This study was approved by the University of Bristol Ethics Committee.

2.2.4 Data Processing

I obtained these data for the purposes of this validation study prior to any processing. I therefore carried out all analyses described hereafter.

Firstly, I filtered and re-referenced PSG recordings using MATLAB with EEGlab and Fieldtrip toolboxes (Delorme & Makeig, 2004; Oostenveld et al., 2010). EEG and EOG channels were bandpass filtered between 0.3–35 Hz and re-referenced to the linked mastoids (M1, M2). EMG

channels were bandpass filtered between 10–100 Hz and re-referenced to each other in a bipolar derivation. I did not filter or re-reference Dreem recordings beyond Dreem's internal processing. However, I resampled respiration channels from the accelerometer from 50 to 250 Hz.

To enable synchronisation of the Dreem and PSG recordings, I truncated PSG files to exactly two hours after the start of the Dreem recording and hence Dreem's automatic scoring. This was accomplished by accessing the timestamp of each recording, deleting the necessary raw data, then creating a new EDF file. This was possible because all recordings were started early in the evening with several hours before sleep onset. This ensured that there was an even number (240) of whole 30-second epochs, all of wake before sleep onset, which could be removed after scoring to match with PSG. Finally, I coded all file names using a random number generator to avoid bias during scoring.

I scored all PSG and Dreem recordings according to AASM guidelines, using the Python-based software *Visbrain Sleep* (Combrisson et al., 2017). I also utilised the respiration channels provided by Dreem's accelerometer to assist sleep stage classification (see Douglas et al., 1982, for an explanation of how respiration varies across sleep stage). I checked my PSG sleep scoring accuracy via two recordings which were independently scored by another experienced sleep scorer (Dr Ross Purple, University of Bristol). The results of this agreement are presented in section 2.3.2.

Finally, I re-matched recordings of the same sleep as scored by PSG and Dreem. The PSG scoring was exactly two hours (240 epochs) ahead of Dreem; therefore, these epochs were deleted from algorithmic and my scoring of Dreem – all were scored as wake. Following this, further extraneous wake was removed from the beginning and the end of each file, according to the epoch of sleep onset and offset as defined by PSG. Each night was therefore scored three times via two recordings: PSG, Dreem-algorithm, and Dreem-manual.

2.2.5 Statistical Analyses

To compare the sleep scoring of Dreem against PSG, I calculated Cohen's Kappa, sensitivity, specificity, positive predictive value, and negative predictive value. I tested differences between the scoring methods with repeated measures ANOVAs or t-tests, with a significance threshold of $p < .050$.

Cohen's Kappa is a widely used statistical technique to compare agreement between two raters who classify items into mutually exclusive categories, accounting for the chance of

agreement if category ratings were random. A suggested interpretation is 0–.20 = no agreement, .21–.40 = minimal agreement, .41–.60 = weak agreement, .61–.80 = moderate agreement, .81–.90 = strong agreement, and .91–1.00 = almost perfect (McHugh, 2012). A confusion matrix is used to calculate Cohen's Kappa (values for illustration only, **Table 2.2**). Each possible category is shown across both rows and columns and the number of times each category is scored is shown across both raters. Each category is wholly independent and reflects the number of epochs scored as each stage across a single night's sleep. Therefore, Kappa does not consider similarity between the stages.

Table 2.2 Illustrative Confusion Matrix Showing Classification for Each Sleep Stage by Two Raters in a Single Recording

Rater 1 (e.g. PSG)

Rater 2 (e.g. Dreem-algorithm)		1	2	3	4	5	6
		N1	N2	SWS	REM	Wake	**Total**
A	N1	6	13	0	0	3	**22**
B	N2	0	210	53	3	0	**266**
C	SWS	0	4	124	0	0	**128**
D	REM	0	39	0	259	0	**298**
E	Wake	1	2	0	0	160	**163**
F	**Total**	**7**	**268**	**177**	**262**	**163**	**877**

Kappa is calculated:

$$\frac{P_o - P_e}{1 - P_e}$$

Where P_o is equal to the sum of observed agreed values, and P_e is equal to the sum of expected values if the categories were assigned randomly.

Therefore: $P_o = A1 + B2 + C3 + D4 + E5$ and $P_e = P_{N1} + P_{N2} + P_{SWS} + P_{REM} + P_{wake}$

Where: P_{N1} = (*F1*/ *F6*) * (*A6*/ *F6*), P_{N2} = (*F2*/ *F6*) * (*B6*/ *F6*), P_{SWS} = (*F3*/ *F6*) * (*C6*/ *F6*), P_{REM} = (*F4*/ *F6*) * (*D6*/ *F6*), P_{wake} = (*F5*/ *F6*) * (*E6*/ *F6*).

Sensitivity, specificity, positive predictive values, and negative predictive values were calculated per sleep stage. For these analyses, one scorer must be considered the ground truth (e.g. rater 1), and true positives, true negatives, false positives, and false negatives are defined by the other scorer's ratings (rater 2) in relation to this (Parikh et al., 2008).

Sensitivity indicates how good rater 2 is at identifying each stage when it occurs. This is equivalent to the % agreement reported in most sleep studies. In contrast, specificity indicates how good rater 2 is at identifying the absence of a stage when it does not occur. Positive predictive value indicates the probability that the stage rated by the tested scorer is that stage, as rated by PSG. In contrast, negative predictive value indicates the probability that when the stage in question is not rated by rater 2, it is not that stage as rated by PSG.

$$\text{Sensitivity} = \frac{True\ Positives}{True\ Positives + False\ Negatives}$$

$$\text{Specificity} = \frac{True\ Negatives}{True\ Negatives + False\ Positives}$$

$$\text{Positive Predictive Value} = \frac{True\ Positives}{True\ Positives + False\ Positives}$$

$$\text{Negative Predictive Value} = \frac{True\ Negatives}{True\ Negatives + False\ Negatives}$$

Where:

- **True Positives**: positive ratings by rater 2 that agree with the ground truth (the diagonal cell in question i.e. *A1* for stage 1) where both scorers agree the stage has occurred.
- **True Negatives**: negative ratings by rater 2 that agree with the ground truth (the sum of all cells excluding the row and column of the sleep stage in question i.e. (*B2:B5)* + (*C2:C5)* + (*D2:D5)* + (*E2:E5)* for stage 1). This is the total number of instances where both raters agree the stage has not occurred.
- **False Positives**: positive ratings by rater 2 that disagree with the ground truth (the row total minus the stage in question i.e. *A6 – A1* for stage 1). This is the total number of instances falsely classified by rater 2 as the stage in question.

- **False Negatives**: negative ratings by rater 2 that disagree with the ground truth (the column total minus the stage in question i.e. *F1 – A1* for stage 1). This is the total number of instances falsely classified by rater 2 as not the stage in question.

Statistics were carried out in Matlab 2019b or IBM SPSS 26. Spectrograms were calculated with the Chronux toolbox (Bokil et al., 2010). I used a 10 second window moving in 0.1 second steps and a multi-taper spectral estimate at a 0.5 Hz resolution (9 tapers).

Since I did not collect these data, I conducted a post-hoc sensitivity analysis with G*Power 3.1 (Faul et al., 2007) to indicate the minimum effect size that the study could reliably yield a statistically significant result (Perugini et al., 2018). My hypotheses were based on the difference between the algorithm's agreement with PSG and manual scoring's agreement with PSG (a single matched-pairs comparison). Accordingly, a sensitivity analysis (two-tailed α = .05, β = .80) with my sample size of 15 indicated a large effect size of .78 would be reliable. This is illustrative of sensitivity across the experiment and indicates that small or medium effect sizes may not be reliably detected.

2.3 Results

2.3.1 Sleep Recordings

The same sleep was captured differently by PSG and Dreem, this also varied over different nights. For example, in a recording that showed high agreement between PSG and Dreem, power across sleep frequencies (0.4–20 Hz) and sleep scoring showed some consistency (**Figure 2.1**). In contrast, in a recording that showed low agreement between PSG and Dreem, power and sleep scoring showed considerable deviation (**Figure 2.2**). I have shown the EEG signal from a frontal channel in each case. However, in the latter, agreement was limited by all Dreem frontal-occipital channels being corrupted. I therefore show channel Fpz-F7, which may account for the lower power.

Even when epochs were scored as the same stage, the EEG signal varied. This can be seen in illustrative epochs where both algorithmic and manual scoring of Dreem scored correctly i.e. agreed with the sleep stage classified by PSG – the ground truth (**Figure 2.3**), and epochs where algorithmic scoring was incorrect but manual scoring was successful (**Figure 2.4**). These epochs were all taken from the congruent night.

In general, Dreem is likely to give higher power readings than PSG due to an increase in noise, possibly attributable to greater movement of the headband on the head and the use of dry electrodes (discussed further in section 2.4). This is demonstrated by the particular increase in signal variability in wake (seen in **Figure 2.3**), compared to PSG where electrodes are affixed to the scalp.

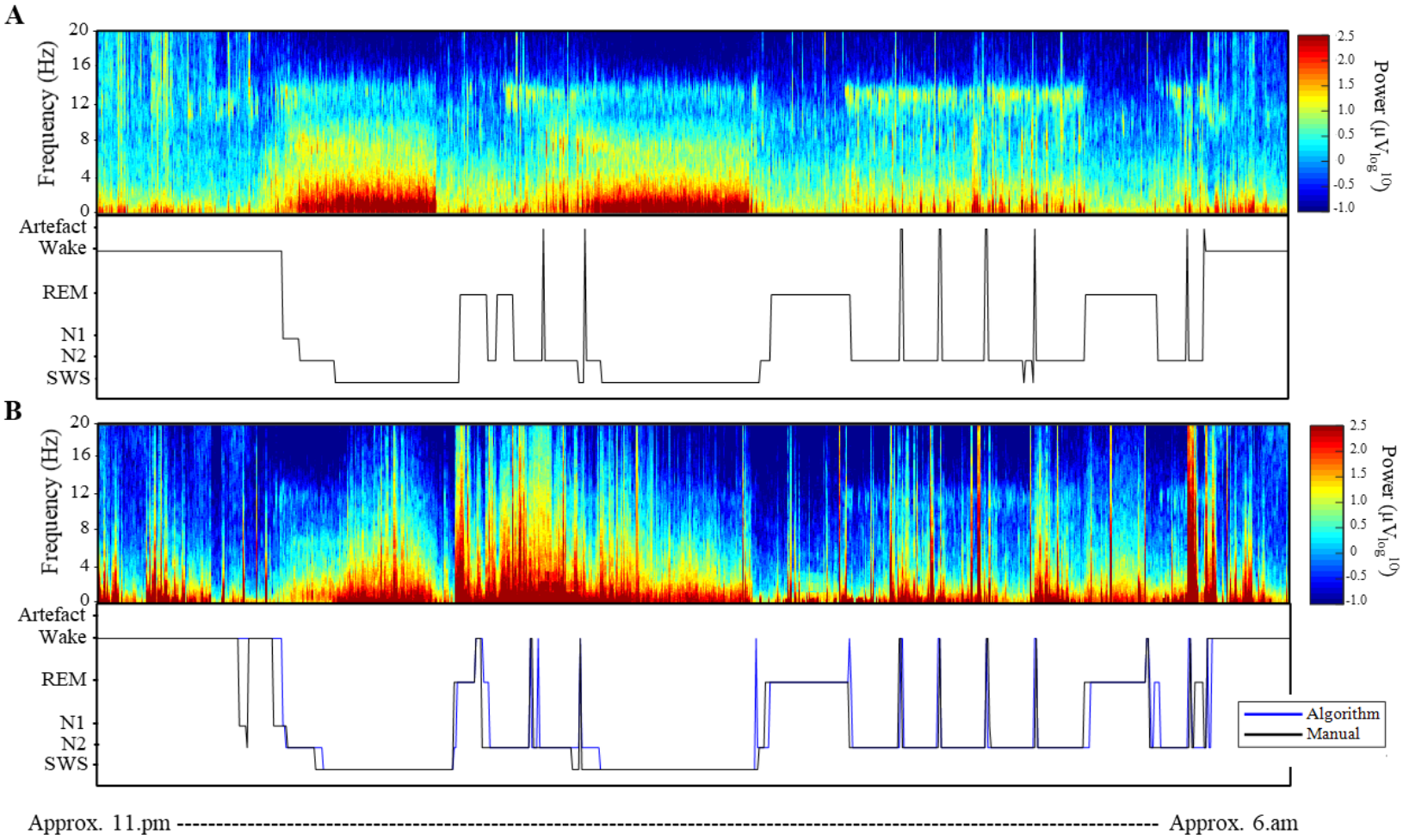


Figure 2.1 A Congruent Night Between PSG and Dreem

A spectrogram showing frequency power and hypnogram showing sleep scoring of the same night as recorded by PSG channel F3 (**A**), and by Dreem channel Fpz-O1 (**B**). There was good agreement (κ = .79–.83) between scoring methods in this recording.

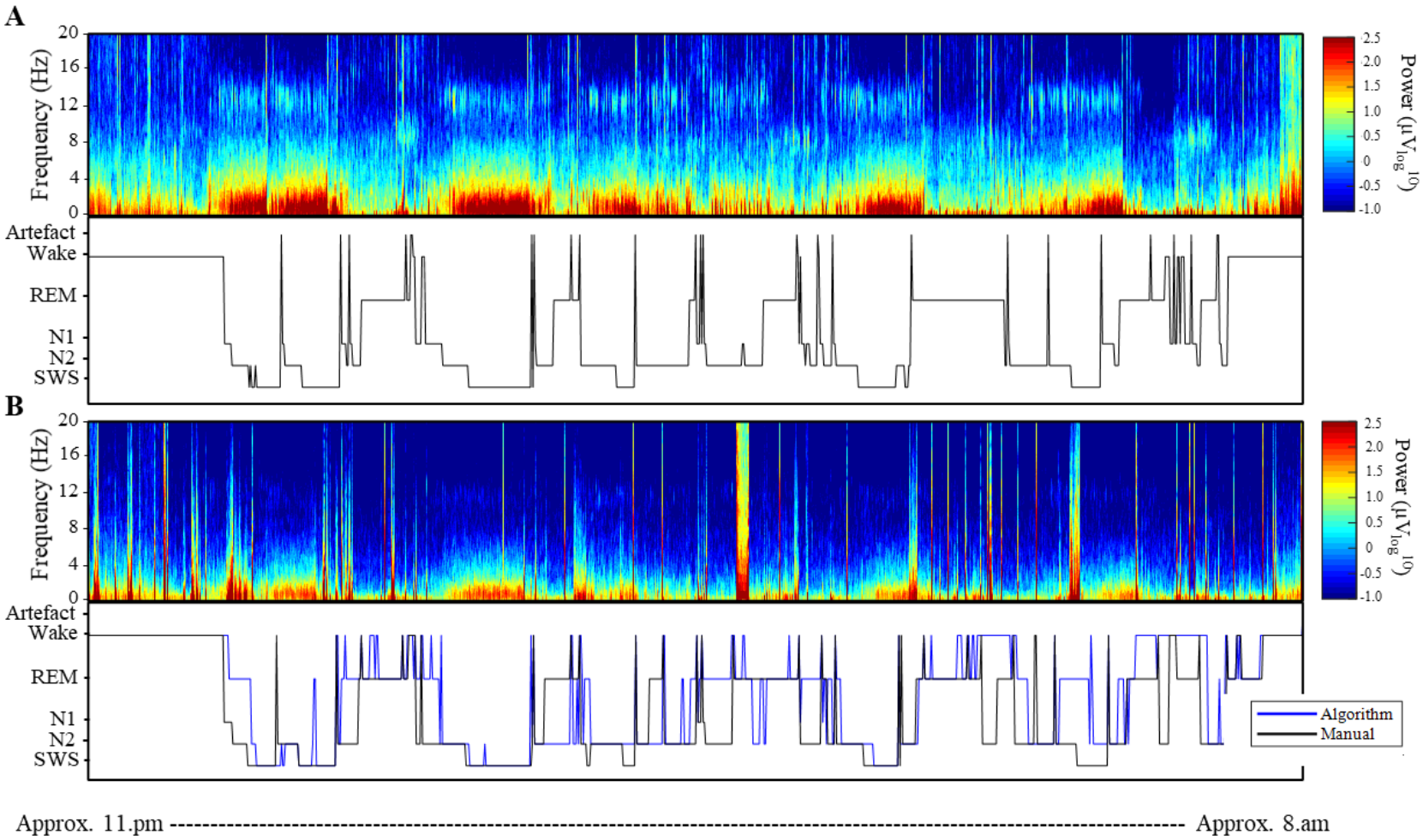


Figure 2.2 An Incongruent Night Between PSG and Dreem

A spectrogram showing frequency power and hypnogram showing sleep scoring of the same night as recorded by PSG channel F3 (**A**), and by Dreem channel Fpz-F7 (**B**). There was poor agreement (κ = .51–.53) between scoring methods in this recording.

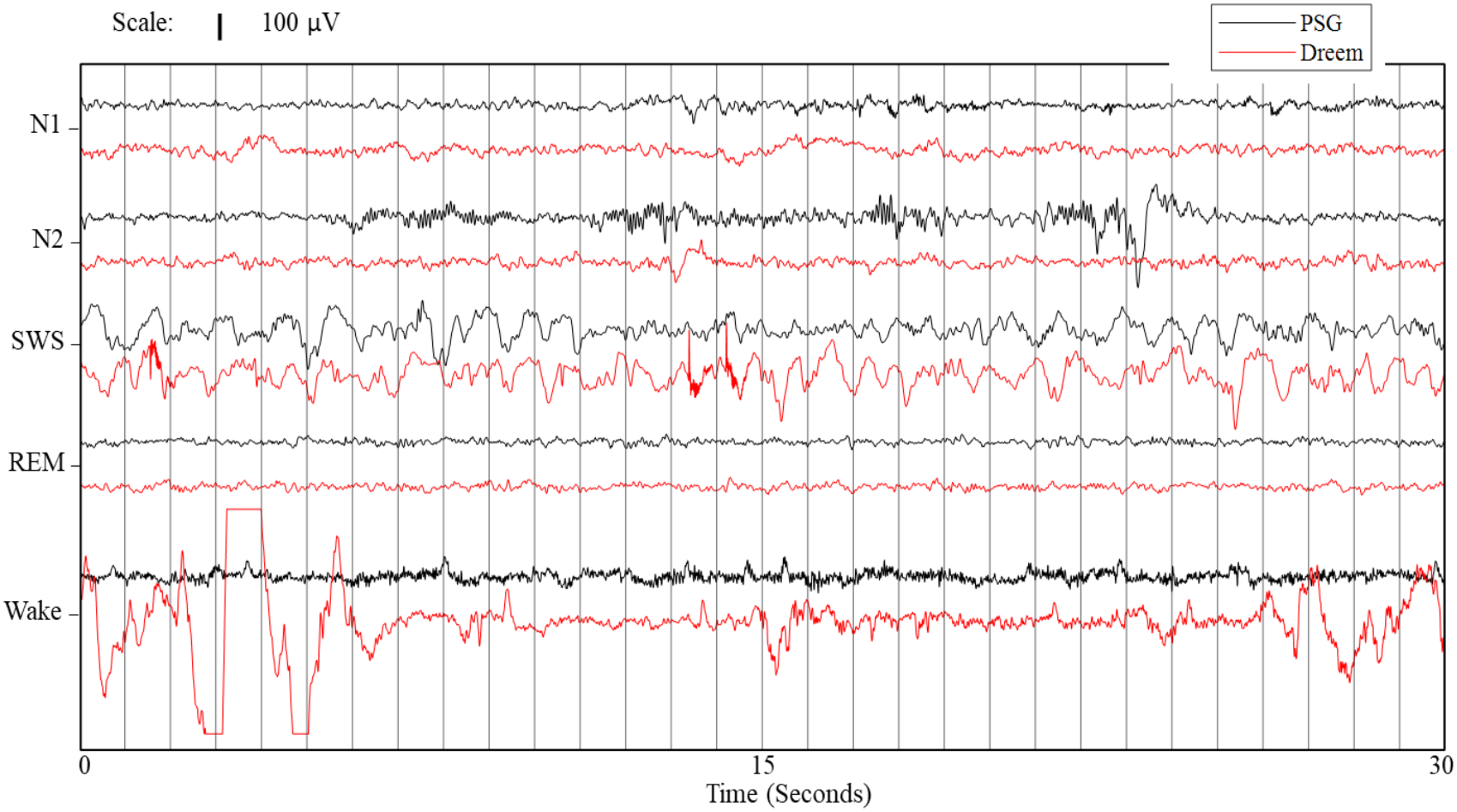


Figure 2.3 EEG Sleep Data: Congruent Epochs Between PSG and Dreem

An illustrative 30-second epoch of each sleep stage as recorded by PSG at channel F3 and Dreem at channel Fpz-O1. Each epoch was scored in agreement as the stage in question via PSG, Dreem-algorithm, and Dreem-manual.

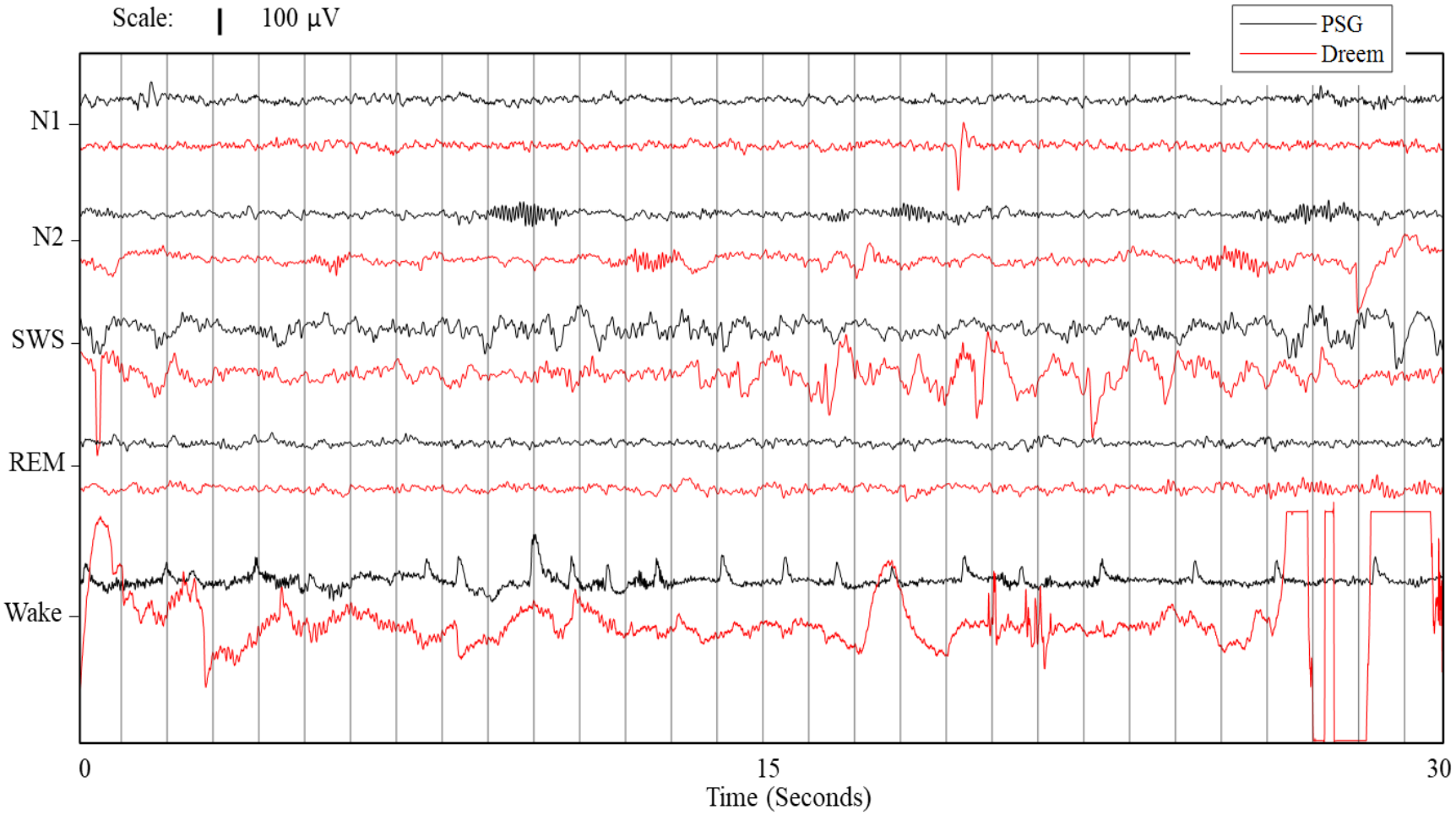


Figure 2.4 EEG Sleep Data: Incongruent Epochs Between PSG and Dreem

An illustrative 30-second epoch of each sleep stage as recorded by PSG at channel F3 and Dreem at channel Fpz-O1. Each epoch was scored as that stage by PSG and Dreem-manual, but differently by Dreem algorithm (the algorithm scored N1 as wake, N2 as REM, SWS as N2, REM as N2, and wake as N2).

2.3.2 PSG Scoring Accuracy

To test the accuracy of my sleep scoring, a second experienced (5+ years) sleep scorer independently scored two PSG recordings: the best (κ = .79) and worst (κ = .27) nights in scoring agreement between PSG and algorithmic scoring of Dreem. This was designed to indicate the range of accuracy across all nights (**Table 2.3**). In both, there was good agreement across the whole night but poor agreement in N1 and wake. On further investigation, I found a large difference in the number of epochs scored in these stages (**Table 2.4**).

Table 2.3 Agreement Between Two Scorers of Two PSG Recordings

		'Worst' Night	'Best' Night	Average
Sensitivity (%)	N1	41.18	21.88	31.53
	N2	86.45	91.37	88.91
	SWS	95.60	94.47	95.04
	REM	83.57	100	91.79
	Wake	18.42	0.00	9.21
Cohen's Kappa (%)		69.49	84.59	77.04
% Agreement		76.59	89.06	82.83

I tested my scoring against Dr Purple's as the ground truth. Kappa values expressed as percentages.

Table 2.4 Number of Epochs Scored Over the Worst and Best Nights

	'Worst' Night			'Best' Night		
	Scorer 1	Scorer 2	Algorithm	Scorer 1	Scorer 2	Algorithm
N1	82	68	3	7	32	3
N2	294	251	265	259	255	273
SWS	180	183	117	190	200	184
REM	215	208	274	128	95	109
Wake	19	81	157	0	4	25

Although there were differences in the number of epochs scored per sleep stage, Dr Purple's and my scoring showed comparable agreement against Dreem's algorithmic scoring: poor in the worst night, 47% and 45% agreement, κ = .31 and .29; good in the best night, 81% and 86% agreement, κ = .74 and .80 respectively. Overall, agreement between Dr Purple and myself surpassed the 80% benchmark and was high across N2, SWS, and REM; therefore, my scoring was likely to be adequate, although analyses of N1 and wake could warrant some caution.

2.3.3 Sleep Scoring Agreement Between PSG and Dreem

I primarily aimed to investigate the performance of the Dreem Headband's algorithmic sleep stage scoring (Dreem-algorithm) when tested against my scoring of PSG. Secondly, I also investigated whether my scoring of the Dreem raw data (Dreem-manual) against my scoring of PSG exhibited significantly greater agreement. Finally, I show agreement between Dreem-algorithm when tested against Dreem-manual for each analysis as an indicator of the variance due to differences in hardware rather than scoring method (discussed in section 2.4.2).

2.3.3.1 Total Agreement

I first investigated sleep scoring agreement across all stages. Since Kappa values are not always reported in the literature, I also present percentage agreement (the number of epochs scored the same by both scoring methods divided by the total number of epochs). Because this does not account for chance, it is expected that these values are slightly higher. In addition, sleep may vary more between participants than over repeated recordings of the same person, I therefore also investigated differences between night 1 and night 2 recordings. The results suggested that both Kappa and percentages showed significantly greater agreement between Dreem-manual and PSG, compared to Dreem-algorithm and PSG; this was stronger when collapsing across night, i.e. treating all nights independently (**Figure 2.5**).

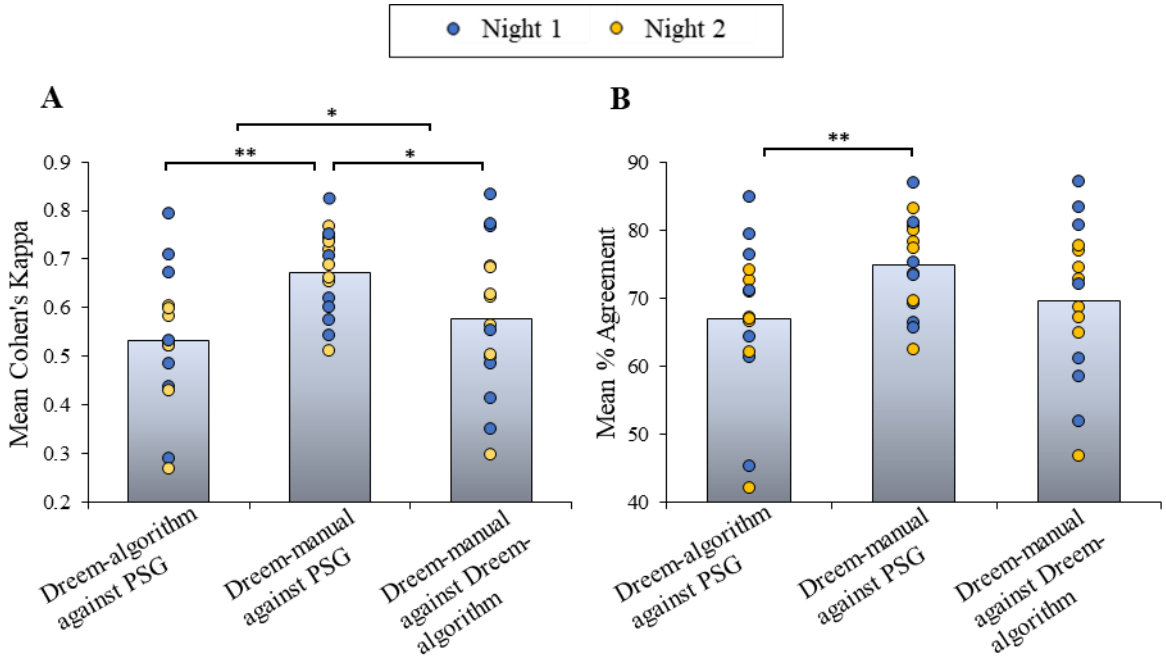


Figure 2.5 Total Scoring Agreement

Dreem-manual scoring tested against PSG showed significantly greater agreement than Dreem-algorithm in Kappa (**A**) and percentage agreement (**B**). There were no differences between night 1 (n=7) and night 2 (n=8). *p < .050, ** p < .010.

Across Kappa values, a 3 x 2 repeated measures ANOVA indicated a significant effect of scoring method, F (2) = 8.72, p = .006, but no effect of night, F (1) = 0.21, p = .669, nor a night * method interaction, F (2) = 1.49, p = .272. There was, similarly, a significant effect of scoring method in percentage agreement, F (2) = 4.77, p = .035, but no effect of night, F (1) = 0.18, p = .686, nor a night * method interaction, F (2) = 1.36, p = .301. Subsequent pairwise comparisons largely indicated significant differences (**Table 2.5**).

However, when collapsing across night, 3-way repeated measures ANOVAs (testing differences between scoring method only) showed stronger differences between scoring methods: Kappa, F (1.33) = 16.49, p < .001; percentage agreement, F (1.31) = 9.14, p = .004. This led to greater pairwise differences (also **Table 2.5**).

Table 2.5 Pairwise Comparisons Between Scoring Methods

	Comparison	*p*-value		
		Dreem-algorithm against PSG **and** Dreem-manual against PSG	Dreem-algorithm against PSG **and** Dreem-algorithm against Dreem-manual	Dreem-manual against PSG **and** Dreem-algorithm against Dreem-manual
Cohen's Kappa	Comparing Across Night	.002	.005	.006
	Collapsed Across Night	< .001	.002	.002
Percentage Agreement	Comparing Across Night	.066	.065	.117
	Collapsed Across Night	.004	.023	.022

The comparison between Dreem-algorithm tested against PSG and Dreem-manual tested against PSG is highlighted as most relevant for my hypotheses.

These results do not indicate a significant effect of night 1 versus night 2. In addition, testing for differences between night 1 and night 2 may hinder the detection of differences in scoring method. All nights were therefore treated as independent in further analyses.

2.3.3.2 Sensitivity and Specificity

I then investigated scoring agreement per sleep stage. Testing against PSG as the ground truth, sensitivity and specificity illustrate the effectiveness of Dreem-manual and Dreem-algorithm at identifying when each stage does and does not occur respectively (correct stages as defined by PSG). Three-way repeated measures ANOVAs indicated significant differences in sensitivity in every sleep stage except N2, while specificity differed in every sleep stage except REM (**Figure 2.6**, **Table 2.6**). For these significant effects, I investigated pairwise comparisons between scoring methods. Of particular note for my hypotheses are differences between Dreem-manual tested against PSG and Dreem-algorithm tested against PSG, but I show the other comparisons for additional information.

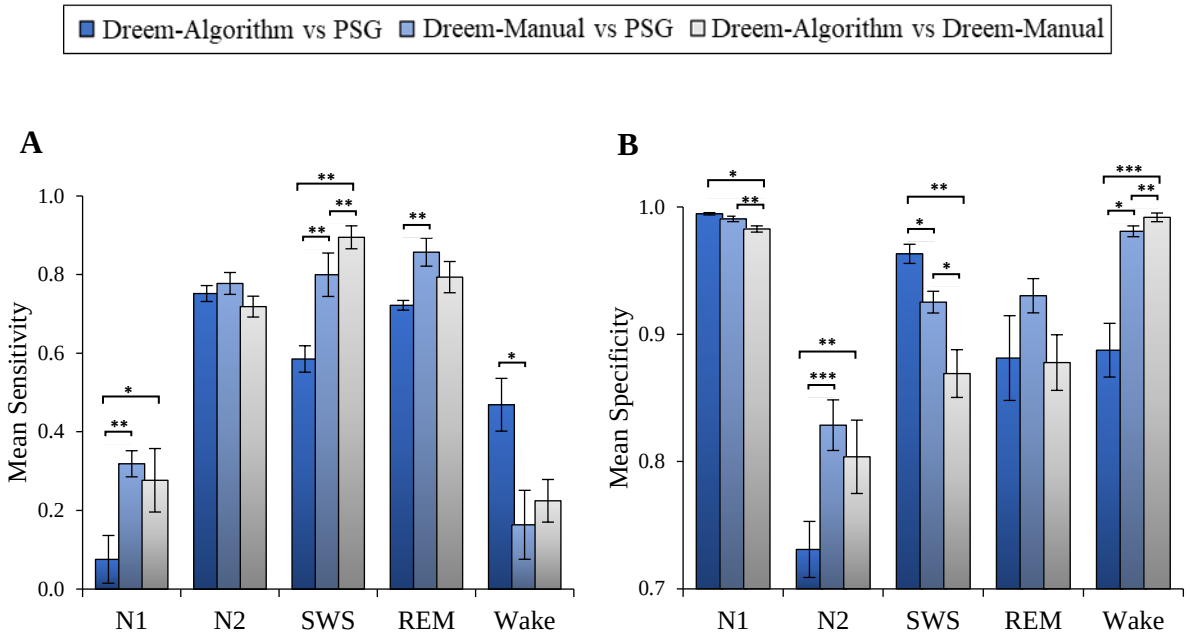


Figure 2.6 Dreem Sensitivity and Specificity per Sleep Stage

There were significant differences in sensitivity in N1, SWS, REM, and wake: generally (except in wake), greater agreement with PSG in manual scoring than algorithmic scoring (**A**). In specificity, there were significant differences in N1, N2, SWS, and wake: manual scoring showed higher agreement in N2 and wake, but algorithmic scoring was greater in SWS (**B**). Error bars show ± one standard error of the mean (SEM). *p < .050, ** p < .010, *** p < .001.

Table 2.6 Differences in Sensitivity and Specificity Between Scoring Methods per Sleep Stage

		Three-way Repeated Measures ANOVAs			*Subsequent Pairwise Comparisons (p-values)*		
	Sleep Stage	*df*	F	*p*	Dreem-algorithm against PSG **and** Dreem-manual against PSG	Dreem-algorithm against PSG **and** Dreem-algorithm against Dreem-manual	Dreem-manual against PSG **and** Dreem-algorithm against Dreem-manual
Sensitivity	N1	2.00	6.25	.006	.002	.007	.657
	N2	1.27	2.06	.167	-	-	-
	SWS	1.15	22.71	< .001	< .001	< .001	.001
	REM	2.00	6.04	.014	< .001	.154	.101
	Wake	1.44	7.92	.006	< .001	.002	.256
Specificity	N1	2.00	8.96	< .001	.582	.004	.003
	N2	2.00	14.03	< .001	< .001	.003	.229
	SWS	1.36	12.42	.001	.005	.001	.001
	REM	1.31	2.61	.116	-	-	-
	Wake	1.02	26.17	< .001	< .001	< .001	< .001

The comparison between Dreem-algorithm tested against PSG and Dreem-manual tested against PSG is highlighted as most relevant for my hypotheses.

2.3.3.3 Positive and Negative Predictive Values

Positive and negative predictive values suggest the probability that epochs scored by Dreem-manual and Dreem-algorithm are in fact correct, i.e. as scored by PSG. Again, I conducted three-way repeated measures ANOVAs for each sleep stage and pairwise comparisons following significant results. Like specificity, positive predictive values differed between scoring method in every sleep stage except REM; meanwhile, negative predictive values differed in every sleep stage (**Figure 2.7, Table 2.7**).

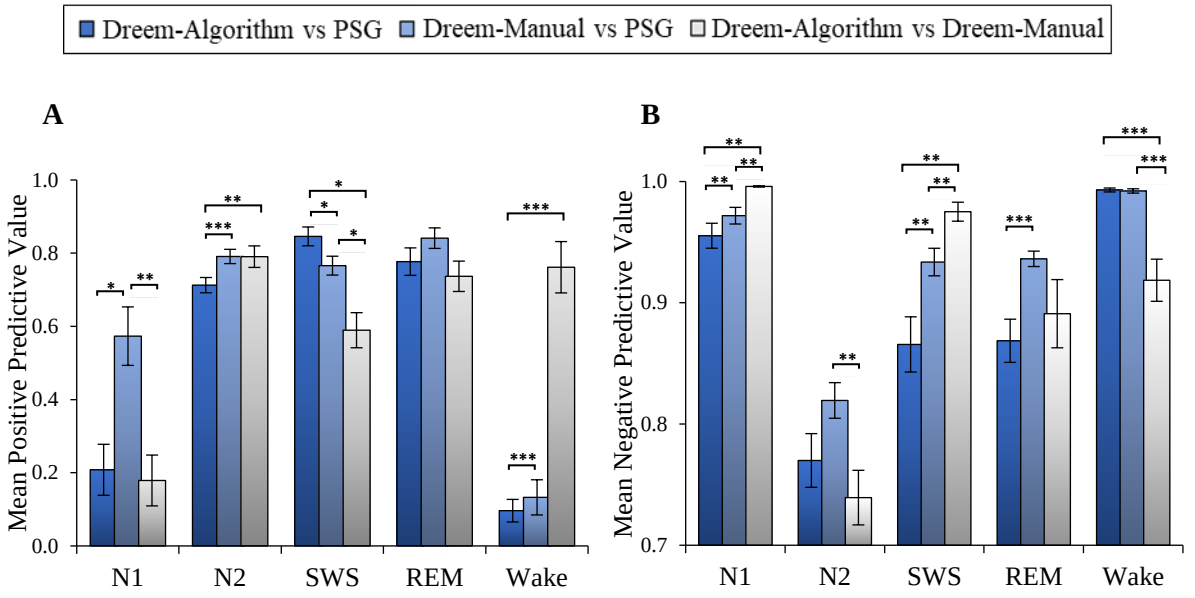


Figure 2.7 Dreem Positive and Negative Predictive Values per Sleep Stage

There were significant differences in positive predictive value in N1, N2, SWS, and wake; in particular, manual scoring showed significantly greater agreement with PSG than algorithmic scoring (**A**). In contrast, in negative predictive value, algorithmic scoring showed greater agreement in N1, SWS and REM (**B**). Error bars show ± SEM. *p < .050, ** p < .010, *** p < .001.

Table 2.7 Differences in Predictive Values Between Scoring Methods per Sleep Stage

		Three-way Repeated Measures ANOVAs			*Subsequent Pairwise Comparisons (p-values)*		
	Sleep Stage	*df*	F	*p*	Dreem-algorithm against PSG **and** Dreem-manual against PSG	Dreem-algorithm against PSG **and** Dreem-algorithm against Dreem-manual	Dreem-manual against PSG **and** Dreem-algorithm against Dreem-manual
Positive Predictive Value	N1	2.00	11.73	< .001	.003	.661	.001
	N2	2.00	12.01	< .001	< .001	.001	.951
	SWS	1.27	12.59	< .001	.013	.002	.007
	REM	1.44	3.66	.057	-	-	-
	Wake	1.11	55.38	< .001	.179	< .001	< .001
Negative Predictive Value	N1	1.06	12.08	.003	< .001	.003	.008
	N2	2.00	5.23	.012	.108	.277	< .001
	SWS	1.15	15.35	.001	.003	.003	.002
	REM	1.42	5.03	.026	< .001	.294	.125
	Wake	1.00	14.63	.002	.164	.002	.002

The comparison between Dreem-algorithm tested against PSG and Dreem-manual tested against PSG is highlighted as most relevant for my hypotheses.

2.3.4 Number of Epochs Scored as Each Sleep Stage

2.3.4.1 Sleep Epochs

The number of 30-second epochs scored by PSG, Dreem-algorithm and Dreem-manual indicate the time spent in each sleep stage. This is a less stringent measure than temporal agreement; for example, if PSG and Dreem-algorithm both scored 200 epochs of REM in one night, they would not necessarily overlap. Nevertheless, three-way repeated measures ANOVAs per sleep stage indicated differences between the scoring methods. Dreem-algorithm significantly overestimated N2 and wake, and underestimated N1 and SWS. In contrast, Dreem-manual only underestimated N1, and significantly less so than the algorithm (**Figure 2.8**, **Table 2.8**).

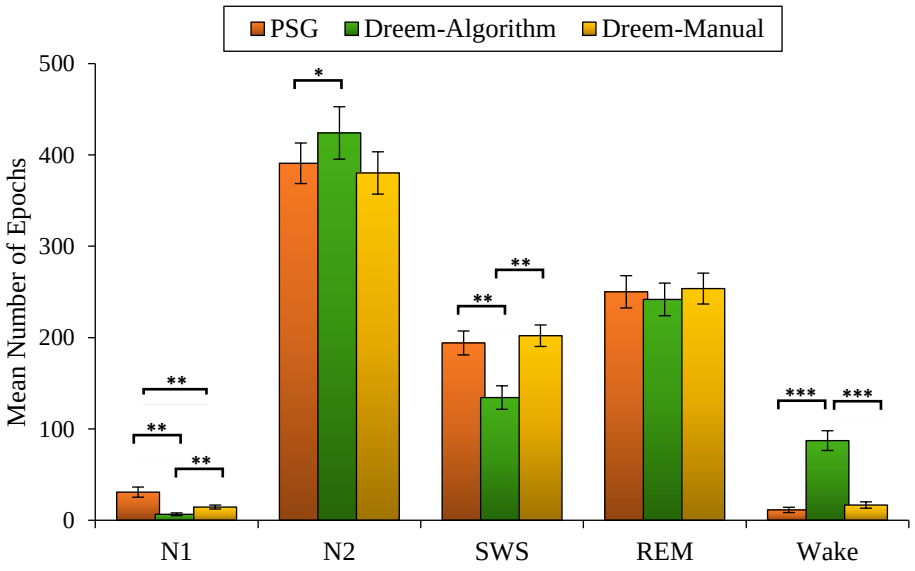


Figure 2.8 Mean Number of Epochs Scored Between Recording Methods

The mean number of epochs scored by PSG, Dreem-algorithm, and Dreem-manual across all recordings (n=15). There were significant differences between PSG and Dreem-algorithm in N1, N2, SWS and wake. In contrast, there was only a significant difference between PSG and Dreem-manual in N1. Error bars show ± SEM. *$p < .050$, ** $p < .010$, *** $p < .001$.

Table 2.8 Number of Epoch Differences Between Scoring Methods

		Three-way Repeated Measures ANOVAs			*Subsequent Pairwise Comparisons (p-values)*		
	Sleep Stage				PSG against	PSG against	Dreem-algorithm against
		df	F	*p*	Dreem-algorithm	Dreem-manual	Dreem-manual
Number of	N1	1.12	14.70	.001	.001	.009	< .001
Epochs	N2	1.38	4.89	.029	.013	.402	.036
	SWS	2.00	13.65	< .001	.002	.546	< .001
	REM	1.40	3.66	.583	-	-	-
	Wake	1.11	41.58	< .001	< .001	.137	< .001

2.3.4.2 Artefact Epochs

I then investigated artefact scoring across the recording and scoring methods. No artefacts were scored by Dreem-algorithm; however, significantly more artefacts were scored per night via Dreem-manual scoring compared to PSG, t (14) = -2.37, p = .033 (**Figure 2.9A**). I then explored how correct (i.e. PSG-scored) artefacts were attributed by both scoring methods of Dreem data. I found that these epochs were attributed similarly according to manual or algorithmic scoring: most likely to be scored as N2 and unlikely to be scored as artefacts (**Figure 2.9B**).

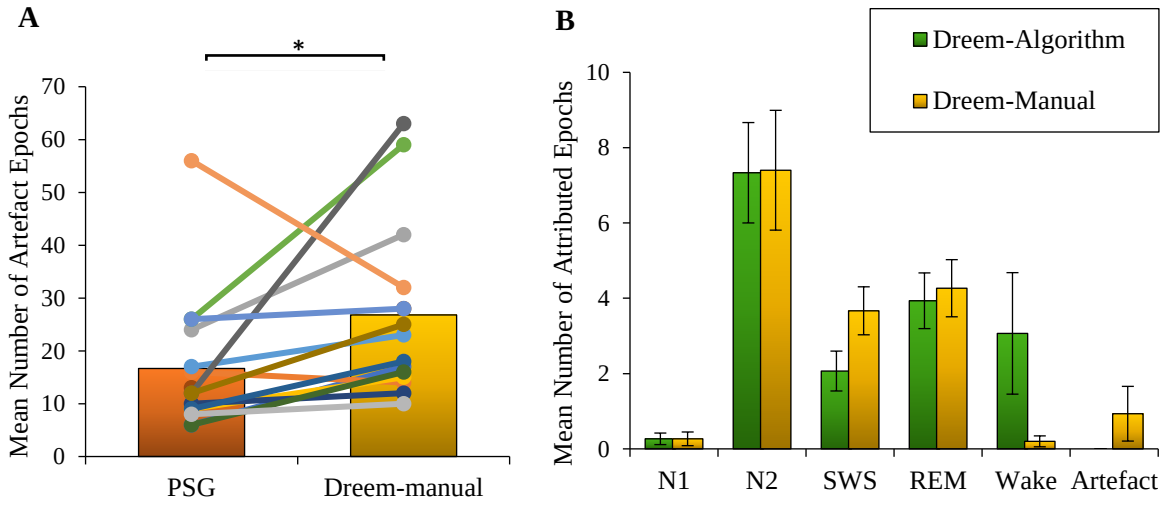


Figure 2.9 Artefact Epochs as Scored in PSG and Dreem

Dreem-manual scoring led to significantly more artefact epochs than PSG while Dreem-algorithm scored none; scatter shows individual recordings (**A**). PSG-scored artefact epochs as scored by Dreem-algorithm and Dreem-manual, on average per recording, were most often attributed to N2 (**B**). Error bars show ± SEM, significant differences between sleep stages are shown in Table 2.9. * p < .050.

To investigate whether the number of artefact epochs wrongly attributed was significantly different between stages, a 6 x 2 repeated measures ANOVA indicated a significant difference across sleep stages, F (1.93) = 17.59, p < .001, but no difference between Dreem-algorithm and Dreem-manual, F (1) = 1.00, p = .334, and no significant interaction, F (1.21) = 3.62, p = .068. Subsequent pairwise comparisons (**Table 2.9**) suggested that artefact epochs were significantly more likely to be scored as N2, SWS, or REM than an artefact, but this did not differ between manual and automatic scoring of Dreem.

Table 2.9 Pairwise Comparisons Between Dreem-Scored Stages of PSG-Scored Artefact Epochs

Comparison		*p*-value
N1	N2	< .001
	SWS	< .001
	REM	< .001
	Wake	.143
	Artefact	.641
N2	SWS	.007
	REM	.013
	Wake	< .001
	Artefact	< .001
SWS	REM	.129
	Wake	.219
	Artefact	.001
REM	Wake	.004
	Artefact	< .001
Wake	Artefact	.047

2.3.5 A Test of Scoring Method: Personality Traits

An investigation of how personality traits are associated with sleep was not an aim of this study; however, I utilised these data to test the effects of scoring method, i.e. the impact of differences in scoring (PSG, Dreem scored algorithmically, Dreem scored manually) on associations with potential predictors of sleep architecture. I explored, with no a priori hypotheses, associations between sleep as scored by PSG and personality traits. For significant associations only, I then investigated the effects of Dreem-manual and Dreem-algorithm scoring. To limit the number of analyses, I focussed on the commonly used sleep metrics of time spent in SWS and REM.

Each trait was considered independently as a predictor of SWS or REM (scored by PSG) in a linear regression model. Where participants contributed sleep recordings on two nights (n=5), time in SWS or REM was averaged. I found a strong association between agreeableness and time spent in SWS (all other associations were non-significant, these results are shown in Appendix D); therefore, I tested for a similar association when relying on Dreem-algorithm and Dreem-manual sleep scoring (**Figure 2.10**). The same analyses were conducted using these

SWS values (**Table 2.10**). Agreeableness was not a significant predictor of SWS when scored by Dreem-algorithm or Dreem-manual, although values were closer to PSG with manual scoring.

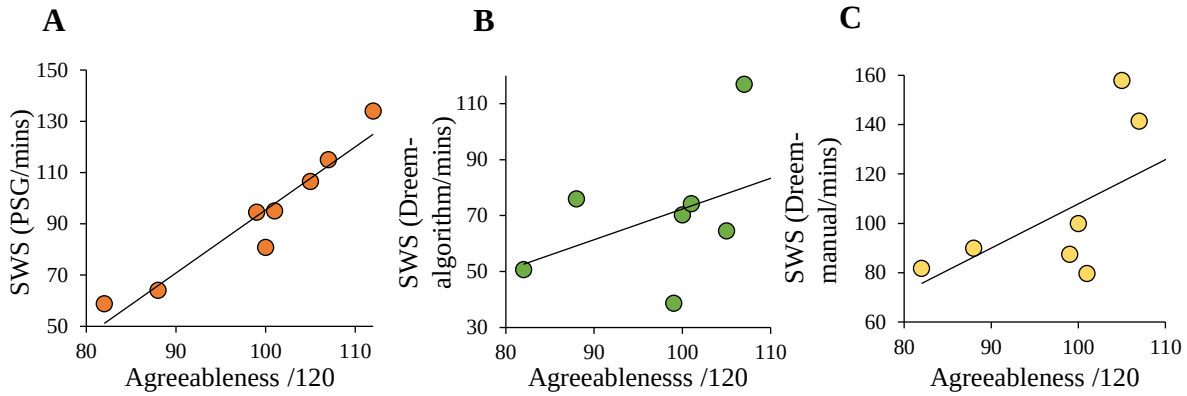


Figure 2.10 Agreeableness and SWS as Scored by PSG and Dreem

Agreeableness was strongly positively associated with minutes spent in SWS as scored by PSG (**A**). However, there was no significant association between agreeableness and SWS when scored by Dreem-algorithm (**B**) or Dreem-manual (**C**), n = 8.

Table 2.10 Associations Between SWS and Agreeableness

SWS Measurement	R^2	F (*1,6*)	*p*	Unstandardised Coefficients	
				B [SE]	95% CI
PSG	.92	65.95	< .001	2.46 [0.30]	1.72, 3.20
Dreem-algorithm	.22	1.69	.241	1.10 [0.84]	-0.97, 3.16
Dreem-manual	.37	3.53	.109	1.79 [0.96]	-0.54, 4.13

Linear Regression.

2.4 Discussion

2.4.1 Summary of Results

In this chapter I aimed to replicate the previous validation of the Dreem Headband against PSG, specifically, greater than 80% agreement in sleep stages N2, SWS and REM. I found that agreement for algorithmic scoring did not reach the targeted 80% in any sleep stage. However, I also investigated manual scoring of Dreem raw data as an alternative to the automatic algorithm, finding that manual scoring was significantly closer to PSG across the night and reached 80% in SWS and REM (**Figures 2.5–2.6**). This suggests that manual scoring of Dreem data is more accurate than algorithmic scoring, sufficiently so for Dreem to be suitable for the measurement of SWS and REM.

I found a moderate 67% agreement between Dreem-algorithm and PSG across the whole night, though there was a marked reduction when taking chance into account, $\kappa = 53\%$. In contrast, manual scoring of Dreem yielded a significantly greater 75% agreement with PSG and with less reduction when accounting for chance, $\kappa = 68\%$. Neither achieved the 80% benchmark for two trained sleep scorers scoring PSG; however, some sleep stages surpassed this target when assessed separately. In sensitivity, my primary measure of sleep stage agreement, PSG and algorithmic scoring agreement achieved 75%, 59% and 72% in the targeted stages N2, SWS and REM respectively. However, I found 80% and 86% agreement for manual scoring in stages SWS and REM, with agreement at 78% in N2 approaching this level. This suggests that manual scoring of the Dreem Headband is an adequate alternative to the more costly and time-consuming gold standard, PSG.

This was confirmed in other measures of agreement. In the balance between sensitivity and specificity, there is generally a trade-off where an overestimation of one sleep stage results in a good ability to detect the stage when it occurs, but a correspondingly poorer ability to detect when it does not occur and vice versa. However, when both Dreem-algorithm and Dreem-manual were tested against PSG, there was largely a more favourable balance for Dreem-manual: both sensitivity and specificity were equal or greater than Dreem-algorithm in sleep stages N1, N2, and REM. There were only two instances where algorithmic scoring significantly outperformed manual scoring. Sensitivity was greater for wake at 47% compared to 16%, and specificity was greater for SWS at 96% compared to 92%. Yet, in both cases there was worse performance in the other measure: the algorithm's better ability to detect the presence of wake and absence of SWS was marred by worse performance detecting the absence of wake and presence of SWS. This suggests that some feature of slow oscillation

detection is particularly problematic for the Dreem headband, discussed in section 2.4.2 and 2.4.3.

I also explored positive and negative predictive values to assess whether the epochs scored by Dreem were correct, regardless of how many were scored in each stage. Like sensitivity and specificity, manual scoring of Dreem mostly resulted in greater correct staging for both positive and negative identification. In fact, there was only one instance of better identification for Dreem's algorithm: significantly greater positive predictive value in SWS at 85%, compared to 77% for manual scoring. This suggests that an epoch scored as SWS by the algorithm is more likely to be real SWS as defined by PSG, while manual scoring yields more false positives and so each SWS-scored epoch is less likely to be true SWS. However, since manual scoring showed significantly greater sensitivity for SWS compared to the algorithm, and this difference was larger at 21%, the algorithm's superior positive identification is traded for a poorer ability to detect all the SWS that occurs throughout the night. Therefore, these agreement measures generally suggest that manual scoring offers a better balance of detection and probability of all sleep stages. However, algorithmic scoring could be utilised if an analysis depended on the SWS epochs identified being true SWS and it was of less importance whether all SWS was identified.

While algorithmic scoring of Dreem offered poor temporal agreement with PSG, time spent in each sleep stage is a commonly used metric more forgiving to discrepancies. Considering the time investment needed to manually score Dreem raw data rather than rely on the automatic scoring algorithm, I also investigated whether algorithmic scoring was sufficient for this simpler statistic. I found that the algorithm significantly underestimated time spent in N1 and SWS and overestimated time spent in N2 and wake. Apart from N2, these differences were considerable: the algorithm scored 43.5 minutes of wake, 38 more than PSG; 3.5 minutes of N1, 12 less than PSG; and 67 minutes of SWS, 30 less than PSG. In contrast, manual scoring of Dreem underestimated time in N1 by 3.5 minutes, but with no difference in any other sleep stage. These results support manual scoring as worthwhile in the evaluation of overnight sleep recorded by the Dreem Headband.

I found inaccurate artefact scoring in both algorithmic and manual scoring of Dreem data. There were no artefacts scored by Dreem's algorithm during the sleep period in this sample, yet both PSG and manual scoring yielded a significant number of artefacts. This suggests that the algorithm wrongly attributes noise in the data as sleep. I investigated how these artefacts were scored by Dreem; surprisingly, algorithmic and manual scoring methods were similar – both attributed artefact epochs across the stages but most often to N2. Manual scoring of Dreem resulted in significantly more artefacts, but these nearly always disagreed with PSG:

of an average 17 artefact epochs per recording as scored by PSG, on average only 1 of these was also scored as an artefact by Dreem-manual. This suggests a problematic signal-to-noise ratio for Dreem that is not improved by manual scoring. Yet, since time spent in any sleep stage (except N1) did not significantly differ between manual scoring and PSG, these wrongly classified epochs do not appear to adversely affect the efficacy of most manual scoring.

Finally, I utilised the personality data for this sample to test how different scoring methods affected external associations. This was exploratory and the sample size was low; nevertheless, I found a clear association between PSG-measured SWS and agreeableness which was still significant if corrected for multiple (10) comparisons. When exploring whether Dreem scoring could detect the same effect, Dreem-manual was more comparable to PSG than Dreem-algorithm but neither showed the association to be significant. This suggests that the 80% SWS agreement between Dreem-manual and PSG was insufficient, albeit with the reduced power of a very small sample. It is therefore likely that a greater sample size (i.e. more statistical power) is required with Dreem to detect effects that are seen more easily with PSG.

2.4.2 Dreem's Scoring Algorithm: Distinguishing Hardware and Software

The Dreem Headband uses an in-house scoring algorithm to classify sleep stages. This technology might rival expert visual scoring. There are many isolated automatic scoring algorithms that claim to accurately sleep score PSG data, though like wearables, with mixed success. For example, one algorithm (Tautan et al., 2019) was tested against the Massachusetts General Hospital dataset of 994 participants and reported agreement of 72%. Stronger results may be achieved using deep learning methods. For example, SleepEEGNet and Deep Sleep Net have been reported to achieve κ = 79% and 80% of 62 and 197 subjects respectively (Supratak et al., 2017; Mousavi et al., 2019). Yet, despite these promising indications, automatic sleep scoring is yet to replace expert scoring in mainstream sleep literature. To replace visual scoring, confidence in automatic algorithms may need to be built up over time.

When comparing algorithmic scoring of the Dreem Headband to PSG, variance originates from the difference in software: an automatic scoring algorithm compared to manual sleep scoring. However, there are also differences in hardware: the headband records from dry electrodes at frontal and occipital regions, omitting several features of PSG such as central EEG and eye movement. While these data do not provide a conclusive measurement of differences between hardware and software, this would require Dreem's automatic algorithm

(not openly available) to be applied to the PSG data. I have, nevertheless, estimated these effects by comparing agreement between PSG, Dreem scored manually and Dreem scored algorithmically.

Sleep is highly heterogenous and sleep scoring relies on subjective judgements, hence why the gold standard, PSG, accepts agreement between two scorings of the same night as low as 80%. We cannot, therefore, assume that the error between Dreem-algorithm and PSG is all due to differences in hardware or software, some is undoubtedly due to the error inherent in sleep scoring. In this study I utilised all comparisons between PSG, Dreem-algorithm and Dreem-manual and each should have a similar level of this 'random' error. Therefore, comparing the agreement of two scoring methods when they differ according to hardware or software can approximate the level of error caused by each. The scoring methods are reiterated below (with differences of hardware and/or software) and average Kappa values as found in this sample:

1. Dreem-algorithm -> PSG (hardware + software), κ = 53%
2. Dreem-manual -> PSG (hardware), κ = 68%
3. Dreem-algorithm -> Dreem-manual (software), κ = 58%

My primary aim in this study was to test Dreem-algorithm against PSG (comparison 1). Here, some of the variance will be due to hardware, some due to software (scoring method), and the rest due to random error, as would occur between two scorers of PSG (the same hardware and scoring method). To estimate the effects of software I tested comparison 2 against comparison 1: greater agreement for manual scoring against PSG (κ = 68%) indicates how much better it is compared to the algorithm against PSG (κ = 53%), this difference was around 15%. Similarly, to estimate the effects of hardware I tested comparison 3 against comparison 1: greater agreement for Dreem-algorithm against Dreem-manual (κ = 58%) indicates how much better it is compared to the algorithm against PSG (κ = 53%), this difference was around 5%.

I focussed on differences in software in this study, evaluating the efficacy of manual scoring of Dreem raw data compared to algorithmic scoring. Yet, my third comparison illustrates that the Dreem Headband itself contributes some error. Testing comparison 3 against comparison 1 between sleep stages, there were no significant differences in N2, REM and wake suggesting no effect of hardware. However, in N1 and SWS, agreement was 20% and 30% greater in comparison 3 respectively when Dreem-algorithm was compared to Dreem-manual. This is especially prominent in the 89% agreement between Dreem-algorithm and Dreem-manual for SWS. This suggests that the appearance of N1 and especially SWS recorded by

the Dreem Headband differs from that recorded by PSG, and that this is a source of error for both the automatic algorithm and manual scoring.

In summary, I found a small effect of hardware on the differences between Dreem-algorithm and PSG across the night of 5%, compared to a 15% effect of scoring method. However, in N1 and SWS, hardware differences have a significant effect and so are likely to reduce accuracy in these stages.

2.4.3 Is Dreem a Promising Sleep Wearable?

Compared to previous validation of other devices, a total agreement of 67% between automatic scoring of Dreem and PSG is encouraging. Against arguably the next most promising device, the Oura ring, Dreem performed better in light sleep at 72% compared to 65%, deep sleep at 59% compared to 51%, and REM at 75% compared to 61%. However, my results do not match those reported by the previous Dreem validation study (Arnal et al., 2020). While the previous Dreem validation reported agreement at 74–85% for all stages except N1, I found lower agreement in every stage at 59–75%. Although Arnal et al. reported poor agreement for N1 at 48%, my results are again lower at 8%. One contribution to this difference could be the way agreement was calculated across the sample. In the previous validation, epochs were summed across all nights before agreement statistics were calculated, whereas I calculated agreement for each night individually and then averaged across nights. This may have meant that poorer nights of sleep, which tend to be shorter, had a greater impact on average agreements.

That being said, individual agreement statistics per night captured the variation between recordings. Figure 2.5 shows greater scatter between agreement of Dreem-algorithm and PSG than between Dreem-manual and PSG. Furthermore, every night in Dreem-manual achieved $\kappa > 50\%$ and all but three achieved at least moderate agreement at $\kappa \geq 60\%$ (McHugh, 2012). In contrast, two nights for Dreem-algorithm showed minimal agreement at $\kappa < 30\%$ and the majority (10/15) fell below 60%. This gives an important indication of variability between recordings that was not present in the previous validation.

I found Dreem's algorithm to have surprisingly low agreement with PSG in SWS at 59%, considering that a primary feature of the headband is the optimisation of slow oscillations and Arnal et al. (2020) reported SWS agreement at 83%. One factor behind this discrepancy could be sample age. The previous validation recruited a wider age range of 23–50 years (mean=35) than my study aged 20–37 years (mean=25). Previous literature suggests a marked decrease in EEG power below 10 Hz and reduced SWS duration with age (Landolt & Borbély, 2001;

Dijk et al., 2010). The effects of age should be investigated in larger samples to clarify this issue.

Alternatively, agreement in SWS has been poorer than N2 and REM in previous literature, as discussed in section 2.1 (Griessenberger et al., 2013; Zambotti et al., 2019), suggesting that wearable devices in general may struggle to accurately score this stage. There was also high variability (SD = 21%) in SWS scoring agreement among the consensus of five sleep scorers in the previous validation. This could be impacted by the use of dry electrodes for slow frequencies. A recent summary of dry electrodes suggested they were equivalent to traditional wet electrodes in some circumstances (Lopez-Gordo et al., 2014); however, a substantial increase in noise has been reported elsewhere (Bertelsen et al., 2019; Mathewson et al., 2017).

2.4.4 Strengths and Limitations

To my knowledge, this study provides the first evidence that Dreem data can (and should) be manually sleep scored. This provides support for the use of the Dreem Headband and perhaps wearables in general across sleep science. My application of manual AASM sleep scoring to the Dreem raw data is novel to the Dreem Headband but has been previously reported in the Philips SmartSleep Deep Sleep Headband (Garcia-Molina et al., 2018). While this is not analogous to Dreem manual scoring considering the different devices, it provides a precedent for this technique.

However, this study is limited by the size and homogeneity of the sample. Due to the variation expected between nights of sleep it is advisable to have as large a sample as possible, although the time and resources required for overnight PSG studies make this challenging. Most previous validation studies use more than 15 nights and therefore these results should be consolidated with more data. A common issue among sleep studies, this sample also consisted of only young, healthy participants. To evaluate the validity of the Dreem Headband for a range of uses, it should be assessed over a more representative sample.

In addition, the original study design recruited participants for two consecutive nights with a sample size unlikely to facilitate accounting for either night or participant effects. A ‘first night effect’, where a lack of comfort and familiarity promote a poorer night’s sleep in a new environment, is well established in sleep literature (Byun et al., 2019; Toussaint et al., 1995). I found no significant night effect in this study, though the lack of power (only six participants contributed two nights of data) means this result is somewhat unreliable. In a future study, it would be informative to evaluate how the headband performs against PSG in the first night

effect. This would also enable an investigation into participant effects: sleep is highly individualised which could affect the accuracy of the Dreem Headband, for example, it may perform better in certain demographic groups.

Finally, analyses in this study were derived from my sleep scoring. This enabled a consistent comparison between Dreem and PSG, yet there is a distinct advantage to a consensus of scorers, as in Arnal et al. (2020), because of the variability expected in this metric. To check scoring accuracy, two of my PSG recordings were scored by another independent scorer. Agreement was high for N2, SWS and REM at 89–95%, but low for N1 and wake at 32% and 9%. Previously, low agreement has been reported in N1 (Stepnowsky et al., 2013). Also, in only two recordings, agreement may have been strongly affected by a few difficult epochs. Both myself and Dr Purple agreed similarly strongly with the algorithm in the best night (κ = 71% and 79%) and poorly with the algorithm in the worst night (κ = 29% and 28%), suggesting that scoring error did not strongly contribute to the total agreement across the sample. However, additional scorers would add weight to these findings.

2.4.5 Conclusions and Future Directions

This study validates the Dreem Headband against the gold standard of sleep scoring, PSG, testing the findings of a previous validation study by the manufacturers. I found lower agreement between PSG and Dreem's algorithm in every sleep stage; critically, this fell below the 80% benchmark that two scorers should achieve in PSG. It is not immediately clear what drove these differences, so future studies should aim to test larger and less homogenous samples. Nevertheless, my results capture the variation between nights not reported in the previous study.

Looking beyond the previous validation, I also investigated manual scoring of the Dreem raw data. To my knowledge, this is novel to the Dreem Headband. I found that manual scoring of Dreem yielded higher agreement with PSG (compared to Dreem's algorithm) in N1, SWS, and REM. Agreement was high enough – greater than 80% – that SWS and REM duration as recorded by Dreem should be suitable for sleep analyses. Although agreement in N1 and wake was poor, I found 78% agreement of N2; therefore, Dreem may in fact be suitable for the analysis of most overnight sleep. Future work should aim to replicate this finding, corroborating visual scoring of Dreem raw data among a consensus of sleep scorers. I explore these EEG data further in Chapter 4 with spectral power and event detection analyses.

Chapter 3

Associations Between Sleep and Fear Conditioned Responses

In this chapter I present a novel fear conditioning experiment to test fear acquisition, overnight consolidation, and extinction in healthy people. I utilised the Dreem Headband – a wearable device which I validated for sleep measurement in Chapter 2, and employed skin conductance, shock expectancy ratings, and heart rate variability to measure fear responses. The results indicated that SWS was associated with overnight fear consolidation while REM sleep was associated with extinction learning. This suggests dissociable roles for these stages in the sleep-dependent processing of fear conditioned memories.

3.1 Introduction

The origin of documented fear conditioning is often traced back to the infamous case of Little Albert (Watson & Rayner, 1920). Albert was an 11-month-old child who was taught to fear a white rat. Every time Albert was given the rat, he was deliberately frightened with a loud sound. Soon, Albert began to show signs of distress at the sight of the rat, even before the sound occurred. In short, Albert had acquired a learned fear. The rat itself had never frightened Albert, but its presence had come to predict a frightening event (the loud sound) and eventually, the rat alone started to elicit a similar fear. In additional tests, this conditioned response showed generalisation to other items that shared characteristics with the rat, such

as those that were white. The fear was also long-lasting, evident even a month after the first encounter. Although the methods are not reproducible today, this study informed a whole literature on fear learning. Much of this research has replicated the longevity and generalisation of fear that Watson and Rayner illustrated with Little Albert a hundred years ago.

Conditioning is a simple model of behaviour which relies on a learned relationship between two stimuli. It is not specific to fear. For example, at a similar time, physiologist Ivan Pavlov was awarded the 1904 Nobel Prize for his work on digestion, which incidentally allowed him to observe conditioning behaviour (Clark, 2004). When Pavlov noticed that his dogs salivated at the sight of his equipment, he assumed this was because they were correctly anticipating the arrival of food. In subsequent famous experiments, he tested this effect by ringing a bell before feeding. When the dogs started to salivate at the sound of the bell it demonstrated that they were learning through association, exhibiting behaviour based on an expected outcome.

Conditioning is generally thought to require some level of conscious awareness, especially where it results in action (Greenwald & De Houwer, 2017; Skora et al., 2021). In these cases, the unconditioned stimulus (US) inherently produces a measurable response, e.g. a loud sound frightens Albert or food stimulates the dogs' salivation. The conditioned stimulus (CS) is present before the US, e.g. the white rat or the bell, and acquires its expectational properties via associative learning. This can happen over repeated experiences, as in Watson and Pavlov's controlled experiments; however, sometimes just one salient event can cause a lasting effect, for example, after trauma.

Fear learning has a clear evolutionary benefit as an adaptive response to dangerous situations. Problems may arise, however, when the fear response generalises to other stimuli or does not fade with time. It is not clear what happened to Little Albert after Watson's experiment, but whether he suffered a longer-term fear of rats is likely to have depended on his individual traits and tendencies. For example, fear is normal after trauma, but in some people an abnormal continuation of fear can lead to the development of a condition like PTSD. Why some people and not others develop such afflictions is a prime question facing this field of research.

Sleep supports the processing of emotional memories, as discussed in Chapter 1, and is therefore a key facet in understanding how maladaptive fear arises and persists. In this chapter, I investigate how sleep architecture relates to fear responses in young, healthy people, developing and testing a novel fear conditioning design to explore sleep-dependent fear memory consolidation.

3.1.1 REM Sleep and Fear Conditioned Memories

As introduced in Chapter 1, sleep has been associated with memory consolidation (Born et al., 2006; Marshall & Born, 2007; Spencer et al., 2017), while emotional processing has been most strongly linked to REM sleep (van der Helm & Walker, 2009; van der Helm et al., 2011; Krause et al., 2017). This is mirrored in the fear conditioning literature, where there is convergent evidence for the role of REM in the consolidation of fear conditioned responses.

Most often, the simple metric of REM duration has been correlated with fear responses. In one study, healthy participants (n=40, all male, mean age 25 years) were conditioned to two CS+ (paired with an aversive shock) and one CS- (Menz et al., 2013). Immediate extinction was carried out for one CS+, leaving the other unextinguished. This was followed by either PSG-recorded sleep or overnight sleep deprivation in the laboratory and recall was tested after an additional night of recovery sleep. Sleep, compared to wake, led to increased discrimination between the unextinguished CS+ and CS- in both expectancy ratings and SCRs. This consolidation of fear memory was correlated with time spent in REM sleep. In particular, lower fear discrimination after sleep deprivation was driven by greater responses to the CS-. This could be explained by fear generalisation, which may reflect a common real-world maladaptive response after a fearful experience. Participants who slept showed a more adaptive response in lower fear to the safe CS-, suggesting that REM sleep promotes an adaptive (i.e. increased discrimination) consolidation of fear learning.

In a later study, Menz et al. extended these findings by directly comparing SWS and REM sleep. After the same conditioning and immediate extinction task, another 40 healthy male participants (mean age 26 years) slept for three hours of either early SWS-dominant or late REM-dominant sleep (Menz et al., 2016). These results were combined with those of total sleep deprivation from the previous study. REM-rich, but not SWS-rich sleep, led to improved discrimination between fear and safe stimuli. In addition, both REM-deprived groups (SWS-rich sleep and no sleep) showed greater SCR fear responses to the extinguished CS+ relative to the CS-, paralleled by a discriminatory increase of activation in the amygdala and ventromedial prefrontal cortex (vmPFC). This suggests that a lack of REM sleep leads to greater fear to both safe stimuli and previously extinguished fear stimuli. Again, this could be explained by fear generalisation.

These findings complement a prior nap study. After a 90-minute daytime nap (n=16, all male, mean age 25 years), the participants (n=7) who reached REM sleep after fear acquisition and immediate extinction showed a lack of significant CS discrimination, indicating greater consolidation of extinction (Spoormaker et al., 2010). In contrast, those who had no REM sleep

still showed a significantly higher SCR fear response to the CS+, as well as lower activation of the vmPFC and lingual gyrus to the extinguished CS. REM duration did not predict changes in CS discrimination, but this could be because participants who did reach REM only had 15 minutes on average.

Together, these results indicate a role for REM in extinction memory consolidation and suggest this effect is not limited to overnight sleep. However, the MRI results are inconsistent. Spoormaker et al. (2010) found stronger activation in the vmPFC to the extinguished CS+ in the REM group, whereas Menz et al. (2016) found the same in REM deprived participants. It has been suggested that the vmPFC acts as a moderator and inhibitor of the amygdala in emotion regulation (Andrewes & Jenkins, 2019); therefore, if REM promotes adaptive responses (i.e. discrimination between the CS+ and CS-), the results of Menz et al. may align more closely with prior understanding of this region. The results of Spoormaker et al. may be due to the low sample size and the REM group reporting significantly greater difficulty in getting to sleep. In addition, REM deprivation over a whole night is not equivalent to a naturally occurring lack of REM in a 90-minute daytime nap.

Across these studies, the gender imbalance may also have affected the results. Removing previously reported effects of sex and menstrual cycle on fear conditioning and sleep (Baran et al., 2009; Glover et al., 2012) by only recruiting male participants probably improved study power. However, especially since fear-based conditions such as anxiety and PTSD are more common in women (Li & Graham, 2017; McLean & Anderson, 2009), the implications for the general population are somewhat limited.

Nevertheless, additional properties of REM sleep have been associated with overnight changes in men and women. Participants (n=42, 18 female, mean age 24 years) had baseline sleep, fear acquisition on day 1, post-conditioning overnight sleep, and then a recall test and extinction on day 2 (Marshall et al., 2014). REM sleep was assessed by REM duration as a percentage of total sleep time, REM efficiency (the proportion of epochs in each episode of REM scored as REM) and REM onset latency. These REM sleep factors in post-conditioning sleep were together associated with stronger CS discrimination at recall, measured by fear-potentiated startle. These results suggest that REM metrics other than duration affect emotional processing and consolidation. However, there was no association between REM and post-recall extinction on day 2 indicating that preceding sleep does not affect subsequent extinction, at least in startle response.

Furthermore, overnight amygdala adaptation has been positively associated with REM sleep duration, but only if REM was undisturbed (Wassing et al., 2019). Participants (n=29, 15

female, aged 18–70 years) were exposed to two odour cues, one paired with their own out of tune singing (CS+) and the other paired with someone else's singing (CS-). This unusual design may have elicited self-consciousness rather than fear, but still yielded activation of the amygdala prior to sleep. After a full night's recorded sleep, participants were tested with the same stimuli. The extent of amygdala adaptation – overnight change in bilateral amygdala BOLD response – was significantly related to REM sleep. Specifically, fragmented or 'restless' REM (the number of other epochs within REM episodes, as well as cortical arousals of 3–15 seconds in REM epochs) was associated with a disruption in emotional consolidation. Additionally, the beneficial effect of REM for emotional processing was enhanced by time spent in 'transition to REM' – spindle rich N2 sleep. This suggests that good quality REM sleep supports emotional processing and provides evidence for sleep stages working together overnight.

Wassing et al. (2019) also tested a subset (n=29, 14 female, mean age 41 years) of participants who were exposed to CS odour cues during REM sleep (13=cued, 16=control). Targeted memory reactivation (TMR), the presentation of sounds or odours during sleep to elicit an unconscious reaction and a reactivation of the memory, has been previously shown to enhance effects of sleep such as improved memory (Hu et al., 2020). Wassing et al. found that TMR enhanced both the beneficial effect of REM duration and the damaging effect of REM restlessness on amygdala adaptation. This provides evidence of a causal relationship between emotional processing and REM sleep. However, this is limited by the wide sample age of 18–70 years. Twelve participants also met the clinical criteria for insomnia disorder, whereas most sleep studies limit their sample to young healthy participants. This study is more representative of the general population, but the results may not accurately reflect healthy sleep processes.

REM sleep has also been associated with lasting memory effects over longer periods of time. For example, REM duration has been associated with a short-term increase in emotion but long-term reduction. As mentioned in section 1.1.4, participants who viewed negative images before and after a daytime nap showed a positive association between overnight REM duration and aversiveness ratings the same day, but a reduced intensity, number, and duration of intrusive memories of the images three days later (Werner et al., 2020). However, there is no research to my knowledge on longer-term effects of post-conditioning REM on fear conditioned responses. This should therefore be investigated.

3.1.2 Is Fear Conditioned Memory Processing Confined to REM Sleep?

Fewer studies provide evidence for the role of non-REM in sleep-dependent emotional processing, which could suggest a small or inconsistent role. In fear conditioning, evidence appears to be confined to TMR studies suggesting that non-REM effects are difficult to detect within the conventions of typical experiments and are more specifically related to reactivation.

TMR during SWS has been reported to enhance extinction of the fear conditioned response. Participants (n=15, 8 female, mean age 25 years) underwent olfactory fear conditioning of four neutral faces, two paired with a shock, while two neutral contextual odours were paired with one CS+ and one CS- each (Hauner et al., 2013). During a subsequent daytime nap, one odour was presented during SWS and responses were tested after sleep. SCR reduction pre- to post-sleep was greater for the reactivated CS+ and CS- and the magnitude of SCR reduction for the reactivated CS+ (relative to the non-reactivated CS+) was correlated with the duration of exposure during sleep. A follow-up experiment with odour re-exposure during wake confirmed that the effect was specific to sleep. However, while SCR reduction was associated with odour re-exposure time, this coincided with SWS duration and so either could be driving the effect. It may also have been expected that duration of SWS would predict change in SCR in the non-targeted stimuli, though the limited sleep obtained in the nap could have been insufficient for such an effect to be observed in a low sample size (n=15). It also would have been informative to explore reactivation in REM.

Similar results have been reported in rodents. In one study, mice (n=16, all male, 8–10 weeks old) were conditioned to a CS+ odour with a footshock and CS- odour without (Rolls et al., 2013). After 24 hours, they were exposed to the CS+ odour during 2 hours of non-REM sleep and recall was tested with another presentation of the CS+ odour after another 24 hours. Freezing behaviour was significantly reduced in mice who had been exposed to the odour during sleep compared to those who were exposed to the CS- odour. This suggests that exposure of the CS+ itself during non-REM also creates an extinction of the learned fear response. However, another reactivation study has reported evidence in the opposite direction. Mice (total n=29, all male, 8–13 weeks old) were conditioned to an auditory CS+ with a time delay before a shock (Purple et al., 2017). The tone was then presented during subsequent REM or non-REM sleep. Exposure during non-REM only led to a greater fear response to the CS+ after sleep, compared to a control group who heard white noise. This conflicting result could be explained by the delay between tone and shock reflecting different learning processes. On the other hand, a decrease in fear in the previous studies may be specific to odour learning.

In summary, TMR provides causal evidence that cued CS reactivation during non-REM sleep can affect fear consolidation. However, it is unclear whether it promotes an extinction or a strengthening of the learned fear response. This could be dependent on methodological detail such as the use of odour. Therefore, more research is required, especially in people, to determine whether this occurs across a greater range of fear conditioning designs.

3.1.3 Aims

Previous literature suggests that sleep supports the consolidation and extinction of fear. Both have been consistently associated with REM sleep, and there is some evidence for contributions by non-REM; however, there is little evidence for these stages working in concert. Consequently, I aimed to replicate findings of a positive association between REM sleep and overnight fear consolidation while investigating a role for the non-REM sleep recorded over the same night.

Secondly, while there is evidence that REM supports extinction consolidation when extinction occurs before sleep, there is less evidence when extinction occurs after sleep, especially across a range of fear measures. In a real-life situation, extinction is unlikely to occur the same day as fear learning. Therefore, this warrants exploration. I aimed to investigate the relationship between sleep (REM and non-REM) and subsequent post-sleep extinction learning.

Many studies of classic memory tasks (vocabulary learning, paired-associates task, etc.) have shown that preferential encoding continues to have an effect a week later, for example when information is rehearsed before or after exercise, it is recalled better than control information both the next day and seven days later (McNerney & Radvansky, 2015). There is also indication that emotional memory in particular could change over the days following encoding (Werner et al., 2020). However, there is also little long-term investigation into fear conditioned and extinguished responses, I therefore also tested extinction learning after seven days.

Building on the findings reported in Chapter 2, I used wearable technology – the Dreem Headband – which I found to be suitable for the estimation of SWS and REM when scored manually. This provides further support for the value of wearable technology in sleep science and allowed me to test a greater sample size. For this reason, I confined my assessment of non-REM sleep to SWS only. In addition, considering that previous studies using targeted memory reactivation have presented convincing evidence, I aimed to design a paradigm amenable for future use with TMR by testing two CS+ and two CS-.

3.1.4 Hypotheses

1. REM sleep duration in a full night of post-conditioning sleep will be associated with greater consolidation of discriminative unextinguished fear responses the next day.
2. REM sleep duration in a full night of post-conditioning sleep will be associated with greater fear extinction (responses towards zero), both the next day and after seven days.

Non-REM sleep may also play a role in fear conditioning and extinction learning, but there is scant evidence outside TMR designs. I therefore additionally explored associative relationships for SWS duration across these same hypotheses. Considering the findings of Chapter 2 regarding the accuracy of the Dreem Headband, I confined my analyses of non-REM sleep to SWS.

3.2 Methods

3.2.1 Participants

I recruited 38 healthy people (28 female, 10 male) aged 19–30 years (mean = 23.00) from Cardiff University and the surrounding area through posters and online advertisements. I initially recruited 20 participants (18 female, 2 male) aged 19–30 years (mean = 21.95), this formed sample 1. Approximately six months later, I recruited a further 18 participants (10 female, 8 male) aged 20–30 years (mean = 24.17) for the same experiment with an additional session a week later, this formed sample 2.

All participants reported a negative history of mental health, sleep or neurological disorder, current medication, and recent sleep disturbance. All were non-smokers, had a regular sleep/wake cycle, reported their ability to sleep as good or excellent, and agreed to abstain from caffeine, alcohol, naps, and extreme exercise for 24 hours prior to each session.

3.2.2 Materials

3.2.2.1 Screening

I created an online questionnaire (Google Forms: Free Online Surveys, 2020) to screen participants' suitability for the experiment. Because of the stimuli used, this included familiarity with the languages, Korean, Hungarian, Hebrew, and Turkish. The full questionnaire and exclusionary criteria are shown in Appendix A.

3.2.2.2 Questionnaires

I measured state and trait anxiety with the State Trait Anxiety Inventory (Spielberger, 1983) and prospective and inhibitory anxiety with the 12-item Intolerance of Uncertainty Scale (Carleton et al., 2007). Because of the risk that the Dreem Headband would disrupt sleep, I also tested participants for sleepiness/alertness at the beginning of each session with the Stanford Sleepiness Scale (Hoddes et al., 1973).

3.2.2.3 A Novel Fear Conditioning and Extinction Design

I designed a novel fear conditioning task for fear (CS+) and safe (CS-) learning, and a complementary extinction/reinstatement task to extinguish learned fear responses and then

test reinstatement through a reminder of the aversive stimulus. The tasks were written and presented using Matlab R2017a and the Cogent 2000 toolbox (Cogent 2000, 2018).

Conditioning and extinction did not require user input. However, both tasks incorporated subjective shock expectancy ratings every eight trials, waiting for a correct keypress each time. This served to maintain participants' attention as well as record their changing judgements of shock pairings.

3.2.2.3.1 Stimuli

I sourced four images from The Novel Object and Unusual Name Database. This resource offers images of distinct and neutral complex objects for research. When 32 participants (20 female) were asked to describe each image, language analysis indicated that the objects were most likely to be described by their colours (Horst & Hout, 2016). I therefore selected four greyscale images; all are photographs of real but unusual objects (288 x 288 resolution) on a blank background (**Figure 3.1**).

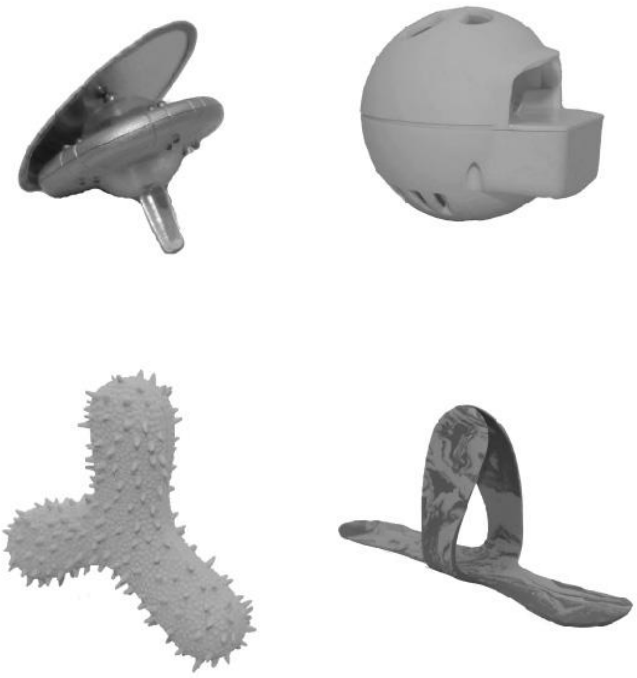


Figure 3.1 Experimental Stimuli

Greyscale images of novel, neutral objects. All participants saw these four images.

I sourced four spoken word recordings from *forvo.com* – a pronunciation website. I chose a single word spoken in Turkish (Karaciğer), Hungarian (Mennydörgés), Hebrew (תכשיטים), and Korean (당신을 사랑해요). These were selected for good recording quality and comparable length (all were 3–4 syllables). Since participants were screened to be unfamiliar with these languages, meaning was not considered, but all were sourced from common words. Each was spoken by a different female speaker and had an approximate 1.5-second length. A slight pause at the beginning and end of the sound gave a more realistic experience of hearing an object be named for a total sound length of two seconds. These words were randomly matched to the images to form four unfamiliar image/sound pairs designed to elicit a neutral response. Stimuli were not rated prior to conditioning; however, to mitigate any unwanted effects (e.g. some image/sound pairs being perceived as more or less threatening), assignment of CS+ and CS- to each image/sound was counterbalanced across the sample.

I chose electrical stimulation as the most suitable aversive unconditioned stimulus for this experiment; it is commonly used in conditioning across animal and human studies, offers precise timing, and intensity is easily calibrated and measured. Each 'shock' consisted of 30 stimulations at 200 volts, each lasting 500 μs and separated by a 1 ms interval (total 45 ms). The shock was generated with a Digitimer DS7A constant current stimulator for transcutaneous stimulation of nerve and muscle tissue and delivered through BioPac disposable electrodes placed on the left index finger. Intensity was individually calibrated to an aversive level for each participant by varying the milliamperes (mA) of the shock prior to the conditioning task (discussed further in section 3.2.3).

3.2.2.3.2 Fear Conditioning Task

The fear conditioning task was presented on a desktop computer in an individual testing room and lasted approximately 15–20 minutes, while sounds were delivered through noise-cancelling headphones. The task started with instructions asking participants to pay attention to the pattern of images, sounds and shocks and explaining how to make shock expectancy ratings (shown in Appendix C). Participants used a keypress to start the task once they were alone.

In each trial, the image/sound pair appeared for two seconds, centred on a black background. Each CS was presented 16 times (total 64 trials), and each trial was separated by a jittered inter-stimulus interval of 8–10 seconds. During these intervals a white fixation cross was centred on a black background (see **Figure 3.2**). For both CS+, the shock co-terminated with image/sound presentation on 9 out of 16 trials. The shock was never paired with the CS-. I

used partial reinforcement (the shock was not paired with the CS+ every time) because it is common among human conditioning studies and promotes less rapid extinction (Grégoire & Greening, 2020; Kitamura et al., 2020; Kredlow et al., 2018).

In the task structure, I aimed to ensure an even distribution of CS presentation while giving the perception of randomness so that the next trial was not predictable (**Figure 3.2**). To achieve this, trial order was determined in an underlying block format: every eight trials contained each CS presented twice, where one of each CS+ trial was reinforced (whether the first or second time was random). Order within each block was random, and the first four and last four trials were controlled to ensure that learning started and ended at the same time: all participants saw each CS in the order [CS-, CS+, CS-, CS+], both CS+ were reinforced, and which CS+ and CS- came first was counterbalanced.

For subjective ratings at the end of each block, each CS appeared sequentially in a random order (without a shock), separated by a 2-second fixation cross. On screen instructions presented alongside the image/sound asked participants: '*When you see this image, how often do you expect to receive a shock? 1 = never … 5 = always'*. The task waited indefinitely for a correct keypress (1, 2, 3, 4 or 5). If an invalid key or multiple keys were detected, participants were shown an error message: '*Sorry, that was not a single number between 1 and 5. Please press a number between 1 and 5 to rate the image/sound now'*. The image remained on the screen but the sound was not repeated.

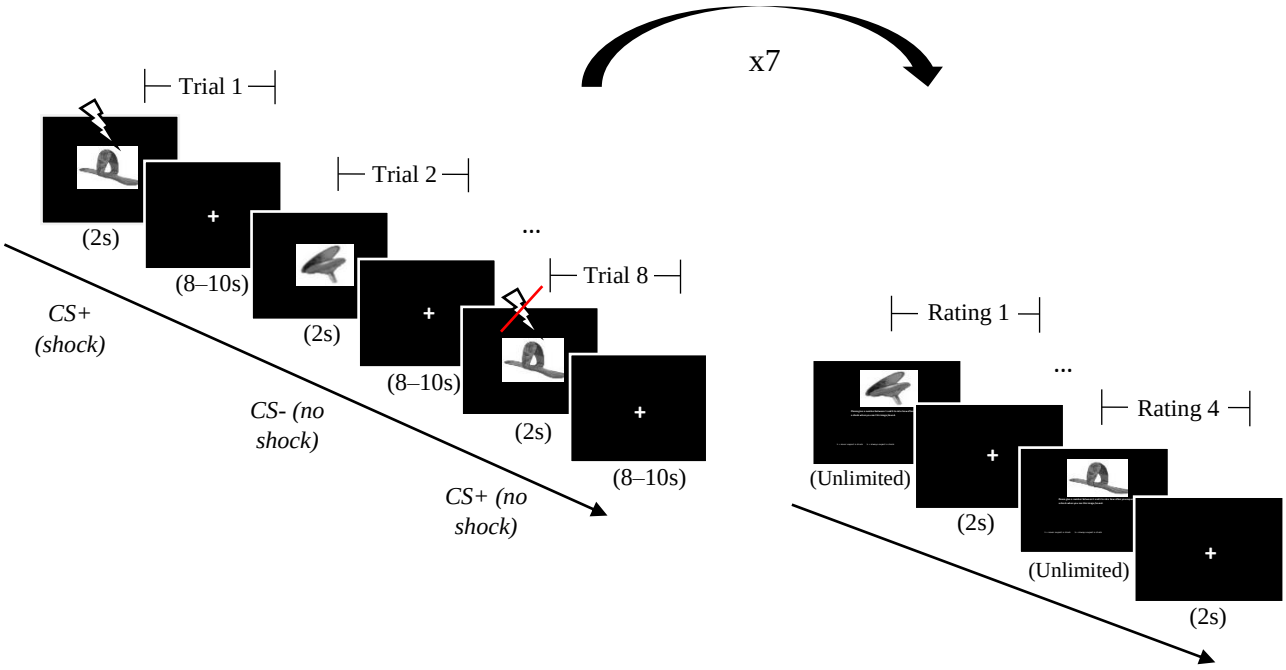


Figure 3.2 Fear Conditioning Task Structure

Participants experienced 64 conditioning trials plus 28 expectancy ratings. The underlying structure of the task consisted of seven blocks of eight trials (two of each CS, one of each CS+ paired with the shock) and then four expectancy ratings (one of each CS). Trials were separated by a variable interval between eight and ten seconds. Expectancy ratings were separated by a shorter two-second interval. This block structure was repeated seven times for the middle 56 trials. It was preceded and followed by the first and last four trials: one of each CS where both CS+ were paired with the shock.

3.2.2.3.3 Fear Extinction and Reinstatement Task

The extinction and reinstatement task consisted of three sections: extinction, reinstatement, and post-reinstatement. Participants were unaware of this and were told they were completing the same task as the previous day with the only contingency that '*the pattern of images, sounds, and shocks may have changed*'. Like conditioning, the task took approximately 15–20 minutes and instructions were identical.

Extinction contained 32 trials structured in the same way as conditioning: blocks of eight trials followed by an additional four expectancy ratings. Unbeknownst to participants, the shock ceased to be paired with any of the stimuli. The first four trials were not controlled because there was no reinforcement. After 32 trials, participants received four un-signalled shocks (unpaired with any image/sound) with a variable interval of 10–20 seconds at the same intensity chosen the previous day. Post-reinstatement consisted of another 32 trials without

shocks, plus expectancy ratings, in the same structure as before. There were no warnings, instructions, or breaks between these phases; all trials were presented continuously.

3.2.2.4 Physiological Recording

I chose skin conductance responses (SCRs) as my main measure of fear. This is commonly used in the fear conditioning literature as a marker of sympathetic nervous system activity and is responsive to aversive electrical stimulation (Jones et al., 2017; Leuchs et al., 2019; Pineda & Al-Rabadi, 2016). I also utilised heart rate variability as an exploratory secondary measure. This has been rarely explored in fear conditioning, and even so, only in relation to a resting baseline (Pappens et al., 2014; Sevenster et al., 2015; Wendt et al., 2015). In contrast, I tested heart rate variability on a trial-by-trial basis.

There are several metrics under the umbrella of heart rate variability. I chose to use the root mean sum of squared differences (RMSSD) as it has been reported the most suitable for short time frames (Wang & Huang, 2012). Although these short time frames generally refer to minutes rather than seconds, more recently, 10-second trials have been reported as highly accurate (r = .85-.86) against standard 5-minute recordings for RMSSD (Tegegne et al., 2019). In addition, while heart rate is mediated by both the sympathetic and parasympathetic systems, RMSSD reflects mainly parasympathetic components (Mackersie & Calderon-Moultrie, 2016), providing a measure complementary to SCRs.

Skin conductance and heart rate were recorded using BrainProducts EXG AUX amp and electrodes (BrainProducts, Germany), sampled at 5000 Hz. For both, skin was prepared with a mild abrasive (NuPrep Skin Prep Gel) to improve recording quality. Silver–silver chloride electrodes were placed on the skin with conductive paste (Ten20 Conductive Paste) and secured with medical tape. Two electrodes recorded skin conductance from the left palm thenar and hypothenar muscle sites, which feature a high concentration of eccrine sweat glands (Klarkowski et al., 2016), while an electrode on each forearm recorded heart rate.

3.2.2.5 The Dreem Headband

I used ‘Dreem 1’ headbands to remotely measure overnight sleep, as described in Chapter 2. Briefly, the Dreem Headband records from five dry EEG electrodes (FpZ, F7, F8, O1, O2) sampled at 250 Hz, referenced to each other. Dreem recordings are internally processed with a Butterworth bandpass (order 2) 0.4–18 Hz filter and (order 3) 50 Hz, 60 Hz and 62.5 Hz notches applied to the EEG channels: Fpz-O1, Fpz-O2, Fpz-F7, F8-F7, F7-O1, F8-O2, and

Fpz-F8. A 3D accelerometer measures movement, position, and breathing while a red-infrared pulse oximeter measures heart rate (Arnal et al., 2020).

3.2.3 Procedure

Participants attended Cardiff University for fear conditioning on day 1, their sleep was recorded at home that night, they then returned the next morning for fear extinction and reinstatement. Eighteen participants also returned a week later for an additional fear extinction/reinstatement session. Testing was scheduled at 3–4 pm on day 1 and 10–11 am on day 2 and day 8 to ensure a consistent time between conditioning and extinction. This timeline is illustrated in **Figure 3.3**.

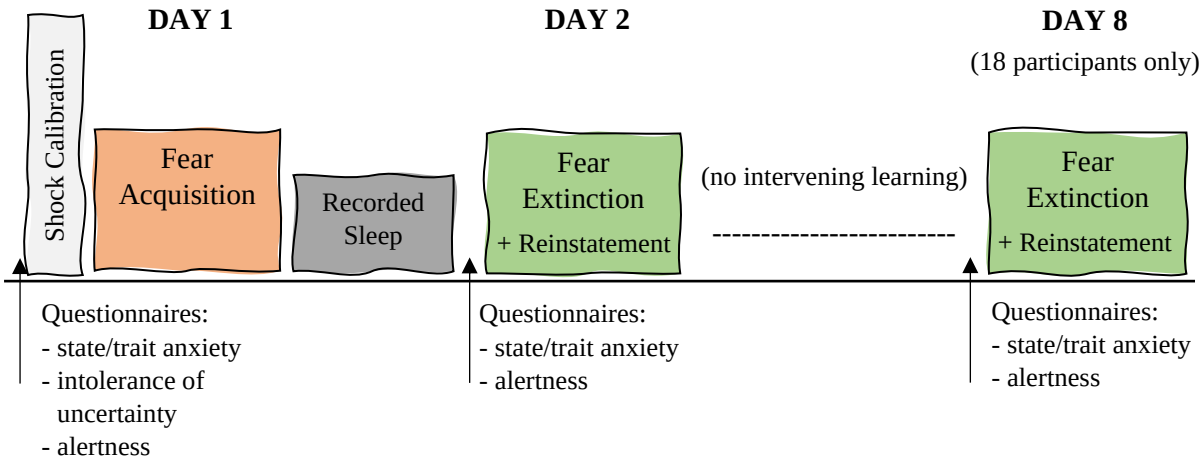


Figure 3.3 Experimental Timeline

All participants were conditioned through my fear acquisition task on day 1, had overnight sleep recorded at home with the Dreem Headband, and then completed my extinction and reinstatement task on day 2. A subset of 18 participants also returned on day 8 to complete the extinction and reinstatement task for a second time.

I aimed to provide a consistent context across participants and testing sessions. All sessions were conducted in the same place (same computer, chair, room etc.), while outside sounds were minimised by signs asking passers-by to stay as quiet as possible. The testing room within the sleep laboratory at Cardiff University was two doors away from the nearest corridor and maintained an even temperature (surrounding testing bedrooms were temperature controlled). Lighting was controlled with overhead room lights on and closed blackout blinds.

On day 1, participants gave informed consent, completed questionnaires measuring anxiety and alertness (IU, STAI and SSS) and were 'wired up' to the recording and shock equipment. Participants were encouraged to ask questions or express concerns about the study; none chose to withdraw.

Shock intensity for the tasks was individually calibrated with increasingly aversive shocks to find a level that was highly unpleasant but not painful, in line with previous studies (Koenig et al., 2017; Leuchs et al., 2019). Calibration started at 1.0 mA (pilot testing had indicated most people could not detect a shock at a lower intensity) and was guided by the participant using a 1–10 scale until a rating of highly unpleasant was reached (**Figure 3.4**). Participants did not interact directly with the shock equipment.

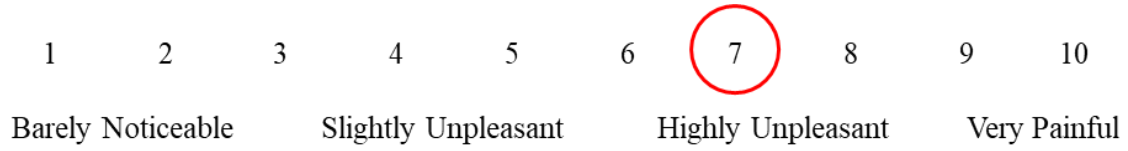


Figure 3.4 Shock Intensity Calibration Scale

Participants were given and asked to refer to this scale to guide them through the calibration procedure. As shock intensity increased, they were advised that they should move towards highly unpleasant but not reach as far as painful, aiming for 7/10. During calibration, participants could ask to repeat the same intensity or return to a lower intensity until they were satisfied the level was correct.

After calibration, participants completed the fear conditioning task alone in a testing room while electrodermal activity and heart rate were recorded. Before leaving, participants were given a Dreem Headband which was set up to record sleep without auditory stimulation or alarm. They practised turning on and wearing the headband correctly and were instructed to go to bed and wake up at their normal time. This session lasted approximately 60 minutes.

On day 2, participants completed the STAI, SSS, and the fear extinction task while electrodermal activity and heart rate were again recorded. Calibration was not repeated, shock intensity was set to the same level as acquisition. For the 18 participants who returned for another session on day 8, this was identical to day 2, although participants were not aware of this. They were again instructed that '*the pattern of images, sounds, and shocks may have changed*'. All participants who took part on day 1 returned for day 2, but one person failed to return for day 8. These sessions lasted approximately 45 minutes.

Cardiff University Psychology Ethics Committee approved this experiment on condition that special consideration was taken for participant wellbeing. Following these discussions, participants completed a short series of questions to indicate whether their mood had been affected by the experiment at the end of every session (see Appendix B). Anyone who reported negative effects would have been assigned 10 minutes of quiet relaxation in the building and given support information, though this was never required. Participants received financial compensation at the final session.

3.2.4 Data Processing

3.2.4.1 Sleep

I sleep scored all Dreem recordings according to AASM guidelines, as described in Chapter 2. Dreem does not use a specific reference channel, instead referencing each electrode to another (Fpz-O1, Fpz-O2, Fpz-F7, F8-F7, F7-O1, F8-O2, Fpz-F8). Accelerometer channels were resampled from 50 to 250 Hz, data were not re-referenced or filtered beyond Dreem's internal processing, and extraneous wake before the first epoch of sleep and after the last epoch of sleep was discarded. Data loss due to uploading issues (n=7), participant error e.g. failing to turn the headband on (n=3), or reported inability to sleep with the headband (n=1), meant intact data were available for 27/38 nights.

3.2.4.2 Electrodermal Activity

I used Matlab 2017b and the Autonomate toolbox (Green et al., 2014) to calculate SCRs (**Figure 3.5**). Failure of recording equipment led to missing SCR data for one participant on day 1 and one different participant on day 2. Raw data were downsampled to 625 Hz and trial duration was cut to the minimum time of 10 seconds (2 seconds CS duration + 8 seconds minimum inter-stimulus interval).

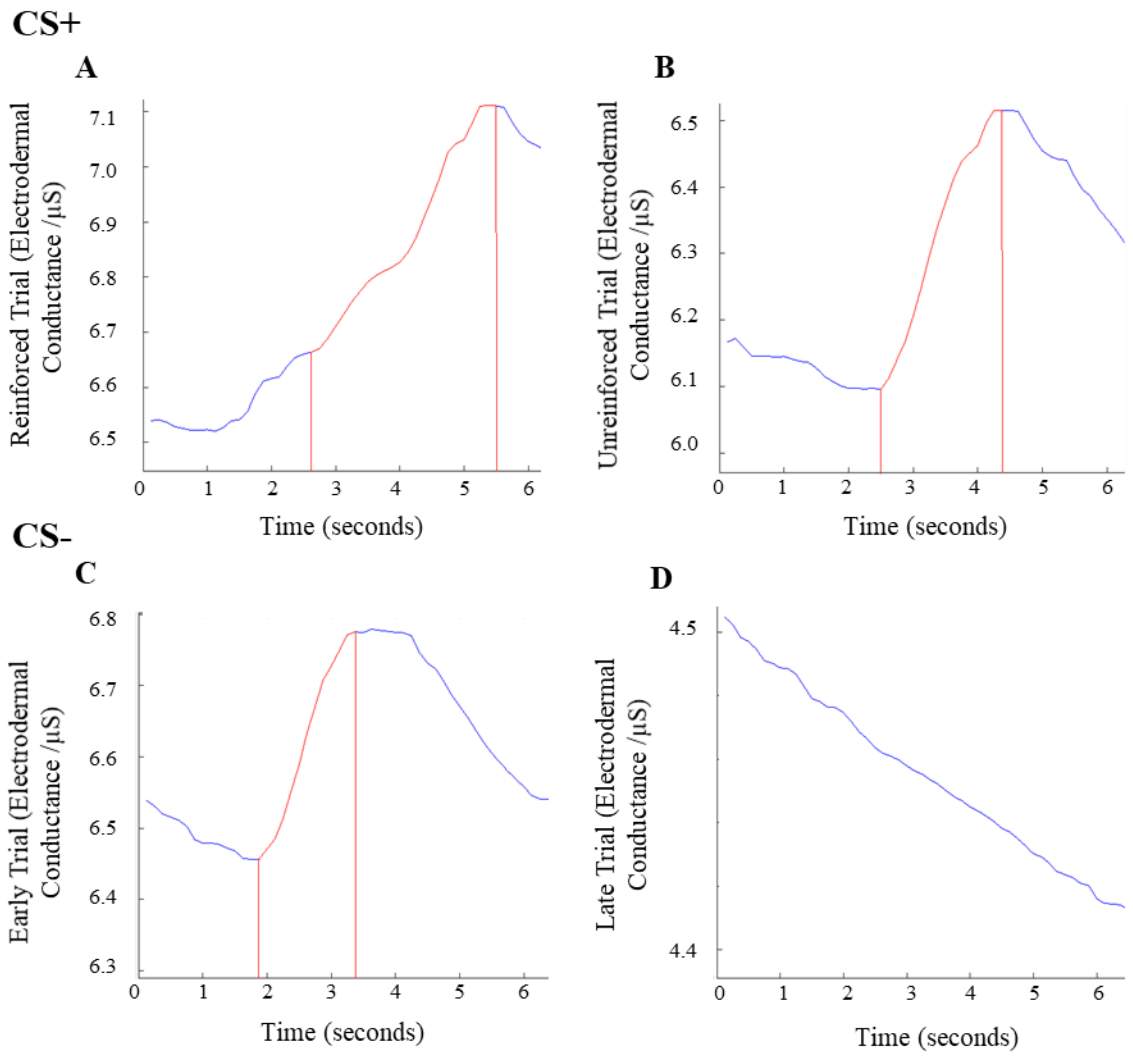


Figure 3.5 Example Trials: Autonomate-Calculated Skin Conductance Responses

Typical calculated SCRs (red) indicate that a reinforced CS+ trial paired with a shock (**A**), shows a similar response to the same CS+ on a trial not paired with a shock (**B**). In contrast, CS- responses changed across early and late trials: an early CS- trial shows a fear response (**C**), but a late CS- trial shows no response (**D**), in fact, skin conductance decreases across this trial, although only by < 0.1 µS.

I limited detection of SCR initiation to 0.8–3.5 seconds after CS onset (the CS was presented at 0–2 seconds of each trial). While previous studies have generally limited SCR initiation to within CS duration, I extended this window due to the short CS length. I did not make use of reinforced (with shock) trials, so detection was not limited by the need to exclude a response induced by the shock itself, rather than the CS. All SCRs were visually inspected to ensure sensible automatic detection and decreases were recorded as zero. Values were square root

transformed to reduce right skew, as previous studies (Morriss, Christakou, et al., 2016; Geller et al., 2017; Lonsdorf et al., 2017). Finally, to facilitate comparison between the 7 unreinforced CS+ trials and 16 CS- trials across acquisition, the number of CS- trials was reduced (trials 2, 4, 6, 8, 9, 11, 12, 14 and 15 discarded).

3.2.4.3 Heart Rate Variability

I wrote a custom Matlab script to calculate RMSSD. One participant was completely removed due to technical failure. Like SCRs, 10-second trials (2-second CS presentation + 8-second minimum inter-stimulus interval) were treated independently. Raw data were filtered with a 5–30 Hz bandpass filter and QRS peaks (the electrical signature of a heartbeat) were identified using a Matlab-based detection package (Pan & Tompkins, 1985). The detection output generated the time in milliseconds between heartbeats detected during the trial, these were squared, summed, averaged, and then square rooted (**Figures 3.6–3.7**). This method has been previously validated (Shaffer & Ginsberg, 2017).

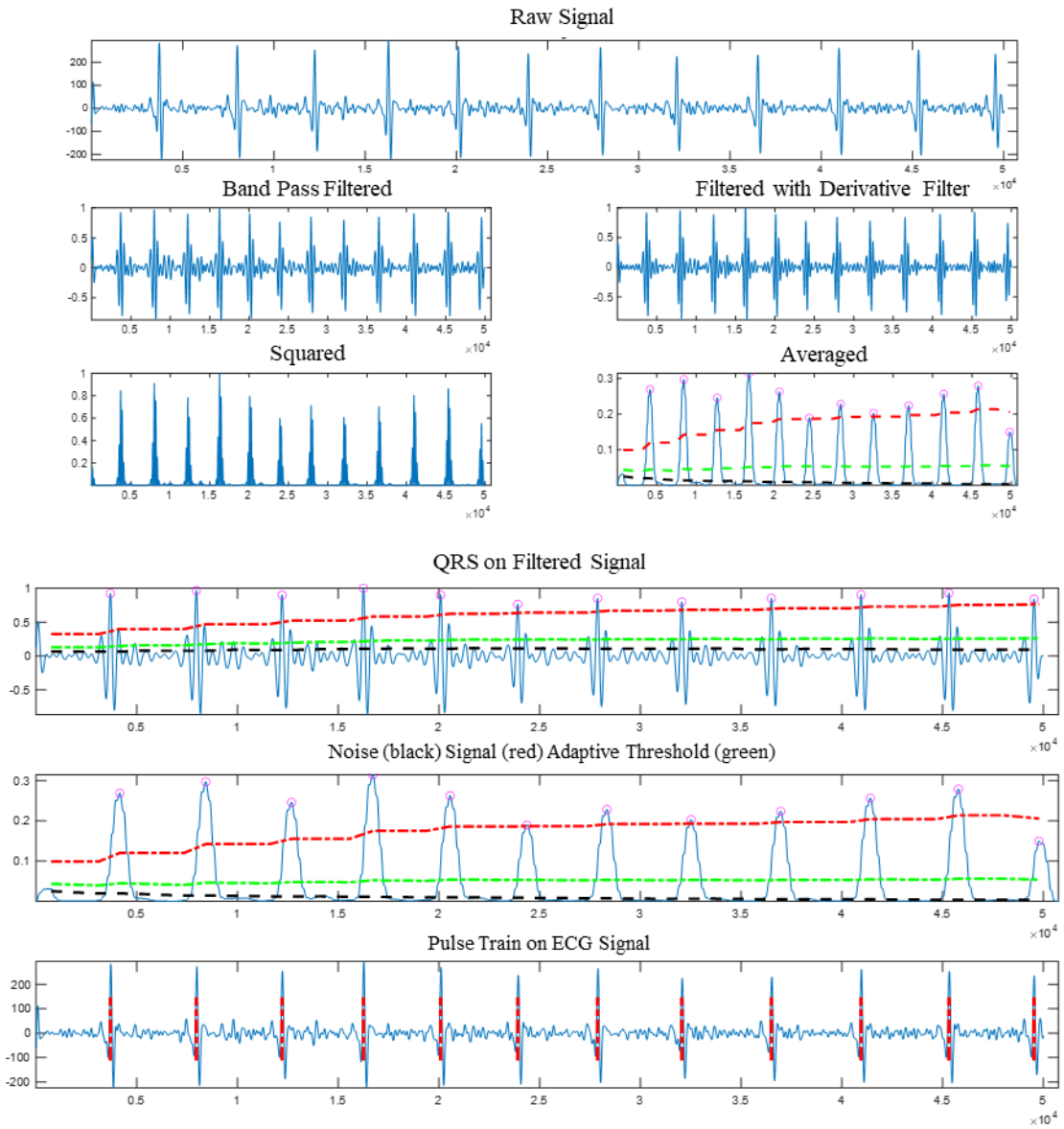


Figure 3.6 QRS Detection Output

Raw data were filtered and squared to determine likely QRS peaks and calculate a moving threshold. Peaks exceeding the threshold (green line) were counted as heartbeats, they did not have to exceed the average signal (red line).

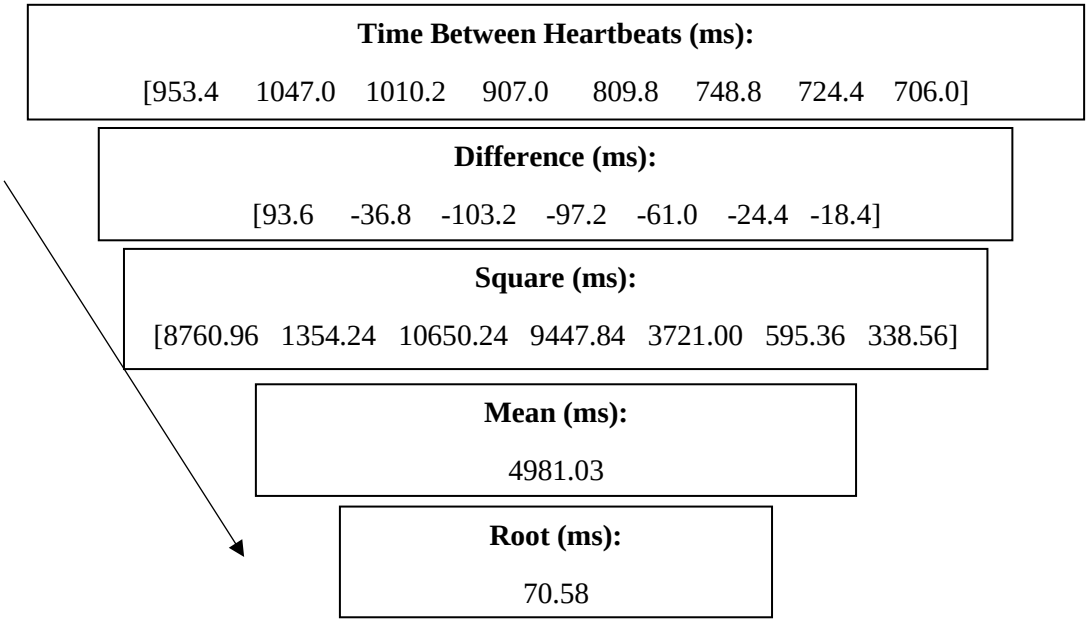


Figure 3.7 RMSSD Calculation

The detection output (time between heartbeats/ms) per trial was transformed into the root mean sum of squared differences. Values shown are from one typical trial.

I removed trials which had a high likelihood of reflecting erroneous values. Firstly, trials with less than eight detected heartbeats in 10 seconds were discarded as likely to contain missing QRS peaks. This eliminated 282/4820 trials (5.85%). Despite this, some remaining values were greater than 2000 ms. RMSSD has previously been reported at a range of 8–108 ms in a time frame of 10-minutes (Pappens et al., 2014). Considering the lack of previous reports on 10-second RMSSD values, I defined outliers as greater than three standard deviations from the mean (mean = 80.37 ms, SD = 130.47). This led to a cut-off of 471.79 ms, a further 56 trials removed (1.16%), and a resultant mean of 69.79 ms (SD = 69.29).

Finally, values were normalised by dividing each trial by the participant mean across all non-shocked trials during acquisition. This was to account for individual differences in RMSSD previously reported according to cardiac fitness and health (Kiviniemi et al., 2017; Habibi et al., 2019), age and gender (Rajkumari et al., 2019; Spina et al., 2019), and cognitive performance (Schaich et al., 2020).

3.2.5 Statistical Analyses

SCR data showed some positive skew despite the square root transformation, particularly for CS- and extinction trials. However, as means and medians were similar, I report the mean and standard error of the mean (SEM). In contrast, subjective shock expectancy ratings showed consistent deviation from normality and so I report the median and interquartile range (IQR). After normalisation by each participant's mean score, heart rate variability data were normally distributed and so I report the mean and SEM.

To indicate differences between CS type at multiple trials across the experiment, I used repeated measures ANOVAs which are robust to deviations of normality. If the assumption of sphericity was violated, I report values calculated with the Greenhouse-Geiser correction. I used linear regression to assess associative relationships. For all analyses, responses to both CS+ and both CS- were averaged.

Statistics were carried out in Matlab 2019b or IBM SPSS 26. An a priori power analysis with G*Power 3.1 (Faul et al., 2007) for linear bivariate regression ($\alpha = .05$, power = .80) indicated that 26 participants were required to detect an effect size of .50 and 82 participants were required to detect an effect size of .30. A post-hoc sensitivity analysis with the 38 participants recruited indicated this sample had 80% power to detect a minimum effect of .42.

3.3 Results

3.3.1 Participant Variables

Self-reported sleepiness/alertness and anxiety remained stable across days and so were unlikely to systematically influence measures of fear conditioning (**Table 3.1**).

Table 3.1 Anxiety and Sleepiness

	Day 1	Day 2		Day 8		Average (all days)
	Mean ± SD	Mean ± SD	t (*df*)	Mean ± SD	t (*df*)	Mean ± SD
State Anxiety	31.95 ± 9.22	31.16 ± 7.22	0.74 (36)	34.94 ± 8.56	0.89 (16)	31.81 ± 7.34
Trait Anxiety	37.82 ± 8.90	37.41 ± 8.22	1.30 (34)	37.76 ± 9.45	0.06 (16)	37.76 ± 8.46
Sleepiness (1–7)	2.45 ± 1.11	2.26 ± 0.98	-0.57 (36)	2.35 ± 0.93	1.58 (16)	2.32 ± 0.79

Paired-samples t-tests. There were no significant differences from day 1 on any measure, all *ps* > .05. Lower sleepiness scores indicate higher alertness.

I also examined the range of shock intensity chosen by each participant. This indicated that six people selected a very low intensity – either to stay at the initial 1.0 mA test shock or only allow a small increase up to 1.5 mA (**Figure 3.8A**). I considered whether this was affected by trait anxiety, finding a significant negative association between shock intensity and trait anxiety, R^2 = .18, F (1,36) = 7.98, *p* = .008, B = -0.10, SE = 0.04, CI = [-0.17, -0.03]. However, this was strongly driven by the six individuals with very low intensities – see **Figure 3.8B** (without them, R^2 = .02, F (1,30) = 0.56, *p* = .459, B = -0.04, SE = 0.01, CI = [-0.14, 0.06]). I also considered whether shock intensity affected learning strength, but there was no significant association with CS discrimination at the last trial of acquisition, R^2 = .05, F (1,35) = 1.69, *p* = .203, B = 0.04, SE = 0.01, CI = [-0.02, 0.10].

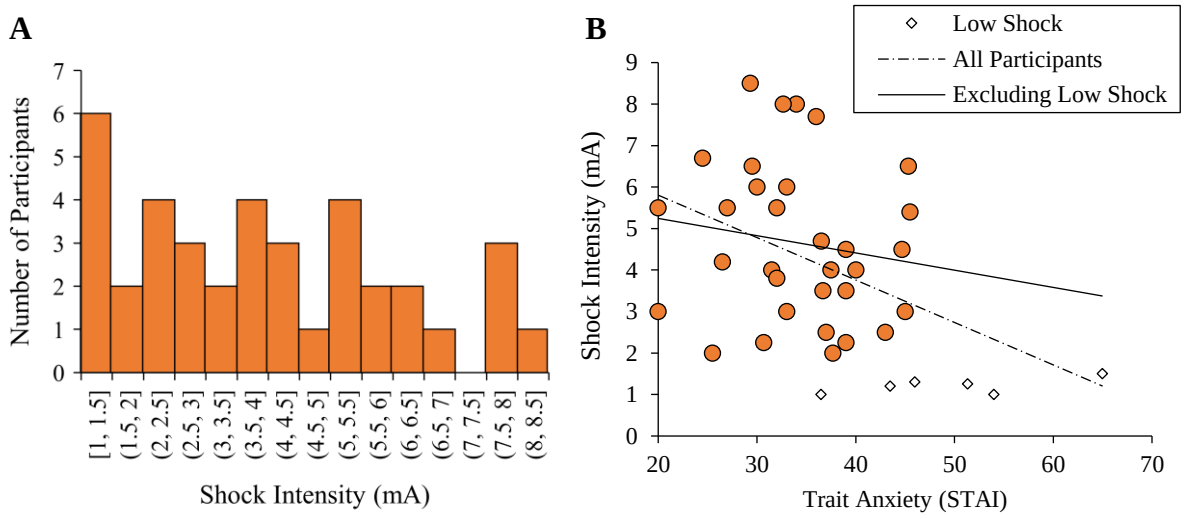


Figure 3.8 Shock Intensity Distribution and Association with Trait Anxiety

Shock intensity distribution showed variation (**A**). Trait anxiety was associated with shock intensity (**B**), but only when including the six participants who chose 1–1.5 mA intensities.

Finally, I investigated the recorded sleep across the sample. Manual sleep scoring of the recorded night via the Dreem Headband indicated a mean time between sleep onset and offset of 7.45 hours (SD = 1.58 hours). Average times spent in each sleep stage (**Table 3.2**) were close to expected levels – as described in the General Introduction (Shrivastava et al., 2014). Since my findings reported in Chapter 2 suggested that participants tend to be asleep (as defined by PSG) for most artefact epochs scored manually in Dreem data, these were included in the calculation of total sleep time.

Table 3.2 Time in Each Sleep Stage

Sleep Stage	Number of Epochs Scored (Mean ± SD)	% Total Sleep Period (Mean ± SD)
N1	21.52 ± 19.43	2.57 ± 2.27
N2	394.63 ± 144.16	44.82 ± 10.98
SWS	179.85 ± 55.57	21.90 ± 8.44
REM	216.15 ± 95.74	23.97 ± 8.54
Artefact	57.52 ± 125.69	6.71 ± 15.24
Wake	23.81 ± 53.11	-

Epochs were 30 seconds. Wake epochs were not included in the calculation of total sleep time.

Sample 2 was tested approximately six months after sample 1. This time difference could have led to changes in the sleep data, for example the headbands used were no longer new. Consequently, I compared algorithmic and manual scoring of both samples to the recordings of Chapter 2 as an indicator of how the data compared to PSG. There were no significant differences in Kappa agreement for manual and algorithmic scoring between sample 1, sample 2, and my Dreem validation study, $F(2) = 1.76$, $p = .185$. This suggests that both samples of these Dreem sleep data, like my Dreem validation data, should be suitable for the summary metrics of time spent in SWS and REM. I present a more in-depth comparison between algorithmic and manual scoring of these data in Appendix E1.

3.3.2 Successful Fear Conditioning and Extinction

Since my conditioning and extinction tasks were novel, I first investigated discriminative learning between CS+ and CS- trials. I compared skin conductance responses (SCRs) and subjective shock expectancy ratings. I was primarily interested in how the difference between CS+ and CS- responses changed across each learning phase, but I also report which trials showed significant differences between stimuli. These were not corrected for multiple comparisons. I also recorded the time taken to make expectancy ratings which generally indicated that participants took longer to rate the CS+ but got faster as trials progressed (shown in Appendix E2).

3.3.2.1 Fear Acquisition on Day 1

On average, participants showed large SCRs to both the CS+ and CS- at the beginning of the acquisition phase on day 1 (**Figure 3.9A**). However, responses gradually diverged across trials as expected. In contrast, shock expectancy ratings showed an immediate divergence between CS+ and CS- (**Figure 3.9B**), although (as described in section 3.2.2.3) the first block of ratings occurred after two trials of each CS, whereas SCRs were recorded alongside CS presentation.

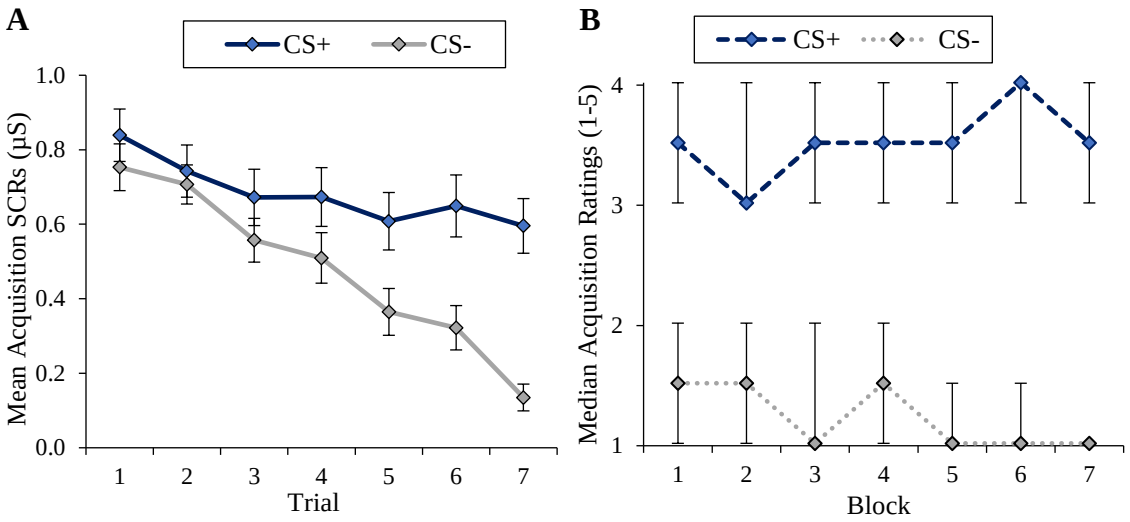


Figure 3.9 Acquisition Training on Day 1

Mean SCRs (n=37) gradually diverged across the learning phase, driven by a steeper decrease in CS- responses (**A**); only the 7/16 trials without shock are illustrated, error bars show ± SEM. In contrast, median ratings (n=38) showed an immediate divergence and a smaller change across the task (**B**), although this was also driven by a decrease in CS- responses. Each block refers to ratings collected after 8 trials (two of each CS, one of each CS+ with shock), error bars show IQR.

A 2 x 7 repeated measures ANOVA comparing CS+ and CS- SCRs across trials indicated a significant CS difference, F (1) = 39.58, $p < .001$, a difference between trials, F (2.94) = 17.03, $p < .001$, and a significant interaction, F (4.33) = 7.38, $p < .001$. This is consistent with successful discriminative learning. Post hoc paired-samples t-tests indicated significant differences between CS+ and CS- in trials 3–7, *ps* <.001–.037.

In shock expectancy ratings, a 2 x 7 repeated measures ANOVA indicated a significant CS difference, F (1) = 250.73, $p < .001$, no difference across blocks, F (3.59) = 0.87, $p = .473$, but a significant interaction, F (2.79) = 5.21, $p = .003$. This suggests an increasing divergence in CS responses across the task, although this is not apparent from the median values. Post hoc paired-samples t-tests indicated significant differences between CS+ and CS- in all trials, all *ps* < .001.

3.3.2.2 Fear Extinction and Reinstatement on Day 2

At the start of fear extinction training on day 2, participants on average showed no immediate CS discrimination in SCR and a decrease in both CS+ and CS- responses across trials (**Figure 3.10A**). Initially, there was a difference in shock expectancy ratings, but this diminished rapidly (**Figure 3.10B**). Likewise, after reinstatement shocks there was no immediate CS

discrimination in SCR (**Figure 3.10C**), but there was a difference in shock expectancy ratings (**Figure 3.10D**). After reinstatement, responses in both measures reduced evenly across subsequent trials.

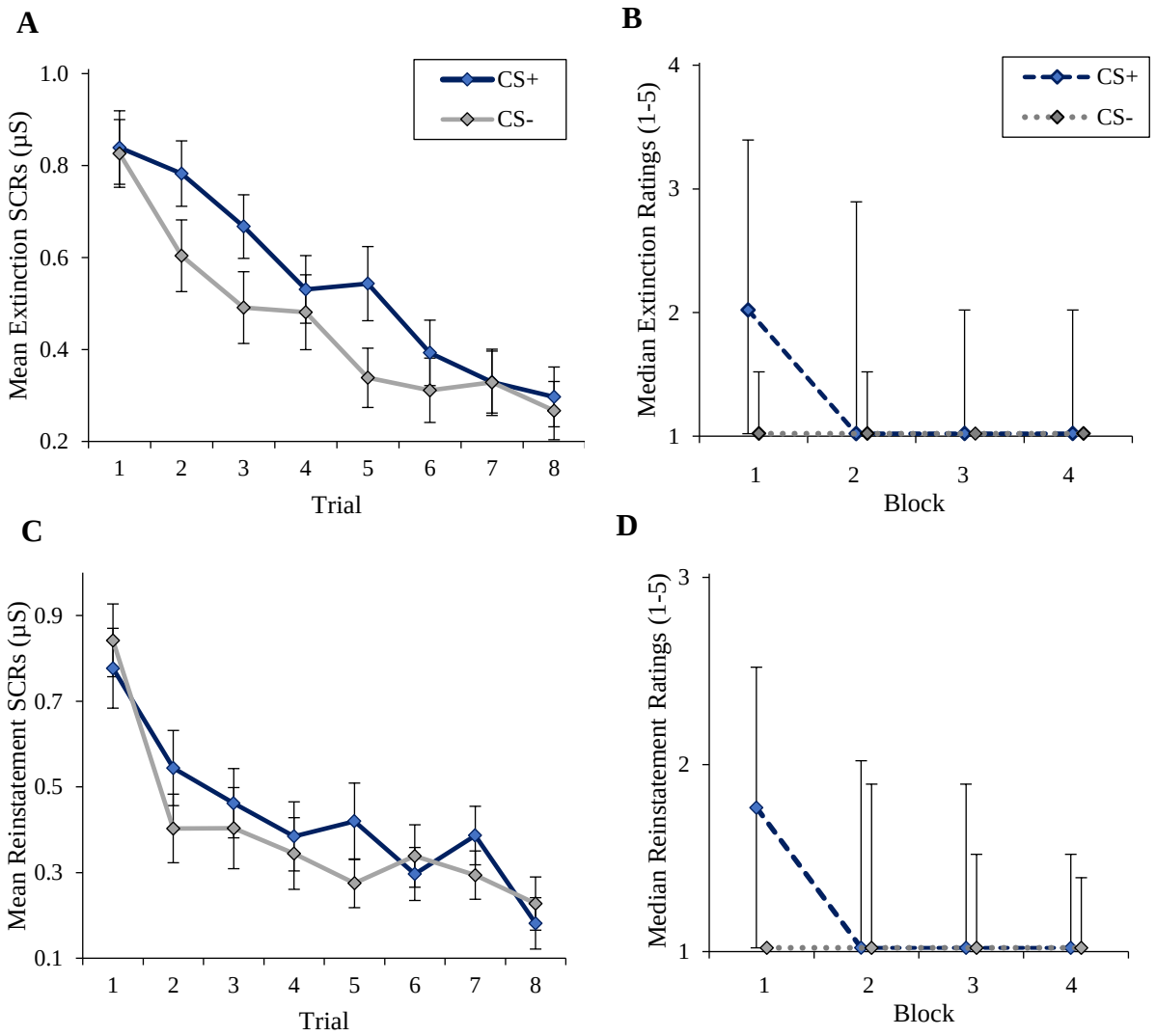


Figure 3.10 Extinction and Reinstatement on Day 2

Mean SCRs (n=37) decreased similarly over extinction although some trials showed a divergence between CS+ and CS- (**A**); in contrast, median ratings (n=38) showed a difference between the CS+ and CS- at the first block and then rapid extinction (**B**). Error bars show ± SEM. After reinstatement, SCRs to both the CS+ and CS- increased but decreased similarly over the following eight trials (**C**); in contrast, ratings showed a small discrimination after one block but then convergence (**D**). Ratings for the CS+ and CS- are slightly offset for better illustration, error bars show IQR.

Across extinction on day 2, a 2 x 8 repeated measures ANOVA comparing CS+ and CS- SCRs across trials indicated a significant CS difference, F (1) = 9.54, $p = .004$, a significant difference between trials, F (3.28) = 28.85, $p < .001$, and approached a significant interaction, F (7) = 1.83, $p = .083$. Post hoc paired-samples t-tests indicated significant differences between the CS+ and CS- in trials 2, 3, and 5, *ps* = .005–.006. Shock expectancy ratings were similar: a 2 x 4 repeated measures ANOVA indicated a significant difference in CS, F (1) = 22.71, $p < .001$, across blocks, F (1.67) = 19.18, $p < .001$, and interaction, F (2.41) = 13.63, $p < .001$. Here, post hoc paired-samples t-tests indicated significant differences between the CS+ and CS- in all trials, *ps* <.001–.019.

Following reinstatement, another 2 x 8 repeated measures ANOVA comparing CS+ and CS- SCRs across trials indicated a significant difference across trials, F (1) = 4.05, $p < .001$, but not between the CS+ and CS-, F (1) = 1.78, $p = .189$, nor a significant interaction, F (4.71) = 1.28, $p = .278$. I therefore did not explore CS differences in each trial. In shock expectancy ratings, a 2 x 4 repeated measures ANOVA indicated a significant CS difference, F (1) = 8.53, $p = .006$, a significant difference across blocks, F (1.56) = 16.91, $p < .001$, but no interaction, F (1.47) = 1.50, $p = .233$. Post hoc paired-samples t-tests indicated significant differences between the CS+ and CS- in all trials, all *ps* <.001.

3.3.2.3 Fear Extinction and Reinstatement on Day 8

Like day 2, participants on average showed large SCRs to both the CS+ and CS- at the beginning of the session. However, there were no differences between the CS+ and CS- across eight trials of extinction (**Figure 3.11A**). Shock expectancy ratings showed no discrimination (**Figure 3.11B**). Following reinstatement, however, (unlike day 2) there was a clear CS+/CS- discrimination immediately after reinstatement in SCRs (**Figure 3.11C**). There was also a small discrimination in shock expectancy (**Figure 3.11D**).

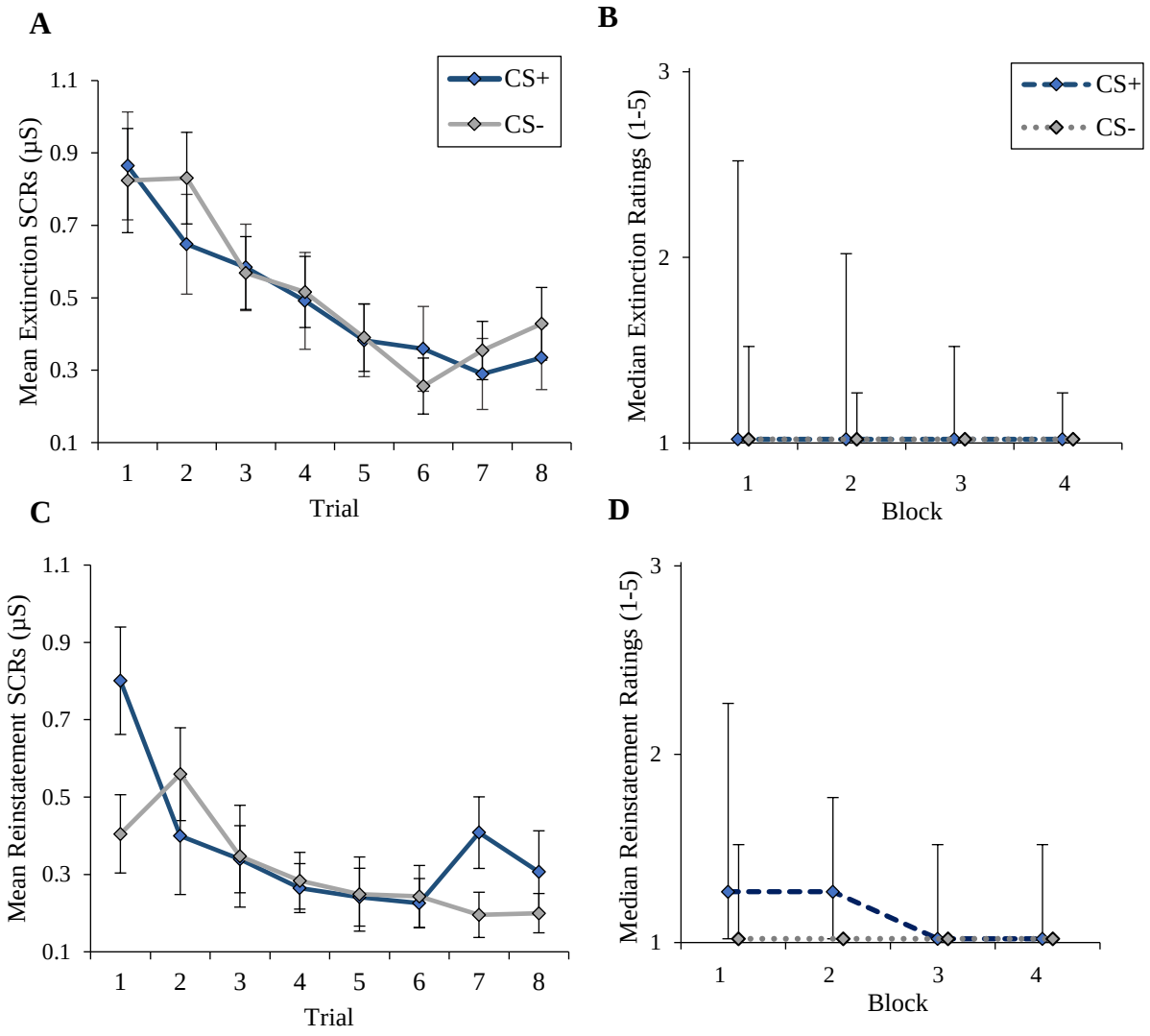


Figure 3.11 Extinction and Reinstatement on Day 8

Mean SCRs (n=17) decreased non-discriminately over extinction (**A**), while median ratings (n=17) were minimal for both CS+ and CS- throughout (**B**). Error bars show ± SEM. After reinstatement, SCRs increased discriminatively to the CS+ after un-signalled shocks (**C**), there was also a small discrimination in ratings (**D**). Ratings for the CS+ and CS- are slightly offset for better illustration, error bars show IQR.

Across extinction on day 8, a 2 x 8 repeated measures ANOVA comparing CS+ and CS- SCRs across trials indicated a significant difference between trials, F (2.98) = 13.23, $p < .001$, but unlike day 2, no significant difference between the CS+ and CS-, F (1) = 0.34, $p = .566$, nor a significant interaction, F (7) = 1.22, $p = .297$. In shock expectancy ratings, a 2 x 4 repeated measures ANOVA indicated a significant CS difference, F (1) = 9.09, $p = .009$, but no difference across blocks, F (1.23) = 3.11, $p = .088$, nor an interaction, F (1.70) = 1.78, $p =$

.192. Post hoc paired-samples t-tests indicated significant differences between the CS+ and CS- in blocks 1–3, *ps* = .014–.028, but not block 4, *p* = .086.

Finally, following reinstatement, another 2 x 8 repeated measures ANOVA comparing CS+ and CS- SCRs across trials indicated a significant difference between trials, F (2.72) = 3.83, *p* = .019, a non-significant difference between the CS+ and CS-, F (1) = 3.21, *p* = .092, and a significant interaction, F (7) = 2.25, *p* = .035. Post hoc paired-samples t-tests indicated a significant difference in trial 1 only, *p* = .042. In shock expectancy ratings, a 2 x 4 repeated measures ANOVA indicated a significant CS difference, F (1) = 7.83, *p* = .014, and a significant difference across blocks, F (1.51) = 3.80, *p* = .048, but no interaction, F (3) = 0.70, *p* = .556. Again, post hoc paired-samples t-tests indicated significant differences between the CS+ and CS- in blocks 1–3, *ps* = .013–.049, but not block 4, *p* = .072.

3.3.2.4 Summary of Task Efficacy and Approach to Hypotheses

I designed this fear conditioning experiment to capture changing responses to CS+ and CS- image/sound pairs across fear acquisition training, extinction learning, and reinstatement. Defining success by my primary dependent variable, SCRs, I found strong evidence of a learned CS discrimination across acquisition trials on day 1, indicating successful associative learning. On day 2, there was no immediate significant maintained discrimination on average, although there was a divergence between CS+ and CS- responses at trials 2, 3 and 5, and CS discrimination decreased as expected over extinction trials. However, reminder shocks did not lead to greater CS+ responses, instead there was an increase to all stimuli. On day 8, there was no maintenance of CS discrimination on average; however, there was a small discriminative reinstatement effect after reminder shocks suggesting that longer-term cued reinstatement was more effective.

I defined overnight consolidation and extinction learning by a single trial, as the results suggested that responses were still changing across the final trials of each phase. For example, the largest gap between the CS+ and CS- during acquisition training on day 1 was in the final trial. Consequently, I defined overnight consolidation as the CS discrimination change between the last trial of acquisition on day 1 and the first trial of extinction on day 2. I defined extinction learning as CS discrimination at the last trial of extinction on day 2 or day 8.

There was no association between reinstatement and sleep: R^2 = .00–.06, *ps* = .104–.993, full results presented in Appendix E3. I explore associations between reinstatement and anxiety in Chapter 4.

Finally, while I found evidence for discriminatory learning on average across this sample, 10/37 participants showed a zero or negative CS discrimination in SCRs at the end of acquisition training. None of these participants showed negative CS discrimination in shock expectancy ratings – greater expectancy rating to the CS- compared to the CS+. This positive discrimination in conscious ratings suggests that they were aware that the shock was paired with the CS+ and not the CS-. Therefore, these participants can be considered to have learned in the declarative sense but for some reason have lacked the implicit physiological learning that is central to fear. This demonstrates the separation between conscious and unconscious learning which may be crucial to our understanding of fear-based pathology.

While it is common to find such 'non-learners' based on SCRs to fear conditioning and they are often excluded (Lonsdorf et al., 2019), this promotes bias as it is unclear if conditioning was wholly unsuccessful. Therefore, I included all participants in the appraisal of my hypotheses but also investigated how the results changed when excluding non-learners. I defined non-learners as participants who showed a CS discrimination of zero or lower at the last trial of acquisition on day 1. This criterion was indicative of an impaired acquisition curve (**Figure 3.12**). Learners and non-learners did not differ in the shock level chosen, p = .545.

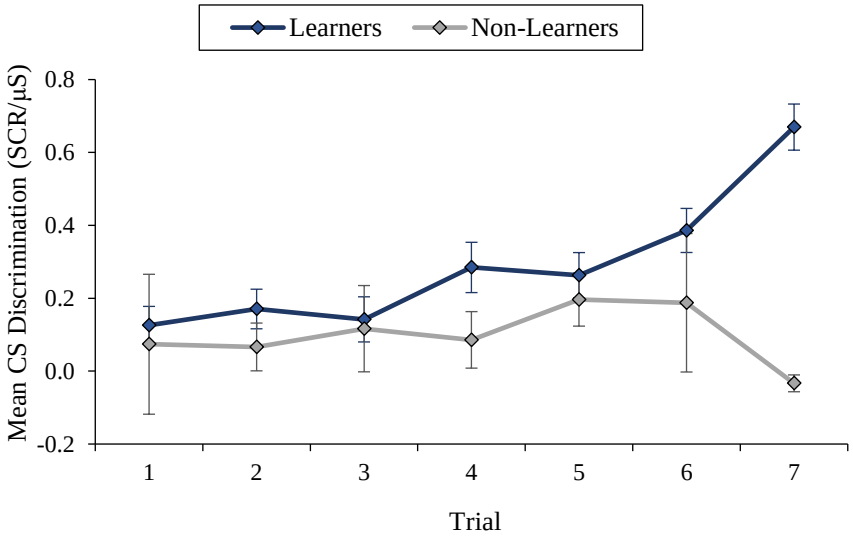


Figure 3.12 CS Discrimination Curve Across Acquisition for Learners and Non-Learners

Non-learners (n=10) showed an impaired CS discrimination curve across the acquisition phase on day 1. The expected increase was seen in the majority of 'learner' participants (n=27). Error bars show ± SEM.

Comparing learners and non-learners, a 2 x 7 factorial ANOVA indicated a significant between-subjects difference in CS discrimination, F (1) = 10.66, p = .002, no significant difference across trials, F (4.24) = 1.99, p = .095, but a significant interaction, F (6) = 3.80, p = .005. This suggests that learners showed greater CS discrimination compared to non-learners, with an increasing difference across trials.

3.3.3 Sleep and Fear Learning

3.3.3.1 Skin Conductance Responses

For these analyses, I tested for associations between REM or SWS and fear conditioned outcomes. Participants who had more REM tended to have more SWS (r = .35, p = .070). However, when adjusting REM and SWS duration as a percentage of total sleep time, REM % and SWS % were not correlated with each other (r = -.10, p = .626), and so were considered as separate predictors in all outcomes. How each analysis changed by excluding non-learners is illustrated in **Table 3.3**.

I first hypothesised that REM duration in a full night of post-conditioning sleep would be associated with greater consolidation of unextinguished fear responses the next day. In contrast, I found that SWS % was significantly associated with greater overnight consolidation (**Figure 3.13A–B**). Secondly, I hypothesised that REM % would be associated with better extinction learning on day 2 and day 8, that is, a diminished CS discrimination towards zero at the final trial. However, I found REM % to be significantly associated with a positive maintained discrimination and SWS % to be unrelated. Conversely, after additional extinction learning on day 8, I found SWS % to be significantly associated with a positive maintained discrimination and REM % to be unrelated (**Figure 3.13C–F**).

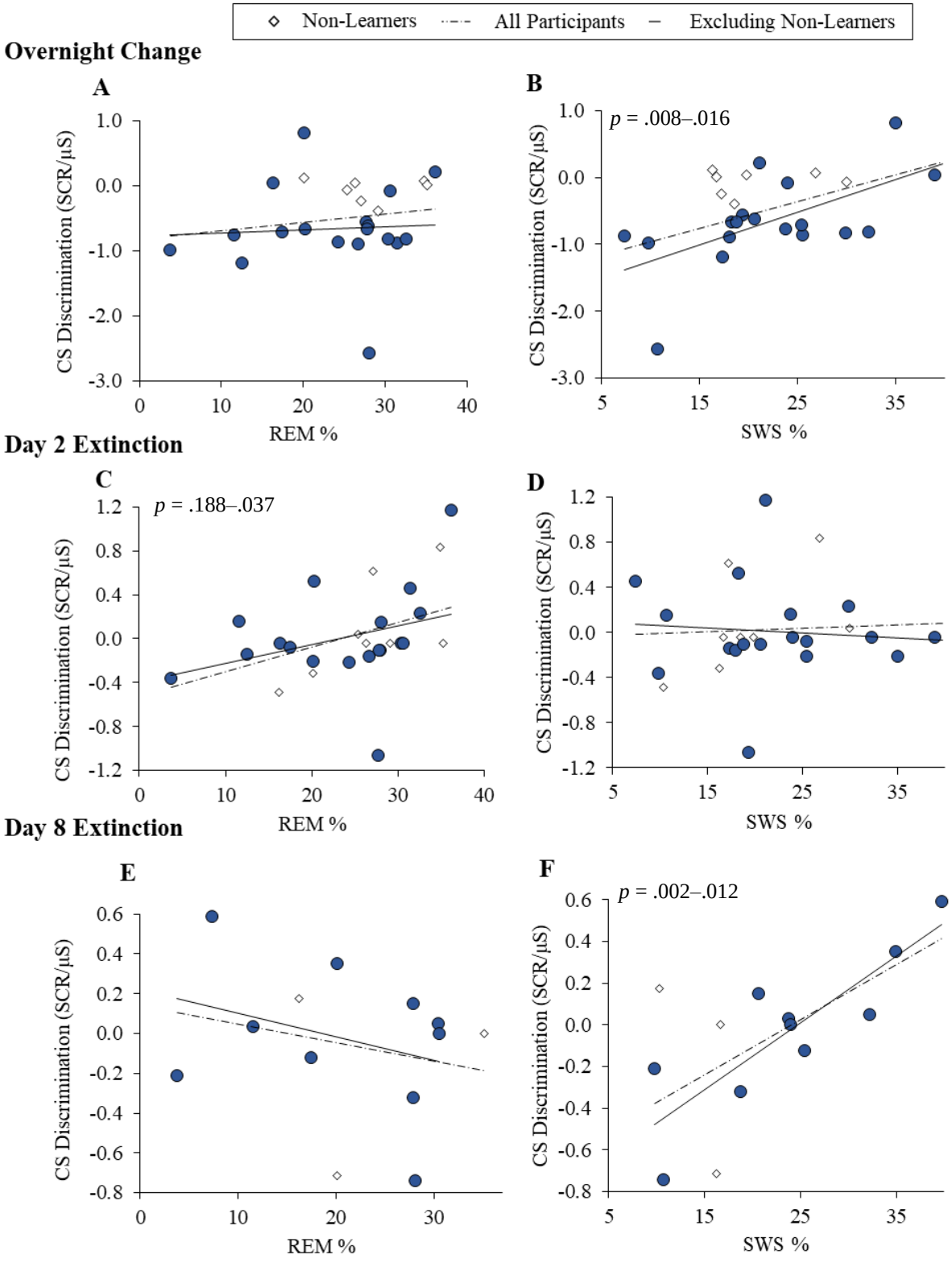


Figure 3.13 Associative Relationships Between Sleep and Overnight/Extinction Learning

REM % was not associated with overnight maintenance of CS discrimination (**A**), but SWS % was positively associated (**B**). On day 2, REM % was positively associated with CS discrimination after extinction learning (**C**), SWS % was not associated (**D**). In contrast on day 8, REM % was not associated with CS discrimination (**E**), but SWS % was positively associated (**F**). Significant *p*-values are shown.

Table 3.3 Associations Between Sleep and Overnight/Extinction Learning: SCRs

		Non-Learners	R^2	F (*df*)	*p*	Unstandardised Coefficients	
						B [SE]	95% CI
Overnight	REM %	Included	.02	0.57 (1,23)	.459	0.01 [0.02]	-0.02, 0.05
		Excluded	.01	0.31 (1,16)	.829	-0.01 [0.02]	-0.04, 0.05
	SWS %	Included	.23	6.77 (1,23)	.016 [a]	0.04 [0.02]	0.01, 0.07
		Excluded	.36	9.04 (1,16)	.008	0.05 [0.01]	0.01, 0.08
Extinction Day 2	REM %	Included	.17	4.86 (1,23)	.037 [b]	0.02 [0.01]	0.00, 0.04
		Excluded	.11	1.89 (1,16)	.188	0.02 [0.01]	-0.01, 0.04
	SWS %	Included	.00	0.07 (1,23)	.796	0.00 [0.01]	-0.02, 0.03
		Excluded	.01	0.11 (1,16)	.744	0.00 [0.01]	-0.03, 0.03
Extinction Day 8	REM %	Included	.06	0.68 (1,11)	.429	-0.01 [0.01]	-0.03, 0.02
		Excluded	.10	0.98 (1,8)	.364	-0.01 [0.01]	-0.04, 0.02
	SWS %	Included	.45	8.97 (1,11)	.012 [c]	0.03 [0.01]	0.01, 0.05
		Excluded	.73	21.45 (1,8)	.002	0.03 [0.01]	0.02, 0.05

[a] This effect was driven by more positive CS+ responses: R^2 = .23, F (1,23) = 6.86, *p* = .015, B = 0.03, SE = 0.01, CI = [0.01,0.05]. There was no significant association for CS- responses, *p* = .409.

[b] This effect was driven by more negative CS- responses: R^2 = .19, F (1,24) = 5.63, *p* = .026, B = -0.02, SE = 0.01, CI = [-0.04, 0.00]. There was no significant association for CS+ responses, *p* = .871.

[c] This effect was not significantly driven by CS+ or CS- responses, *ps* = .496–.532.

Positive associations between SWS % and CS discrimination in overnight maintenance and after extinction on day 8 were strengthened by excluding non-learners. This could suggest that SWS supports consolidation of learned fear responses dependent on the strength of learning. I therefore explored an association between SWS % and the strength of learning before sleep (**Figure 3.14A**). This indicated that CS discrimination at the last trial of acquisition was negatively associated with subsequent SWS %, R^2 = .16, F (1,24) = 4.50, *p* = .044, B = -0.02, SE = 0.01, CI = [-0.04, 0.00]. This was also stronger excluding non-learners, R^2 = .41, F (1,17) = 11.79, *p* = .003, B = -0.03, SE = 0.01, CI = [-0.04, -0.01]. This suggests that the association between SWS and overnight consolidation may be driven by these participants displaying poorer learning and potentially having more ground to make up across sleep.

However, I also found a positive association between SWS % and CS discrimination at the first trial of extinction on day 2 (**Figure 3.14B**), R^2 = .17, F (1,24) = 4.99, *p* = .035, B = 0.02,

SE = 0.01, CI = [0.00, 0.04]. This was similar but weaker when excluding non-learners, R^2 = .16, F (1,16) = 2.99, *p* = .103, B = 0.02, SE = 0.01, CI = [0.00, 0.04]. This in fact suggests that greater SWS % also promotes enhanced CS discrimination after sleep, regardless of learning. Pre-sleep fear discrimination, therefore, does not completely explain the consolidation effect in this sample.

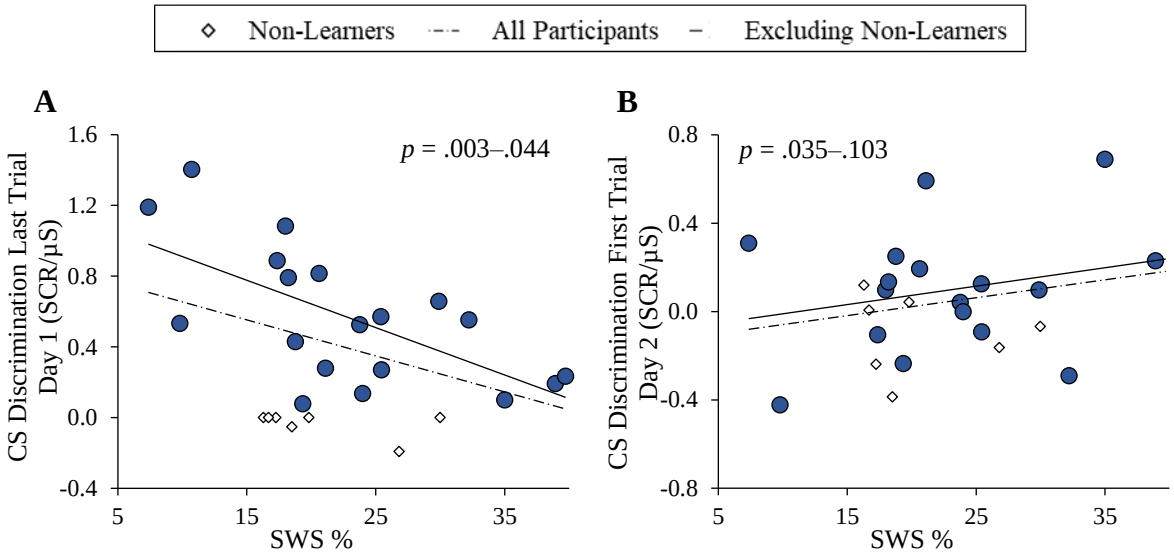


Figure 3.14 Driving Factors Behind SWS and Overnight Change Association

SWS % was negatively associated with CS discrimination at the last trial of acquisition training on day 1, this was stronger when excluding non-learners (**A**). In contrast, SWS % was positively associated with CS discrimination at the first trial of extinction training on day 2, this was weaker when excluding non-learners (**B**).

3.3.3.2 Subjective Shock Expectancy Ratings

In subjective ratings change overnight, the data met the assumptions for linear regression; however, there were no significant associations with REM or SWS % (R^2 = .00 in both cases, *ps* = .851–.913). Given the lack of variation across the sample at the end of extinction, I did not expect to find associations with sleep, which was supported, R^2 = .00–.07, *ps* = .180–.876, I present full results in Appendix E4.

3.3.4 Heart Rate Variability as a Measure of Fear Learning

Finally, I explored HRV as a dependent measure, to investigate associations between SWS % and REM % with overnight changes and extinction learning, as found in SCRs. RMSSD

values were normalised by dividing each trial by the participant's mean (as described in 3.2.4.4). HRV and SCR values were not significantly correlated with one another in overnight CS discrimination change, r = -.11, p = .558, extinction on day 2, r = .00, p = .999, or extinction on day 8, r = -.15, p = .579, suggesting that these metrics reflect dissociable processes.

I found no evidence for HRV as an indicator of discriminatory learning on average across the sample (*ps* = .135–.820, full results in Appendix E5), though HRV as a dependent measure (rather than SCR) was highly exploratory so this is not surprising. Nevertheless, I investigated differences between participants in regard to their sleep. I found a significant negative association between REM % and HRV-measured CS discrimination maintenance overnight, while there was no association with SWS % (**Figure 3.15A–B**). In extinction learning on day 2, HRV-measured CS discrimination at the last trial was not associated with REM %, but there was a negative effect for SWS %. On day 8, neither REM % nor SWS % were associated with HRV-measured extinction learning (**Figure 3.15C–F**). Non-learners were still defined by SCRs; I compare results excluding non-learners in **Table 3.4**.

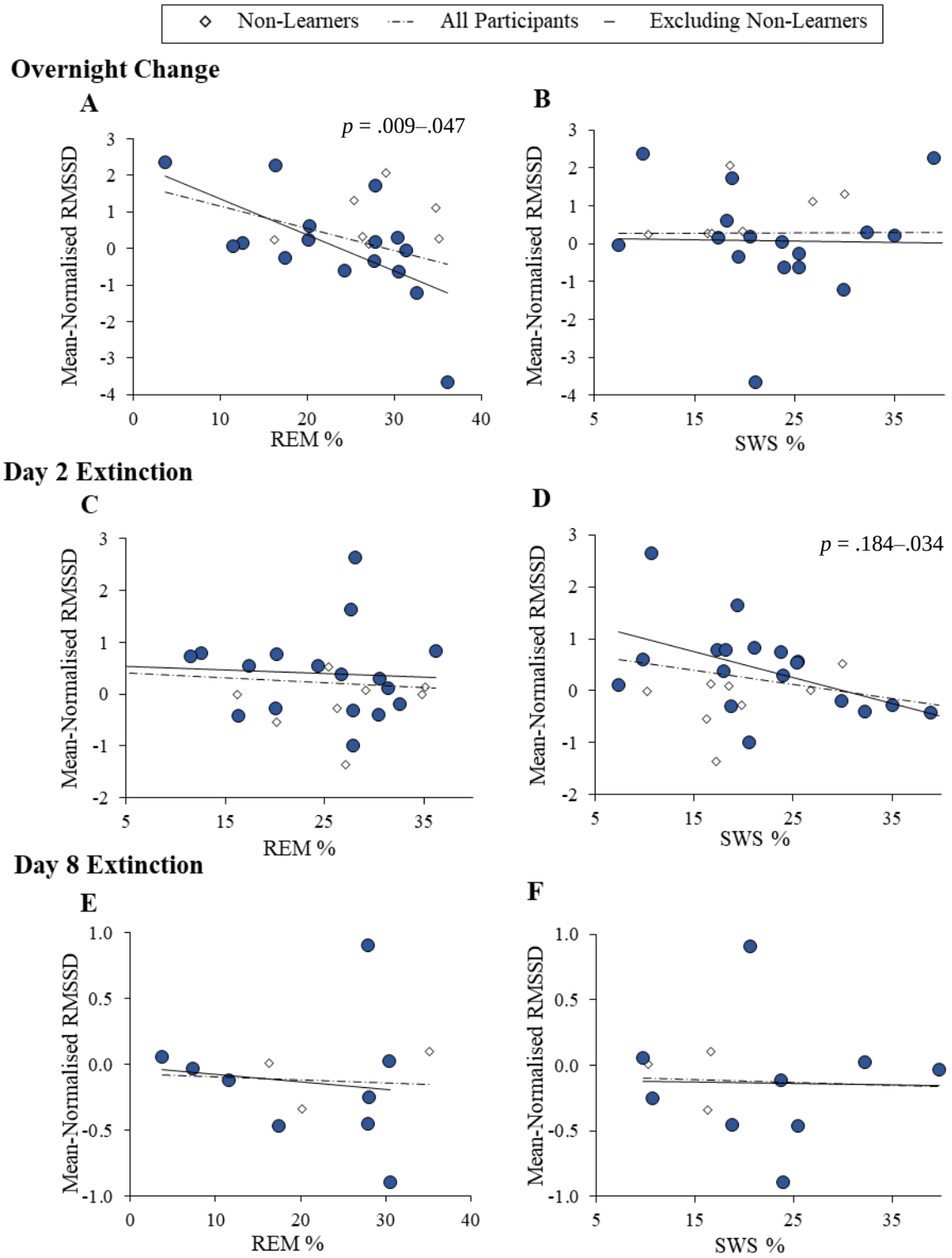


Figure 3.15 Associations Between Sleep and Overnight/Extinction Learning When Measured by HRV

REM % was associated with an overnight reduction in CS discrimination (**A**), while there was no association for SWS % (**B**). In contrast, REM % was not associated with CS discrimination at the last trial of extinction (**C**), but there was a negative effect for SWS % when excluding non-learners (**D**). On

day 8, neither REM % (**E**) nor SWS % (**F**) were associated with extinction learning. Significant *p*-values are shown.

Table 3.4 Associations Between Sleep and Overnight/Extinction Learning: HRV

		Non-Learners	R^2	F (*df*)	*p*	Unstandardised Coefficients	
						B [SE]	95% CI
Overnight	REM %	Included	.17	4.44 (1,22)	.047 [a]	-0.06 [0.03]	-0.12, 0.00
		Excluded	.39	9.05 (1,14)	.009	-0.10 [0.03]	-0.17, -0.03
	SWS %	Included	.00	0.00 (1,22)	.986	0.00 [0.03]	-0.07, 0.07
		Excluded	.00	0.01 (1,14)	.944	0.00 [0.05]	-0.10, 0.09
Extinction Day 2	REM %	Included	.01	0.20 (1,24)	.663	-0.01 [0.02]	-0.05, 0.03
		Excluded	.01	0.07 (1,16)	.793	-0.01 [0.02]	-0.06, 0.05
	SWS %	Included	.07	1.87 (1,24)	.184	-0.03 [0.02]	-0.07, 0.01
		Excluded	.25	5.37 (1,16)	.034	-0.05 [0.02]	-0.10, 0.00
Extinction Day 8	REM %	Included	.00	0.03 (1,10)	.875	0.00 [0.01]	-0.04, 0.03
		Excluded	.02	0.11 (1,7)	.748	-0.01 [0.02]	-0.05, 0.04
	SWS %	Included	.00	0.03 (1,10)	.878	0.00 [0.02]	-0.04, 0.03
		Excluded	.00	0.00 (1,7)	.965	0.00 [0.02]	-0.05, 0.05

[a] This effect was driven by more positive CS- responses: R^2 = .20, F (1,24) = 6.01, *p* = .022, B = 0.07, SE = 0.03, CI = [0.01,0.12]. There was no significant association for CS+ responses, *p* = .875.

Like SCRs and SWS %, the association between overnight change in RMSSD and REM % was reflected in an association between CS discrimination at the final trial of day 1 learning, R^2 = .30, F (1,23) = 9.63, *p* = .005, B = 0.05, SE = 0.02, CI = [0.02, 0.08], and also stronger excluding non-learners, R^2 = .69, F (1,15) = 33.56, *p* < .001, B = 0.08, SE = 0.01, CI = [0.05, 0.11]. There was no significant association between REM % and RMSSD (CS+/CS-) discrimination at the first trial of day 2 (*p* = .468), suggesting the overnight effect was driven by pre-sleep learning.

3.4 Discussion

3.4.1 Summary of Results

In this study I designed a novel fear conditioning protocol. I found evidence for discriminatory learning, suggesting my design was successful in promoting fear to the CS+ over the CS-. I also measured overnight sleep after fear acquisition using sleep wearable technology: the Dreem Headband. I hypothesised that REM sleep would promote greater overnight fear consolidation and extinction learning, although ambiguity in previous literature led me to explore SWS as well. In contrast to my hypotheses, I found that SWS % was associated with greater overnight consolidation and a maintenance of CS discrimination after extinction on day 8, whereas REM % was only associated with extinction on day 2 (**Figure 3.13**).

Across the sample, some participants showed no evidence of learning i.e. SCR discrimination between the CS+ and the CS- at the final trial of acquisition on day 1. Excluding these non-learners strengthened some associations, particularly, between CS discrimination consolidation and SWS. While SWS was associated with CS discrimination at the final trial of acquisition, this was also strengthened by excluding non-learners suggesting that sleep-dependent consolidation may be associated with the strength of initial learning before sleep, but only for participants who showed at least some learning. In alignment with this, excluding non-learners weakened the association between SWS and CS discrimination at the first trial of day 2, suggesting evidence for overnight consolidation in SWS (between day 1 and day 2) above that explained by differences in learning on day 1.

I also investigated how shock expectancy ratings differed from SCRs, finding that shock expectancies were acquired and changed more rapidly. For example, participants learned that CS+ trials were paired with shocks during conditioning and ceased to be paired with shocks during extinction after only one block (two trials of each CS). Ratings after reinstatement on day 2 also suggested that participants consciously understood that this was likely to signal a resurgence of the CS+/shock pairing, even though it was not echoed in greater SCRs. This suggests that autonomic learning lags behind conscious awareness, which may reflect the presentation of fear-related disorders: affected individuals consciously know their feelings are irrational but continue to experience fear, panic, or anxiety regardless (Horwitz & Wakefield, 2012).

Finally, I measured heart rate variability (HRV) as an exploratory metric of fear conditioning. I found no evidence that HRV measures fear learning, yet HRV-measured consolidation and extinction discrimination were associated with post-conditioning REM and SWS % respectively. Surprisingly, these presented the opposite pattern to SCR findings: REM % was

associated with overnight consolidation and SWS % was associated with CS discrimination after extinction on day 2. In view of these parallels, my findings suggest future avenues for investigation into the role of HRV in fear learning and consolidation across sleep.

3.4.2 Implications for Emotional Memory Consolidation

Contrary to my hypothesis, I found that SWS duration was associated with overnight consolidation of fear discrimination. Specifically, this was driven by greater CS+ responses, suggesting that SWS promotes consolidation of learned fear to dangerous stimuli. In keeping with this, SWS was also associated with a maintenance of discrimination after extinction on day 8. This suggests that a high proportion of SWS following conditioning leads to a stronger fear memory which is resistant to extinction. This finding was unexpected, but aligns with prior research such as that supporting the Active Systems Consolidation Theory, which suggests that non-REM sleep promotes a strengthening of memories (Born et al., 2006; Diekelmann & Born, 2010). My findings indicate that participants who had a very low SWS % showed negative discrimination (greater responses to the CS- than the CS+). This suggests that a lack of consolidation after learning could leave participants susceptible to long-term maladaptive responses to safe stimuli.

I did not find that REM supports overnight consolidation of CS maintenance. However, Marshall et al. (2014) previously found that a combination of REM duration, efficiency and latency was together associated with a greater consolidation of fear recall after post-conditioning sleep. This is equivalent to the first trial of extinction in my study. Meanwhile, Wassing et al. (2019) found that fragmented REM was associated with disrupted emotional consolidation. It is not clear whether my finding that REM did not support emotional consolidation was due to my focus on REM duration, when this evidence suggests that the quality of REM is also important. Although, these studies used startle response and amygdala activity to define fear responses, so the differences could also be due to my choice of dependent measure. I confined my sleep analyses to sleep stage duration because Dreem is relatively unproven. However, some of these additional analyses are likely to be possible with further exploration.

I also hypothesised that REM would promote better extinction learning, i.e. CS discrimination towards zero. Instead, I found that REM was related to greater CS discrimination; however, this was driven by smaller responses to the CS-. This suggests that REM was associated with extinction learning, but specifically to the safe stimuli. In short, REM may support adaptive extinction learning but not necessarily reduced CS discrimination. Previously, a lack of REM

has been associated with a generalisation of fear (Menz et al., 2013, 2016; Spoormaker et al., 2010). Although my finding was not as expected, this result still aligns with the previous literature, since participants who had a low proportion of REM sleep after conditioning tended to have greater fear responses to the CS-. Fear responses to a CS- experienced in the same context are generally interpreted as reflecting a generalisation of fear (Baker et al., 2019; Dibbets et al., 2015; Kull et al., 2012).

3.4.3 Causal Effects Between Sleep and Fear Learning?

I found both REM and SWS to significantly relate to several fear conditioned outcomes; however, the data do not confirm the causality of these relationships. Sleep has been strongly linked to memory consolidation, as discussed in Chapter 1. Therefore, my results are likely to suggest that sleep-dependent consolidation affected subsequent fear responses. However, since I did not measure baseline sleep, it is possible that fear conditioning itself affected sleep, which in turn affected consolidation. There is some literature – albeit from rodent studies – which suggests that fear conditioning changes subsequent sleep architecture.

For example, fear conditioning in mice (n=8, all male, 3–4 months old) led to a decrease in the number of REM episodes, average REM duration, and increased REM latency (Sanford et al., 2001). These results were replicated in a subsequent study (n=14, all male, 7–9 weeks old), while further evidence suggested that the effects extended to 4–5 days post-conditioning and varied in strength according to mouse strain (Sanford et al., 2003). This suggests that fear conditioning effects on sleep are not confined to the immediate sleep after conditioning and may also have a high dependence on individual differences.

In another study to support these findings, rats (total n=21, all male, 2 months old) were conditioned to associate an auditory tone with a footshock; fear was tested with presentation of the tone after 24 hours and two weeks (DaSilva et al., 2011). Stress-sensitive Wistar-Kyoto rats, but not control Wistar rats, showed a 27% increase in REM sleep from baseline immediately following the conditioning procedure. REM microarchitecture also changed, with significantly more sequential REM episodes. After two weeks, the amount of REM had decreased to baseline levels, but there were still significantly more sequential REM episodes i.e. fragmented REM. There were no sleep changes in control animals that received the same shocks unpaired with the tone, which suggests that fear learning and not simply a stressful experience can induce REM changes. The stress-sensitive rats did not exhibit normal extinction even at day 14, suggesting that the lingering effects of conditioning on REM sleep could lead to a long-term continuation of fear.

There is also evidence for non-REM changes following conditioning. Mice (total n=43, all male, 3–6 months old) exposed to fear conditioning exhibited a greater time spent in subsequent non-REM sleep (Hellman & Abel, 2007). There was also an increase in delta power (a marker of deep non-REM sleep) and a decrease in theta power (a marker of REM sleep). This study found no evidence of REM changes and the previous studies discussed found no evidence of non-REM changes; however, this study had a far greater sample size (12–16 subjects per group) and so the results may be more robust. Alternatively, differences in methodology (timing, stimuli, species strain) may account for these discrepancies. For all of these rodent results, it is unclear how females respond because of the unilateral use of males.

Few human studies have explicitly reported a focus on whether fear conditioning affects subsequent sleep, although including a baseline night controls for this. For example, Marshall et al. (2014), as discussed in section 3.1, recorded sleep before and after conditioning. There was no change in any sleep measure, including time spent in each sleep stage, REM efficiency or REM latency. This suggests that fear conditioning in people does not affect subsequent sleep, unlike previous rodent studies. However, it is likely that fear conditioning is a more salient experience for an animal. When people agree to take part in a psychological experiment, they are aware that no real harm can come to them which probably dampens the fearfulness of the experience.

In summary, while fear conditioning may affect subsequent sleep in (male) rodents, there is no evidence to my knowledge that these effects translate to people. Furthermore, all my participants underwent fear conditioning, and so even if this experience caused changes in sleep architecture, this would not necessarily counter my findings regarding SWS % and fear consolidation, or REM % and extinction. This would depend specifically on whether the level of learning affected sleep stage duration. Therefore, while my SWS results could be interpreted as better fear learning leading to more SWS %, previous studies of memory consolidation and sleep (Diekelmann & Born, 2010), suggest that my results are more likely to reflect sleep-dependent memory consolidation. In other words, differences between participants' sleep contributed to changes in post-sleep fear responses. With more resources, my design could be adapted to include baseline sleep before conditioning and explicitly test for this possibility. However, there is not necessarily a causal effect: people who tend to have more SWS may also tend to have better overnight consolidation and maintenance of CS discrimination due to other factors that I did not measure.

3.4.4 The Exclusion of Non-Learners

As reported in a recent systematic literature search, a quarter of recent fear conditioning studies excluded participants if they showed a zero or negative SCR discrimination by the end of the acquisition phase (Lonsdorf et al., 2019). In my study, 10 out of 37 participants failed to show discriminative fear learning on the basis of SCRs at the last trial. Given that non-learners are a common occurrence in fear conditioning studies, I investigated the impact of their exclusion.

Non-learners are not a trivial issue. If participants do not show learning, it could be argued that subsequent changes in discrimination are meaningless. If this were the case, their results would add unnecessary noise to the data, reducing the power of the study to detect real effects. In my study, a lack of learning was not just evident at the last trial, I show in **Figure 3.12** that the last trial criterion was sensitive to an impaired learning curve across acquisition training. Elsewhere, participants who fail to show discriminative SCR fear learning have been previously found to exhibit hypoactivation of fear and inhibitory regions (amygdala, anterior cingulate cortex, insula) in the brain (Marin et al., 2020). This suggests that people who do not show significant fear conditioning (as measured by SCRs) may process these stimuli differently. On the other hand, in my study, shock expectancy ratings showed that non-learner participants were consciously aware of CS+/CS- attributions. It is possible, therefore, that they would show an improvement after sleep. Alternatively, confounding factors in the measurement of skin conductance may have affected their data (e.g. skin differences, susceptibility to temperature), and so when other measures of fear are also utilised it may not be necessary to wholly exclude them. Given these conflicting aspects, more evidence as to the effects of non-learners is of clear value to the fear conditioning literature.

I found that SWS-driven associations were strengthened by excluding non-learners, despite the reduced sample size. There was a particularly large effect in the association between sleep and strength of learning, increasing the proportion of explained variance from 16% to 41%. This suggests that non-learners add considerable noise to some data. However, the association between REM and CS- responses at extinction on day 2 was weakened (to non-significance) by excluding non-learners. This could suggest these participants show expected responses in extinction. Defining non-learners by SCRs also affected associations measured by HRV. Excluding non-learners strengthened associations between REM % and overnight consolidation from 17% to 39%, between REM % and learning strength from 30% to 69%, and between SWS % and extinction learning on day 2 from 7% to 25%. This suggests that SCR learning interacts with HRV responses to a considerable degree.

On balance, these findings suggest that non-learners add noise to SWS-driven analyses, but some outcomes after further learning (e.g. extinction) may be similar to other participants. However, I did not explore interaction effects. In a larger sample, it would be prudent to investigate the effect size and statistical significance of this observation by comparing non-learners and learners across outcomes.

3.4.5 Heart Rate Variability as a Marker of Fear Learning

HRV has gained momentum in recent years as a marker for physical and mental resilience, especially emotion regulation. Specifically, high beat-to-beat variability reflects faster adaptive responses to a changing environment through the autonomic nervous system (for a review, see Shaffer & Ginsberg, 2017). HRV could therefore provide a complementary measure to SCR in the study of the conditioned fear response: while SCRs reflect mainly sympathetic activity, HRV reflects autonomic (sympathetic/parasympathetic) balance, and RMSSD specifically reflects mainly parasympathetic components. However, I found no evidence that RMSSD values indicated fear to the CS+ compared to the CS-.

Previously, resting HRV (rather than trial-by-trial) has been linked to fear conditioning. In healthy participants (n=57, 10 male, aged 18–30 years), higher 10-minute resting RMSSD was associated with better extinction of the startle response to an unpleasant period of breathlessness (achieved via breathing apparatus) and safety learning to a period without breathlessness (Pappens et al., 2014). RMSSD was not related to SCRs. In addition, when healthy participants (n=114, 56 female, aged 18–33 years), underwent fear conditioning with geometric shapes and an unpleasant shock, higher 5-minute resting RMSSD was associated with better extinction, again in startle response but not SCRs (Wendt et al., 2015). These results suggest that startle response-measured extinction learning is related to resting HRV. However, my investigation into 10-second RMSSD trials was without precedent.

Nevertheless, I did find that HRV measured in this way for overnight consolidation and extinction was significantly associated with sleep. Interestingly, the separation between REM and SWS was reflected in a divergence between SCRs and HRV. While in SCRs, SWS % was associated with overnight consolidation and REM % was associated with extinction, I found in HRV that REM % was significantly associated with overnight consolidation and SWS % was significantly associated with extinction. These results suggest that the parasympathetic components measured by RMSSD and sympathetic components measured by SCRs could relate to the roles of REM and SWS % in the consolidation of fear and extinction learning respectively. It cannot be ruled out that unknown factors drove these converging associations,

but further investigation in future studies may clarify the connection between HRV and SCR in fear conditioned responses that vary according to sleep.

3.4.6 Strengths and Limitations

Strong evidence of discriminatory acquisition learning across the sample on day 1 suggests that my development of a novel fear conditioning task was successful in promoting acquired fear responses to specific stimuli. It could be argued that the uncommon use of both images and sounds for my conditioned stimuli affected the results, for example, increased the number of non-learners. However, since real-life fearful experiences are multimodal, the results may have a higher real-world application. In addition, the use of sounds means this design has the potential for sleep-dependent reactivation, providing a precedent for future TMR studies.

Use of the Dreem Headband allowed me to test a larger sample than would have been practical using the standard approach, PSG. It also extends my previous Dreem validation study (Chapter 2), adding evidence for the value of wearables in sleep science. I found in Chapter 2 that the Dreem Headband was suitable to estimate time spent in SWS and REM when manually scored, providing a justification for its use in my investigation of emotional memory. In further support of Dreem's accuracy, I found close to the expected average levels of each sleep stage: 5% in N1, 50% in N2, 20% in SWS and 25% in REM (Shrivastava et al., 2014). In addition, agreement between manual and algorithmic scoring of Dreem did not significantly differ from that in Chapter 2. While not necessarily indicative of how the results would compare to PSG, this suggests that Dreem performed consistently across both samples and is therefore likely to be similarly suitable for the estimation of sleep stages.

I did not allow for an adaptation night wearing the Dreem Headband. Given time and resource constraints, I chose to prioritise sample size over this potential advantage. Sleep data loss was mainly due to technical issues which I encountered sporadically throughout the experiment, so adaptation nights would not have alleviated this issue. I also minimised the risk of participants struggling with the headband as far as possible by limiting my sample to young, healthy people who reported their ability to sleep as good or excellent, and subsequently only one participant removed the headband in the night. Nevertheless, Dreem sleep data were lost for 11/38 recordings. Normally, a consumer would synchronise their headband to an app on their mobile phone where the data would be uploaded to Dreem. Using multiple headbands across many participants, I sought advice from Dreem, but had to re-synchronise each headband to one app many times which may have caused technical issues. Although summary statistics always presented Dreem's algorithmic scoring, some nights failed to

upload correctly and the raw data for manual scoring were not available. This meant that the second round of data collection had only 13 participants. These results should therefore be interpreted with caution, as low sample sizes can lead to reduced generalisability and a greater rate of false discovery.

Finally, I did not investigate hormonal effects as a confounding factor. Menstrual cycle has been reported to affect discriminative fear conditioning and extinction, primarily based on cycling oestrogen (Hwang et al., 2015; Kobayashi et al., 2020). Consequently, the use of hormonal contraceptives may affect discriminative fear learning (Lonsdorf et al., 2015). While I collected data on early versus late menstrual cycle for eligible participants, I did not record use of hormonal contraceptives in sample 1 (n=18). Since 70% of eligible participants (n=10) in sample 2 reported using hormonal contraceptives, it is unlikely there would have been sufficient statistical power to assess differences between hormonal contraceptive users and early or late cycle phases in the remaining people, but I did not have the data to explore this.

3.4.7 Conclusions and Future Directions

In this chapter I present a novel fear conditioning design. This allowed a comprehensive investigation into how fear responses change over various learning phases across one week. I also utilised the Dreem Headband to increase my sample size and demonstrate how a sleep study can make use of this evolving technology.

My results provide further evidence towards understanding the relationship between sleep and fear learning. I found that the proportion of time dedicated to SWS within the post-conditioning night supported overnight consolidation and a week-long maintenance of CS discrimination. In contrast, time spent in REM during the same night promoted lower responses to the safe CS- after extinction learning the next day. In more exploratory analyses, I also found evidence that HRV calculated on a trial-by-trial basis did not define fear learning, yet when taken as the measure of consolidation and extinction it was significantly associated with REM and SWS respectively – the opposite pattern to SCRs.

Together, these results suggest different but perhaps complementary roles of REM and SWS % for the consolidation of fear discrimination and extinction learning respectively. This could be specific to unextinguished responses and so previous studies which extinguish before sleep may have missed these divergent roles. Since extinction is unlikely to occur before a night's sleep after a traumatic event, unextinguished responses as measured in my study could better reflect real-world fearful events.

In further research, longer-term associations between post-conditioning sleep and CS discrimination should be replicated with a greater sample size, while HRV should be further investigated in relation to fear conditioned responses. This fear conditioning design also provides a basis for the investigation of targeted memory reactivation, while my results suggest this should be explored during both REM and SWS. Finally, these results should be extended with an exploration of spectral analyses and event detection. I present an investigation of these factors in Chapter 4.

Chapter 4

Exploring Sleep Neurophysiology with the Dreem Headband: From Validation to Fear Consolidation

In this chapter I present further analyses of my sleep EEG data recorded by the Dreem Headband. Moving beyond the sleep stage duration metrics of previous chapters, I explored slow oscillations, spindles, and their interactions using spectral analysis, event detection, and phase-amplitude coupling. I first investigated whether Dreem was suitable for these analyses by extending my validation against PSG (Chapter 2). I used these results to inform further analyses of my fear conditioning experiment (Chapter 3), investigating whether my findings relating SWS duration to overnight fear consolidation were reflected in these more precise quantifications of non-REM sleep. I found mixed results across spectral power, but there were indications Dreem was suitable for event detection. Consequently, detected slow oscillation events were significantly associated with overnight fear consolidation. This extends both my validation of the Dreem Headband and evidence for the association between SWS and fear memory consolidation.

4.1 Introduction

In Chapter 2, I found that manual scoring of Dreem raw data provided sufficient (> 80%) agreement with PSG-recorded sleep of the same night, providing evidence for Dreem as suitable for the estimation of SWS and REM duration. I also found 78% agreement in N2, so

Dreem may be suitable for all non-REM sleep, though I confined my fear conditioning analyses to SWS. As reported in Chapter 3, I used the Dreem Headband to record participants' overnight sleep at home, finding that SWS percentage during the night following fear acquisition was significantly associated with a greater maintenance (less reduction) of CS discrimination overnight. I interpreted this as sleep-dependent fear consolidation. Consolidation was also evident after one week, where the same post-conditioning SWS % was associated with greater CS discrimination on day 8.

I initially focussed on sleep stage duration because this metric has often been associated with emotional memory (Tucker & Fishbein, 2009; Lau et al., 2010; Diekelmann et al., 2012). Sleep staging was also the focus of the previous Dreem validation (Arnal et al., 2020), so there was a greater precedent for such analyses. However, further to my results in Chapter 2, relating behavioural measures to hallmark physiological features of the EEG signal extends these analyses towards underlying neural mechanisms. Such analyses are commonly based on the EEG features of non-REM sleep: slow oscillations (SOs) and spindles. Considering that my previous results support the potential utility of Dreem data in sleep science, a logical next step is to explore how far these analyses can be taken. In addition, my fear conditioning results regarding SWS duration would be strengthened – and related more directly to neural activity – by complementary findings in spectral power and event detection.

In this chapter I explore SOs and spindles in my Dreem-recorded non-REM sleep data. First, I quantify how Dreem performs against PSG in the measurement of SO and spindle activity using my validation data (Chapter 2), I then use these analyses to strengthen my evidence towards non-REM sleep and emotional memory consolidation (Chapter 3).

4.1.1 Oscillatory Activity in Non-REM Sleep and Memory Consolidation

4.1.1.1 Slow Oscillations and Sleep Spindles

The Active Systems Consolidation Theory suggests that phase locking between cortical slow oscillations, thalamic sleep spindles, and hippocampal sharp wave ripples during non-REM sleep promotes key mechanisms supporting sleep-dependent memory consolidation, as discussed in Chapter 1 (Diekelmann & Born, 2010; Born & Wilhelm, 2012), see **Figure 4.1**. Because these events are required to score N2 and SWS, time spent in non-REM sleep will reflect these events. However, a higher-resolution quantification of SOs and spindles (and ripples, primarily in rodent data) provides more specific evidence for their roles in memory consolidation, informing potential mechanisms relying on coordinated network activity.

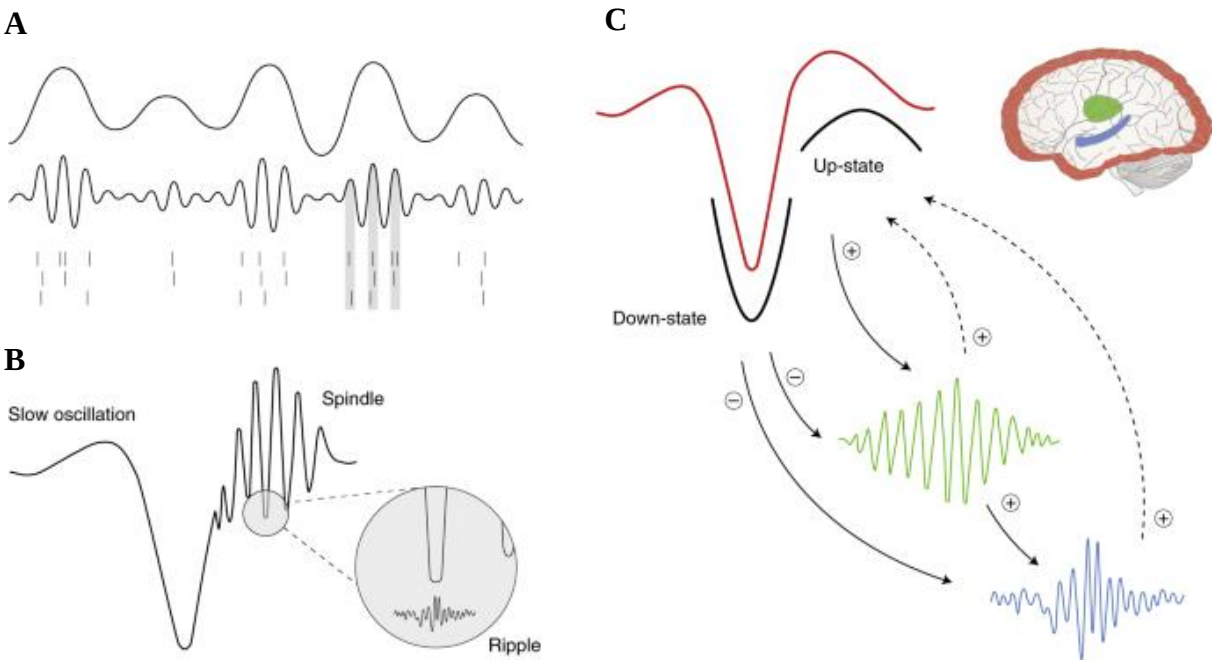


Figure 4.1 Systems Memory Consolidation During Sleep

There is a co-occurrence between cortical low frequencies, sub-cortical higher frequencies, and local network neuronal firing (**A**); systems consolidation relies on such coordination between slow oscillations, spindles, and ripples (**B**); brain regions involved are the cortex (red), thalamus (green), and hippocampus (blue) respectively (**C**). Image taken from Klinzing et al. (2019).

In one previous study to demonstrate the utility of these more specific analyses, when participants with schizophrenia, their first-degree relatives, and a control group (n=47, 20 female, mean age 30 years) had overnight sleep recorded with PSG after an auditory learning task, there were no differences in N2 or SWS duration. However, schizophrenia patients showed reduced fast spindle density (the average number of detected spindle events per epoch), which in turn was related to poorer post-sleep recall (Schilling et al., 2017). This also occurred to a lesser extent in first-degree relatives of the patients, compared to the control group. This suggests that sleep spindles relate more strongly to some types of memory consolidation than non-REM duration, they may also be indicative of genetically influenced memory consolidation.

In an example of healthy participants (n=25, all male, mean age 33 years) after overnight PSG-recorded sleep, slow oscillation amplitude during SWS predicted working memory performance in an n-back task for participants who had improved overnight, while there was

no effect of N2 or SWS duration (Ferrarelli et al., 2019). This suggests that SO power supports the consolidation of task performance (rather than memory of the content), and again sleep stage duration may not be the most sensitive measure of the relationship between non-REM sleep and memory.

In support of this, boosting slow oscillations – which increases SO power but not always SWS duration – causally leads to better declarative memory consolidation in various tasks (Marshall et al., 2006; Ngo et al., 2013; Garcia-Molina et al., 2018). Meanwhile, further evidence suggests that SO activity reflects enhanced limbic-thalamic-cortical coordination and the alignment of reactivated memory ensembles encoding task-relevant information (Fernandez & Lüthi, 2019; Jiang et al., 2017, 2019; Manoach & Stickgold, 2019; Wei et al., 2018).

SOs and spindles have been investigated less often in relation to emotional memory, but there is mounting evidence for their contributions. For example, in a daytime nap study, participants (n=57, 29 female, mean age 21 years) completed an encoding task where they viewed negative or neutral object images (Payne et al., 2015). They were then assigned to either a nap group or two wake control groups to account for differences in time of day, and all participants spent four hours in structured activities before memory was tested. The results indicated that recognition memory was better in the nap group for negative objects. However, SWS duration was correlated with both emotional and neutral object memory, while spectral power in the delta 1–4 Hz frequency was associated only with emotional object recognition. In contrast, there were no associations between memory performance and REM sleep. This suggests that SWS promotes memory consolidation in general while delta power specifically supports preferential emotional memory, evident even after a daytime nap.

In a subsequent study, spindle activity during SWS was associated with emotional memory (Alger et al., 2018). Young (18–39 years) or middle-aged (40–64 years) participants (n=80, 52 female) encoded negative or neutral objects on a neutral background. Participants were then either kept awake, had a 90-minute nap, or a delayed 90-minute nap. During testing four hours later, negative objects were remembered better but only after an immediate nap. In young adults, SWS was positively associated with negative recall, as were slow oscillation 0.5–1 Hz and delta 1–4 Hz power as well as spindle density, amplitude, and power (11–15 Hz). In contrast, the older group had less SWS, and spectral associations showed less significant effects. These measures were all derived from C3, C4, F3, and F4, to confirm that they were not driven by one electrode site. However, this study defined sleep spindles between 11–15 Hz, which omits many slow spindles at 9–12 Hz (Cox et al., 2017; Mölle et al., 2011). Overall, these results suggest that not only time in SWS, but slow oscillation and (mainly fast) spindle

spectral dynamics promote emotional consolidation. This may, however, depend on a young sample and sleep occurring shortly after encoding.

There is also evidence from conditioning models for associations between non-REM EEG features and fear learning. In one study, rats (n=28, all male, 8–10 weeks old) were exposed to the single prolonged stress procedure, a model of PTSD. After this stress, increased REM sleep and reduced spindle (10–15 Hz) power during 'transition to REM' sleep were associated with greater freezing behaviour during fear extinction training one week later (Vanderheyden et al., 2015). In another conditioning study, rats (n=4, all male, 12 weeks old) learned the location of an aversive air puff while running along a track (Girardeau et al., 2017). Reactivation patterns (coordinated firing between the hippocampus and amygdala) that were present during encoding peaked with hippocampal sharp wave ripples during post learning non-REM sleep. This was stronger for runs with the air puff (CS+) compared to safe (CS-) runs. Finally, in mice (n=6, all male, 3–5 months old), optogenetic suppression of hippocampal ripples impaired contextual fear conditioned memory the day after acquisition learning (Wang et al., 2015). Together, these studies provide consistent evidence that slow oscillations, spindles, and sharp wave ripples support emotional memory consolidation.

4.1.1.2 Slow Oscillation-Spindle Coupling

In addition to SO, spindle, and ripple events during non-REM sleep, recent evidence suggests, as proposed in the Active Systems Theory, that the strength of coupling between these events also predicts memory consolidation. This has generally been limited to SOs and spindles, which are more accessible to study via human EEG. For example, participants (n=28, 14 female, mean age 22 years) were tested with a verbal memory task after PSG-recorded sleep (Niknazar et al., 2015). In a repeated measures design, participants were administered zolpidem (to increase GABA-A receptor-mediated signalling), sodium oxybate (to increase GABA-B receptor-mediated signalling), or a placebo, before sleep. The results indicated that spindle and SO power were correlated with memory performance across groups. After zolpidem particularly, more spindles occurred in the slow oscillation transition from the down-to up-state which was associated with better verbal memory. This concurs with previous findings, where spindles at this specific phase have been associated with better memory (Mölle et al., 2011).

Similar findings have also been reported in a rodent model. Optogenetically stimulated thalamic spindles in mice (n=25, all male, 11–14 weeks old) caused an increase in coupling between SOs, spindles, and ripple events as well as an increase in memory performance, but

again only if stimulation occurred in phase with a slow oscillation up-state (Latchoumane et al., 2017). Meanwhile, suppression of thalamic spindles impaired memory performance. Together, these studies suggest a causal link between SO-spindle-ripple coupling and memory consolidation.

Despite these findings, like event detection, SO-spindle coupling remains underexplored in relation to emotional memory. In one recent study, the first to my knowledge to report this, coupling unexpectedly predicted poorer emotional memory. Participants (n=65, 34 female, mean age 22 years) underwent the Trier Social Stress Task which provokes social stress by asking participants to perform a 5-minute speech and mental arithmetic in front of judges (Denis et al., 2021). Comparison against a control task without judges (the social stress) was sufficient to elicit significantly greater cortisol in the stress group. Participants then completed an emotional image task where they viewed 300 International Affective Picture System images and were asked whether they would approach the situation in real life to promote deep encoding. Finally, participants had PSG-recorded sleep overnight before a surprise memory test the next morning.

The results indicated better recognition memory for negative and positive images compared to neutral, while time spent in SWS was associated with better memory for all image types, but only in the stress group. Further investigation indicated that this effect was driven by high cortisol responders. Greater coupling between frontal SOs and central spindles was then negatively associated with recognition memory for emotional (positive and negative) images, again in the stress group only. These results suggest that SWS is associated with better memory, but SO-spindle coupling is associated with poorer emotional memory after stress. Therefore, stressful encoding potentially leads to greater coupling as a compensatory mechanism, but this requires replication. Stress has been consistently reported to affect the relationship between sleep and learning due to the interaction between stress hormones and subsequent noradrenaline release during encoding (Kim & Payne, 2020; Payne & Kensinger, 2018). However, this is not often considered in human fear conditioning which represents a relatively low stress event. Overall, evidence for SO-spindle coupling in emotional memory consolidation is thus somewhat limited.

4.1.1.3 Summary

There is good evidence for the mechanistic roles of sleep-dependent memory consolidation that form the basis of the Active Systems Theory: cortical slow oscillations, thalamic sleep spindles, and hippocampal sharp wave ripples, as well as coupling between these events.

Though the Active Systems Theory does not explicitly make predictions concerning emotional memory, there is also evidence that emotional memory is supported by these same mechanisms during non-REM sleep. This concurs with my findings in Chapter 3, where SWS duration was significantly associated with fear consolidation. However, slow oscillations and spindles should be explored in relation to human fear conditioned responses.

4.1.2 Aims

In Chapter 3, I found that SWS duration was associated with overnight fear consolidation, while previous literature suggests that the EEG hallmarks of SWS – slow oscillations and spindles – also relate to emotional memory consolidation. Consequently, I aimed to explore whether spectral power, event detection, and phase-amplitude coupling of slow oscillations and spindles were also associated with overnight consolidation of the human fear conditioned response. I also investigated N2 sleep since it shares the same oscillatory hallmarks as SWS.

However, while the Dreem Headband may be suitable to estimate sleep stage duration, it is not analogous to PSG. Based on my previous findings in Chapter 2, the EEG signal is noisier, more prone to artefacts, and has limited coverage. There is also little precedent for such analyses in Dreem Headband (or similar) data. Given this, I expected oscillatory analyses to present challenges. I therefore first compared the matched PSG and Dreem sleep data (Chapter 2), using this to inform my approach to the fear conditioning data.

These analyses are largely exploratory and so I did not make explicit hypotheses. I aimed to quantify slow oscillations and spindles in regard to power spectra, event detection, and phase-amplitude coupling, ultimately providing further evidence for the utility of the Dreem Headband, as well as a greater understanding towards non-REM sleep events and emotional memory consolidation.

4.2 Methods

In this chapter I present further analyses of the data previously presented in Chapters 2 and 3. I therefore only briefly reiterate details of the sample and previous data processing.

4.2.1 Samples

For my validation data, 10 healthy participants (8 female, aged 20–37 years, mean = 25) had overnight sleep in a laboratory environment. This was measured by simultaneous PSG and a Dreem Headband over two consecutive nights. Four recordings were missing and one was discarded for loss of signal, so the final sample consisted of 15 Dreem and 15 PSG recordings of matched overnight sleep. While some of these nights are from the same participants, I collapsed across night in Chapter 2 after finding no significant differences between night 1 and night 2. Likewise, I treat all nights independently in these analyses.

For my fear conditioning data, 38 healthy participants (28 female, aged 19–30 years, mean = 23) underwent fear conditioning on day 1 and fear extinction/reinstatement on day 2, 18 returned for an additional test of extinction and reinstatement on day 8. All participants took a Dreem Headband home after fear conditioning on day 1 to record overnight sleep. Sleep data were lost for 11 nights, leaving a final sample of 27 Dreem recordings.

4.2.2 Data Processing

4.2.2.1 Prior Data Processing

For the validation data (Chapter 2), an ambulatory PSG system recorded six EEG channels F3, F4, C3, C4, O1, and O2 at 256 Hz. After recording, these were bandpass filtered at 0.3–35 Hz and re-referenced from Cz to the linked mastoids (M1, M2). I scored these data according to AASM guidelines.

For both datasets (Chapters 2 and 3), the Dreem Headband recorded five EEG channels Fpz, F7, F8, O1, and O2 at 250 Hz, referenced to each other (Fpz-O1, Fpz-O2, Fpz-F7, F8-F7, F7-O1, F8-O2, Fpz-F8), and bandpass filtered at 0.4–18 Hz. A 3D accelerometer measured movement, position, and breathing, while a red-infrared pulse oximeter measured heart rate (Arnal et al., 2020). I did not use the pulse oximeter, but I resampled the accelerometer from 50 to 250 Hz to match the EEG channels and utilised this measure of breathing frequency to aid sleep stage classification. With this addition, I also scored these data according to AASM guidelines.

4.2.2.2 Subsequent Data Processing

For this chapter, I retrieved and concatenated all 30-second epochs of EEG scored as either N2 or SWS for each recording. Because my focus was slow oscillations and spindles which are most clearly seen in frontal and central regions, I limited my analyses of PSG to the frontal (F3, F4) and central (C3, C4) channels. For Dreem, I compared all frontal-occipital channels as the closest approximation to PSG: 'CH1 Fpz-O1', 'CH2 Fpz-O2', 'CH5 F7-O1', and 'CH6 F8-O2'. I maintained a separation between N2 and SWS.

Although some epochs (where the majority of the EEG signal was disrupted) were scored as artefacts during sleep scoring, these SO and spindle analyses required a cleaner signal and thus a more stringent selection process. Therefore, I reviewed every epoch of N2 and SWS across the selected channels, removing those still containing artefacts (**Figure 4.2**). I employed visual artefact rejection using the Fieldtrip toolbox (Oostenveld et al., 2010), since it was unclear how automatic rejection would apply to Dreem data. Initially, I rejected whole channels containing a large number of corrupt trials, then trials (30-second epochs) were assessed individually.

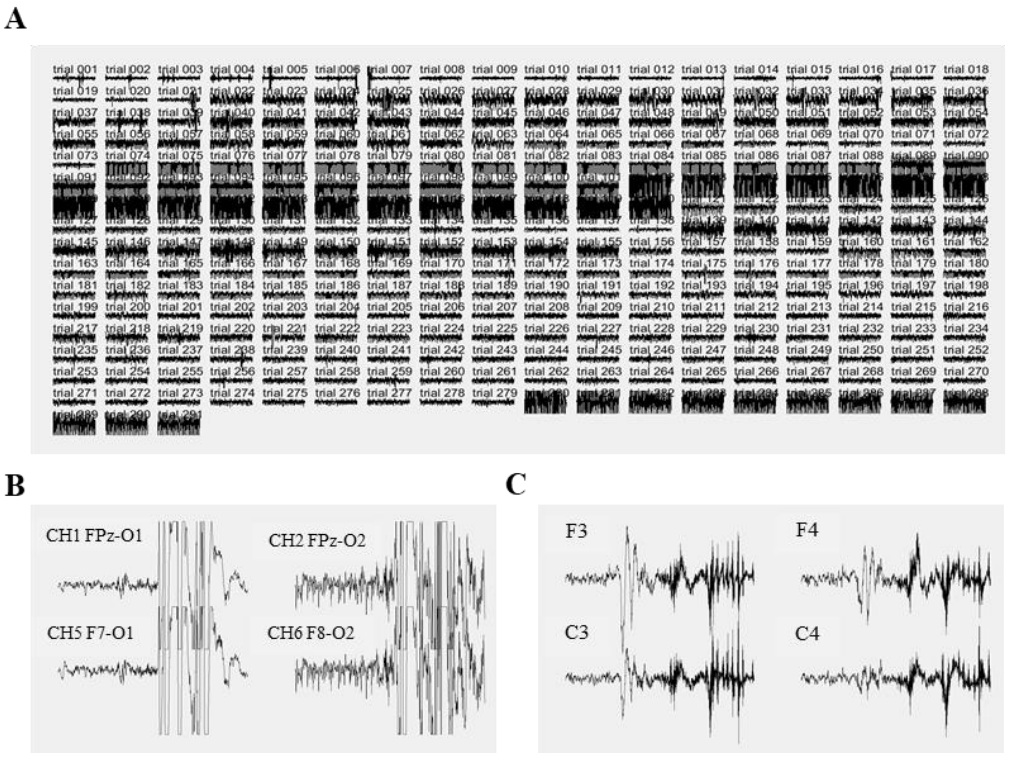


Figure 4.2 Example Rejected Channel and Trials

First, channels with a large number of corrupted trials were rejected, this only occurred in Dreem recordings (**A**). Remaining individual trials were then reviewed. Those containing artefacts were rejected; for example, Dreem (**B**) and PSG (**C**).

4.2.3 Data Analyses

I defined slow and fast spindle frequencies at 9–12 Hz and 12–15 Hz respectively (Cox et al., 2017; Mölle et al., 2011). For slow oscillations, the AASM defines 0.5–2 Hz (Parrino et al., 2009), but slow oscillations modulating spindles have been previously defined at < 1 Hz (Mölle et al., 2011), or 0.5–1.5 Hz (Cox et al., 2012). Since Dreem filters out frequencies below 0.4 Hz, I followed the latter 0.5–1.5 Hz slow oscillation definition.

I calculated power spectra using the Chronux toolbox (Bokil et al., 2010). Frequencies between 0.5 and 20 Hz were analysed using a Fast Fourier Transform based spectral analysis with 0.5 Hz resolution and a 10-second multi-taper window: (resolution*window*2) - 1 = 9 tapers. This analysis separates distinct frequencies within a complex signal and plots the relative magnitudes. I used the $\log_{10}$ decibel (dB) scale to illustrate power across frequencies.

I employed an automatic algorithm for spindle and slow oscillation event detection (Navarrete, 2017). This algorithm detects spindles at 9-16 Hz over a 0.5–2 second duration and single oscillations at 0.3–2 Hz, based on Silber et al. (2007); it does not distinguish slow and fast spindles. Detection occurs only in N2 and SWS scored epochs, and an adaptive noise-signal threshold is used based on the EEG data of each recording. This software illustrates detected events plotted onto the EEG signal input (shown in Appendix F).

Phase-amplitude coupling describes a form of covariance between oscillations of different frequencies when the phase of a slower (modulating) oscillation is consistently associated with the amplitude of a faster (modulated) signal (Jensen & Colgin, 2007). I calculated phase-amplitude coupling (PAC) using MATLAB code which was previously developed in the lab (Onslow et al., 2011; Onslow, 2012). I used the modulation index calculation method which has been suggested for short epochs and noisy data (Onslow et al., 2011; Hülsemann et al., 2019), with a phase and amplitude frequency resolution of 0.5 Hz. This code shuffles the data 50 times to determine statistically significant PAC values, so only those where $p < .05$ are retained.

I used paired-samples t-tests to test for differences between PSG and Dreem, and linear regression with 95% confidence intervals to test for associations between PSG and Dreem. Statistics were carried out in Matlab 2019b and IBM SPSS 26.

4.3 Results

I first compared PSG and Dreem for the analysis of slow oscillations (SOs) and spindles using the validation data presented in Chapter 2. I then investigated these metrics in the post-conditioning Dreem data of Chapter 3.

4.3.1 Dreem Validation Data

I investigated artefact rejection within Dreem and PSG. Two Dreem recordings were discarded because all frontal-occipital channels were corrupted. I compared the remaining recordings (n=13) matched for the same sleep as recorded by PSG and Dreem, finding significantly greater channel and trial rejection in Dreem across both N2 and SWS (**Table 4.1**). This was driven by high removal of CH2 and CH6 (**Table 4.2**), suggesting these sites may have been particularly vulnerable to movement or disruption by simultaneous PSG.

Table 4.1 Average Rejected Channels and Trials per Recording for Dreem and PSG

		Mean ± SD			
		Dreem	PSG	t (*12*)	*p*
Channels (max = 4)	N2	1.92 ± 0.64	0 ± 0	-10.82	< .001
	SWS	1.62 ± 0.96	0 ± 0	-6.06	< .001
Trials	N2	119.62 ± 86.73	44.08 ± 46.50	3.03	.011
	SWS	32.08 ± 18.97	5.15 ± 2.41	4.90	< .001

Paired-samples t-tests. Mean total number of trials for N2/SWS: PSG (391/194), Dreem (380/202).

Table 4.2 Dreem Channels Retained

	CH1 Fpz-O1	CH2 Fpz-O2	CH5 F7-O1	CH6 F8-O2
N2	12	1	13	1
SWS	12	3	13	3

Maximum retention = 13.

I then investigated power between the selected channels. First, I show a previous study of high-density EEG to demonstrate a clear spectral distinction between frontal and central electrodes in slow and fast spindle frequency peak (**Figure 4.3**).

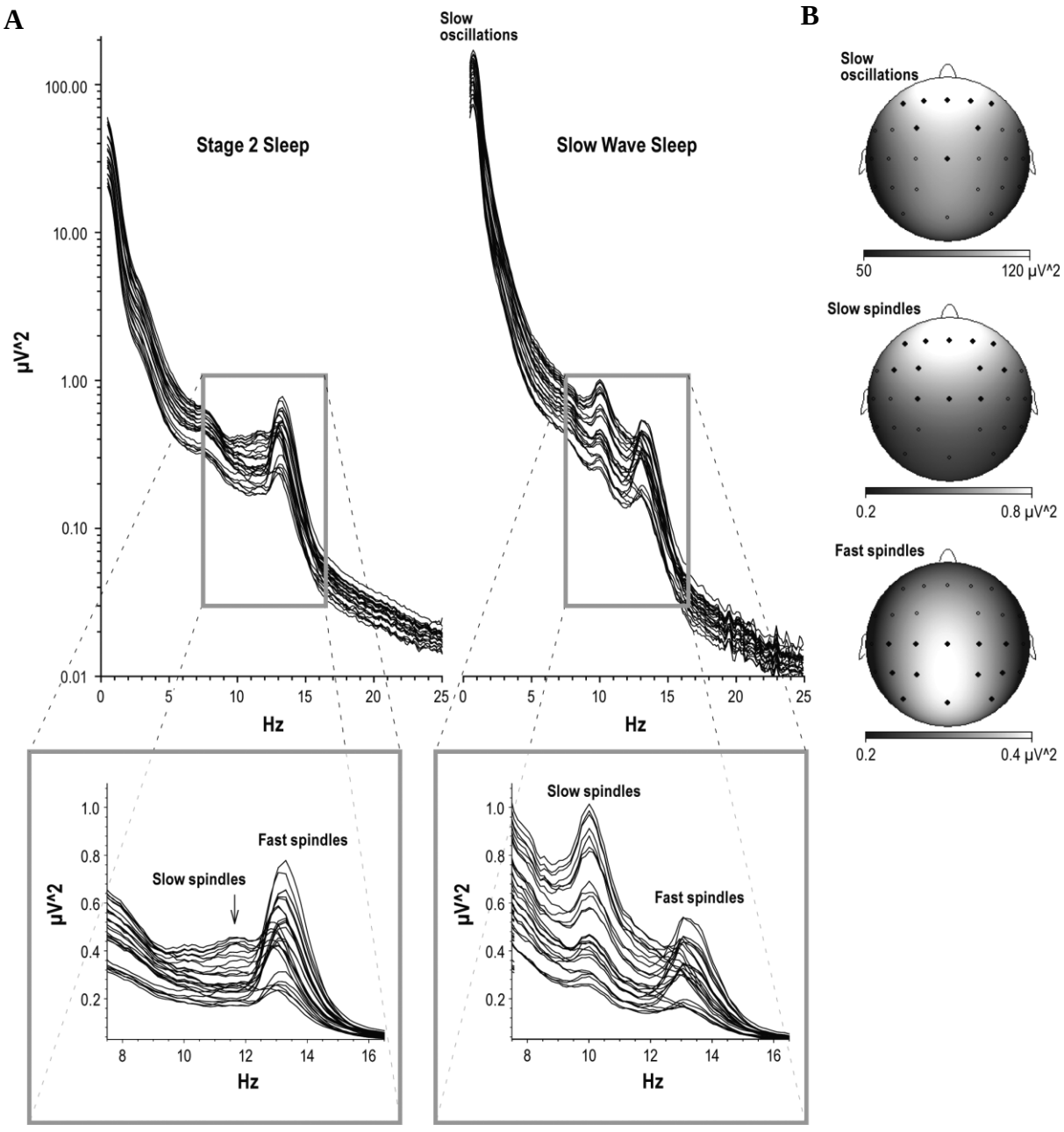


Figure 4.3 Example Power Spectra Showing Fast and Slow Spindles

Example of high density EEG data showing fast and slow spindle power (Mölle et al., 2011). There tends to be greater power in slower frequencies, but there is a distinct spindle peak in both the slow and fast spindle frequency range in SWS (**A**). Slow oscillations and slow spindles are strongest in frontal electrodes, while fast spindles are strongest in central electrodes (**B**).

In my data, I was interested in SO (0.5–1.5 Hz), slow spindle (9–12 Hz), and fast spindle (12–15 Hz) power. Average spectral peaks in the slow oscillation band of around 0.85 Hz indicated that this range was suitable for PSG and Dreem. PSG also showed a spindle peak at 9–14 Hz for frontal channels and 14 Hz for central channels, although Dreem power was greater across all frequencies with no clearly discernible spindle peak (**Figure 4.4**).

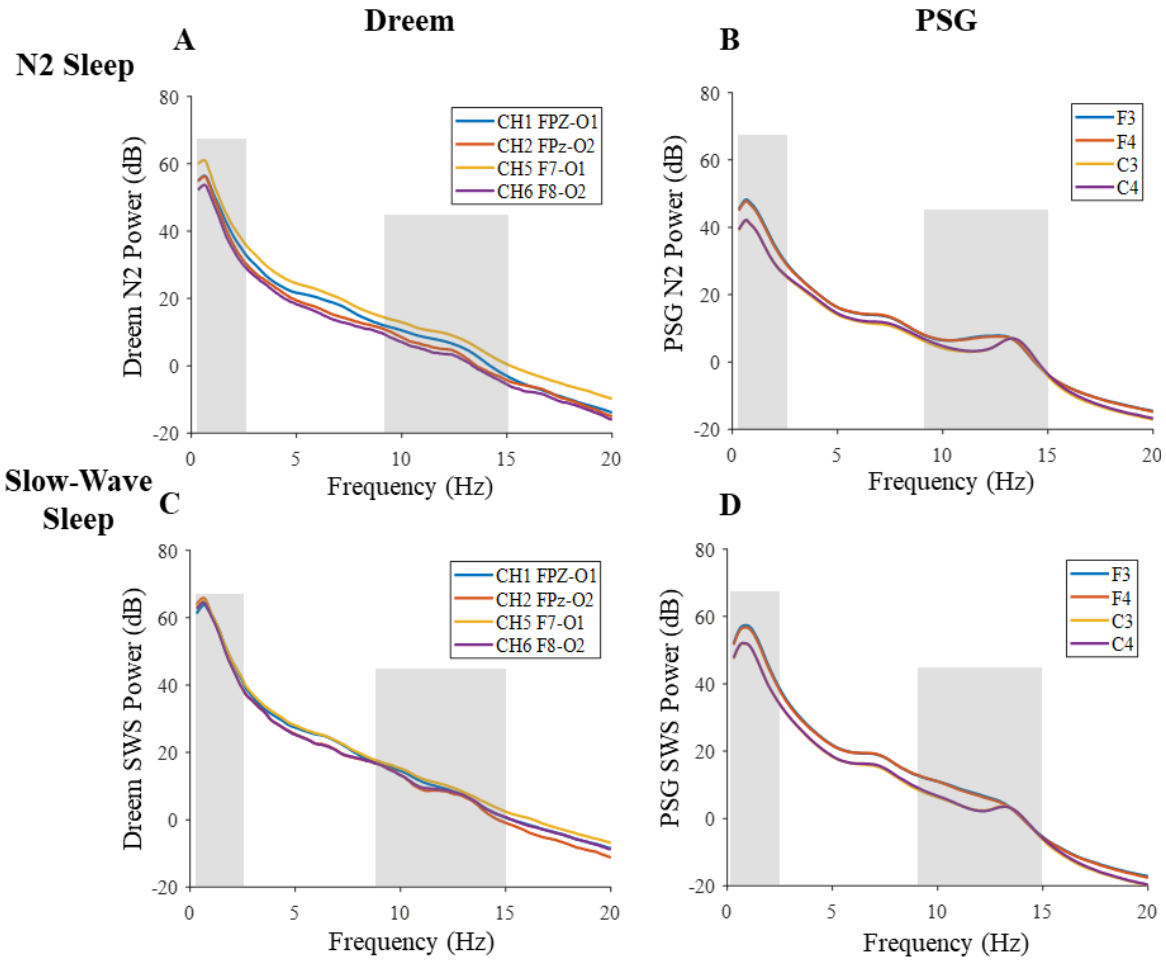


Figure 4.4 Power Spectra Across Frequencies in Dreem and PSG

Spectral power (dB), averaged across recordings (n=13), indicated that Dreem channels similarly showed greater SO power compared to PSG and no discernible spindle peak, for N2 (**A**) or SWS (**B**). In contrast, PSG showed a spindle peak at 9–14 Hz in frontal channels and ~14 Hz in central channels for both N2 (**C**) and SWS (**D**). Slow oscillation and spindle frequency bands are highlighted.

Average power spectra indicated little difference between Dreem channels. However, considering prior rejection, I averaged CH1 Fpz-O1 and Channel CH5 F7-O1 per recording (**Figure 4.5**). For PSG, I averaged the frontal (F3, F4) and central electrodes (C3, C4).

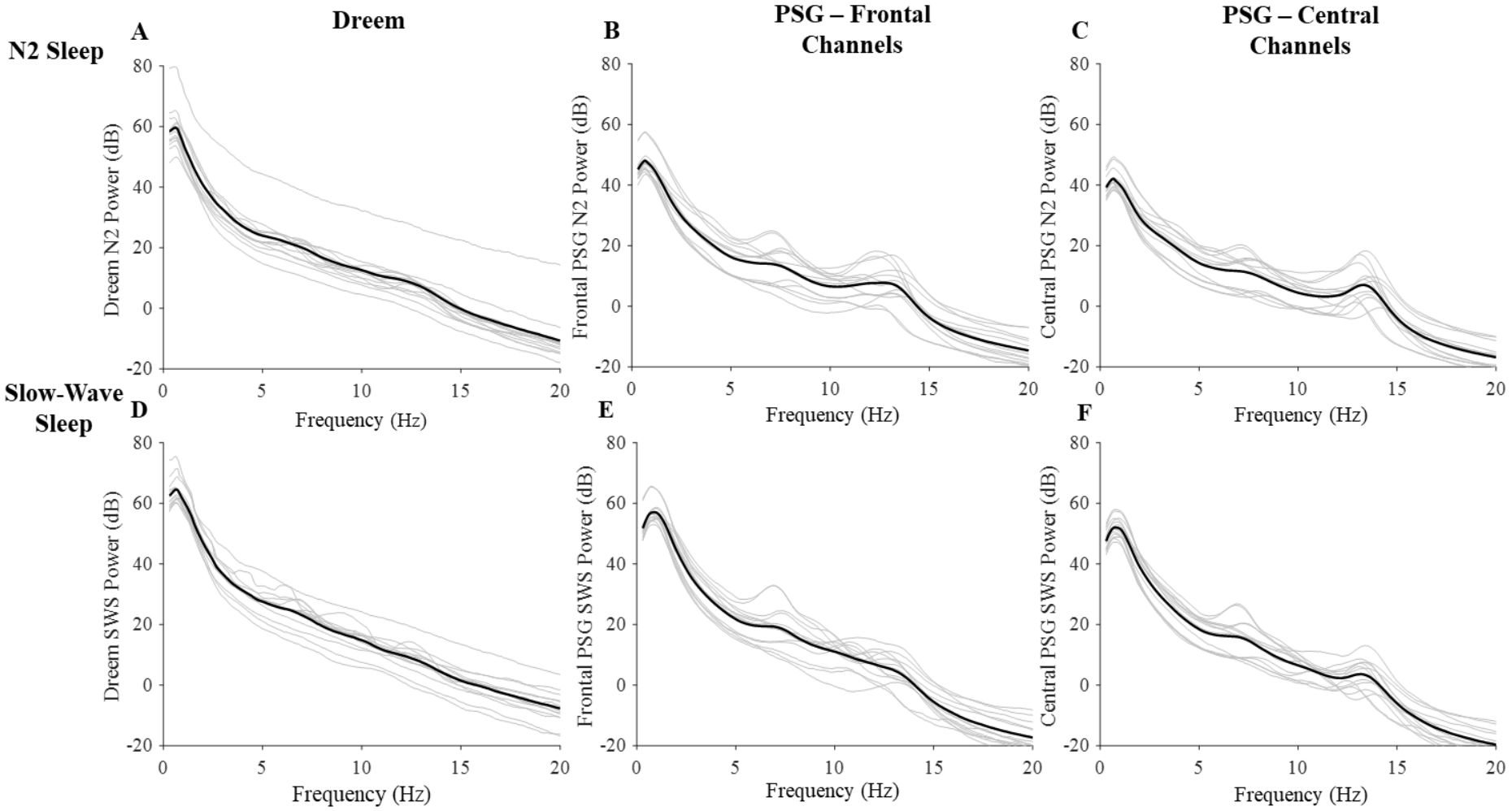


Figure 4.5 Power Spectra per Recording

Channel CH1/CH5, F3/F4, and C3/C4 averaged power (dB) for N2 and SWS across Dreem (**A**, **D**), frontal PSG (**B**, **E**) and central PSG (**C**, **F**). Mean across recordings (n=13) is shown in bold. Where CH1 was rejected (n=1), I used CH5 only.

To quantify differences between Dreem and PSG, I averaged power within the frequency bands of interest (0.5–1.5, 9–12, 12–15 Hz). Since Dreem showed greater power across all frequencies, I also quantified power as a proportion of total power: average power in the specified range divided by average power across all measured frequencies (0.4–20 Hz). I focussed on frontal PSG channels as the closest comparison to Dreem.

As indicated by the power spectra (**Figure 4.5**), I found significantly greater power in Dreem compared to PSG in N2 and SWS for SOs, and in SWS for slow and fast spindles (**Figure 4.6**). Broadly, adjusting power by the proportion of total power reduced the differences between Dreem and PSG in SWS but increased them in N2. However, the effect of outliers appears to be reduced. This suggests that calculating proportional power does not account for the raw power difference yielded by Dreem recordings, though it may enable a more consistent estimate in relation to PSG.

I also investigated associations between Dreem and PSG power with linear regression. This indicated that a significant group difference did not necessarily translate into strength of association: all power metrics suggested that Dreem values significantly predicted PSG values. As a proportion of total power, all metrics across N2 showed a significant association but Dreem slow spindle power in SWS no longer predicted PSG. However, associations were generally stronger when values were calculated as a proportion of total power (**Figure 4.7**, **Table 4.3**).

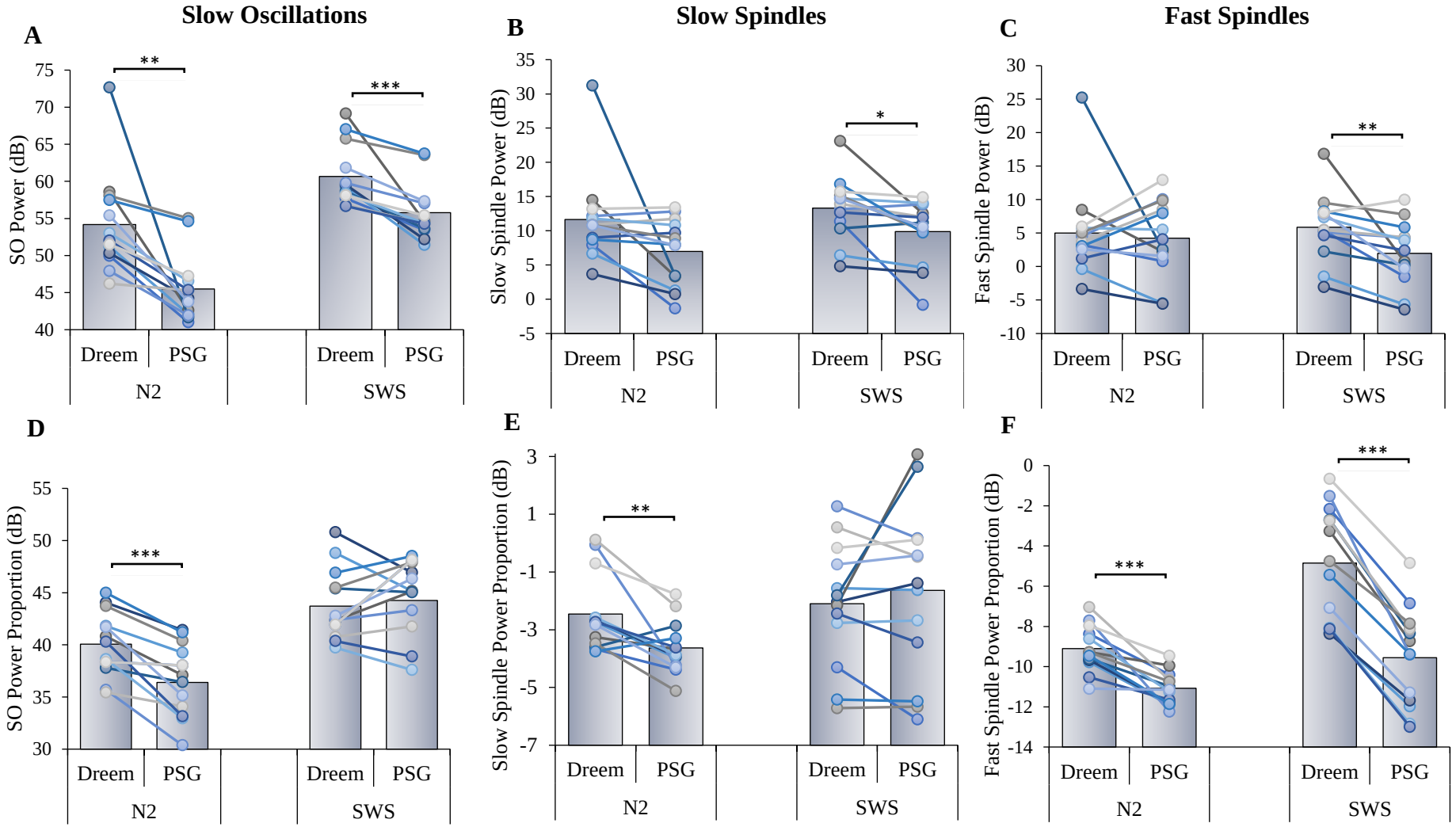


Figure 4.6 Power in Slow Oscillation and Spindle Frequencies Across Dreem and PSG

Dreem recordings showed significantly increased power across SO in N2 and SO, slow spindles, and fast spindles in SWS (**A**–**C**). As power proportional to total power, Dreem was greater in SO, slow spindles, and fast spindles in N2, but only in fast spindles in SWS (**D**–**F**). * $p < .050$, ** $p < .010$, *** $p < .001$.

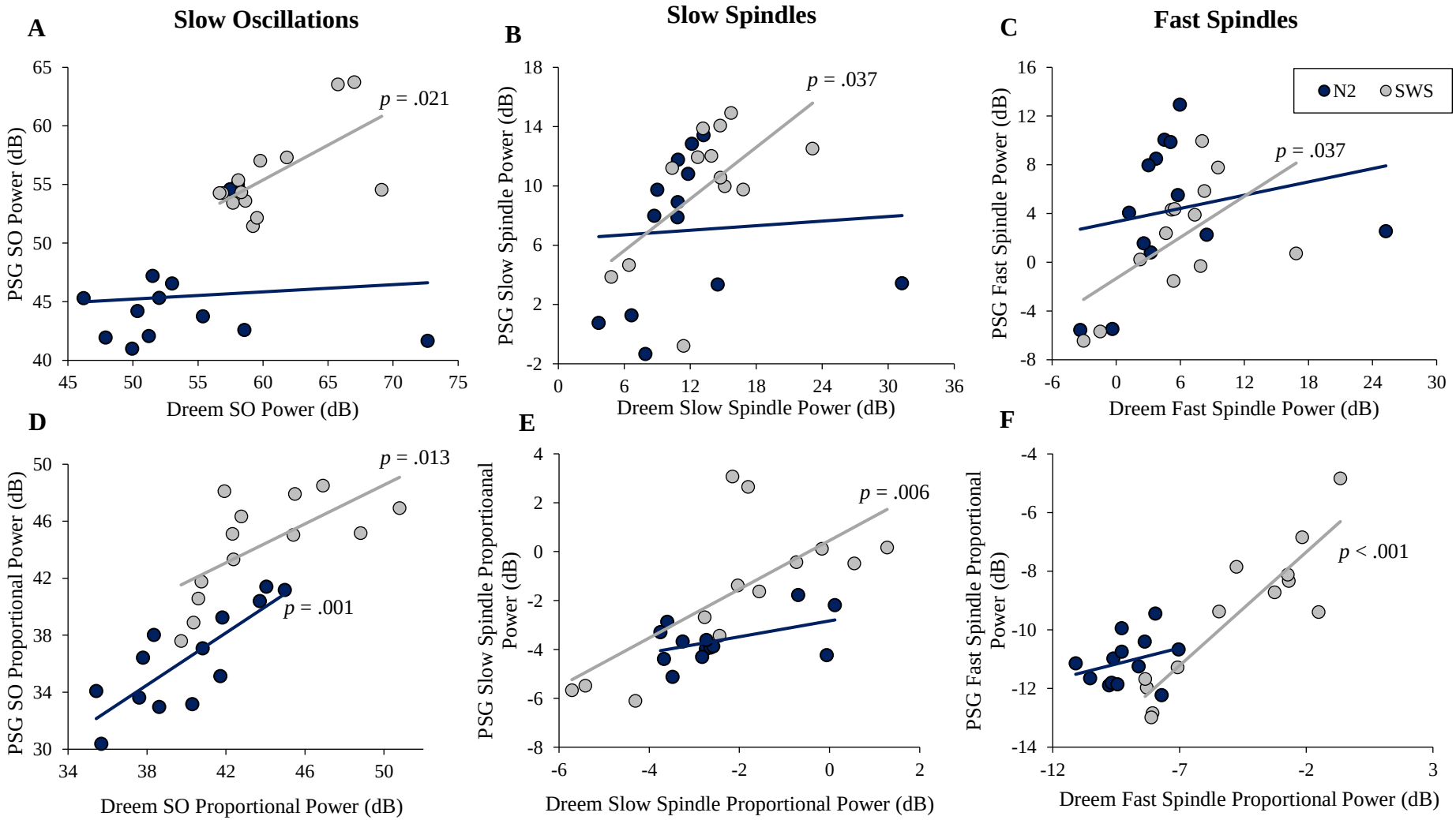


Figure 4.7 Associations Between Dreem and PSG in Slow Oscillation and Spindle Frequency Power

Dreem power was significantly associated with PSG power across SWS in SO (**A**), slow spindle (**B**), and fast spindle (**C**) frequencies; there were no associations in N2. Still, except N2 fast spindles, proportional power was significantly associated in all frequencies across N2 and SWS (**D**–**F**). Significant *p*-values shown.

Table 4.3 Power Differences and Associations Between Dreem and PSG Across SO and Spindle Frequencies

			Paired-Samples t-test		*Linear Regression (Unstandardised Coefficients)*				
	Frequency (Hz)		t (*12*)	*p*	R^2	F (*1,11*)	*p*	B [SE]	95% CI
Power	SO: 0.5–1.5	N2	4.02	.002	.01	0.09	.768	0.06 [0.20]	-0.39, 0.51
		SWS	5.15	< .001	.40	7.23	.021	0.60 [.22]	0.11, 1.08
	Slow Spindle: 9–12	N2	2.12	.055	.07	0.05	.825	0.05 [0.23]	-0.45, 0.55
		SWS	2.93	.013	.58	5.62	.037	0.58 [0.25]	0.04, 1.12
	Fast Spindle: 12–15	N2	0.35	.730	.22	0.54	.478	0.18 [0.25]	-0.36, 0.73
		SWS	3.13	.009	.34	5.66	.037	0.56 [0.24]	0.04, 1.08
Proportional Power	SO: 0.5–1.5	N2	6.35	< .001	.66	21.10	.001	0.91 [0.20]	0.48, 1.35
		SWS	-0.66	.520	.44	8.71	.013	0.68 [0.23]	0.17, 1.19
	Slow Spindle: 9–12	N2	3.53	.004	.24	3.46	.090	0.33 [0.18]	-0.06, 0.72
		SWS	-0.80	.438	.51	11.40	.006	1.00 [0.30]	0.35, 1.65
	Fast Spindle: 12–15	N2	5.90	< .001	.08	0.97	.345	0.21 [0.21]	-0.25, 0.67
		SWS	13.63	< .001	.81	47.87	< .001	0.78 [0.11]	0.53, 1.03

I then investigated event detection of SOs and spindles. Because the high rejection of Dreem data could have affected the results and the detection algorithm uses an adaptive threshold to account for noise, I used all trials scored as N2 or SWS. Again, I averaged PSG channels F3/F4 and all Dreem frontal-occipital channels (excluding rejected channels per recording). This indicated significantly more detected SOs across N2 and fewer spindles across both N2 and SWS in Dreem, though there was no significant difference in SOs across SWS. Meanwhile, linear regression indicated that Dreem detections significantly predicted PSG detections in SO count across SWS but not N2, and PSG spindle count across N2 but not SWS (**Figure 4.8**, **Table 4.4**).

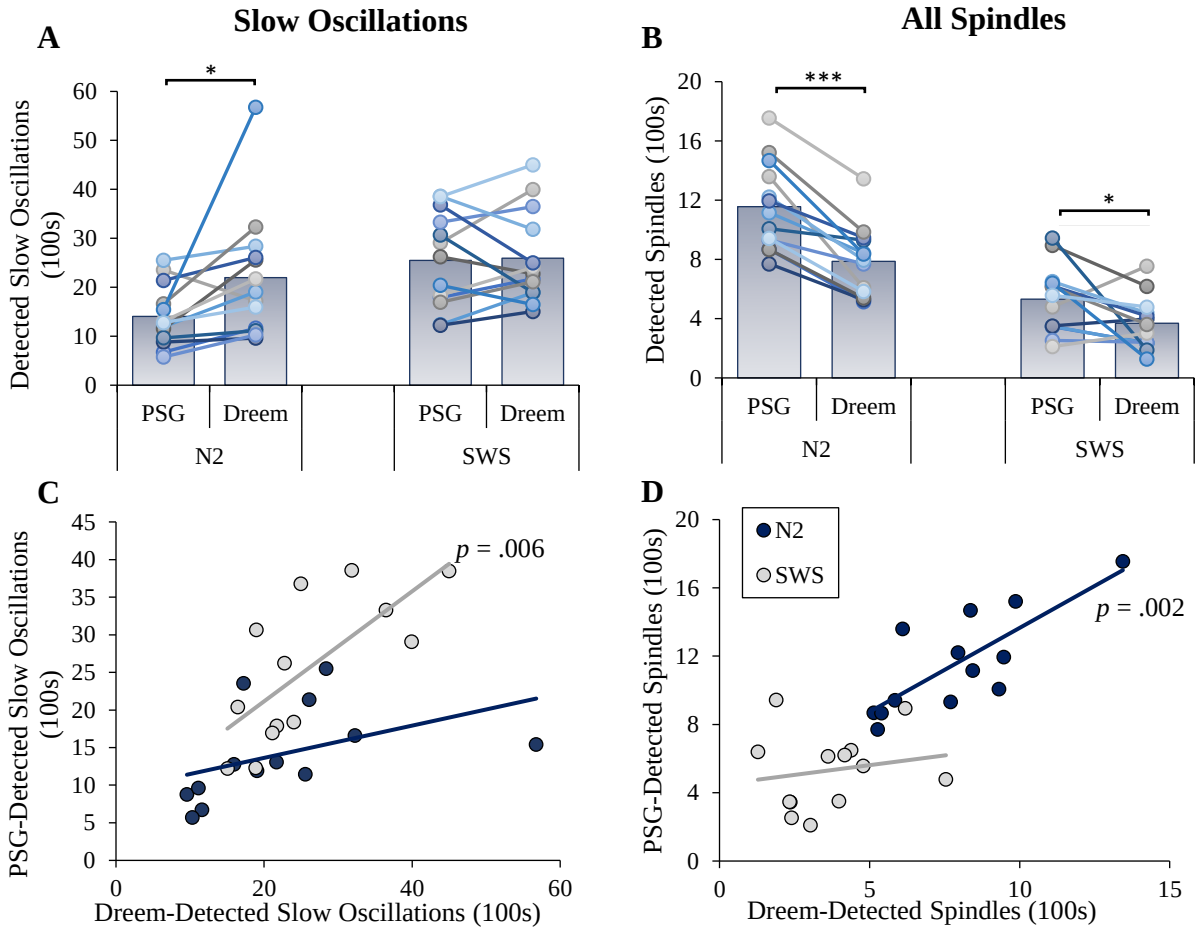


Figure 4.8 Slow Oscillation and Spindle Event Detection in Dreem and PSG

More slow oscillations (**A**) and fewer sleep spindles (**B**) were detected in Dreem recordings across N2. There was no significant difference in SOs and a smaller difference in spindles in SWS. * $p < .050$, *** $p < .001$. There were positive associations between Dreem and PSG in detected SOs in SWS (**C**) and spindles in N2 (**D**), but not SOs in N2 or spindles in SWS. Scatter shows individual recordings (n=13). Significant *p*-values are shown.

Table 4.4 Differences and Associations in Slow Oscillation and Spindle Detection

		Paired-Samples t-test		*Linear Regression (Unstandardised Coefficients)*				
		t (*12*)	*p*	R^2	F (*1,11*)	*p*	B [SE]	95% CI
Slow Oscillations (100s)	N2	-2.77	.017	.16	2.13	.172	0.20 [0.14]	-0.10, 0.51
	SWS	-0.22	.827	.51	11.33	.006	0.69 [0.21]	0.24, 1.15
Spindles (100s)	N2	7.14	< .001	.61	17.28	.002	0.98 [0.24]	0.46, 1.50
	SWS	2.23	.046	.03	0.36	.562	0.23 [0.38]	-0.61, 1.07

Potentially, event detection could have been affected by the number of epochs scored in N2 and SWS as this differed across PSG and Dreem recordings of the same night. However, density results (SO or spindle count divided by the number of epochs scored in N2 or SWS) were similar: Dreem-detected density positively predicted PSG-detected density in SO across SWS (p = .004) but not N2 (p = .365), and spindle density across N2 (p = .018) but not SWS (p = .683). Full results are shown in Appendix F.

Finally, I investigated PAC between slow oscillation (0.5–1.5 Hz) phases and spindle (9–15 Hz) amplitudes. I simulated EEG data with a phase-amplitude coupling between a 0.5 Hz phase modulating a 10.5 Hz amplitude, with a secondary coupling between a 1 Hz phase modulating a 14 Hz amplitude. Analogous to my sleep EEG data, I created 200, 30-second trials with a random phase shift (≤ pi/2) to distinguish each trial, code developed by Onslow (2012). I concatenated trials and calculated PAC in the same way as my sleep data. I also show the simulated raw EEG trace (**Figure 4.9**). Each pixel represents the coupling power within a 0.5 Hz range; if this did not reach significance (p < .05) the value was recorded as zero.

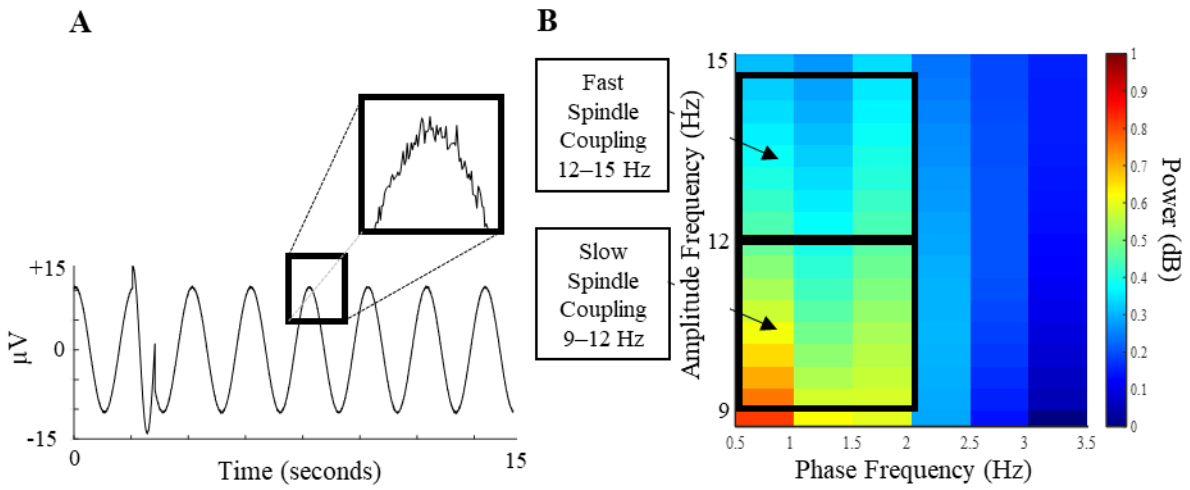


Figure 4.9 Simulated Data: SO-Spindle Phase-Amplitude Coupling

An illustrative 15-second segment of the simulated raw EEG signal (**A**) used to calculate phase-amplitude coupling across 200, 30-second trials (**B**). Warmer colours indicate greater power.

I used this phase-amplitude coupling method to compare PSG and Dreem recordings across N2 and SWS. Coupling in Dreem was strongest at a phase of 1–1.5 Hz and an amplitude around 9–12 Hz. This reflects slow spindle frequencies. PSG coupling was more widely spread across a phase of 0.5–1.5 Hz and amplitude of 9–15 Hz. This reflects both slow and fast spindle frequencies (**Figure 4.10**).

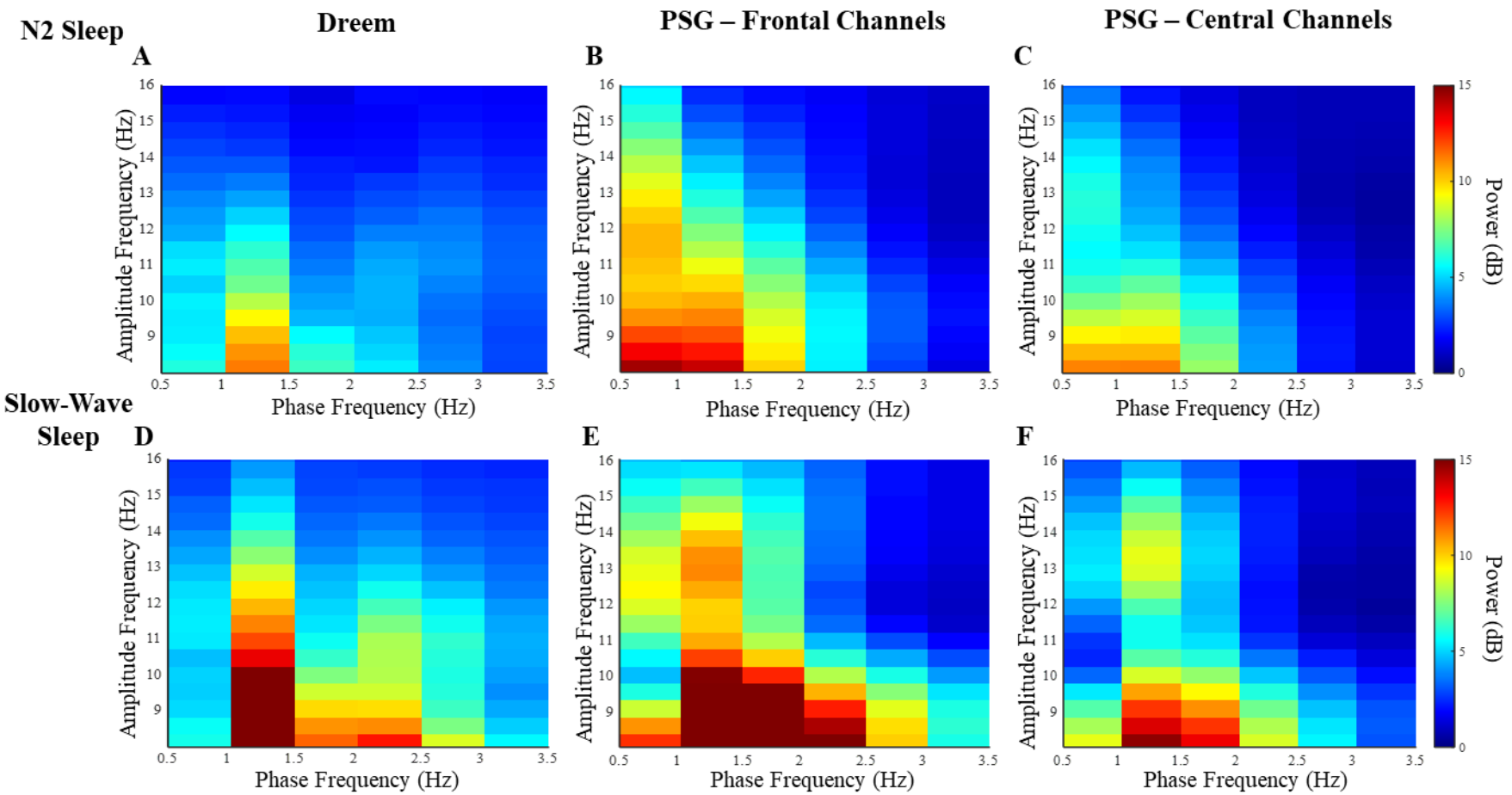


Figure 4.10 PACgrams Showing SO-Spindle Phase-Amplitude Coupling in Dreem and PSG

Mean (n=13) PAC values for 0.5–3.5 Hz phases and 8–16 Hz amplitudes were greater in PSG compared to Dreem, in N2 sleep (**A**–**C**), and SWS (**D**–**F**). Across methods, PAC tended to be greater in SWS than N2. All power axes are set to the same scale.

As with the power spectra, I averaged PAC values within slow oscillation 0.5–1.5 Hz (phase) and slow spindle 9–12 Hz / fast spindle 12–15 Hz (amplitude) frequencies and then compared Dreem and PSG. I found significantly greater coupling in PSG at fast spindle amplitudes in N2, but no significant differences in SWS or for slow spindle amplitudes. However, linear regression indicated that Dreem was an effective predictor of PSG in fast spindle coupling (**Figure 4.11, Table 4.5**).

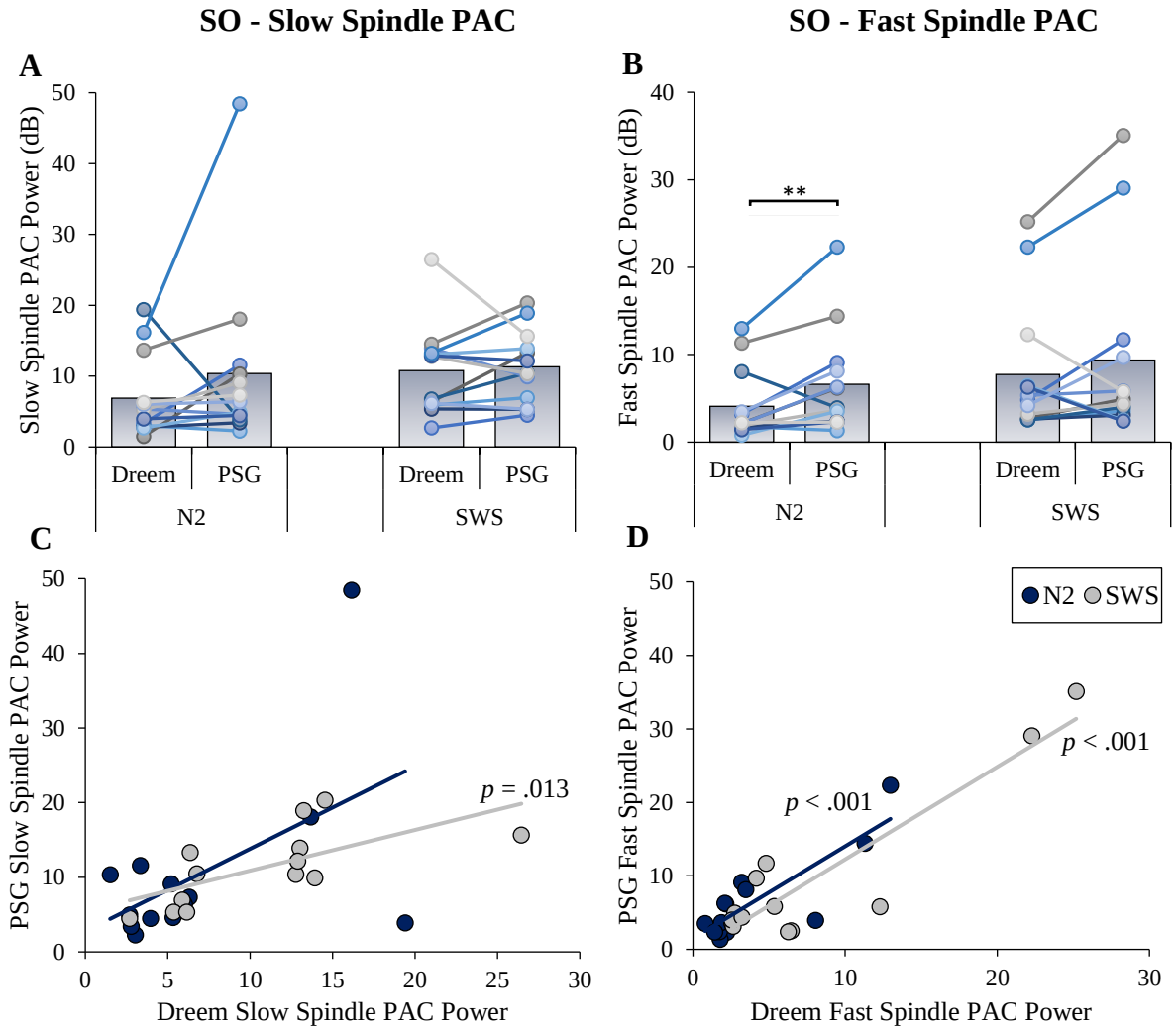


Figure 4.11 Phase-Amplitude Coupling Differences and Associations Between Dreem and PSG

There were no significant differences between PAC for slow spindle amplitudes (**A**), but PSG showed greater PAC in N2 for fast spindle amplitudes (**B**). There was a significant association for slow spindle amplitudes between Dreem and PSG coupling in SWS but not N2 (**C**). However, in fast spindle amplitudes there were significant positive associations in both N2 and SWS (**D**). Significant *p*-values are shown. ** $p < .010$.

Table 4.5 Phase-Amplitude Coupling Differences and Associations Between Dreem and PSG

		Paired-Samples t-test		*Linear Regression (Unstandardised Coefficients)*				
Frequency (Hz)		t (12)	*p*	R^2	F (1,11)	*p*	B [SE]	95% CI
Slow Spindle: 9–12	N2	-1.20	.253	.27	4.05	.069	1.11 [0.55]	-0.10, 2.31
	SWS	-0.41	.689	.44	8.79	.013	0.55 [0.18]	0.14, 0.95
Fast Spindle: 12–15	N2	-2.73	.018	.72	27.58	< .001	1.25 [0.24]	0.73, 1.78
	SWS	-1.26	.233	.83	54.66	< .001	1.26 [0.17]	0.89, 1.64

In summary, Dreem was generally a poor indicator of PSG-measured SOs and spindles, showing overestimated spectral power, no discernible spindle peak, and reduced SO-spindle coupling. However, event detection was more successful with strong associations between Dreem and PSG for SOs in SWS and spindles in N2 sleep.

4.3.2 Fear Conditioning Data

Following analysis of my Dreem validation data, I investigated event detection and spectral power in the sleep recorded as part of my fear conditioning experiment. In Chapter 3, I found a positive association between SWS duration and overnight change in discriminatory learning of the fear conditioned response, so I confine my analyses here to this outcome. These data were processed as the Dreem data above.

Of 27 intact Dreem sleep recordings, three were discarded because all frontal-occipital channels were corrupted (final n=24). Trial and channel rejection were slightly lower than the Dreem data of Chapter 2 (**Table 4.6**). Again, channel rejection was primarily from CH2 Fpz-O2 and CH6 F8-O1, but not as severe as the validation study (**Table 4.7**).

Table 4.6 Dreem Channels and Trials Rejected: Fear Conditioning Data

	Sleep Stage	Mean ± SD
Channels (max = 4)	N2	1.28 ± 1.06
	SWS	0.76 ± 1.01
Trials	N2	96.08 ± 82.78
	SWS	17.32 ± 18.51

Mean total number of trials for N2/SWS: 395/180.

Table 4.7 Dreem Channels Retained: Fear Conditioning Data

	CH1 Fpz-O1	CH2 Fpz-O2	CH5 F7-O1	CH6 F8-O1
N2	22	13	21	12
SWS	23	17	24	17

Maximum retention = 24.

Visual analysis of power spectra between the channels indicated few differences. Therefore, unlike the validation data, I averaged across all available channels for every participant (**Figure 4.12**).

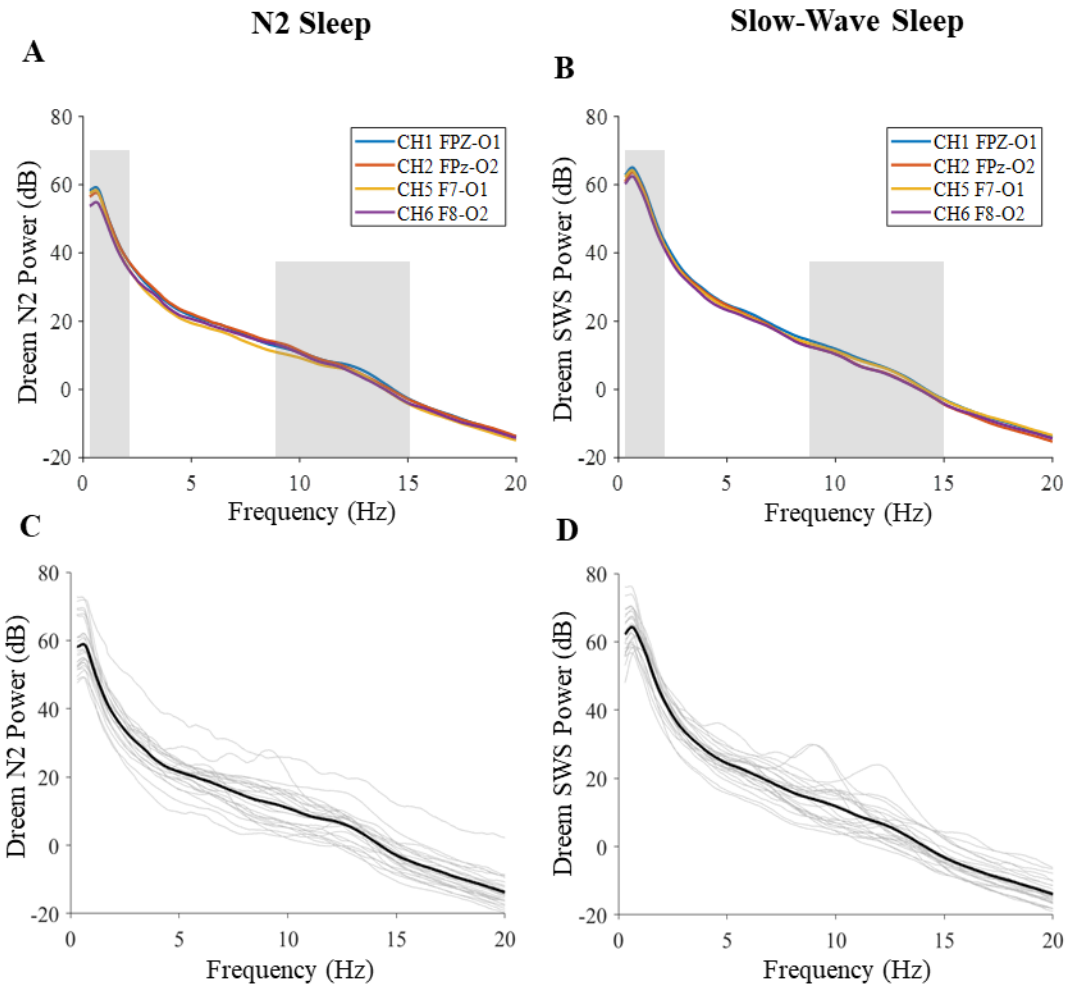


Figure 4.12 Power Spectra in Fear Conditioning Data

Dreem power (dB) averaged across recordings (n=24) was similar to the validation data, for N2 (**A**), and SWS (**B**). Slow oscillation and spindle frequencies are highlighted. Spectra per participant, however, showed greater variation, in N2 (**C**), and SWS (**D**). The mean is shown in bold.

I then calculated power and event detection for SO and spindle frequencies. Based on my previous findings in the validation data, I limited power analyses to a proportion of total power. I investigated associations between these metrics and overnight consolidation of the fear conditioned response (**Table 4.8**). There was a negative but non-significant association between fast spindle power in N2 sleep and overnight fear consolidation, and a positive association between SO count in SWS. These were significantly driven by CS- change and CS+ change respectively (**Figure 4.13**).

Table 4.8 Power and Event Detection Associations with Overnight Fear Consolidation

Power/Event		R^2	F (*1,20*)	*p*	Unstandardised Coefficients	
					B [SE]	95% CI
Slow Oscillation Power	N2	.02	0.37	.549	-0.03 [0.05]	-0.13, 0.07
	SWS	.00	0.01	.923	-0.01 [0.05]	-0.10, 0.09
Slow Spindle Power	N2	.01	0.18	.676	0.01 [0.01]	-0.02, 0.04
	SWS	.01	0.25	.623	0.03 [0.06]	-0.10, 0.17
Fast Spindle Power	N2	.12	2.75	.113 [a]	-0.15 [0.09]	-0.33, 0.04
	SWS	.09	1.88	.185	-0.12 [0.08]	-0.29, 0.06
Slow Oscillation Count (100s)	N2	.01	0.18	.676	0.01 [0.01]	-0.02, 0.04
	SWS	.27	7.20	.014 [b]	0.04 [0.02]	0.01, 0.07
Spindle Count (100s)	N2	.04	0.88	.361	-0.04 [0.05]	-0.14, 0.05
	SWS	.10	2.13	.160	0.14 [0.09]	-0.06, 0.33

[a] Driven by CS- change: R^2 = .35, F (1,20) = 10.97, *p* = .003, B = 0.19, SE = 0.06, CI = [0.07, 0.31]. This in turn was strengthened by excluding non-learners: R^2 = .38, F (1,13) = 8.00, *p* = .014, B = 0.23, SE = 0.08, CI = [0.06, 0.41]. There was no association for CS+ change, *p* = .554.

[b] Driven by CS+ change: R^2 = .40, F (1,20) = 10.27, *p* = .004, B = 0.03, SE = 0.01, CI = [0.01, 0.05]. This in turn was strengthened by excluding non-learners: R^2 = .46, F (1,13) = 11.27, *p* = .005, B = 0.04, SE = 0.01, CI = [0.01, 0.06]. There was no association for CS- change, *p* = .510.

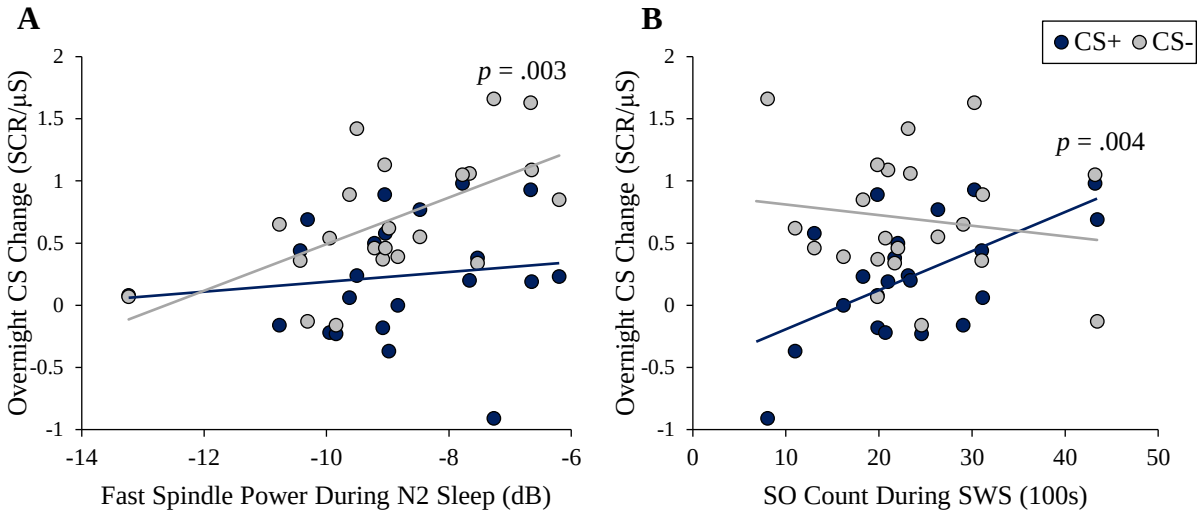


Figure 4.13 Spindle and SO Associations Overnight Fear Consolidation

Fast spindle power in N2 was positively associated with overnight change in CS- responses, while there was no association for CS+ change (**A**). SO count in SWS was positively associated with overnight change in CS+ responses, while there was no association for CS- change (**B**). Significant *p*-values are shown (n=21).

I also investigated whether the finding in SO count was reflected in SO density (SO count/number of scored epochs), and found a significant positive association between SO density in SWS and CS+ change overnight, R^2 = .20, F (1,20) = 4.96, *p* = .038, B = 0.07, SE = 0.03, CI = [0.01, 0.13].

Finally, I calculated the PAC between slow oscillation phases and fast or slow spindle amplitudes. There was coupling within these frequencies similar to my previous Dreem (Chapter 2) data (**Figure 4.14**), but no associations with overnight change in CS discrimination (**Table 4.9**).

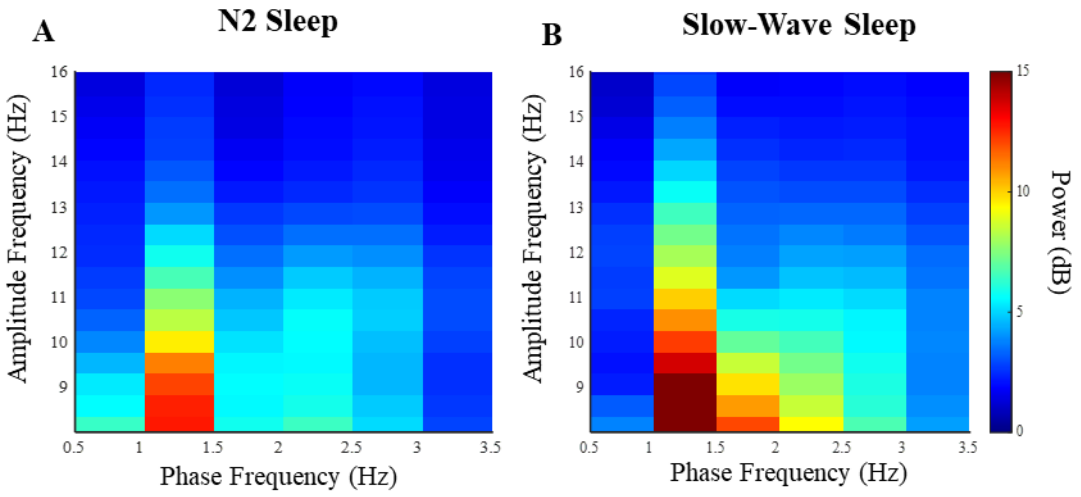


Figure 4.14 PACgrams Showing Slow Oscillation-Spindle Coupling Across N2 and SWS During Post-Conditioning Sleep

There was significant phase-amplitude coupling in the expected frequencies, mainly in slower spindle amplitudes in N2 sleep (**A**). This was stronger and extended into faster spindle frequencies in SWS (**B**). Power is set to the same scale.

Table 4.9 Associations Between PAC Power and Overnight Fear Consolidation

					Unstandardised Coefficients	
Power Range		R^2	F (*1,21*)	*p*	B [SE]	95% CI
Slow Spindle Coupling	N2	.00	0.05	.834	0.01 [0.02]	-0.04, 0.05
	SWS	.01	0.23	.636	0.01 [0.01]	-0.02, 0.04
Fast Spindle Coupling	N2	.01	0.14	.709	-0.02 [0.06]	-0.15, 0.10
	SWS	.00	0.02	.888	0.00 [0.03]	-0.07, 0.06

Linear Regression.

4.4 Discussion

4.4.1 Summary of Results

In this chapter I explored my Dreem EEG data from Chapters 2 and 3 for the analyses of slow oscillations (SOs) and sleep spindles. I first compared matched nights of sleep recorded by Dreem and simultaneously by the gold standard of sleep measurement, PSG. Subsequently, I explored whether SOs and spindles were associated with overnight fear consolidation, finding that detected SO events in SWS were associated with a more positive change in CS+ (SCR) responses (**Figure 4.13**).

In spectral analyses, Dreem showed significantly greater spectral power than PSG across SO and spindle frequencies. However, this was driven by a wideband increase in power across all frequencies. I attempted to correct for this by calculating power as a proportion of the total power across all measured frequencies. This was successful in reducing outliers, but significant differences between PSG and Dreem remained. Linear regression indicated that Dreem was largely more successful in proportional power, but the PSG variance explained by Dreem was still irregular (e.g. very good in fast spindle power in SWS, but non-existent in fast spindle power in N2). This suggests that Dreem overestimates power and may not be indicative of the variation in PSG in some metrics. Nevertheless, power spectra of my fear conditioning data showed greater variation and a discernible spindle peak for three participants. This suggests that Dreem can detect spindles in a minority of individuals; it may also be reflective of better-quality data, as indicated by the lower artefact rejection. An exploration of these metrics in relation to my fear conditioning results indicated that fast spindle power was associated with a more negative change in CS- fear response overnight, but this result requires replication.

In subsequent event detection, Dreem was relatively accurate in the defining features of each stage: spindles in N2, and SOs in SWS. This disparity between power and event detection could be caused by poor signal quality, suggesting that the Dreem EEG signal contains noise in the SO and spindle frequency bands even after removal of visually identifiable artefacts. In SWS in particular, Dreem predicted 51% of the variance in PSG and there was no significant group difference. For spindles in N2, there were significantly fewer spindles detected in Dreem, but Dreem predicted 61% of the variance in PSG. Dreem was less accurate for spindles in SWS and SOs in N2, with significantly fewer spindles and more SOs; there were also no significant associations between Dreem and PSG detections in these metrics. However, in the fear conditioning data, SO count was significantly associated with overnight fear consolidation in accordance with the association with SWS duration (Chapter 3). SO

density (the average number of SO events in each 30-second SWS epoch) was similarly associated with fear consolidation, suggesting this effect is independent of SWS duration.

Finally, I found that quantification of the phase-amplitude coupling (PAC) between SO phases and spindle amplitudes indicated significant coupling on average in Dreem, but this was greater and more specific in PSG. That being said, some Dreem coupling significantly predicted PSG coupling, explaining 72–83% of the variance in fast spindle frequencies. I found similar coupling in my fear conditioning Dreem data; however, there were no significant associations with overnight fear consolidation.

Overall, Dreem, when compared to PSG, was inaccurate in spectral power, showing no discernible spindle peak and reduced SO-spindle coupling. Nevertheless, event detection was successful, especially for the characteristic signatures of each stage i.e., SOs in SWS and spindles in N2 sleep. I subsequently found a positive association between SO event detection and overnight fear consolidation in my fear conditioning data. There was also an association between fast spindle power in N2 and CS- change overnight, though I did not find any effect of SO-spindle coupling. However, these results suggest that some event detection is appropriate for Dreem-recorded data and that Dreem-detected SOs promote fear memory consolidation.

4.4.2 Fear Memory Consolidation in Non-REM Sleep

In Chapter 3 I found that SWS duration as a proportion of total sleep time was significantly associated with a maintenance of CS discrimination overnight: change in CS+/CS- responses from the last trial of acquisition training on day 1 to the first trial of extinction training on day 2. In this chapter, I explored whether this consolidation was reflected in SO and spindle power spectra, event detection, and PAC. In Chapter 3 I also found an association between SWS % and CS discrimination on day 8, but I chose to focus on overnight change, considering the low day 8 sample size.

I did not find that power spectra or SO-spindle PAC was related to overnight fear consolidation. However, the positive association with SO count suggests evidence for the neural mechanisms underlying memory consolidation, specifically, the maintenance of learned fear discrimination overnight. Like SWS %, the association with SO count was driven by CS+ changes: more detected oscillations during SWS were associated with a more positive change in fear response (as measured by SCR) to the danger stimuli overnight. This was also strengthened by excluding non-learners, despite the reduced sample size. This suggests that the coordinated neural activity reflected by SOs promotes consolidation of fear learning, in line

with previous literature (Krugliakova et al., 2020; Menicucci et al., 2020; Tatsuno et al., 2020). This overnight association was also reflected in SO density suggesting that the number of SOs in each SWS-scored epoch, regardless of the number of scored epochs, has a beneficial memory consolidation effect.

I also found a positive association between fast spindle power in N2 and overnight change in fear response to the CS-. However, this result is tenuous, considering that my Dreem validation data suggested Dreem was highly inaccurate in this measure. In addition, Dreem is not expected to detect many fast spindles, since they are seen most clearly from central locations which Dreem does not record. Furthermore, I found no evidence that detected spindle events in N2 were related to CS- change.

If the association between fast spindle power and an increase in CS- response overnight were substantiated, it could suggest that fast spindles in N2 following fear learning play a role in fear generalisation (from the CS+ to the CS-). Previously, fast spindles have been associated with the generalisation of non-emotional declarative memory (Hennies et al., 2016; Chatburn et al., 2021). One possible mechanism is a tighter coupling than slow spindles with slow oscillations and hippocampal ripples (Clemens et al., 2011; Mölle et al., 2011). Fast spindles have also been associated with memory reactivation during sleep. In 25 female participants (mean age 20 years), presentation of a contextual odour during non-REM sleep, previously present during the learning of word pairs, elicited greater fast spindle amplitude and density, although this was not related to improved post-sleep memory (Cox et al., 2014). On balance, my result fits with previous literature but should primarily be viewed as showing potential for further investigation.

4.4.3 Limitations of EEG Analyses in the Dreem Headband

Arguably, the Dreem Headband was not designed for the analyses I have presented in this chapter. While the previous Dreem validation study assessed spectral power, reporting a mean percentage error of 10–16 % across alpha, beta, delta, and theta frequencies, Dreem were able to develop an algorithm to determine spectral similarity between Dreem and concurrent PSG which automatically selected the best channel for each frequency band per 30-second epoch. This was not replicable in my data. PSG channels were also referenced to occipital channels; this provided greater similarity between PSG and Dreem but may not reflect the typical PSG signal. Consequently, my validation of sleep wearable technology (and by extension the investigation of emotional memory consolidation using this method) was still

somewhat exploratory. While these wearables will continue to develop, current limitations curtail some analyses.

Firstly, the Dreem Headband lacks the basic coverage of PSG. This is most notable in the absence of central electrodes, but the frontal electrodes are also further forward than standard PSG positions F3 and F4 (shown in **Figure 1.1**, General Introduction). Dreem also lacks the mastoid electrodes which normally provide the reference for a PSG-recorded EEG signal. Instead, Dreem references frontal channels to either other frontal channels or the occipital channels. I analysed the frontal-occipital electrodes because, based on the topography, they are most likely to represent a signal closest to PSG. However, it is difficult to establish exactly what effect referencing had on the data. For example, PSG channel F3 shows the electrical signal from this point minus the signal averaged from the mastoids. In contrast, CH1 FPz-O1 shows a (further forward) frontal signal minus that from the back of the head. This means that even if the recording from Dreem versus PSG electrodes were identical, the EEG would not look the same.

The other major disadvantage of Dreem (compared to PSG) is the use of dry electrodes which are not fixed in position. This is likely to increase impedance and reduce the signal-to-noise ratio. This was reflected in my power spectra results. Event detection, along with visual examination of the data during the sleep scoring of Chapter 2, suggested that sleep spindles can be seen in Dreem data; therefore, the lack of spindle peak in spectral power suggests that noise around these frequencies obscures the usual pattern. This is despite the substantial artefact rejection I employed before spectral analyses to clean the data. In contrast, I found event detection to be relatively accurate, at least for spindles in N2 and SOs in SWS. This suggests that the more specific measure of event detection is more suitable than power band estimates in Dreem EEG data.

Poor quality Dreem data in my validation study could be a direct consequence of unwanted interactions between Dreem and PSG, for example, PSG electrodes causing the headband to sit outside the normal position. I rejected nearly half of all Dreem channels and then 31% of N2 trials and 16% of SWS trials. This level of rejection meant that my estimates of spectral power were based on reduced data and so may be less reliable. Nearly all of the channel rejection in Dreem came from Channel 2 Fpz-O2 and Channel 6 F8-O2, which could suggest that Dreem's O2 electrode was particularly sensitive to disruption. In contrast, the previous validation study (Arnal et al., 2020) only reported a 2.1% rejection; however, this is likely to be due to switching between channels per epoch. My approach was arguably less refined, but more replicable. Artefact rejection in my fear conditioning data was also not as severe as my validation study: channels 2 and 6 were rejected more often than the others but were still

retained for approximately half the recordings, while subsequent trial rejection at 24% and 9% for N2 and SWS respectively was also improved. This indicates a higher quality of Dreem data when it was the only recording device worn during sleep.

Finally, the Dreem Headband was designed for closed loop auditory stimulation: short bursts of sound to boost SOs (Debellemaniere et al., 2018). If designed with SO detection in mind, it is conceivable that the headband actively overestimates SOs in the EEG signal to target as many as possible. This could explain why Dreem overestimated SOs in N2, although it showed good accuracy in SWS. A consistent overestimation of SOs in N2 would need to be replicated in a larger dataset to be confirmed.

4.4.4 Strengths and Limitations

A strength of this study is that the event detection algorithm I used offers a visual representation of detected events on the EEG input signal, as well as event histograms and power spectra per epoch (see Appendix F). Since these analyses of Dreem EEG data were novel, it was advantageous to view the data in this way. I did not count SOs and spindles manually, but I visually checked every recording for sensible detection. My finding that detected SOs were positively associated with fear consolidation concurs with the finding in Chapter 3 regarding SWS duration. This was based on my sleep scoring of Dreem data and so agreement provides a corroboration of both measures.

However, a limitation of my Dreem validation is the small sample size. In Chapter 2, I collapsed across night for measurements of sleep stage, but SO and spindle metrics may be more prone than sleep stage duration to stronger consistency across the same individuals (Massimini et al., 2004; Purcell et al., 2017; Cox et al., 2017). After additional rejection of two nights (from the same participant), only five people contributed both consecutive nights of data for these analyses; therefore, statistical comparisons within and between individuals would not have been particularly meaningful. In the future, a larger sample which records multiple nights would be informative. My validation could have also been affected by the PSG system, which only comprised of six EEG channels. Higher density recording would have better captured fast and slow spindles. In contrast, my fear conditioning data offered a larger sample which was reflected in lower artefact rejection and more typical power spectra; although, there is no indication of how the results would compare to PSG-recorded sleep after fear conditioning.

Furthermore, because of the limitations of Dreem, I did not synchronise event detection, i.e. attempt to detect the same events in Dreem and PSG as defined by their time stamp. I expected that differences in recording quality, coverage, and referencing would make such an

analysis unreliable. Although my analysis of SO/spindle count and density is less precise, it gives some indication of the utility of Dreem for such analyses, especially when this agrees with sleep stage duration – as was the case with my findings between SWS duration and emotional memory consolidation.

My quantification of phase-amplitude coupling may also have lacked precision. In a previous investigation of emotional memory consolidation (Denis et al., 2021), SO–spindle coupling was measured from channels F3/F4 for SOs and channels C3/C4 for spindles. Another study reported the isolation of events and then the detected coupling of spindles specifically within each slow oscillation (Mikutta et al., 2019). My coupling analyses were arguably a simplified version of this, adapted to the Dreem Headband's lack of central channels and atypical referencing. Consequently, I only looked for coupling between slow oscillation frequency phases with spindle frequency amplitudes across the whole EEG; this may not reflect actual SOs and spindles. While I did find significant coupling in the expected frequencies, these results are likely to be a broad estimation of the true coupling in these data.

Finally, my assessment of non-REM sleep would have been strengthened by the exploration of delta oscillations. Distinguishing between slow oscillations and delta oscillations is complicated by a lack of standard approach to precise parameters in the literature. SOs have been defined at < 1 Hz, < 2 Hz, or 0.5–1.5 Hz (Cox et al., 2012; Lanquart et al., 2018; Mölle et al., 2011; Parrino et al., 2009), whereas delta oscillations have been defined from 0.5–4 Hz, to 1.5–4 Hz (Amzica & Steriade, 2002; Dang-Vu et al., 2005). Delta power during non-REM sleep has been associated with greater emotional object recognition after sleep in the absence of an effect for slow oscillations at 0.5–1Hz (Payne et al., 2015). Although, in a subsequent study, both SO and delta power were associated with post-sleep recall for negative items (Alger et al., 2018). Alternatively, slow oscillations and delta waves may have competing roles. In one rodent study (n=12 rats, all male, 12 weeks old), reactivation during SOs and delta waves led to a weakening and strengthening of the memory respectively (Kim et al., 2019), though this was not emotional memory but brain-machine interface learning. Slow and delta oscillations were defined by their waveforms, with average frequencies of 0.41 and 1.12 Hz respectively. By these definitions, my results would span both of these effects. This issue requires clarification in a well-powered study and the comparison of small frequency bands against emotional memory performance. Possibly, this is a question unsuited to the use of wearable technology.

4.4.5 Conclusions

In this chapter I investigated the Dreem Headband for spectral power and event detection of slow oscillations and spindles. Dreem showed mixed efficacy across power spectra and phase-amplitude coupling. This was somewhat expected considering the results of Chapter 2. However, automatic detection of events in their defining sleep stage was accurate, especially SO events in SWS. Correspondingly, I found that the association in Chapter 3 between overnight fear consolidation and SWS duration was reflected in both SO count and density. This suggests that Dreem is suitable for such non-REM sleep event detections, but there is less indication it should be utilised for spectral analyses. This requires replication, yet the results extend the findings of Chapters 2 and 3 for the utility of the Dreem Headband and the relationship between SWS and fear memory.

Chapter 5

Fear Responses: Associations with Anxiety and Bad Dreams

In this chapter I investigate how fear conditioned responses relate to self-reported anxiety. I found that state, trait, and intolerance of uncertainty anxiety measures similarly predicted maladaptive reinstatement of fear, while post-hoc analyses suggested this was driven by female participants. In a subset of participants, bad dreams were unrelated to anxiety but people who reported bad dreams showed more maladaptive fear responses across the experiment. These results suggest that anxiety and bad dreams could be relevant indicators of poor fear learning and consolidation.

5.1 Introduction

Anxiety is a complex emotional response that reflects an anticipation of real or perceived threat. It is characterised by worry, restlessness, and impaired concentration (Andrews et al., 2010). State and trait anxiety can be dichotomised as momentary feelings and long-term tendencies respectively, but these facets are highly interconnected with trait anxiety fuelling state anxiety and potentially, vice versa (Endler & Kocovski, 2001; Leal et al., 2017). In fact, state and trait anxiety have been suggested to rely on the same functional network including the orbitofrontal cortex, cingulate cortex, and thalamus (Takagi et al., 2018). The correlation between state and trait anxiety was .35–.70 in a sample of 1058 twin pairs (aged 8–16 years);

this was stronger in monozygotic twins, females, and adolescents over 12 years (Lau et al., 2006). However, state anxiety was primarily influenced by environmental factors while trait anxiety had 30% heritability. This suggests dissociable elements between state and trait anxiety.

As discussed in Chapter 1, anxiety recruits the autonomic nervous system (Bajkó et al., 2012; Mizuno et al., 2017; Thayer et al., 1996). It is therefore intrinsically related to the fear response. Anxiety also recruits top-down executive functions in the brain (Affrunti & Woodruff-Borden, 2015; Hamm, 2020; Zainal & Newman, 2018), though its neural correlates are still centred around the amygdala (Ahrens et al., 2018; Babaev et al., 2018; Tye et al., 2011). Like fear, anxiety can be a normal and valuable response to threat, for example, promoting an awareness about potential danger (Robinson et al., 2012; Thwaites & Freeston, 2005). Anxiety therefore spans a spectrum that can be adaptive but becomes damaging when persistent or excessive. Consequently, the fear response, particularly fear generalisation, has been posited as a driving force behind clinical anxieties (Chen & Lovibond, 2020; Dymond et al., 2015; Via et al., 2018). This is not limited to anxiety-centred conditions (e.g. Generalised Anxiety Disorder), but also those relating to stress and trauma, such as PTSD (Gilbar, 2020; Thome et al., 2017). Given this, understanding how anxiety interacts with fear learning will inform a fuller understanding of the fear response and how it leads to various psychopathologies.

Dreams have also been associated with anxiety and emotion dysregulation, as discussed in Chapter 1 (Levin & Nielsen, 2009, 2007). The mechanisms and causality of this relationship have not been fully clarified, but dreams – particularly negative dreams – have been previously related to the consolidation of emotional experiences (Eichenlaub et al., 2018; van Rijn et al., 2015), and may be an underexplored facet in the context of fear conditioning.

In Chapters 3 and 4 I found that individual differences in sleep architecture were associated with fear learning and consolidation. This was based on the well-established links between sleep, learning and memory (Born et al., 2006; Born & Wilhelm, 2012). However, as discussed in Chapter 3 in the case of Little Albert (Watson & Rayner, 1920), whether or not people develop chronic psychological problems after fear learning may be influenced by their individual traits and tendencies. In this chapter, I therefore investigate how state and trait anxiety relate to fear acquisition, extinction, and reinstatement of fear in young, healthy people. I also explore associations between bad dreams and fear conditioned outcomes.

5.1.1 Anxiety and Fear Conditioning

5.1.1.1 State and Trait Anxiety

Both state and trait anxiety have been related to fear conditioning, particularly a lack of safety learning (low fear responses to the safe CS-) and a generalisation of fear following reinstatement. In short, stimuli that have never been or are no longer associated with danger should evoke little fear response; however, anxiety may promote impaired discrimination between learned fear and safe stimuli, i.e. fear generalisation, in a variety of settings (Baker et al., 2019; Dibbets et al., 2015; Kull et al., 2012).

As discussed in the General Introduction, a review of inter-individual differences in healthy fear conditioned responses suggests that anxiety – perhaps specifically intolerance of uncertainty – is associated with maladaptive fear acquisition, extinction, and return of fear (Lonsdorf & Merz, 2017). Fear generalisation has strong links to understanding how maladaptive fear may promote clinical pathologies. For example, anxiety patients compared to healthy controls show increased fear responses (Duits et al., 2015). Current theories of fear development support the view that maladaptive fear arises from the same generalisation systems that help humans to be so adept at learning and memory (Dunsmoor & Paz, 2015).

Non-clinical trait anxiety has been associated with maladaptive fear acquisition, extinction, and reinstatement. In one study, healthy participants (n=42, 29 female, mean age 20 years) were selected based on high or average STAI-measured trait anxiety (Gazendam et al., 2013). Highly anxious participants showed greater startle responses and shock expectancy ratings to the CS- at the end of acquisition, a slower extinction curve for both CS+ and CS- the next day, and greater expectancy ratings for the CS- after reinstatement. This suggests that trait anxiety promotes greater fear responses during acquisition, extinction, and reinstatement; although, there were no significant effects in SCRs and so this may not be reflected in every physiological measure of the fear response. In contrast, trait anxiety in healthy participants (n=73, 36 female, aged 18–64 years) across a variety of measures including the Penn State Worry Questionnaire and Beck Anxiety Inventory, but not the STAI, predicted greater differential SCR conditioning to coloured shapes, one paired with an aversive shock (Otto et al., 2007). This suggests that the STAI-trait scale may not be strongly related to SCRs.

Elsewhere, state (rather than trait) anxiety modulated return of fear in SCRs after reinstatement: healthy participants (n=36, 21 female, mean age 27 years) completed fear acquisition, immediate extinction, and reinstatement (Kuhn et al., 2016). State anxiety (STAI) predicted generalisation of fear after cued reinstatement: more anxious participants showed an increase in fear response to both the CS+ and CS- after reinstatement shocks; in contrast,

less anxious participants showed a discriminatory increase (greater for the CS+) – a more adaptive response to a re-presentation of danger.

In a replication of Kuhn and colleagues' design, trait anxiety predicted maladaptive consolidation after sleep and reinstatement of fear. Healthy participants (n=152, 81 female, mean age 25 years) were selected on the basis of either childhood or recent adversity (Scharfenort et al., 2016). In the MRI scanner, participants completed fear acquisition and then extinction and reinstatement the next day. The control and childhood adversity groups showed differential SCRs to the CS+ and CS-, both at the first trial of day 2 and the first trial after reinstatement. In contrast, those who had experienced recent adversity – who also had significantly higher levels of trait anxiety – showed a generalised increase to both stimuli. This was reflected in greater activity in the hippocampus and amygdala. This study suggests that trait anxiety, albeit possibly driven by recent adversity, may predict impaired overnight consolidation of fear discrimination and an impaired non-discriminative reinstatement response.

Together, these studies suggest an association between anxiety and maladaptive fear learning, but the results are made ambiguous by various measures of anxiety and fear response, as well as differences in fear conditioning design. For example, Gazendum et al. (2013) found that trait anxiety was associated with SCR extinction and reinstatement expectancy ratings after 24 hours, whereas Kuhn et al. (2016) found that state anxiety was related to reinstatement in SCRs, but before sleep. In addition, Gazendum et al. used human faces, while Kuhn et al. used inanimate shapes. Since faces could specifically recruit social anxiety, the impact of stimuli should also be kept in mind.

5.1.1.2 Anxiety Beyond the STAI

The STAI is a well-validated and widely used measure of trait and state anxiety (Guillén-Riquelme & Buela-Casal, 2011; Ortuno-Sierra et al., 2016). However, anxiety is a complex emotion of which different facets can be assessed by a variety of measurement tools. In particular, the Intolerance of Uncertainty Scale (IU) comprised of prospective and inhibitory subscales has gained momentum in recent years. IU has been described as a trait variable measuring excessive concern over future events regardless of their probability: prospective anxiety as the anticipation of uncertainty and inhibitory anxiety as the tendency towards inaction based on uncertain situations (Mahoney & McEvoy, 2012). Clinically, the IU scale has been associated with Generalised Anxiety Disorder, Obsessive Compulsive Disorder, and

social anxiety (Holaway et al., 2006; Carleton et al., 2010). It has also shown good psychometric properties (Buhr & Dugas, 2002; Gosselin et al., 2008).

In fear conditioning designs, IU has predicted poorer extinction learning. Healthy participants (n=22, 12 female, mean age 24 years) completed fear acquisition and immediate extinction (Morriss et al., 2015). During early extinction learning, higher IU was associated with a lack of CS discrimination in SCRs and greater amygdala activity to the CS-. During late extinction learning, higher IU was associated with greater SCRs to the CS+ and increased ventromedial prefrontal cortex (vmPFC) activity to both the CS+ and CS-. This study was then replicated with a larger sample outside the MRI scanner (Morriss, Christakou, et al., 2016). Healthy participants (n=38, 32 female, aged 18–25 years) completed the same fear acquisition and extinction task. Again, IU was associated with a lack of CS discrimination in early extinction and continued fear expression in late extinction to the safe CS-. In both studies, there was no effect of STAI-measured trait anxiety. This suggests that IU is a sensitive measure of maladaptive extinction learning. However, the 100% reinforcement design (all previously mentioned STAI-measured studies used partial reinforcement) may have affected the results. Some evidence suggests that 100% reinforcement induces faster extinction (Xia et al., 2017), especially in people with a tendency towards anxiety (Allen et al., 2014).

Subsequently, another sample (n=60, 33 female, mean age 24 years) completed the same acquisition and extinction task, but this time with 50% reinforcement (Morriss & van Reekum, 2019). Only participants reporting high IU but also not given explicit contingency instructions showed impaired extinction. This suggests, in keeping with the definition, that the negative effects of high intolerance of uncertainty are mediated by prior knowledge of unpleasant events. These results replicate an earlier study where high IU was more strongly associated with greater fear responses at a lower 50% reinforcement rate, compared to 75% (Chin et al., 2016). In short, as uncertainty increases, the effects of IU anxiety also increase.

Together, these studies suggest that IU as a trait measure is associated with altered extinction learning. However, more research is needed to determine whether it is substantially more sensitive than the STAI to extinction and other fear conditioned outcomes, particularly reinstatement. It is also unclear how IU predicts fear responses when extinction occurs after sleep – as may be more likely in a real-life situation.

5.1.1.3 Summary

There is consistent evidence that anxiety predicts maladaptive responses under a range of experimental settings. In particular, high anxiety has been associated with impaired CS

discrimination resulting from greater maladaptive fear responses to the CS-. The literature also shows inconsistent effects for different outcomes; IU may predict poorer extinction when uncertainty in the task is high, but this has not been explored in relation to fear reinstatement – a situation which also reflects high uncertainty.

5.1.2 Bad Dreams, Anxiety, and Fear Conditioning

Dreams have long been the topic of discussion and debate as to their role in emotional processing. Although dreams occur in non-REM sleep, they are more frequent, vivid, and emotional in REM sleep and hence are more often associated with this sleep stage (McNamara et al., 2010; Nemeth & Fazekas, 2018). However, dreaming of a learning task in non-REM sleep has been associated with greater post-sleep performance, suggesting that dreams may indicate new processing/learning and that this occurs in non-REM sleep (Wamsley et al., 2010). Based on such evidence, sequential hypotheses of sleep and memory have suggested that emotional dreams in REM sleep, reflecting emotional processing, may play some role in the consolidation processes of these memories in non-REM (Paller et al., 2021; Walker & Stickgold, 2010). This would explain why emotional memories tend to show enhanced consolidation, but the mechanisms of such actions are yet to be elucidated.

As discussed in the General Introduction, dreaming has been related to the processing of recent emotional experiences during sleep (Eichenlaub et al., 2018; van Rijn et al., 2015). Further to this, a recent study has suggested that dreams are also related to aversive responses during wake. Healthy participants (total n=89, 58 female, mean age 22 years) kept a sleep and dream diary for one week. They were then tested with neutral and aversive images in the MRI scanner: fear conditioned CS+ and CS- (neutral human faces, one paired with an aversive sound), funny or sad images, and neutral and negative faces (Sterpenich et al., 2020). Participants who reported more fear in their dreams showed greater activation to aversive stimuli in the medial prefrontal cortex and lower activation in the amygdala, insula, and midcingulate cortex. Insula activity was also related to pupillometry during the conditioning task, suggesting that participants who had fearful dreams showed lower autonomic fear conditioned responses.

In an additional smaller sample within this study (n=18, 14 female, mean age 40 years), serial awakenings asking participants to report fear in their dreams throughout the night indicated greater insula and midcingulate cortex activity during fear-related dreams, as measured with high density scalp EEG. This suggests that conditioned fear responses may share neural correlates with fearful dreams themselves. In addition, fearful dreams could promote lower

fearful responses to subsequent and (presumably) unrelated stimuli. This posits fearful dreams as a protective factor towards future fear learning, as well as the consolidation of previous experiences. Overall, this study offers valuable insights, but does not offer causal evidence for these relationships; it is equally likely that fear in dreams and fear learning are driven by other factors not measured here.

Dreaming has also been related to trait anxiety, though this has varied across dream metrics. For example, in children (n=624, 284 girls, aged 10–16 years), trait anxiety predicted distress due to bad dreams independently of bad dream frequency (Schredl, 2020). Elsewhere, in a longitudinal study of adolescents (n=610, 330 girls), disturbing dreams were associated with trait anxiety at age 13 and with symptoms of Generalised Anxiety Disorder, separation anxiety, and Overanxious Disorder at age 16 (Nielsen et al., 2000). In adults, one survey study found that participants (n=30, 20 female, aged 17–45 years) with greater alexithymia (an inability to identify or describe emotions) reported significantly lower dream sharing and creative/problem-solving dreams, while higher STAI-measured trait anxiety was associated with nightmare frequency (Montebarocci & Giovagnoli, 2019). Together, these findings suggest an ambiguous relationship between the various facets of anxiety and dreams.

In summary, Sterpenich and colleagues (2020) provide evidence for a link between fearful dreams and subsequent fear conditioned responses, as well as support for the emotion regulation theory of dreaming. However, this study tested fear acquisition training; it is not clear how overnight consolidation, extinction learning, and reinstatement of fear relate to dreams. In addition, Sterpenich did not find that STAI-measured trait anxiety was related to dream emotion or frequency, but given the uncertainty from retrospective surveys, this would benefit from further investigation with additional measures of anxiety. Finally, Sterpenich only measured fear within dreams, when other types of negative dreams could also reflect emotional learning and consolidation. Therefore, ‘bad dreams’ as have been quantified in large-scale studies and which cover a range of negative dreams and nightmares (Robert & Zadra, 2014; Zadra & Donderi, 2000), could more broadly relate to fear conditioned responses.

5.1.3 Aims

Given mixed evidence, I aimed to investigate state, trait, and intolerance of uncertainty anxiety in a sample of young, healthy adults. The strongest evidence appears to converge on anxiety promoting increased fear to the CS-, this was therefore my focus. Specifically, I aimed to clarify whether the spectrum of anxiety relates to increased CS- responses across a range of time points within fear learning: after acquisition on day 1, after extinction on day 2, and after

reinstatement on day 2. There is also a lack of longer-term investigation in this field, so I aimed to test how anxiety relates to fear extinction and reinstatement after one week (day 8), as well as spontaneous reinstatement – a re-emergence of the fear response over time without additional learning.

Trait and state anxiety as measured by the STAI are common in this literature. However, intolerance of uncertainty has shown promising indications that it may be specifically related to conditioned responses. A recent factor analysis indicated that anxiety sensitivity and intolerance of uncertainty may not be separate constructs and structurally both are manifestations of neuroticism (Naragon-Gainey & Watson, 2018). However, the STAI does not necessarily wholly reflect anxiety sensitivity. An exploration of both the STAI and IU scale in regard to fear conditioning suggested a substantial shared variance, but a specific association between STAI-trait scale and CS-discrimination in SCRs, and IU with CS-discrimination in fear-potentiated startle (Sjouwerman et al., 2020). Considering these issues and the scope of this project (measuring SCR but not startle responses), I tested all three types of anxiety (STAI-trait and state scales, IU scale) against my hypotheses but did not test for differences between anxiety types.

Since most cases of impaired discrimination resulted from greater fear to the safe CS- in previous literature, I focussed on the CS- responses, though I tested associations with CS+ responses as well. Based on previous research linking dreams to trait anxiety and fear conditioned responses, I also aimed to explore bad dreams in relation to sleep metrics and the fear conditioned outcomes measured in this sample.

5.1.4 Hypotheses

1. Greater anxiety will predict greater responses to the CS- immediately after fear acquisition training.
2. Greater anxiety will predict greater responses to the CS- immediately after fear extinction training, after 24 hours and after 7 days.
3. Greater anxiety will predict greater responses to the CS- immediately after fear reinstatement, after 24 hours and after 7 days.

Additionally, I explored self-reported bad dreams in the week between fear acquisition and the final fear extinction a week later. Specifically, I investigated how bad dreams were associated with trait anxiety and fear conditioning in this healthy sample.

5.2 Methods

These data were collected within the fear conditioning experiment outlined in Chapter 3, where the experimental timeline is described in more detail.

5.2.1 Participants

I recruited 38 healthy participants (28 female, 10 male) aged 19–30 years (mean = 23.00) from Cardiff University and the surrounding area. All completed the fear conditioning and extinction/reinstatement protocol. A subset of 18 participants (10 female, 8 male) aged 20–30 years (mean = 24.17) completed further extinction and reinstatement on day 8, one failed to return for the final session. These participants were also asked to complete sleep and dream reports of the preceding night between and including the morning of day 2 and day 8.

Participants were asked about their gender, not biological sex, and all stated either male or female. In relevant analyses I therefore report on self-identified gender: male or female.

5.2.2 Measures

As described in Chapter 3, I recorded skin conductance responses (SCRs) as my primary measure of fear. Participants also gave subjective shock expectancy ratings (1–5) every eight trials. I measured overnight sleep using the Dreem Headband. These data were manually scored according to AASM guidelines.

I tested state and trait anxiety with the State Trait Anxiety Inventory (Spielberger, 1983). This measure has been widely studied and accepted for good psychometric properties (Guillén-Riquelme & Buela-Casal, 2011; Ortuno-Sierra et al., 2016). Cronbach's Alpha indicated excellent internal consistency for my sample: STAI-trait = .95, STAI-state = .92. In addition, I tested intolerance of uncertainty (comprising prospective and inhibitory anxiety) with the 12-item Intolerance of Uncertainty Scale. This more recently developed short scale has shown better psychometric properties than the original 27-item scale (Carleton et al., 2007; Helsen et al., 2013). Cronbach's Alpha indicated good internal consistency for my sample: IU = .84.

For a measure of sleep and dreams, I designed a short online survey using PsyToolkit (Stoet, 2010, 2017) to be completed each morning upon waking (**Figure 5.1**). Survey progression was shown, answers could be changed before submission, and participants were reminded of the research email address at the instruction screen to report questions or concerns.

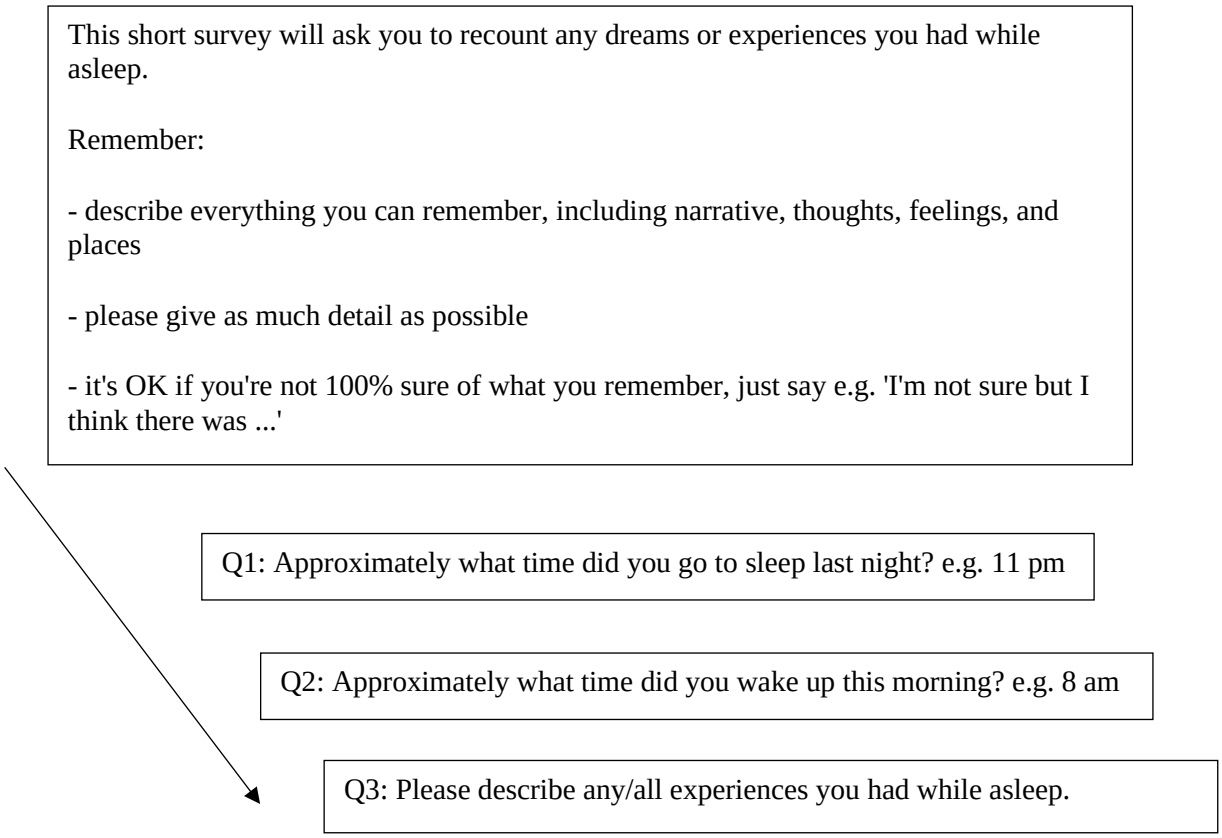


Figure 5.1 Online Sleep Survey

Each question was presented on a new screen to which participants could progress in their own time. The text is shown exactly as it appeared. Each question was followed by an empty text response box.

5.2.3 Procedure

Anxiety measures were recorded via pen and paper questionnaires prior to fear conditioning and extinction. Intolerance of uncertainty was completed once at the first testing session, while state and trait anxiety were completed at every session (the experimental timeline is shown in Chapter 3).

Sleep and dream reports were collected remotely each morning from day 2 to day 8 (total 7 days). Before the experiment began, participants were emailed survey instructions, a unique 4-digit code, and the online survey hyperlink. Their understanding of the instructions was discussed at the first testing session. Participants were prompted to enter their code (linked elsewhere to their participant ID) before and after the survey and so all data were immediately anonymised. There were no reminders to complete the survey throughout the week and no technical issues, questions, or concerns were reported.

5.2.4 Data Processing

5.2.4.1 Raw Data

Anxiety questionnaires were scored according to published instructions (see Appendix B). One participant failed to complete the trait anxiety measure on day 2. For all other participants, trait anxiety was averaged across testing sessions (there were no significant differences between days, reported in Chapter 3, Table 3.1).

I employed a simplified content analysis to quantify dream reports as bad dreams using criteria from a previous publication which were developed from the Typical Dreams Questionnaire, refined with pilot testing, then used to classify 9,796 dream reports (Robert & Zadra, 2014). Bad dreams were dependent on the identification of at least one theme: being chased, physical aggression, interpersonal conflict, environmental abnormality, evil presence, accidents, disaster/calamity, failure or helplessness, insects/vermin, health-related concerns or death, apprehension/worry, or others. A description of each category is shown in Appendix G. Two participants who did not complete the dream survey at least once were excluded.

All descriptive sleep/dream entries (my sleep survey, Q3) were collapsed across participant, separated from sleep/wake times, and shuffled to a random order. This ensured that answers from the same participants were not clustered together during analysis. Entries were assessed for whether a dream was reported and if so, whether the dream met the criteria for a 'bad dream'. Finally, these were classified into one of the bad dream categories. The classification of dream/no dream was not critical to my analyses and only facilitated the removal of non-dream entries (see example in Table 5.9). For this reason, the only parameter for this decision was whether any narrative was determined in the text. Finally, following the methodology of Robert and Zadra (2014), all entries were re-randomised and rated independently by another researcher (Dr Ross Purple, University of Bristol). I calculated agreement between our classifications, then the small number of entries for which we disagreed were discussed. All were successfully resolved.

5.2.4.2 Content Analysis: Dream Reports

Agreement between Dr Purple's and my independent content analyses (stage 1) was 98% and 93% at the first and second question, though 67% on the third question regarding which category best fitted the dream (**Figure 5.2**). Following the resolution of disagreed entries (stage 2), 60 dreams were identified, 16 of which were classified as bad dreams.

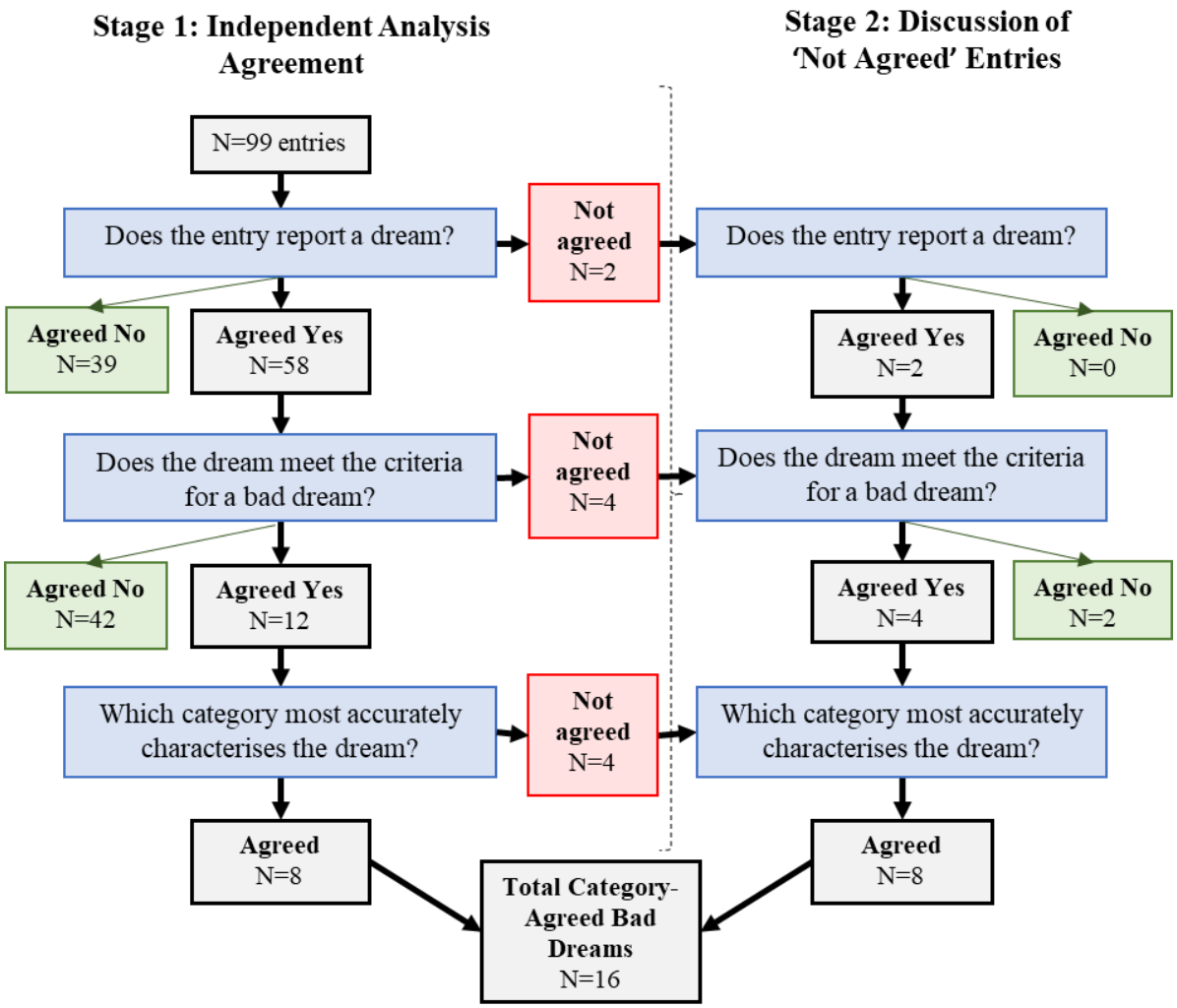


Figure 5.2 Content Analysis Agreement of Sleep and Dream Survey Descriptive Entries

Stage 1 shows agreement between independent classification of each entry according to the bad dream criteria. Those not agreed were resolved with discussion in stage 2 – those agreed 'yes' then fed into the next question. Agreed bad dream categorisations are illustrated in Figure 5.9.

5.2.5 Statistical Analyses

I used linear regression with 95% confidence intervals to assess the relationships between anxiety and SCRs. Assumptions for multicollinearity (if applicable) and heteroscedasticity were met unless otherwise indicated. Prior analyses in Chapter 3 of subjective shock expectancy ratings suggested highly uneven distributions. I therefore employed a median-split approach (creating 'high' and 'low' groups for each anxiety measure) and used the non-parametric Mann-Whitney U test to assess the significance of differences.

5.3 Results

5.3.1 Anxiety Demographics

Anxiety measures showed expected distributions, while a Friedman's ANOVA indicated no significant differences in state anxiety between days, χ^2 (2) = 0.64, p = .725 (**Figure 5.3**). Most anxiety measures and subscales showed strong and significant positive associations with one another, though prospective anxiety was unrelated to state anxiety (**Table 5.1**).

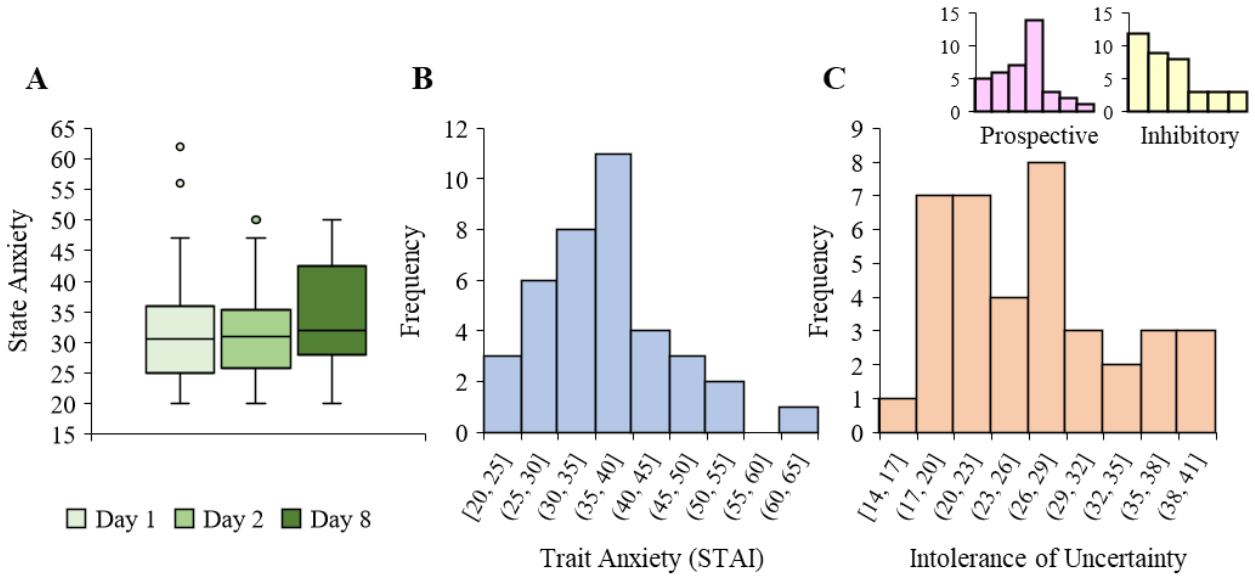


Figure 5.3 Anxiety Measure Distributions

There was no change in state anxiety across testing days (**A**). Average trait anxiety showed a normal distribution (**B**). Intolerance of uncertainty showed a largely normal distribution (**C**); of its subscales, prospective anxiety was normally distributed but inhibitory anxiety was slightly skewed towards lower responses.

Table 5.1 Correlations Between Anxiety Measures

	Prospective Anxiety	Inhibitory Anxiety	Total Intolerance of Uncertainty	State Anxiety (day 1)	State Anxiety (day 2)	State Anxiety (day 8)	State Anxiety (mean)	Trait Anxiety (mean)
Prospective Anxiety								
Inhibitory Anxiety	*.53* **							
Total Intolerance of Uncertainty	*.90* ***	*.84* ***						
State Anxiety (day 1)	*.23*	*.42* *	*.36* *					
State Anxiety (day 2)	*.19*	*.33* *	*.29*	*.70* ***				
State Anxiety (day 8)	*-.09*	*.42*	*.24*	*.63* *	*.40*			
State Anxiety (mean)	*.26*	*.44* **	*.39* *	*.93* ***	*.87* ***	*.81* ***		
Trait Anxiety (mean)	*.46* **	*.57* ***	*.58* ***	*.66* ***	*.57* ***	*.82* **	*.72* ***	

* $p < .050$, ** $p < .010$, *** $p < .001$.

5.3.2 Trait Anxiety and Fear Conditioning

While I hypothesised associations between anxiety and CS- responses, I also tested CS+ responses. As in Chapter 3, I used the last trial of each phase to indicate learning and did not correct for multiple comparisons.

The median split of shock expectancy ratings meant 22/38 participants were assigned the same group for all anxiety types. I considered this variation sufficient to explore each anxiety individually. As expected, following this split, anxiety scores in the high groups were significantly greater: trait anxiety, t (35) = -7.13, $p < .001$; state anxiety, t (35) = -6.85, $p < .001$; intolerance of uncertainty, t (35) = -8.68, $p < .001$. Two participants (one male, one female) who scored exactly the median value in trait anxiety were excluded from this variable.

Finally, testing for associations between anxiety and total sleep time, SWS %, and REM % suggested that anxiety was independent of post-conditioning sleep, *ps* = .188–.969 (full results in Appendix G).

5.3.2.1 Fear Acquisition and Extinction

No anxiety measure was significantly associated with CS+ or CS- responses (SCRs) after acquisition on day 1, or after extinction on day 2 or day 8 (**Figure 5.4**, **Table 5.2**). Further to this, I did not find an association between anxiety and overnight change in CS+ or CS-, *p*s = .315–.890 (full results in Appendix G).

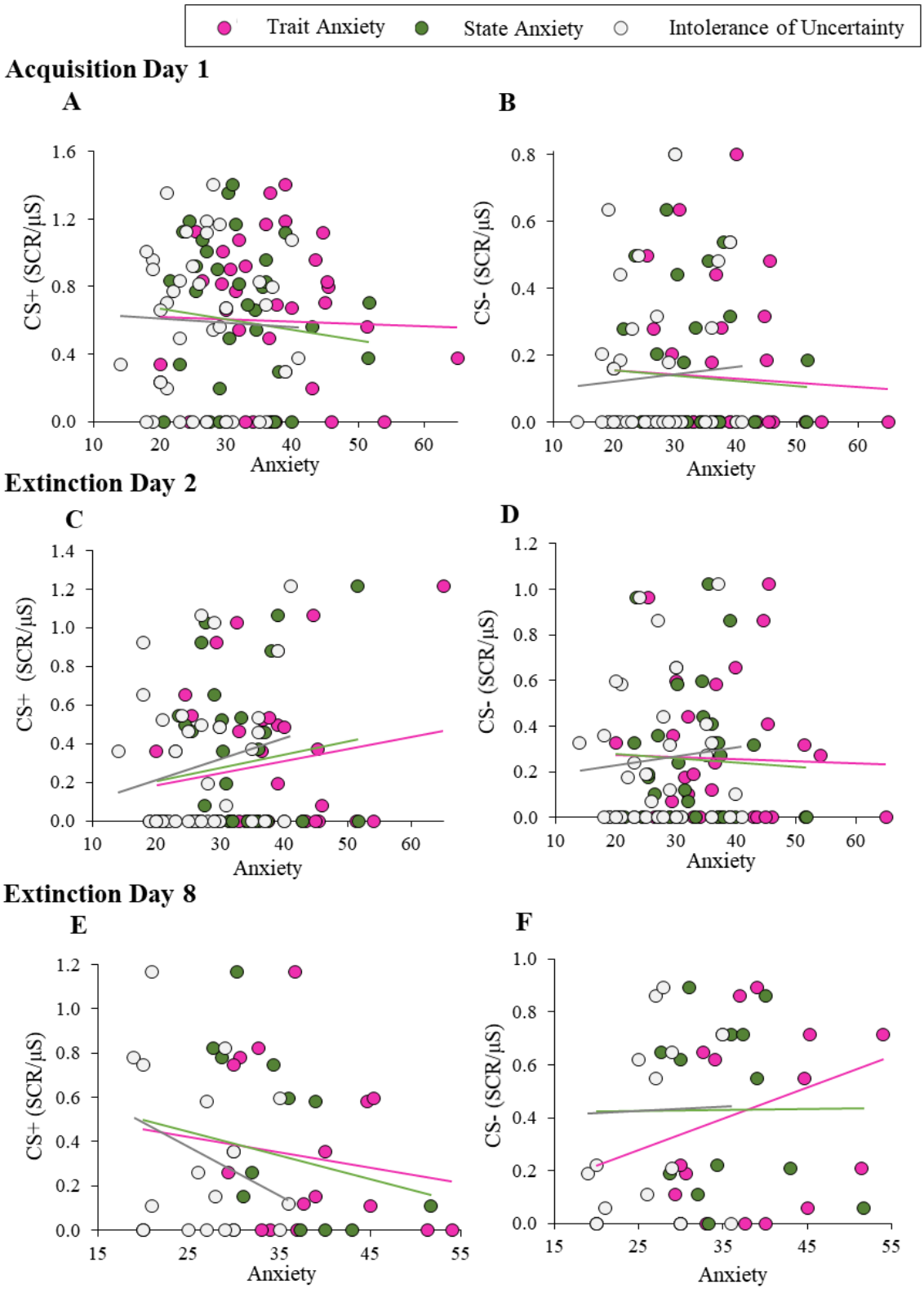


Figure 5.4 Associations Between Anxiety and SCRs After Fear Acquisition and Extinction

There were no significant associations between trait, state, or intolerance of uncertainty anxieties and CS+ or CS- responses after acquisition (**A**–**B**). Likewise, there were no associations with responses after extinction on day 2 or day 8 (**C**–**F**).

Table 5.2 Associations Between Anxiety and SCRs After Acquisition and Extinction

						Unstandardised Coefficients	
		Anxiety Type	R^2	F (*1,35*)	*p*	B [SE]	95% CI
Acquisition	CS+	Trait	.00	0.03	.865	0.00 [0.01]	-0.02, 0.02
		State	.01	0.31	.583	-0.01 [0.01]	-0.03, 0.02
		IU	.02	0.06	.812	0.00 [0.01]	-0.02, 0.02
	CS-	Trait	.01	0.23	.635	0.00 [0.01]	-0.01, 0.01
		State	.00	0.10	.751	0.00 [0.01]	-0.01, 0.01
		IU	.01	0.19	.668	0.00 [0.01]	-0.01, 0.01
Extinction Day 2	CS+	Trait	.03	0.94	.339	0.01 [0.01]	-0.01, 0.02
		State	.02	0.52	.474	0.01 [0.01]	-0.01, 0.02
		IU	.04	1.49	.231	0.01 [0.01]	-0.01, 0.03
	CS-	Trait	.00	0.03	.860	0.00 [0.01]	-0.01, 0.01
		State	.01	0.18	.679	0.00 [0.01]	-0.02, 0.01
		IU	.01	0.19	.662	0.00 [0.01]	-0.01, 0.02
Extinction Day 8	CS+	Trait	.03	0.03	.535	-0.01 [0.01]	-0.04, 0.02
		State	.04	0.69	.421	-0.01 [0.01]	-0.04, 0.02
		IU	.10	1.70	.212	-0.02 [0.02]	-0.06, 0.01
	CS-	Trait	.09	1.42	.252	0.02 [0.01]	-0.01, 0.04
		State	.00	0.00	.982	0.00 [0.02]	-0.03, 0.03
		IU	.00	0.01	.937	0.00 [0.02]	-0.04, 0.05

Linear Regression.

In subjective shock expectancy ratings, there were no significant differences between high and low anxiety groups at the end of fear acquisition. On day 2, there was a non-significant difference where high trait anxiety was associated with greater CS+ responses, but this was not present on day 8 or across other anxiety measures (**Figure 5.5, Table 5.3**).

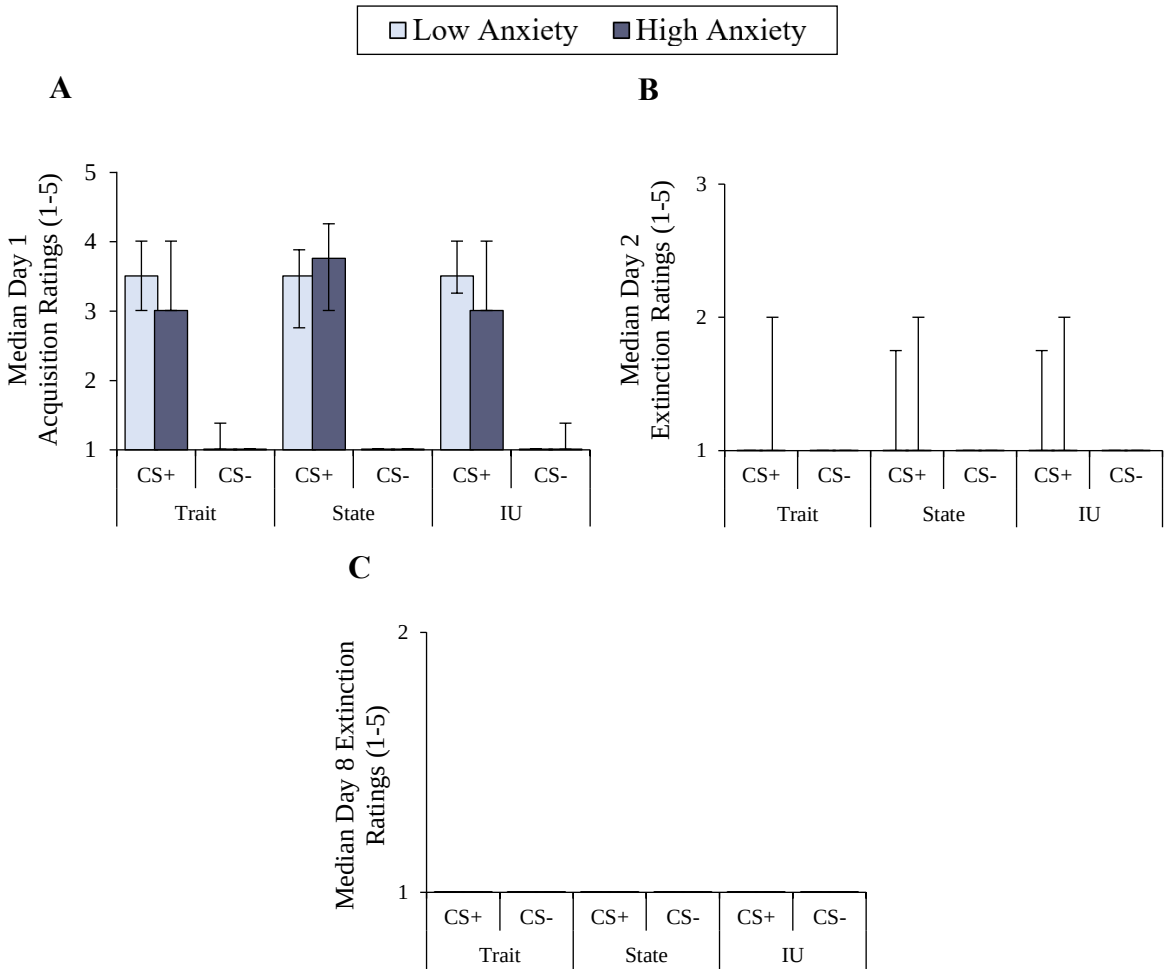


Figure 5.5 Subjective Shock Expectancy Ratings by High and Low Anxiety After Fear Acquisition and Extinction

There were no significant differences in subjective shock expectancy ratings between all low and high anxiety groups after acquisition on day 1 (**A**). There was a non-significant difference in trait anxiety after extinction on day 2, though this is not evident from the median values (**B**). There were no differences after extinction on day 8 (**C**). On day 8, low and high anxiety groups were redefined by participants who returned for this session. Error bars show IQR, though in many cases this was 0.

Table 5.3 Subjective Rating Differences Between High and Low Anxiety Groups After Acquisition and Extinction Learning

Learning Phase	Stimulus	Anxiety	Z	*p*
Acquisition (Day 1)	CS+	Trait	-0.54	.587
		State	-0.58	.565
		IU	-1.25	.213
	CS-	Trait	-1.11	.266
		State	-0.21	.833
		IU	-0.89	.375
Extinction on Day 2	CS+	Trait	-1.66	.097
		State	-0.24	.813
		IU	-0.21	.826
	CS-	Trait	-0.40	.693
		State	-1.61	.107
		IU	-0.50	.615
Extinction on Day 8	CS+	Trait	0.00	1.000
		State	-0.28	.781
		IU	0.00	1.000
	CS-	Trait	0.00	1.000
		State	-0.18	.854
		IU	0.00	1.000

Mann Whitney U tests.

5.3.2.2 Fear Reinstatement

I then investigated associations between anxiety and reinstatement. I assessed cued reinstatement on day 2 and day 8 as well as spontaneous reinstatement over this 7-day period where no learning occurred. Anxiety predicted greater CS- responses at the first trial after cued reinstatement on day 2, but there were no other significant associations (**Figure 5.6, Table 5.4**). Further analyses of anxiety subscales suggested that the IU and state anxiety results were driven by prospective anxiety and state anxiety on day 2 respectively (**Table 5.5**).

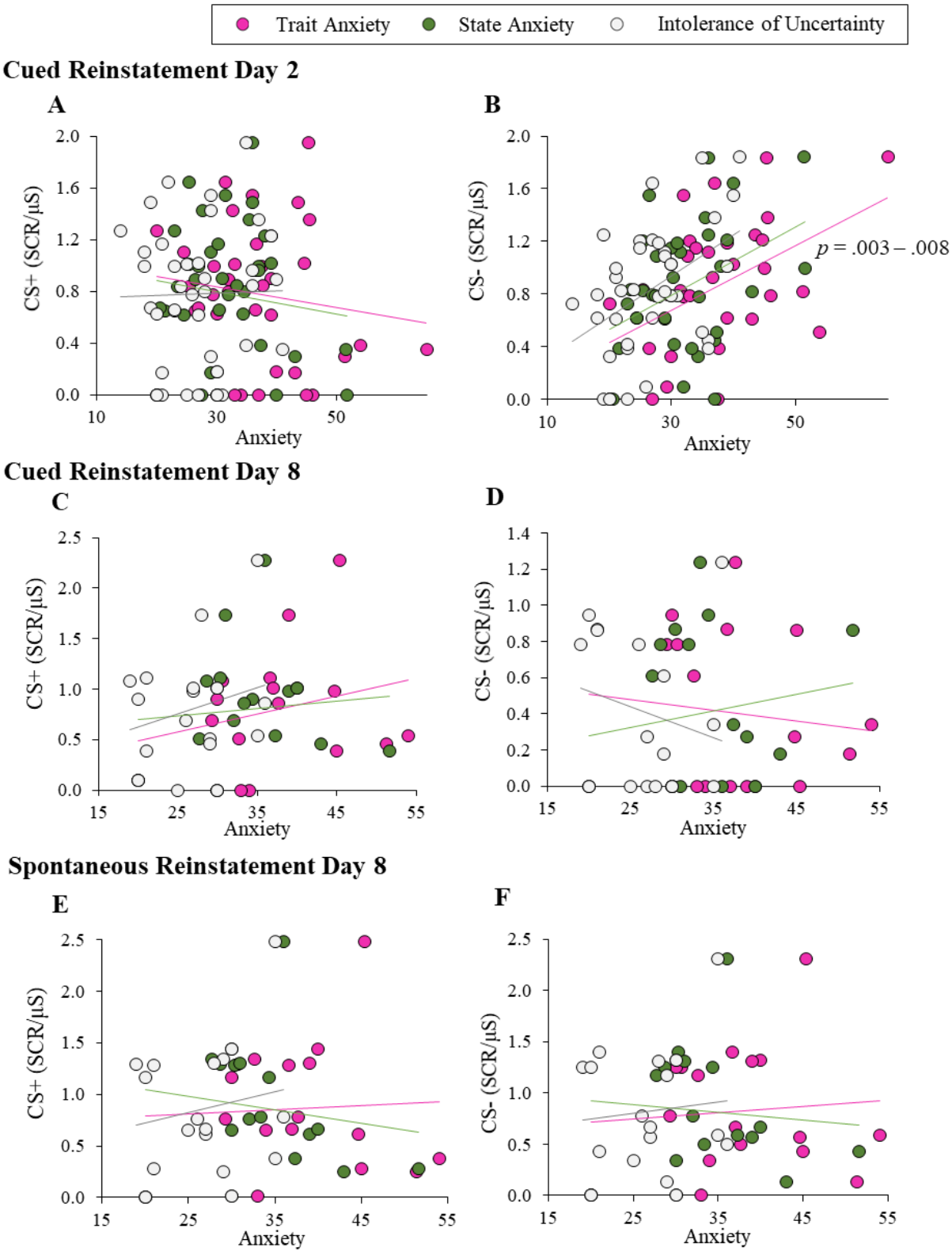


Figure 5.6 Associations Between Anxiety and SCRs After Reinstatement

There were no significant associations between anxiety and CS+ responses (**A**), but all anxiety measures predicted greater CS- responses after cued reinstatement on day 2 (**B**). There were no significant associations on day 8 (**C**–**F**). Significant *p*-values are shown.

Table 5.4 Associations Between Anxiety and SCRs After Reinstatement

						Unstandardised Coefficients	
		Anxiety	R^2	F (*1,35*)	*p*	B [SE]	95% CIs
Cued Reinstatement Day 2	CS+	Trait	.01	0.44	.511	-0.01 [0.01]	-0.03, 0.01
		State	.02	0.64	.429	-0.01 [0.01]	-0.03, 0.01
		IU	.00	0.02	.892	0.00 [0.01]	-0.03, 0.03
	CS-	Trait	.23	10.55	.003	0.03 [0.01]	0.01, 0.04
		State	.18	7.86	.008	0.03 [0.01]	0.01, 0.05
		IU	.20	8.77	.005	0.03 [0.01]	0.01, 0.05
Cued Reinstatement Day 8	CS+	Trait	.08	1.30	.272	0.02 [0.02]	-0.02, 0.06
		State	.01	0.19	.668	0.01 [0.02]	-0.04, 0.05
		IU	.06	0.93	.349	0.03 [0.03]	-0.03, 0.08
	CS-	Trait	.03	0.38	.545	-0.01 [0.01]	-0.04, 0.02
		State	.01	0.20	.660	0.01 [0.02]	-0.03, 0.04
		IU	.50	0.75	.400	-0.02 [0.02]	-0.06, 0.03
Spontaneous Reinstatement Day 8	CS+	Trait	.01	0.11	.747	0.01 [0.02]	-0.04, 0.05
		State	.02	0.27	.620	-0.01 [0.02]	-0.06, 0.04
		IU	.03	0.47	.504	0.02 [0.03]	-0.04, 0.08
	CS-	Trait	.01	0.17	.690	0.01 [0.02]	-0.03, 0.05
		State	.01	0.11	.743	-0.01 [0.02]	-0.05, 0.04
		IU	.01	0.14	.713	0.01 [0.03]	-0.05, 0.07

Linear Regression.

Table 5.5 Driving Factors for Associations Between Anxiety and CS- SCRs After Reinstatement on Day 2

Anxiety		R^2	F (*1,35*)	*p*	Unstandardised Coefficients	
					B [SE]	95% CI
IU	Prospective Anxiety	.21	9.12	.005	0.05 [0.02]	0.02, 0.08
	Inhibitory Anxiety	.10	3.70	.063	0.04 [0.02]	0.00, 0.09
State Anxiety	Day 1	.09	3.46	.071	0.01 [0.01]	0.00, 0.03
	Day 2	.17	7.02	.012	0.03 [0.01]	0.01, 0.05
	Day 8	.09	1.46	.247	0.02 [0.02]	-0.01, 0.05

Linear Regression.

Subjective shock expectancy ratings after reinstatement showed similar but weaker results. There were no significant differences between low and high anxiety. However, despite equal medians, there was a non-significant effect where participants with high IU gave higher ratings to the CS- after cued reinstatement on day 2 (**Figure 5.7, Table 5.6**). In this case, the data met the assumptions for linear regression and further investigation indicated a significant association between prospective anxiety and these CS- ratings, R^2 = .11, F (1,36) = 4.58, *p* = .039, B = 0.04, SE = 0.02, CI = [0.00, 0.08]. There was a non-significant association for inhibitory anxiety, R^2 = .05, F (1,36) = 1.99, *p* = .167, B = 0.03, SE = 0.02, CI = [-0.01, 0.08].

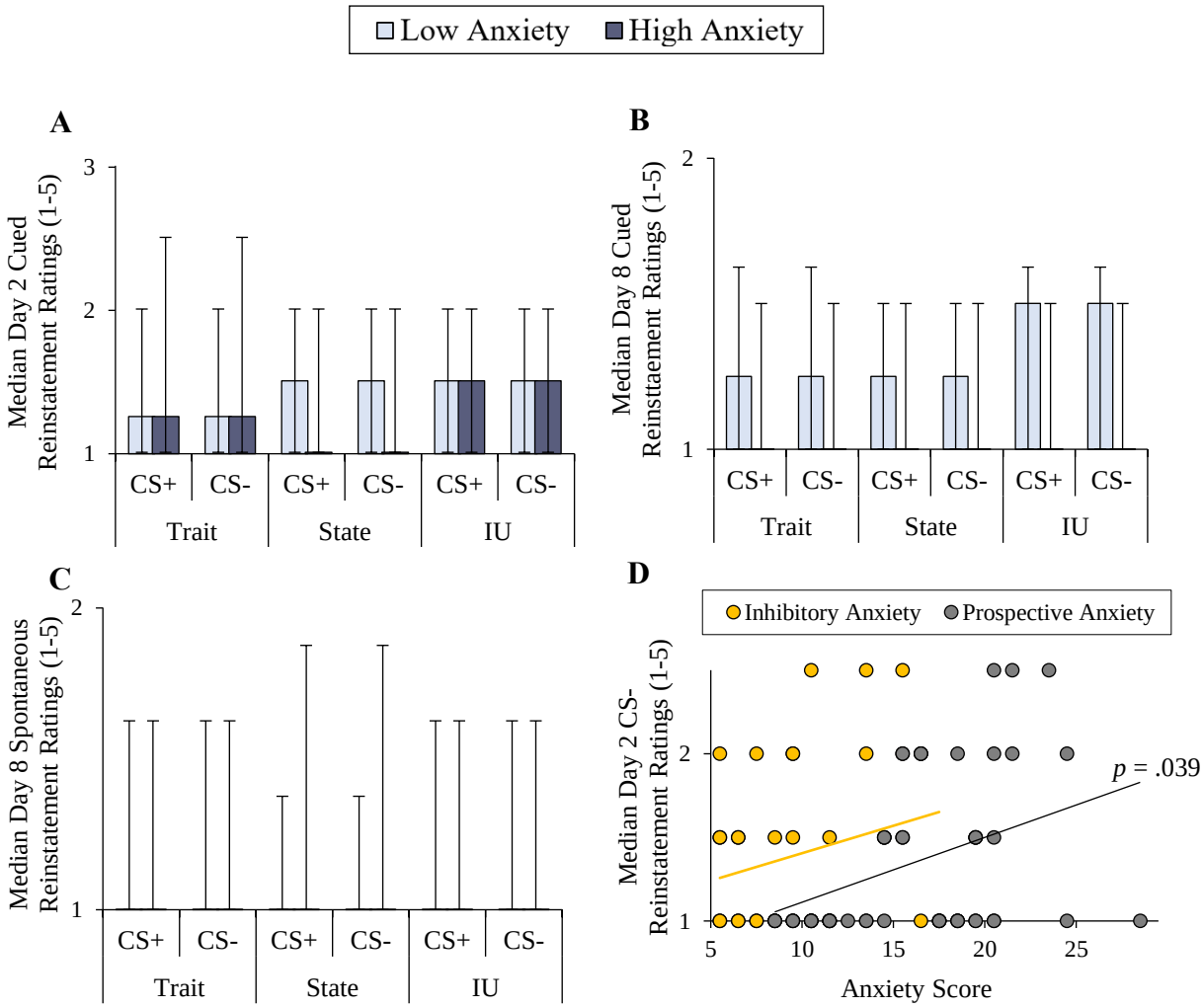


Figure 5.7 Shock Expectancy Ratings by High and Low Anxiety After Reinstatement

There were no significant differences between low and high anxiety groups in shock expectancy ratings after cued reinstatement on day 2 (**A**), cued reinstatement on day 8 (**B**), or spontaneous reinstatement (**C**), error bars show IQR. However, there was a non-significant difference between IU and CS- responses on day 2, not evident from the medians. Subsequent analyses indicated a significant association in prospective but not inhibitory anxiety (**D**). Significant *p*-values are shown.

Table 5.6 Subjective Rating Differences Between High and Low Anxiety After Reinstatement

		Anxiety	Z	*p*
Cued Reinstatement Day 2	CS+	Trait	-0.67	.505
		State	-0.55	.583
		IU	-0.79	.428
	CS-	Trait	-1.25	.213
		State	-0.32	.750
		IU	-1.85	.064
Cued Reinstatement Day 8	CS+	Trait	-0.85	.397
		State	-0.23	.820
		IU	-1.31	.190
	CS-	Trait	-0.19	.854
		State	-0.56	.577
		IU	-0.68	.496
Spontaneous Reinstatement Day 8	CS+	Trait	-0.41	.685
		State	-0.82	.413
		IU	-0.58	.563
	CS-	Trait	-0.19	.854
		State	-0.26	.796
		IU	0.00	1.000

Mann Whitney U tests.

In post-hoc analyses, I investigated gender differences (10 males, 28 females; one male participant was missing from SCR data) within the significant SCR reinstatement effect across the sample on day 2. Moderated multiple regression testing the effect of gender on the relationship between anxiety and CS- responses indicated significant moderation effects in all anxiety measures (**Figure 5.8, Table 5.7**). This cannot be explained by significant differences between males and females in any reported anxiety measure, *ps* = .367–.380 (I show how males and females responded across the experiment in Appendix G).

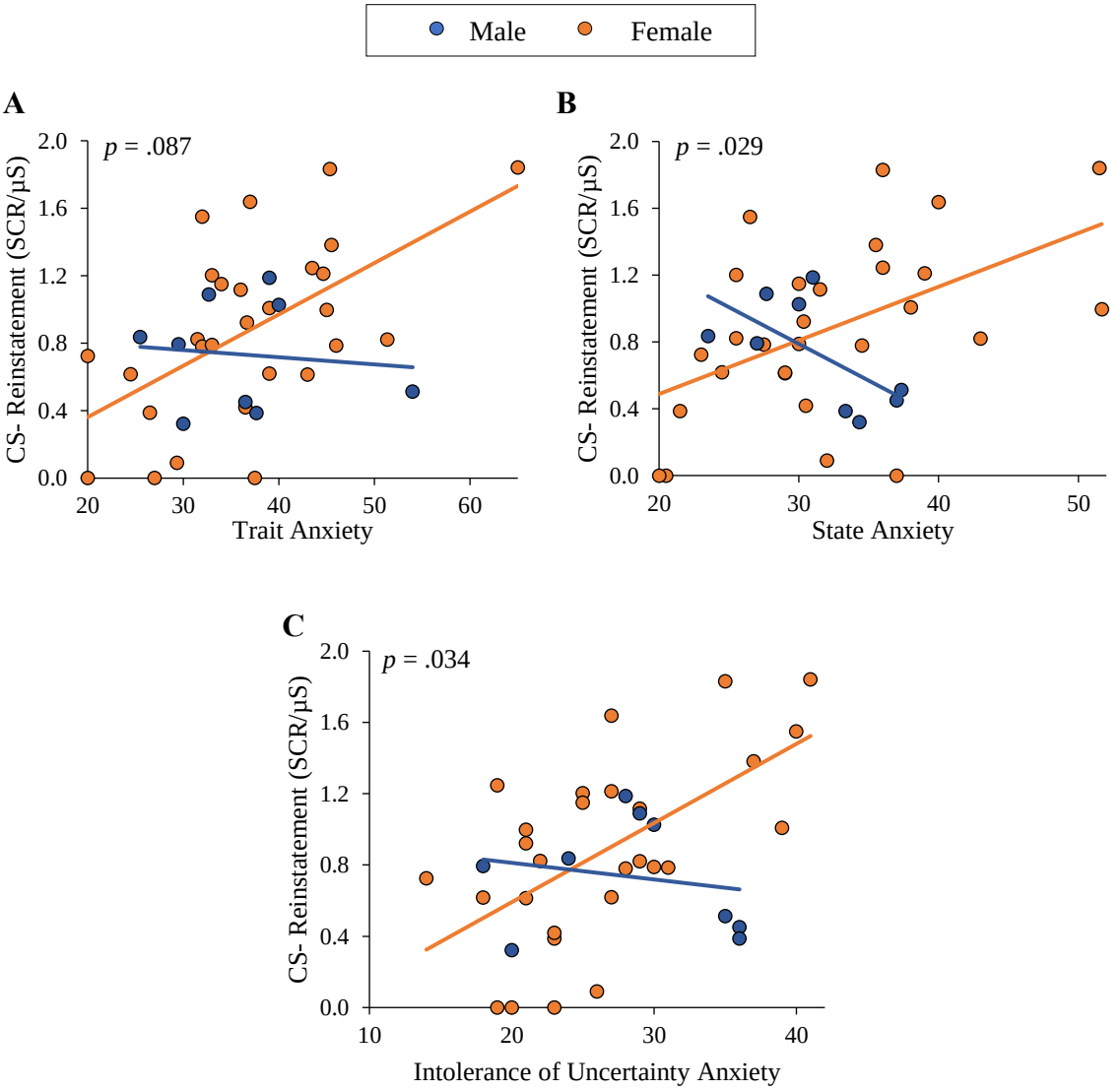


Figure 5.8 Gender as a Moderator for the Association Between Post-Reinstatement CS- Responses on Day 2 and Anxiety

There were similar moderation effects of gender between CS- responses after reinstatement on day 2 and trait anxiety (**A**), state anxiety (**B**), and intolerance of uncertainty (**C**). This was slightly short of significance in trait anxiety. In all measures, females showed a positive association whereas males showed a slightly negative or neutral association. Anxiety groups were not redefined based on gender (males were split evenly between all groups). Error bars show IQR. Significant *p*-values indicating moderation effects are shown.

Table 5.7 Gender Moderation Between Anxiety and CS- SCRs After Day 2 Reinstatement

Model Predictors		t	*p*	Unstandardised Coefficients	
				B [SE]	95% CI
Trait Anxiety and Gender	Constant	5.24	< .001	0.73 [0.14]	0.45, 1.02
	Trait Anxiety	2.92	.006	0.02 [0.01]	0.01, 0.04
	Gender	0.87	.393	0.14 [0.16]	-0.19, 0.46
	Interaction	1.76	.087	0.04 [0.02]	-0.01, 0.08
State Anxiety and Gender	Constant	4.57	.001	0.67 [0.15]	0.37, 0.97
	State Anxiety	1.15	.258	0.01 [0.01]	-0.01, 0.04
	Gender	1.15	.260	0.19 [0.17]	-0.15, 0.53
	Interaction	2.29	.029	0.08 [0.04]	0.01, 0.15
Intolerance of Uncertainty and Gender	Constant	5.34	< .001	0.75 [0.14]	0.46, 1.03
	IU Anxiety	3.13	.036	0.03 [0.01]	0.01, 0.05
	Gender	0.94	.354	0.15 [0.16]	-0.18, 0.47
	Interaction	2.21	.034	0.05 [0.02]	0.00, 0.10

Continuous variables were mean centred. Each section shows a separate linear regression model. R^2 = .31, .29, and .33 respectively, *df* = (3,33), all *p* < .010.

5.3.3 Bad Dreams, Anxiety, and Fear Conditioning

In the second sample of participants within my fear conditioning experiment, I also explored bad dreams. All retained participants (n=16) completed the sleep and dream survey for at least 4 out of 7 nights (mean completed = 6.19, SD = 1.05). Most (n=14) participants reported entries later classified as dreams, the average word count of these entries was 90.04 (SD = 35.75), 27% of these were classified as bad dreams. Examples are illustrated in **Table 5.8**.

An investigation into bad dream frequency per category and per participant indicated that the most common category was interpersonal conflict and nearly half the sample did not have any bad dreams (**Figure 5.9**). I therefore disregarded these factors and, for subsequent analyses, compared participants who reported at least one bad dream throughout the week (n=9) with those who did not (n=7).

Table 5.8 Sleep Survey Examples

Classification	Entry
Bad Dream	*"I remember my mum starting a fight with me over something she had thought but not communicated. Berating me for not having expected and done so for her. I felt misunderstood as she wouldn't listen to me, just saying I was lying. I felt anything good was ignored, and only the apparently disappointing sides were remembered/ falsely recalled.~~~~I also woke myself worrying I had overslept.that was enough to startle me to check my clock."*
Dream (did not meet criteria for a bad dream)	*"All I can remember was I was at a fare with my boyfriend. Just have little snippets of going on ride, eating food and winning toys"*
Non-Dream Entry	*"I had one awakening during the night but I don't remember any dreams."*

Descriptive sleep entries as collected from my sleep and dream survey (Q3). The agreed category for this bad dream was interpersonal conflict.

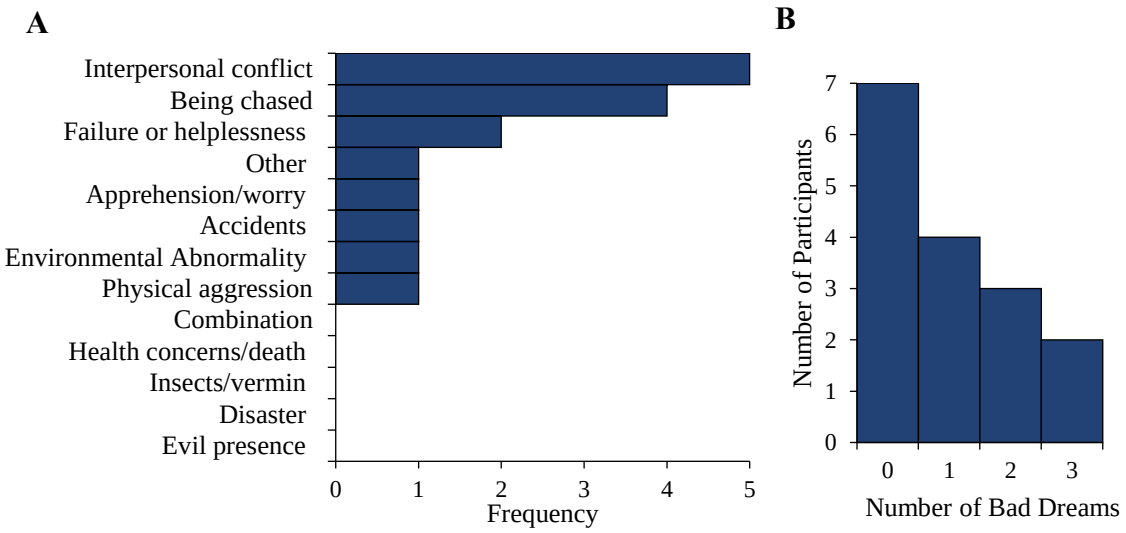


Figure 5.9 Bad Dream Frequency per Category and Participant

The most common category of bad dream was interpersonal conflict, some categories were not observed (**A**). Nearly half of the sample did not report any bad dreams, but of participants that did, it was most common to only report one (**B**).

5.3.3.1 Sleep and Anxiety

I explored whether the presence of bad dreams was associated with anxiety. There was no significant difference between bad dreamers and non-bad dreamers across state, t (14) = -0.25, *p* = .807, trait, t (14) = 0.79, *p* = .443, or intolerance of uncertainty, t (14) = 1.15, *p* = .270 measures (**Figure 5.10A**).

I then explored the presence of bad dreams in relation to self-reported sleep over seven days and the single Dreem-recorded night between day 1 and day 2 of the experiment, though only 11/16 recorded nights were intact (7/9 bad dreamers, 4/7 non-bad dreamers). Bad dreamers had significantly greater average self-reported total sleep times during the week after conditioning, t (14) = -2.33, *p* = .035. A corresponding difference in the recorded post-conditioning night was not significant after correction for unequal variance, t (3.37) = -2.19, *p* = .106 (**Figure 5.10B**). However, total monitored sleep time was positively correlated with self-reported sleep time of the same night, *r* = .75, *p* = .007, although participants significantly overestimated their time spent asleep (mean = 0.51 hours, SD = 0.71; t (10) = 2.39, *p* = .038). Finally, SWS % in the recorded post-conditioning night was lower in bad dreamers, t (9) = 3.43, *p* = .008; there was no difference in REM %, t (9) = -0.32, *p* = .759 (**Figure 5.10C**).

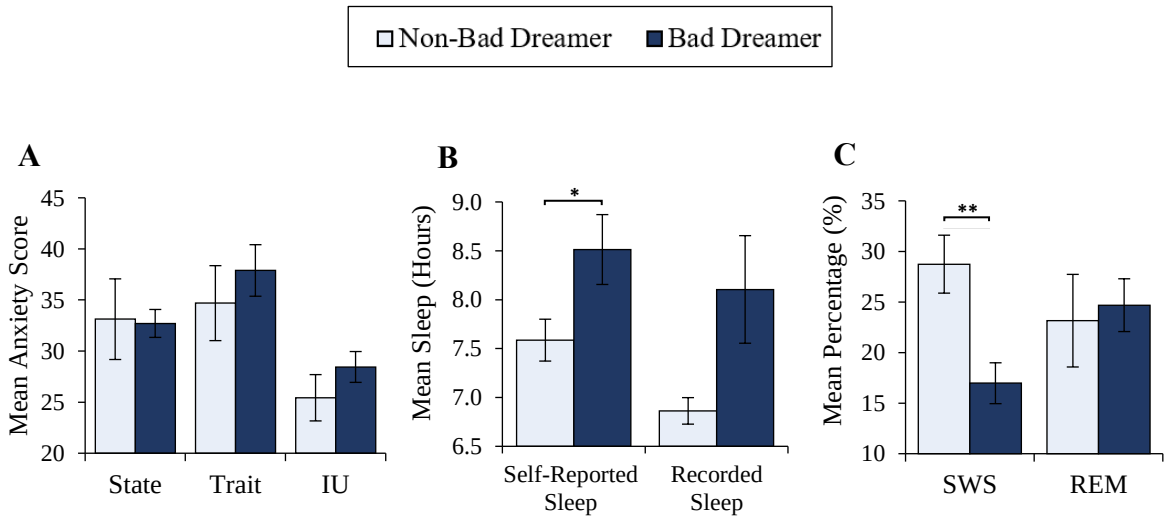


Figure 5.10 Anxiety and Sleep in Bad Dreamers and Non-Bad Dreamers

There were no significant differences in state, trait, or intolerance of uncertainty anxiety measures between participants who did or did not report bad dreams (**A**). However, participants reporting bad dreams had significantly more sleep across the week (total n=16) and had more (though not significantly) recorded sleep immediately following conditioning (total n=11; **B**), they also showed less SWS % but similar REM % (**C**). Error bars show ± SEM. * *p* < .050, ** *p* < .010.

Lower SWS % in the night following conditioning could not be explained by more time spent asleep, as these participants also spent fewer minutes in SWS, t (9) = 2.44, p = .037. There was also no difference in self-reported sleep time averaged between the nights when the bad dreams occurred (mean = 8.45 hours, SD = 0.89) and nights when they did not occur (mean = 8.50 hours, SD = 0.59), t (8) = -0.33, p = .747. This suggests that people with a propensity for bad dreams tend to sleep for longer on all nights, rather than bad dreams themselves causing longer sleep.

5.3.3.2 Bad Dreams and Fear Learning

I then investigated bad dreams and fear learning. I found that participants who reported bad dreams were significantly less likely to show discriminative fear learning at the end of acquisition training on day 1, χ^2 = 5.66, Fisher's Exact p = .034 (**Table 5.9**).

Table 5.9 Contingency Table: Frequency of Bad Dreamers and Non-Learners

	Did Learn	Did Not Learn
Did Report Bad Dreams	4	5
Did Not Report Bad Dreams	7	0

Non-learners were defined by a zero or negative discriminatory (SCR) response between the CS+ and CS- at the last trial of fear acquisition on day 1. This was reflective of an impaired learning curve (see Chapter 3).

Given that bad dreams were related to sleep but not anxiety, I then explored fear conditioned outcomes previously related to sleep: overnight consolidation and extinction. Bad dreamers showed significantly greater CS- responses compared to non-bad dreamers in change overnight and after day 8 extinction; on day 8 this led to significantly reduced CS discrimination (**Figure 5.11**). These results could be driven by bad dreamers being more likely to lack fear learning. However, despite the smaller sample size, I found similar effects with only the 11 participants who showed fear learning, i.e. excluding non-learners (**Table 5.10**).

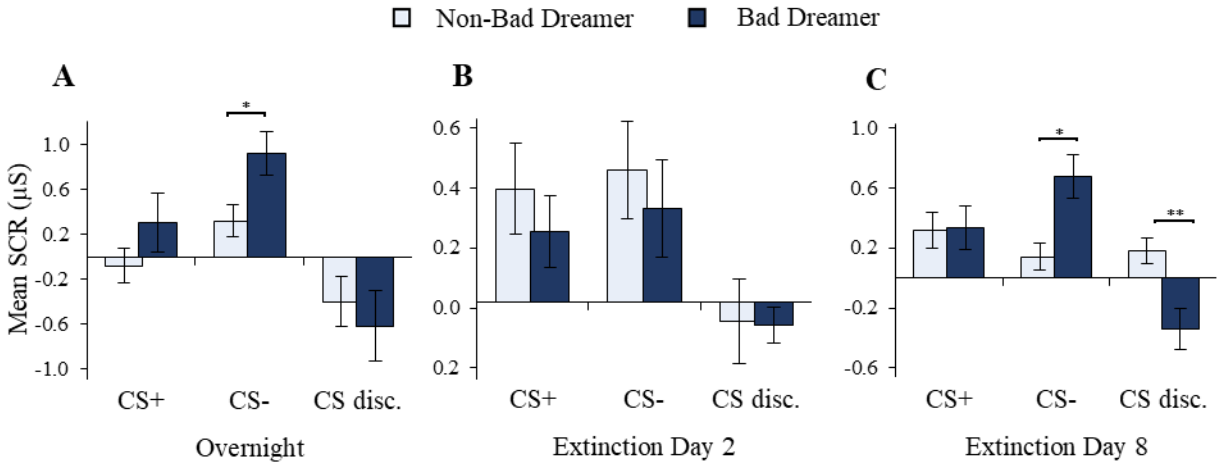


Figure 5.11 Bad Dreamer and Non-Bad Dreamer Fear Responses Overnight and After Extinction

Bad dreamers showed significantly greater CS- SCR changes overnight (**A**). There were no significant differences after extinction learning on day 2 (**B**), but bad dreamers showed greater CS- SCRs and a more negative CS discrimination on day 8 (**C**). N=16, error bars show ± SEM.* $p < .050$ ** $p < .010$.

Table 5.10 Differences Between Bad Dreamers and Non-Bad Dreamers in Overnight Change and Extinction Learning: Including and Excluding Non-Learners

		Original Result (n=16, 9 bad dreamers)		Learners Only (n=11, 4 bad dreamers)	
		t (*df*)	*p*	t (*df*)	*p*
Overnight Change	CS+	-1.22 (13)	.245	-0.39 (9)	.709
	CS-	-2.41 (13)	.032	-3.26 (9)	.010
	CS Disc.	0.54 (13)	.599	1.60 (9)	.143
Extinction (Day 2)	CS+	0.75 (14)	.467	0.48 (9)	.643
	CS-	0.54 (14)	.595	0.72 (9)	.492
	CS Disc.	0.09 (14)	.932	-0.35 (9)	.733
Extinction (Day 8)	CS+	-0.08 (13)	.940	-0.96 (8)	.365
	CS-	-2.75 (13)	.017	-2.65 (8)	.029
	CS Disc.	3.23 (12.56)	.007	2.38 (8)	.045

Independent-samples t-tests.

5.4 Discussion

5.4.1 Summary of Results

In this chapter I investigated the relationship between anxiety and fear conditioned outcomes in healthy people. I hypothesised that anxiety would predict maladaptive fear acquisition, extinction, and reinstatement via greater CS- responses. I found no evidence for an association with fear acquisition or extinction, but greater anxiety predicted maladaptive reinstatement on day 2 in line with previous literature, though I did not find that the effect extended to reinstatement on day 8 (**Figure 5.6**). In a post-hoc exploration of the day 2 result, I found a significant moderation effect of gender whereby the positive association was only present in females. This suggests that the sample-wide effect was driven by the greater proportion of female participants.

I tested trait, state, and intolerance of uncertainty anxiety measures, finding that all predicted CS- reinstatement on day 2. However, further investigation indicated the strongest differences in state anxiety measured on day 2 and the prospective anxiety subscale of IU. State and prospective anxiety were not significantly associated with each other, so these different facets of anxiety may independently predict maladaptive reinstatement, though this would require replication. I did not test for differences between the anxiety measures.

Subjective shock expectancy ratings followed a similar pattern to SCRs. I found no significant differences in acquisition or extinction when splitting the sample into low and high anxiety groups. Anxiety predicted greater CS- shock expectancy ratings at reinstatement on day 2, but unlike SCRs, only in prospective anxiety. This measure could therefore be particularly sensitive to conscious reinstatement, which may be less strongly affected by anxiety than SCRs.

Finally, I explored the presence of bad dreams in a subset of participants. I found no association between bad dreams and anxiety, but participants who reported at least one bad dream in the week between fear acquisition and extinction on day 8 showed a range of maladaptive fear responses. Specifically, bad dreamers showed a greater increase in CS- change overnight following acquisition as well as greater CS- responses after extinction on day 8. In effect, less fear learning. In addition, bad dreamers had significantly longer self-reported sleep across the week, with a corresponding (non-significant) difference towards longer Dreem-recorded sleep on the post-conditioning night, as well as a lower percentage of SWS. In line with Sterpenich et al. (2020), these results suggest an association between maladaptive fear learning and bad dreams, though neither offer causal evidence for bad dreams affecting fear learning or vice versa.

5.4.2 Greater CS- Responses: A Generalisation of Fear

My results suggest that greater anxiety predicts greater fear responses to the CS- after cued reinstatement. This can be explained by a generalisation of fear from the CS+ to other stimuli experienced in the same context. Fear generalisation may be considered an opposing mechanism to fear discrimination. In the context of a fear conditioning experiment, this reflects maladaptive and adaptive learning respectively (Dunsmoor & Paz, 2015). In support of this, fear generalisation and discrimination have been found to engage different circuits within the lateral amygdala, suggesting separable neural correlates (Grosso et al., 2018). However, both are crucial aspects of learning. While discrimination helps us determine danger, we must also be able to generalise, i.e. we do not need to see every possible example of a dangerous category to know to avoid it, but we cannot overgeneralise to be afraid of safe situations. A recent systematic review and meta-analysis suggested that trait anxiety increases vulnerability to anxiety disorders through fear generalisation (Sep et al., 2019). Therefore, the discrimination versus generalisation of fear appears to be a balance disrupted by anxiety, pushing responses towards a *better safe than sorry,* generalisation-heavy approach (Cho et al., 2021).

Anxiety has been strongly associated with fear generalisation, especially when uncertainty in the task is high (Dunsmoor & Paz, 2015; Dymond et al., 2015). In one study, participants (n=80, 43 female, mean age 21 years) were selected for high or low anxiety measured by the Depression Anxiety Stress Scale (Wong & Lovibond, 2018). Relative positions of a black dot indicated an unpleasant shock (CS+) or safety (CS-), while intermediate positions served as generalisation stimuli. Participants were also asked to determine the rule. The results indicated no effect of anxiety when a rule was identified, but excessive generalisation of fear (SCRs) in the high anxiety group when a rule was not identified. This suggests that higher anxiety in an uncertain situation promotes fear generalisation. My finding of greater fear responses to the safe CS- with greater anxiety could similarly represent a generalisation of fear in an uncertain situation – in this case after a reminder shock.

Correspondingly, IU anxiety has also been associated with fear generalisation. For example, participants (n=48, 25 female, mean age 20 years) were presented with a CS+ image paired with a shock and a range of perceptually similar images to test generalisation while EEG was recorded (Nelson et al., 2015). Like my study, participants completed the 12-item IU scale and the STAI. The late positive potential, an index of motivationally salient attention, was greater for the CS+ compared to the generalisation stimuli, but this effect was attenuated in participants reporting higher IU. In another study, participants (n=54, 49 females, mean age 19 years) completed a similar conditioning and generalisation procedure and high IU was

associated with delayed discrimination between threat and safe cues during extinction (Morriss, Macdonald, et al., 2016). In both cases, the effects were independent of STAI-measured trait anxiety.

These studies suggest that anxiety leads to reduced discrimination between fear and safe stimuli, an effect which may be modulated by uncertainty. This corresponds with my reinstatement results, despite generalisation to a known safe stimulus (CS-) arguably being less likely – or requiring a greater level of anxiety – than generalisation to new, perceptually similar stimuli in an experiment designed to promote generalisation. This aligns with fear generalisation as a core feature of clinical anxiety and PTSD (Andrews et al., 2010; Thome et al., 2017). Overall, results are somewhat mixed between different measures, but the literature supports the conclusion that anxiety promotes fear generalisation. My results add to this by suggesting that anxiety, even graded across the average spectrum, promotes an unhealthy generalisation of fear after reinstatement.

Alternatively, another possible factor in fear generalisation is that return of fear may reflect a form of mood-congruent memory (Bouton, 2002; MacLeod & Mathews, 2004). In the case of fear conditioning, since extinction has not erased the original learning (as discussed in section 1.2.2), the memory trace which more closely matches individual's current mood state is most likely to retrieved. This would suggest that anxious people are more likely to display a return of fear because they are more likely to have a negative mood state. This is unlikely to explain why anxiety was specifically related to greater CS- responses (rather than the CS+) but may be a more general factor influencing the relationship between anxiety and return of fear.

Finally, a possible mechanism behind the link between anxiety and return of fear, trait anxiety may enhance connectivity between emotional control centres during emotional memory encoding. Healthy participants (n=65, 33 female, mean age 30 years) underwent resting-state functional MRI and encoding of emotional (fearful, sad, or happy) faces paired with neutral faces (Hakamata et al., 2020). Anxious participants (scoring more than one SD from a previously estimated population mean) showed greater performance in fear-related face memory but impaired happy-related face memory. This bias was associated with greater resting-state connectivity between the basolateral amygdala and dorsal anterior cingulate cortex (dACC). This same connectivity has been linked to pathological fear in PTSD (Morey et al., 2020). To shed further light on these effects, future studies could aim to replicate my results in the MRI scanner.

5.4.3 Anxiety in Fear Acquisition, Extinction, and Reinstatement

I did not find that anxiety affected fear acquisition and extinction, yet this has been suggested in previous literature. Gazendam et al. (2013) reported that high anxiety impaired CS discrimination at the end of acquisition and after extinction learning. However, the average STAI-measured trait anxiety score in my sample was 37, closer to the control group of the previous study (32) than the high anxiety group (47). This suggests that moderate trait anxiety is unrelated to acquisition and extinction learning, though there may be an association too small to be detected in these sample sizes ($n < 45$).

My finding that anxiety is related to maladaptive reinstatement is strongly in line with previous literature. Gazendam et al. (2013) found that more anxious participants showed maladaptive reinstatement the day after conditioning, although only in startle response and not SCRs. Differences in study design (number of trials, type of stimuli, testing environment, equipment) could have caused this discrepancy, or it may be explained by the higher anxiety found in the previous study's sample. In support of this, Kuhn et al. (2016) and Scharfenort et al. (2016) found respectively that state and trait anxiety (STAI) in young, healthy people predicted poorer CS discrimination in SCRs after reinstatement but had no effect on acquisition or extinction. Kuhn et al. found a significant reinstatement effect when extinction and reinstatement immediately followed acquisition. Reinstatement may therefore be somewhat independent of prior overnight consolidation.

Other studies have reported that greater IU predicts poorer extinction learning beyond the STAI (Morriss et al., 2015, 2016). However, with an equal or greater sample size (n=22 and 38 in the previous studies), I found no evidence that either the STAI or IU scales were associated with extinction learning. IU predicted maladaptive reinstatement, but not better than STAI-measured trait or state anxiety. This disparity could be explained by differences in IU between the samples, but this is difficult to determine because the previous study used the longer 27-item IU scale. Therefore, while IU may not be more sensitive to differences in fear acquisition and extinction, there is stronger evidence in the literature of all anxieties predicting maladaptive reinstatement. My results concur with previous literature to suggest this occurs even in a healthy sample.

I did not find that the reinstatement effect of day 2 was replicated on day 8, though there was a stronger reinstatement effect (irrespective of anxiety) across the sample on this final testing day (reported in Chapter 3). Previous studies of long-term reinstatement are uncommon, but one study investigating appetitive reinstatement in rats (n=76, 38 female, 11 weeks old) found that chronic stress (via restraint) caused an attenuation of cue-induced reinstatement in

females but not males after one week; however, a high anxiety phenotype was associated with a decrease in long-term reinstatement for male rats whereas there was no effect for females (Ball et al., 2020). This suggests that females may be more susceptible to the effects of recent chronic stress on appropriate reinstatement responses while males are more susceptible to effects caused by existing anxiety phenotypes. Although, this requires replication in fear conditioning and human subjects. My null finding on day 8 could be due to the reduced sample size, or prior extinction and reinstatement on day 2. Considering the links between anxiety and the development of long-term fear responses into anxiety-related conditions, this deserves further investigation.

5.4.4 Conscious Reinstatement: Subjective Shock Expectancy Ratings

Prospective anxiety was the only metric to show an association with subjective shock expectancy ratings. It may therefore be more sensitive than the STAI as a metric of conscious awareness of fear and safe discrimination after a cued reminder of fear. This result, however, was weaker than those measured by SCRs. In Chapter 3, I found that subjective shock expectancy ratings occurred much faster than physiological learning, suggesting that conscious awareness may supersede autonomic responses. My results in this chapter suggest that anxiety may be less strongly aligned to conscious learning.

Previously, Morriss et al. (2015, 2016) found that participants with high IU scores reported greater uneasiness ratings to the CS+ and CS- across acquisition and extinction, as discussed in section 5.1. This does not concur with my results; however, uneasiness may not wholly reflect a conscious expectation of shock pairings. In another study, healthy participants (n=46, 38 female; mean age 19 years) were taught to expect a shock after a CS+ image; the CS+ was then presented together with a new neutral image (blocking CS) before the shock designed to attenuate the fear response (Boddez et al., 2012). STAI-measured trait anxiety was positively associated with shock expectancy ratings to the blocking CS, while there was no association in SCR. This suggests that higher anxiety promotes an impairment in conscious discrimination of shock pairings; in other words, participants with greater anxiety tend to show a generalisation of conscious fear to safe stimuli, in agreement with my results. In the future, additional research should determine whether prospective anxiety is particularly sensitive to this effect.

5.4.5 Gender Differences

A post-hoc exploration of my results indicated that female anxiety predicted maladaptive responses to cued reinstatement (greater fear responses to the CS-) while there appeared to be a neutral or slightly negative association in male participants. To my knowledge, gender as a moderator for the relationship between anxiety and fear reinstatement in a sample of healthy participants has not previously been reported.

Gender differences may be driven by social/cultural or biological factors. A recent review suggests that social gender roles and gender-mediated qualities such as 'instrumentality' and 'expressivity' are negatively and positively associated with threat appraisal respectively (Pittig et al., 2020). Fear responses have also been suggested to rely on biological differences such as hormonal factors, especially in women. For example, in one large-scale study, participants (n=377, 261 females, aged 18–35) underwent fear acquisition on day 1 and then extinction and a context-reinstatement test on day 2 (Lonsdorf et al., 2015). Females showed lower CS discrimination than males on both days. There were no differences between female participants in the early or late menstrual phase, but those taking hormonal contraceptives showed reduced CS discrimination across day 2. This suggests that females may be more susceptible to impaired fear learning and reinstatement, while this is somewhat dependent on hormones such as oestrogen. This aligns with my results. However, my findings only relate to self-reported gender rather than biological sex and I did not measure hormone levels; therefore, the driving factors are unclear.

Despite the statistically significant results, the lack of power means these may not be detected in another well-powered sample, since statistical power is decreased for interaction effects and when a categorical moderator has non-matched subgroups (Aguinis & Gottfredson, 2010). In particular, a different effect in males may occur with a greater sample size. That being said, my results provide a potential connection between anxiety, maladaptive fear learning, and gender differences. If females with high anxiety are more susceptible to maladaptive generalisation after a cued reminder of fear, this aligns with the greater prevalence of both clinical and non-clinical anxiety among women (Bekker & van Mens-Verhulst, 2007; Altemus et al., 2014; Teymoori et al., 2020). In fact, women are 1.5–2 times more likely than men to receive a clinical anxiety diagnosis (Bandelow et al., 2017). Given this, gender differences are an important issue for future research to explicitly test for these effects.

5.4.6 An Exploration of Bad Dreams in Relation to Fear Learning

Levin and Nielsen (2009, 2007) have suggested that dreams promote emotional resolution and more recently, Sterpenich et al. (2020) found evidence that fear in dreams predicts lower subsequent fearful responses. I found that people who reported at least one bad dream showed greater maladaptive fear learning overnight and after one week. I did not quantify the emotion of each dream, but my results could be interpreted as in keeping with the theory of emotional resolution. I present evidence in Chapter 3 that SWS % is associated with poorer discriminative consolidation and extinction on day 8, and in this chapter, I have found that people who reported bad dreams showed consistent maladaptive learning and lower SWS %. This could suggest that bad dreams reflect poorer fear consolidation and further extinction learning, perhaps as a compensatory mechanism, but further evidence is required to support this association and suggest the causality of the relationship.

Participants who reported bad dreams had longer total sleep times but lower proportions of SWS following conditioning. This could indicate poorer quality sleep, given the known benefits of SWS (Born & Wilhelm, 2012; Diekelmann & Born, 2010; Van Der Werf et al., 2009). However, while disturbed dreaming is often associated with the perception of worse sleep, a study of people with frequent nightmares compared to a control group over three consecutive nights at home (total n = 34, 32 female, mean age 24 years), suggested that self-reported poor quality sleep in the nightmare group was not supported by changes in sleep architecture (Paul et al., 2015). This suggests that bad dreams are unlikely to cause less SWS or longer sleep times, rather that these changes and perhaps the dreams themselves reflect the maladaptive emotional memory consolidation I also found in this group. Nevertheless, it is possible that either poor fear conditioning caused an increase in bad dreams or both were affected by uncontrolled factors such as shared genetic influences. In the future, collecting dream reports prior to fear conditioning would help to clarify the direction of this effect.

Finally, I did not find evidence for an association between bad dreams and anxiety. There is a previous link between anxiety and bad dreams which may interact with gender. Where trait anxiety predicted distress due to bad dreams (Schredl, 2020), this was significantly more common in girls. In addition, where disturbing dreams were associated with symptoms of Generalised Anxiety Disorder, separation anxiety, and overanxious disorder at age 16, girls reported a greater number of overanxious symptoms with disturbed dreaming (Nielsen et al., 2000). However, I did not test for interaction effects, which require a greater sample size for adequate statistical power (McClelland & Judd, 1993). Considering the gender differences that I found, this would benefit from further exploration.

5.4.7 Strengths and Limitations

I did not have sufficient statistical power to detect the medium effect sizes in anxiety on days 1 and 2, while analyses of day 8 responses were further limited by the smaller sample (n=17) that took part in additional extinction, reinstatement, and dream reports. There was also an uneven number of males and females. These issues limit the robustness of my findings. I also disregarded information on the category of bad dream and number of bad dreams across the week – which may have led to a richer understanding of the relationship between dreams and fear responses.

In addition, the testing of three anxiety types resulted in multiple significance tests which can increase the likelihood of false positives, although my results are consistent. I have not corrected for multiple comparisons as it may be overly conservative when comparisons are highly interrelated (Chen et al., 2017). Nevertheless, high correlations between the measures indicates these questionnaires did not assess distinct anxieties, the results could therefore point towards a more general effect. Future research may benefit from a more streamlined approach to outcome, for example focussing only on reinstatement effects.

Finally, my shock expectancy ratings are limited by the highly correlated anxiety measures, as this led to a large proportion of participants being assigned to the same low or high anxiety group for all measures. I used a median-split approach to assess anxiety because the shock expectancy ratings data did not meet the assumptions of linear regression. However, in the future, a more sensitive scale of shock expectancy such as 0–100 or a sliding bar would provide a more precise distribution of results where associative investigations could be closer to those shown via SCRs.

5.4.8 Conclusions and Future Directions

In this chapter I provide evidence for the relationship between anxiety and fear learning outcomes. I found that greater anxiety in a young, healthy sample predicted maladaptive reinstatement after a cued reminder of the fear stimulus, even in the absence of significant effects on fear acquisition or extinction learning. In contrast, when assessed by conscious awareness of shock expectancy, only prospective anxiety predicted this effect.

I also found significant gender differences in reinstatement, suggesting that the results across the sample were driven by the greater number of female participants. In addition, participants who reported bad dreams showed greater maladaptive responses before and after the recorded week, suggesting bad dreams as a marker of poor fear learning and consolidation.

These analyses suggest avenues for future investigations. Further research on anxiety and fear conditioning should consider longer-term reinstatement effects in a larger sample and explore the crossover from anxiety within the normal range to clinical groups such as PTSD.

Chapter 6

General Discussion

In this chapter I summarise my main findings, discuss the strengths and limitations of my experiments, and explore the implications and future directions of this work. My aims for this thesis were:

(1) Provide evidence for the roles of REM and non-REM sleep in emotional memory consolidation.

(2) Investigate how anxiety and bad dreams in a healthy sample are associated with maladaptive fear responses across acquisition, extinction, and reinstatement of fear learning.

(3) Test the validity of the Dreem Headband for sleep measurement against the gold standard, PSG.

My results indicated that non-REM sleep supports overnight fear consolidation while REM sleep in the same night supports fear extinction of safety cues, though these findings were based on associations rather than causal interventions. In addition, anxiety predicted maladaptive reinstatement of fear while bad dreams were also associated with maladaptive fear responses. Finally, when manual AASM scoring was applied to raw data, the Dreem Headband proved suitable for the measurement of most overnight sleep. These results have implications for understanding the roles of sleep, anxiety, and dreams in emotional memory consolidation, as well as the practicality of sleep wearables for research.

6.1 Summary of Main Findings

The first aim of this thesis was to provide further clarity to the roles of REM and non-REM sleep in fear memory. I developed a novel fear conditioning design to test fear learning (day 1), overnight consolidation across measured sleep, extinction learning (day 2 and day 8), and reinstatement of fear (day 2 and day 8). Based on previous literature, I hypothesised that overnight REM duration would be associated with greater overnight consolidation and extinction learning. However, I found that SWS duration was associated with greater overnight consolidation and a lack of extinction learning on day 8. Meanwhile, REM sleep was associated with lower fear responses to the safe CS- on day 2, but not the diminished CS discrimination that is the hallmark of successful extinction learning. Further to this, in spectral and event analysis of the sleep EEG, fast spindle power in N2 sleep was significantly associated with a greater (more positive) CS- change overnight, while slow oscillation count was significantly associated with fear consolidation and specifically, greater (more positive) CS+ change overnight. These results suggest that SWS and REM in the same overnight sleep following fear learning support separable processing of fear consolidation and extinction safety learning respectively.

The next aim of this thesis was to explore interindividual differences besides sleep that may be associated with fear learning. The primary focus of this investigation was self-reported anxiety; however, in my second round of fear conditioning data collection, I also explored bad dreams as an indicator of maladaptive learning. I found that anxiety was strongly associated with greater (SCR) fear responses to the CS- after cued reinstatement on day 2. There was no distinction between trait, state, and intolerance of uncertainty anxiety measures, although prospective anxiety was the only measure to relate to subjective shock expectancy ratings of the CS- at the same time. I then explored, post-hoc, whether this result was driven by the high proportion of female participants, finding a statistically significant moderation of gender on the association between anxiety and CS- responses after reinstatement for all three anxiety measures. Furthermore, participants who reported at least one bad dream during the week between fear acquisition and final extinction showed greater fear response to the CS- change overnight and after extinction on day 8. Bad dreams were not related to anxiety, suggesting that these facets could indicate separable predictors of maladaptive fear learning.

The final aim of this thesis was methodological, testing the utility of a wearable EEG device in the context of my emotional memory studies. I conducted a validation study of the Dreem Headband. In novel analyses of previously collected data, I explored how Dreem's automatic algorithm compared to the gold standard, PSG, when both were used to record overnight sleep simultaneously. I found that Dreem performed better than other devices reported in

previous literature but did not meet the 80% agreement requirements to replace PSG. However, AASM manual sleep scoring of Dreem's raw data yielded significantly greater agreement, such that Dreem was suitable for the estimation of most overnight sleep. Given this, I utilised Dreem for my fear conditioning experiment and also explored these sleep data for spectral analyses and event detection. I found mixed results in power spectra and phase-amplitude coupling. However, my results indicated that Dreem was suitable to estimate detected events, especially in the hallmarks of each sleep stage: spindles in N2 sleep and slow oscillations in SWS.

6.2 Strengths and Limitations

6.2.1 The Development of a Novel Fear Conditioning Design

For the exploration of my hypotheses, I developed a new fear conditioning design to test fear acquisition, sleep, extinction, and reinstatement in healthy, young adults. This enabled the comprehensive evaluation of these factors but carried its own strengths and limitations. My design choices were based on the fear conditioning literature, external collaboration with researchers with substantive experience in fear conditioning protocols (Tina Lonsdorf, University Medical Center Hamburg-Eppendorf; Joseph Dunsmoor, University of Texas), and pilot testing.

I sourced novel images and spoken words for my conditioned stimuli to confer a greater ecological validity than a single modality. Use of a single modality is the default approach in conditioning literature (this has been the case in every conditioning study I have discussed), as conditioning aims to create a simple behavioural response. However, some evidence has suggested that visual and auditory fear conditioned cues are processed with both common and separable neuronal firing patterns in the amygdala (Bergstrom & Johnson, 2014). Therefore, limiting conditioned responses to one modality, which may not accurately represent real-life fearful learning, could also result in a more limited or specific recruitment of fear regions. Previously, one fear conditioning design (n=22–72 male rats over five separate experiments) explicitly tested the effect of simultaneous light and tone stimuli paired with an aversive shock (Jones et al., 2013). The results indicated that a multimodal (CS) fear memory was more resistant to extinction than simple tone-shock pairings. The memory was also disrupted by the presentation of only one feature (tone or light) during extinction. I did not test for such an effect, but this has important implications for future work such as targeted memory reactivation of the sound part of the CS during sleep, discussed further in section 6.4.2.

I did not explicitly inform participants about CS-US contingencies (instructed conditioning). In a meta-analysis of fear conditioning studies comparing instructed and uninstructed designs, greater explicit knowledge was more likely to recruit the hippocampus, prefrontal cortex, and nucleus accumbens (Mechias et al., 2010). Explicit instructions may increase the strength of conditioning (Mertens et al., 2021), but again reduce ecological validity, as fearful experiences are not often preceded by an explanation. I also chose partial 56% reinforcement (the proportion of CS+ shock pairings) to maximise retention of the fear discrimination overnight, since previous literature suggested that lower reinforcement rates promote slower extinction (Chan & Harris, 2019). For this reason, perhaps, partial reinforcement is more common in human conditioning designs (Menz et al., 2013; Morriss et al., 2015).

My results suggest that this fear conditioning experiment strongly promoted acquired fear to the CS+ on day 1. In addition, testing for differences between sample 1 and sample 2, which were collected approximately six months apart, indicated consistency across the results (shown in Appendix H), especially in CS discrimination acquired after acquisition training. This suggests that sample 2 effectively replicated the results of the initial study. I found no overnight maintained discrimination at the first trial of day 2, or discriminative reinstatement on day 2; however, I was primarily interested in differences between individuals and thus the range of responses from negative to positive across the sample. Broadly, therefore, my fear conditioning design was successful in conditioning the sample as a whole while also encouraging a range of discriminative responses.

6.2.2 A Range of Fear Measurement

I investigated psychological and physiological fear outcomes to provide a comprehensive picture of fear responses and how they changed across the fear conditioning design. I used skin conductance responses (SCRs) as my primary measure of fear, which is common across human conditioning designs (for a review, see Lonsdorf et al., 2017). I also investigated heart rate variability on a trial-by-trial basis and asked participants to give shock expectancy ratings to each CS. This gave complementary insight into the difference between sympathetic and parasympathetic activation of the autonomic fear response, as well as the difference between physiological and psychological learning; this latter pairing is also common in previous conditioning studies (Menz et al., 2013, 2016; Zenses et al., 2020). This range of measurement is a strength of the study, but each measure is subject to its own limitations.

Skin conductance has been a popular metric of arousal in human psychology for several decades. However, early studies demonstrated that responses (sudden increases in

conductance over several seconds) can be elicited spontaneously (Nikula, 1991), and that the response shows strong habituation and individual differences. For example, a study of two samples of same-sex monozygotic and dizygotic twins (total 78 pairs, 37 male, mean age 22 years in one sample, 42 years in the second sample), raised together or apart, reported that SCR habituation to loud sounds had a heritability of 59% (Lykken et al., 1988). In addition, the SCR can reflect other emotional responses. In a study of emotion, SCRs were elicited for fear, happiness, and to a lesser degree sadness and peacefulness (Khalfa et al., 2002). Therefore, while the SCR is a useful metric of sympathetic arousal, it may not directly reflect fear.

I also recorded subjective shock expectancy ratings, a measure of the psychological response to fear conditioning, i.e. participants' understanding of shock pairings as the task progresses and changes. Previously, autonomic and subjective measures of fear have been suggested to have dissociable structural neural correlates. In healthy participants (n=52, mean age 22 years) left amygdala volume significantly predicted differential (CS+/CS-) SCR magnitude but had no effect on contingency ratings; meanwhile, bilateral hippocampal volume predicted contingency ratings but not SCRs (Cacciaglia et al., 2015). My results reflect such a divergence: shock expectancy was acquired quickly in every learning phase whereas physiological learning lagged behind. This suggests that psychological understanding of threat may not necessarily be reflected in autonomic responses, which has important implications in the development of anxiety and fear-based pathology. I discuss this in more detail in section 6.3.2.

Finally, I recorded heart rate variability as an exploratory measure. I used the metric of RMSSD as it reflects mainly parasympathetic activity from the autonomic nervous system (Mackersie & Calderon-Moultrie, 2016), and has been reported as the most accurate measure of HRV over short time frames, even 10-seconds (Wang & Huang, 2012; Tegegne et al., 2019). While I did not use full electrocardiogram equipment, heartbeat detection was largely successful with 93% trial retention. However, unlike SCRs, I found no evidence that variation across RMSSD (during the 10-seconds of CS duration and subsequent inter-stimulus interval) was a marker of fear learning. This could suggest that parasympathetic activity does not change as a function of fear anticipation. Alternatively, the variability between detected heartbeats may be too indirect a measure of parasympathetic activity to detect a significant CS+/CS- difference, or the change may occur over a longer time than 10 seconds. However, my finding that HRV-measured CS discrimination change overnight and extinction learning on day 2 were significantly associated with both REM sleep and SWS, suggests that HRV has some relationship to fear learning. This would need to be explored in more detail in subsequent research.

6.2.3 Interpreting Associative Relationships

A primary aim of this thesis was to clarify the roles of REM and non-REM sleep in emotional memory. My design facilitated the comparison between sleep stages recorded over the same post-conditioning night, but the associations I have reported are not necessarily causal. In the context of previous literature, my findings arguably suggest that SWS promotes memory consolidation and REM promotes future safety extinction. Yet, it is possible that fear conditioning had a causal effect on sleep. For example, greater discriminative fear learning led to more SWS that night, which in turn led to better consolidation. As discussed in Chapter 3, there is some evidence from rodent studies which suggests that fear conditioning affects sleep architecture (DaSilva et al., 2011; Hellman & Abel, 2007; Sanford et al., 2001; Sanford et al., 2003). However, this was most often found for REM sleep and has not been replicated in studies of people (Marshall et al., 2014), though this may warrant more research. In my results, it is also possible that people who tended to have more SWS also tended to have better fear conditioned consolidation; in other words, the association could have been driven by factors that were not controlled in this experiment, for example, shared genetic effects.

Furthermore, not all changes that occur across sleep are attributable to sleep itself, since changes in memory also occur across time. Generally, most evidence suggests that recently encoded memories degrade across wake (due to interference) and strengthen across sleep (Gais et al., 2006; Mander et al., 2011; Payne et al., 2012). This is an important factor in how fearful memories consolidate and generalise, for example, wake interference may be preferable after fear learning if it reduces an unhealthy fear generalisation. I could have controlled for this by comparing sleep to an equivalent period of wake. However, as discussed in Chapter 3, this would have substantially increased the time demands of the study. It also introduces circadian effects if the wake group is tested in the morning then the evening and the sleep group vice versa, as Pace-Schott et al. (2009). Otherwise, if the wake group are deprived of sleep overnight, as Zenses et al. (2020), this introduces another confound as sleep deprivation is highly stressful and in itself impairs memory (Gais et al., 2006; Graves et al., 2003). These factors all affect the strength of evidence and invariably some aspect is compromised. In my results, the associative nature of the evidence should be kept in mind.

I measured anxiety prior to each testing session and responses remained stable across days. As a result, anxiety was unlikely to have changed as a function of fear conditioning, although uncontrolled factors may still have affected both anxiety and fear conditioned responses. I can therefore have greater confidence that anxiety predicts maladaptive fear responses to cued reinstatement, but causal interventions would further strengthen this finding. This is also true of my findings relating to bad dreams. My results cannot determine whether people who

happened to have bad dreams that week were particularly affected by the fear conditioning protocol. Emotional experiences may be consolidated via subsequent dreams, but since the salience of my fear conditioning protocol is difficult to assess, further evidence is required to fully understand these relationships. Currently, I can conclude that bad dreams are potentially associated with fear conditioned overnight consolidation and fear extinction learning a week later.

Together, my results indicate associative evidence for separable roles of REM and non-REM sleep for fear consolidation and extinction. To my knowledge, no other fear conditioning study has reported roles of both REM and SWS in the same night relating to responses the next day. I have also extended this finding to fear discrimination responses one week later and provided further evidence for the roles of anxiety and bad dreams towards maladaptive fear responding over one week. However, future studies should be mindful of associative versus causal effects in this field. Adaptations to better account for this could include a baseline sleep night, comparing sleep to an equivalent period of wake, or using targeted memory reactivation. I discuss such potential future work in section 6.4.2.

6.2.4 Sampling and Statistical Power

Like all studies, I have tried to limit confounding factors and recruit a large sample, but this could be improved. In my fear conditioning experiment, the sample was comparable to previous literature (n=38). Also, to minimise common confounds, all participants were young adults, self-reported good sleepers, had no history of mental health or sleep pathology, and reported full compliance with the abstinence from caffeine, alcohol, naps, and extreme exercise. However, analyses of day 8 were limited to 17 participants, reduced to 11 when accounting for sleep data loss. This means that my findings of day 8 – namely that SWS was associated with a lack of extinction but anxiety was unrelated – provide less robust evidence for the impact of sleep or against the impact of anxiety on conditioned responses. Specifically, the effect sizes are less precisely estimated and so there is greater uncertainty about these associations.

My validation of the Dreem Headband was also limited by its sample. The matched nights where sleep was recorded simultaneously by Dreem and PSG only yielded 15 nights of data, while EEG analyses were confined to 13 of these nights. As well as the low number of recordings, the sample was potentially confounded by the recruitment based on neuroticism and the recording of multiple nights from the same individuals. I did not find neuroticism (low [n=5] versus high [n=3]) or night (first versus second [n=6]) to have a significant effect on sleep

agreement; however, these analyses themselves lacked statistical power and are therefore somewhat unreliable. That being said, while these confounds may affect sleep, they are not obviously indicative of differences in agreement between Dreem and PSG. In addition, my findings are broadly comparable with the previous literature on sleep wearables.

Limited sample sizes are most relevant in their effect on statistical power. This is an issue across PSG-measured sleep research, in fact, across science (Anderson & Maxwell, 2017; Lindsay, 2015). Statistical power is the probability that a study will detect an effect of interest, given the effect exists in the studied population. Generally, 80% power – an 80% likelihood of detecting a statistically significant effect if one exists – is considered acceptable (Brysbaert, 2019; Cohen, 1992). An underpowered study decreases the likelihood of finding a true effect (a false negative), but as noted in Chapter 5, also means that significant effects are more likely to be spurious (a false positive) than significant effects in adequately-powered studies (Button et al., 2013; Fraley & Vazire, 2014). In my fear conditioning experiment, the analyses regarding sleep were underpowered after data loss reduced the sample size from 38 to 27. Analyses of bad dreams and sleep/anxiety, particularly on day 8, also lacked sample size, while my exploration of gender moderation was seriously underpowered, considering the greater sample needed for moderation analyses and the uneven number of males and females. My Dreem validation study had sufficient power to detect only large differences.

Finally, these experiments had substantial 'experimenter degrees of freedom'. This refers to the numerous choices made over the course of experiments and analysis, unconsciously increasing the chances of finding positive results (Wicherts et al., 2016). For example, my findings regarding an increase in CS discrimination overnight could have been explained by either processing or consolidation; the former allows for a result showing decreased reactivity and the latter for the increased reactivity (SCR) that I report. I have related my findings to previous literature; however, the robustness of these conclusions would have been enhanced if I had pre-registered this experiment.

In summary, the significant effects I have found are at risk of being false positives. In addition, I did not have enough power to detect medium or small effect sizes. Therefore, the implications are somewhat limited. However, my results are strengthened by the consistency of the findings across this thesis and in the context of previous literature and so warrant replication in larger samples.

6.3 Implications

6.3.1 Emotional Memory Consolidation

The Active Systems Consolidation Theory, a dominant theory of sleep-dependent memory consolidation, suggests that slow oscillations, sleep spindles, and hippocampal sharp-wave ripples support memory consolidation during non-REM sleep (Diekelmann & Born, 2010). While it does not specifically relate to emotional memory, abundant evidence suggests that emotional memories are also supported in this way (Denis et al., 2021; Girardeau et al., 2017; Göder et al., 2015; Jones et al., 2019; Kaestner et al., 2013). My findings align with this. Specifically, the association between SWS duration and a maintenance of CS discrimination overnight provides further evidence for the specific role of non-REM sleep in emotional memory consolidation, not just after one night, but after one week as well.

In Chapter 4, I also provide evidence for the neural mechanisms at play in such consolidation. Complementary to the association between SWS duration and maintenance of fear discrimination, slow oscillation count and density were also associated with this discrimination, suggesting that slow oscillations during non-REM sleep play a mechanistic role in long-term consolidation of fear memory. Previously, the spatial and temporal patterns of slow oscillations have been suggested to determine the synaptic strength between neurons and in turn promote replay of neuronal firing sequences (Wei et al., 2016). While my results are a much broader measure of slow oscillations, they concur with this prior literature, adding evidence for the role of slow oscillations in emotional memory consolidation.

I also found that fast spindle power in N2 sleep related to CS- change overnight. There was poor agreement between PSG and Dreem in this metric which weakens the strength of this finding. However, it could suggest that fast spindles promote generalisation of fear (from the CS+ to the CS-), which also aligns with previous literature (Chatburn et al., 2021; Lewis et al., 2018). Potentially, therefore, my results also indicate a divergence between sleep stages SWS and N2 for fear consolidation and generalisation respectively.

Beyond theories of non-REM, my results suggest that REM and SWS in the same post-conditioning night promote complementary consolidation processes that may impact future responses, even after further learning. This aligns with Wassing et al. (2019), where fragmented REM was associated with poorer negative/neutral discrimination, while the beneficial effect of unfragmented REM was enhanced by spindle rich N2 sleep prior to REM episodes. In support of this, healthy participants (n=15, 3 male, mean age 20 years) viewed positive, negative, and neutral images in an MRI scanner, then had PSG-recorded sleep overnight before a recognition test (Cairney et al., 2014). SWS duration was associated with

better memory for negative images and reduced hippocampal activation during recollection, while REM duration was associated with an overnight increase in hippocampal-neocortical connectivity for these images. This suggests that SWS and REM have complementary roles during overnight sleep which support preferential emotional memory. I am unaware of any fear conditioning design which has reported complementary roles between REM and non-REM in this way. Therefore, my results are novel in the conditioning literature but align with growing evidence for both REM and non-REM sleep in emotional memory consolidation.

The Sleep to Forget, Sleep to Remember Hypothesis suggests that REM promotes a gradual reduction in emotional responses over time and after multiple bouts of REM sleep. I found that REM was associated with reduced fear responses to the CS- after extinction on day 2, but there was no association on day 8. However, I only recorded REM over a single night's sleep. Thus, a gradual attenuation of fear should be investigated with sleep recording over consecutive nights. In addition, since fear responses are the metric of consolidation, fear conditioning may sometimes conflate emotional responses and memory consolidation. A separation between discriminative memory and amelioration of emotion would therefore benefit from additional evidence via a different experimental design.

Nevertheless, my results align with other previous literature linking fear learning to REM (Marshall et al., 2014; Menz et al., 2013, 2016; Spoormaker et al., 2010; Wassing et al., 2019). To my knowledge, no previous study has reported that REM sleep supports extinction learning the next day. My finding that REM promotes more adaptive future responses suggests a role in the separation of danger and safe stimuli consolidation after initial encoding. In support of this, there is evidence that the CS+ and CS- are encoded in separable neuronal ensembles (Corches et al., 2019). In addition, REM duration was recently reported to be associated with increased fear generalisation in healthy people (n=24, 11 female, mean age 23 years), but of learned CS+/CS- responses to novel situations (Lerner et al., 2021). Therefore, while REM may play a complex role, there is consistent evidence that this sleep stage supports the processing of fear conditioned responses.

6.3.2 Anxiety, Stress, and Sleep Problems

My results suggest that anxiety as a trait factor predicts maladaptive responses to a cued reminder of fear; that is, an increase in fear to the safe CS- rather than to the previously known dangerous CS+. Interestingly, these results were only partially replicated in subjective shock expectancy ratings, suggesting that physiological metrics may supersede conscious knowledge in the development of maladaptive generalisation of fear. This is supported by

previous literature, for example, participants (n=124, 72 female, mean age 30 years) with high physical anxiety sensitivity showed a greater attentional bias towards masked and unmasked negative words (Hunt et al., 2006). This suggests that anxious tendencies are driven at least in part by unconscious responses.

Understanding how individual differences in anxiety promote maladaptive fear responses has important implications for a number of psychopathologies, most notably clinical anxiety and PTSD. These disorders are common and stem, at least in part, from an abnormal continuation and generalisation of fear. However, while many people experience unpleasant events, only a minority will go on to develop a condition such as PTSD (Dekkers et al., 2010; Kessler et al., 2017; Kolassa et al., 2010; Shalev et al., 1996, 2019). Therefore, PTSD is not an inevitable response to trauma. My findings were derived from a young, healthy sample but suggest that trait anxiety, REM, and non-REM sleep should be investigated further to explore causal effects. In particular, my fear conditioning design could be adapted to an exploration of targeted memory reactivation to explore how these findings could be applied to not only understand how sleep interacts with fear consolidation, but how fear memories could be manipulated and ultimately ameliorated.

In 2021, my results have additional implications considering the long-term stress, anxiety, and fear of the COVID-19 pandemic. In college students (n=707, 431 female, 32 gender diverse) aged 18–22 across the US, a mental health survey in April and again in July 2020, suggested that most students were suffering from stress and anxiety. In particular, women reported significantly poorer outcomes than men, while gender diverse and sexual minorities reported significantly poorer outcomes than cisgender, heterosexual individuals (Hoyt et al., 2021). This suggests that added stress affects people differently based on their gender and again posits interesting and important avenues for further exploration.

COVID-19 has also impacted sleep. For example, in May 2020 during a national lockdown in India, an online survey (n=958, 393 female, mean age 37 years) indicated that self-reported sleep quality had reduced from a retrospective baseline, while these reductions were significantly associated with depressive symptoms (Gupta et al., 2020). Further to this, a study in China (n=7236, 3952 female, mean age 35 years) found that young people (< 35 years) were affected more than older people by anxiety and depression symptoms during the pandemic (Huang & Zhao, 2020). The Dreem Headband has been used to study these factors. In participants who were already accustomed to the device (n=599, 174 female, aged 36–59), sleep was compared over 5 weeks both before and during the pandemic (specifically during a lockdown). Overall, people slept for longer, had less SWS, more light sleep, and longer REM sleep, while these changes were greater in people who reported an eveningness chronotype

(Pépin et al., 2021). These findings suggest that various interrelated factors (age, gender, chronotype, anxiety, depression) interact with sleep, potentially affecting the propensity for maladaptive fear responses. This is an important avenue for further research as the effects of the pandemic persist.

6.3.3 The Impact of Gender

There is an issue with gender balance across the fear conditioning literature. In general, rodent studies tend to only use males (DaSilva et al., 2011; Hellman & Abel, 2007; Purple et al., 2017; Rolls et al., 2013; Sanford et al., 2001, 2003). This focus on males has also been the case for some human studies (Menz et al., 2013, 2016; Spoormaker et al., 2010). On the other hand, some human studies which rely on psychology undergraduate students are dominated by women (Morriss, Christakou, et al., 2016; Sterpenich et al., 2020). It is difficult to establish what impact this has on the results, but as noted in Chapter 5, clinical anxiety is more prevalent in women (Teymoori et al., 2020), which suggests that gender does affect these processes, or at least, how they manifest.

While my fear conditioning sample heavily comprised of females, my findings potentially suggest that male and female (gender as self-reported) participants are affected differently by anxiety. The positive association between anxiety and reinstatement to the CS- was driven by female participants, while males showed a neutral or even slightly negative association, albeit in exploratory post-hoc analyses. This could be indicative of the greater susceptibility to clinical and non-clinical anxiety in women (Asher et al., 2017; Gao et al., 2020; McLean & Anderson, 2009; Teymoori et al., 2020).

However, while all participants identified as male or female in my moderately-sized sample, minority gender groups may suffer from greater anxiety. For example, in college students (n=43,632) completing the Health Minds Study, people who identified as pansexual, demisexual, asexual, queer, questioning, or transgender/nonconforming reported significantly greater anxiety and depression than heterosexual individuals (Borgogna et al., 2019). An interesting avenue would be to explore fear conditioning and reinstatement in these groups, perhaps distinguishing between biological and social/cultural factors towards gender differences which my results do not consider, since I only asked participants about their self-identified gender. Therefore, while my results do not clarify this issue, they suggest the importance of considering gender in future investigations.

6.3.4 Wearable Technology

Sleep research has historically been dependent on PSG, but this is an expensive, time-consuming procedure which limits the sample size of sleep studies. Meanwhile, a boom in the development of wearable technology may revolutionise health research. This has extended to sleep, despite its complexity. Consequently, sleep wearables have huge potential, but research is still in the early stages. Across the array of sleep wearables currently available, most yielded poor sleep measurement when scientifically evaluated, as discussed in Chapter 2. In contrast, previous validation of the Dreem Headband suggested it performed well against PSG, but this required substantiation.

My results suggest that the Dreem Headband introduces too much error in sleep measurement from differences in both hardware and scoring method. However, when the manual sleep scoring method that was developed for PSG was applied to Dreem raw data, it was suitable for sleep stage metrics. To my knowledge, this is yet unreported using the Dreem Headband. The previous validation suggested that Dreem's automatic sleep scoring algorithm was sufficient against PSG (Arnal et al., 2020), but my results cast doubt on this finding. Dreem must be shown to consistently perform well against PSG in a variety of settings before it can be fully trusted in sleep research for both sleep measurement and analysis.

Even with manual sleep scoring, Dreem is not a perfect replacement for PSG and there will be circumstances where wearables are unsuitable. Dreem sleep data are more difficult to sleep score and carry an impoverished signal coverage and quality, i.e. no eye movement, muscle tone, and central EEG measurement, as well as increased artefacts and poorer signal-to-noise ratio. However, Dreem could be utilised for large-scale studies where estimations of SWS and REM sleep stages take precedence. The convenience of sending a fully autonomous wearable to participants' homes could hugely increase the size of sleep studies, even if the data are manually sleep scored. I also found that Dreem was suitable for the detection of sleep spindles in N2 sleep and slow oscillations in SWS, and I was able to use this to strengthen my findings regarding emotional memory consolidation. In the future, this may be further improved with developments in wearable technology, but currently, my results advocate the use of Dreem – with the caveat of manual sleep scoring – for sleep staging as well as spindle and slow oscillation detection.

6.4 Future Directions

6.4.1 Replicating These Experiments

In a replication of my fear conditioning experiment, I would collect sleep, dream, and anxiety measures one week prior to the first conditioning session. This would enable a more comprehensive evaluation of how these factors may cause (or affect) changes in fear conditioned responses across acquisition, extinction, and reinstatement. It would also be beneficial to recruit a larger sample size with equal numbers of male and female participants, and pending a separate investigation into minority gender groups, ask people about both their biological sex and gender identity so that potential confounds between biological and social factors can be controlled. To limit possible effects of oestrogen, female participants could also be asked to participate within the same menstrual phase, or hormone levels could be quantified if more resources were available.

With greater resources, it would also be informative to test the effects of time between encoding, sleep, and extinction. The stress hormone cortisol peaks in the morning and decreases throughout the day (Gagnon et al., 2018), while the optimal time of day for learning varies between individuals (Delpouve et al., 2014; May et al., 1993; Ngo & Hasher, 2017). Meanwhile, circadian disruption impairs fear extinction and safety learning in rodents (Clark et al., 2020; Kordestani-Moghadam et al., 2020). In my current results, I tested fear acquisition in the afternoon and fear extinction the following morning. While this was the same for all participants, a variation of time of day would inform how these factors affect the relationship between fear conditioning, sleep, and anxiety. In addition, interindividual differences in chronotype could be tested with a measure such as the Morningness Eveningness Questionnaire (Panjeh et al., 2021). This would give an indication of how wake interference before sleep, chronotype, and circadian timing – factors at play in real-life fearful experiences – affect fear learning. This could help to clarify why some people suffer from maladaptive and long-term fear.

In a replication of my Dreem validation study, a larger sample size would also be advantageous, but in particular, I would test whether the accuracy of Dreem is affected by a ‘first night effect’. Participants are generally unfamiliar with sleep measurement and it is not clear from my current findings how much this affected the results. In addition, like most technologies sleep wearables are a fast-moving field and the validation of their efficacy needs to stay apace. Therefore, I would also use the latest ‘Dreem 2’ headband to investigate this newest development against PSG.

6.4.2 Further Study of Emotional Memory Consolidation

My findings indicate several avenues for further research into emotional memory consolidation beyond replication. In particular, my fear conditioning task could be easily applied to targeted memory reactivation (TMR). Specifically, the sound component of the CS (one each of the CS+ and the CS-) would be presented during sleep. This may initially utilise the control of PSG but could potentially be adapted for sleep wearables too.

TMR has gained popularity in recent years as an instrument to understand sleep through manipulation. It is advantageous in that it can be applied translationally to animal and human subjects, is non-invasive, and provides causal evidence (Creery et al., 2015; Hu et al., 2020; Lewis & Bendor, 2019; Oudiette & Paller, 2013; Schouten et al., 2017). Furthermore, as described in Chapter 3, TMR in non-REM sleep has already been applied to fear conditioning designs (Hauner et al., 2013; Purple et al., 2017; Rolls et al., 2013), though there is ambiguity as to whether it strengthens or reduces fear responses.

Since REM was associated with lower CS- responses after extinction, my results could suggest that REM reactivation would promote extinction of the CS-. Although, reactivation does not necessarily enhance the effects associated with that stage. Based on evidence for specific weakening of emotional memories after reactivation (Hauner et al., 2013; Simon et al., 2018), TMR during SWS may also ameliorate fear responses. Therefore, both REM and non-REM sleep warrant investigation. If an amelioration of fear was achieved, TMR could be applied to more complex or older fear memories with a view towards eventual application to fear-based pathologies such as PTSD.

6.5 Conclusions

In this thesis I have provided evidence for the contributions of REM and non-REM sleep towards the consolidation of fear conditioned responses. I have also explored how anxiety and bad dreams relate to maladaptive fear. In addition, I have extended the literature on sleep wearables with a novel validation of the Dreem Headband including spectral analyses and event detection.

My results suggest associations between SWS and overnight fear consolidation as well as anxiety and maladaptive fear reinstatement. Moreover, the Dreem Headband may be suitable to measure time spent in SWS and REM, but only when expertly sleep scored. Finally, in more exploratory analyses, I found that bad dreams may relate to poor sleep-dependent consolidation while anxiety's effect on reinstatement may be specific to female participants.

These findings suggest avenues for further research into emotional processing and dreams as well as the impact of gender on fear reinstatement.

Together, these results will help inform future studies of fear memory consolidation and sleep wearable validation. Ultimately, this research may support the development of more efficient sleep measurement, as well as a better understanding of the fear response and how it manifests into disabling psychopathologies such as PTSD.

Appendices

Appendix A

Screening Forms

I used *Google Forms* to create a screening tool which all participants were asked to complete prior to testing. If forced response, options are shown in brackets - []. Red indicates that the response would exclude the respondent, green indicates the response was acceptable for the experiment.

1. Your age (in years) – less than 18 or greater than 30
2. Gender [male; female; prefer not to say]
3. Left or right-handed [left-handed; right-handed; I use my hands equally]
4. Are you happy to disclose where in your menstrual cycle you are? [yes; no; I may be unsure of this information; N/A]
5. Are you familiar with any of these languages? [Hebrew; Hungarian; Turkish; Korean; none of the above]
6. Do you have any form of hearing impairment? [yes; no]
7. Have you ever suffered from any of the following illnesses? [mental illness (e.g. depression); neurological disorder; I'm not sure; undiagnosed but I feel I may have a disorder; none of the above]
8. Do you have hypersensitive skin or any known contact allergies? [yes; no]
9. Are you currently taking any medications? [yes; no]
10. Do you smoke? [yes; no]
11. Do you agree not to consume caffeine or engage in extreme physical exercise within 24 hours before your visit to the laboratory? [yes; no]
12. Do you agree not to consume alcohol within 24 hours before your visit to the laboratory? [yes; no]
13. At what time do you usually go to bed (enter in format 0:00 - 23:59)? *– times later than 2am were excluded based on an abnormal sleep/wake cycle.*
14. How long does it usually take you to fall asleep? [almost instantly; somewhere between 10 minutes and half an hour; longer than half an hour, I often toss and turn]
15. What time do you usually wake up (0:00 - 23:59)? *– times later than 10am were excluded based on the start time of experimental session 2.*

16. Has your sleep and wake cycle (i.e. the times you get up and go to sleep) remained relatively constant over the past 4 weeks? [yes; no]
17. Have you engaged in any regular night shift work over the past two months? [yes; no]
18. Have you travelled across more than two time zones in the past two months? [yes; no]
19. Do you usually wake up during the night? [yes; no]
20. If yes, how many times and for what reason? *– many participants indicated that they wake up to use the bathroom in the night once. These participants were not excluded.*
21. Have you experienced any severe stressful life event(s) in the past six weeks? [yes; no; I'm not sure]
22. Have you had any form of continuous sleep disturbance for longer than two weeks in the past? [yes; no]
23. If 'Yes' please give details *– all were excluded*
24. How would you generally describe your ability to sleep? [excellent; good; fair; poor]
25. How much do you think wearing the headband will affect your sleep? [I'm confident it will not affect me; it may affect me slightly but I'll still be able to sleep well; it will probably affect me quite a lot, I may struggle to sleep; I'm not sure how much it will affect me]
26. Have you previously taken part in any sleep study at CUBRIC/Cardiff University? [yes; no]

Number of excluded respondents per question: Q7 – 9; Q8 – 1; Q9 – 8; Q10 – 2; Q13 – 2; Q14 – 5; Q15 – 3; Q16 – 10; Q17 – 3; Q18 – 1; Q21 – 3; Q24 – 8; Q25 – 6.

Appendix B

Questionnaires Administered During Fear Conditioning Experiment

I sourced the Intolerance of Uncertainty Scale and State Trait Anxiety Inventory (STAI) to measure anxiety and the Stanford Sleepiness Scale to measure alertness. I created the mood questionnaire to be administered after conditioning in conjunction with Cardiff University's Ethics Committee. All were anonymised with participant IDs: no names or identifying information was written on these questionnaires.

Externally accessed questionnaires: For Intolerance of Uncertainty, participants answer on a scale of 1 to 5 as to how much they agreed with various statements on 11 items. Similarly, for the STAI, participants answered on a scale of 1 to 4 on 20 items for state anxiety and 20 items for trait anxiety. For the Stanford Sleepiness Scale, participants circled one for seven options labelled 1 to 7 describing states of increasing sleepiness.

I wrote guidelines to the mood questionnaire which explain how it would have been used if necessary:

This questionnaire will be administered at the end of every testing session; participants will be reminded to answer as honestly as possible, and that their answers will not affect their results.

If the participant answers a 3 or 4 on the first two questions, a 4 or 5 on the third question, or indicates in the final two questions that they have been negatively impacted emotionally by taking part in the experiment the following procedure will be carried out.

Participants will be asked to sit in a quiet room while relaxing music is played for 10 minutes. Previously, various studies have found that relaxing music reduces physiological indicators of stress (Khalfa et al., 2003; Knight & Rickard, 2001). They will think this is part of the experiment. Before they leave, the participant will also be given the information sheet about various mental health help services to take away, and they will not be invited to take part in subsequent parts of this experiment, or any other similar experiment.

This will also be offered to any participant exhibiting signs of emotional distress, regardless of their answers to this questionnaire

Mood Questionnaire

Please answer the following questions as honestly as you can by indicating the statement which best describes you **in this exact moment**.

How anxious do you feel?

1 I am not at all anxious
2 I am alert but not anxious
3 I feel slightly anxious
4 I am very anxious

How do you feel about leaving the experiment and going about your day?

1 I feel very able to continue my day as planned
2 I feel able to continue my day as planned
3 I feel it will be somewhat difficult to continue my day as planned
4 I feel it will be very difficult to continue my day as planned

How much do you think your mood has changed from when you started the experiment?

1 I feel much more positive
2 I feel slightly more positive
3 I feel about the same
4 I feel slightly more negative
5 I feel much more negative

Has your experience in this experiment brought up any unpleasant memories for you?

Yes

No

Please add any additional information you would like concerning the experiment and how it has affected your mood.

_____
_____
_____
_____

Support Information (*only given to participant if signs of distress were shown*)

Cardiff University Wellbeing Team

If you are a Cardiff University student, the wellbeing team offer a range of free and easy to access services including counselling, interactive workshops, courses, and groups.

You can contact them via email at **wellbeingandcounselling@cardiff.ac.uk** or by phone on **029 2087 4966**

Alternatively, you can find out more about the services on offer on their website:

https://www.cardiff.ac.uk/study/student-life/student-support/counselling-and-wellbeing

CALM

Campaign **A**gainst **L**iving **M**iserably is a service aimed at men who may be struggling with mental health problems. You can access free telephone support by **calling 0800 585858** between 5pm and midnight, 365 days a year. Alternatively, you can use their webchat service by going to their website:

https://www.thecalmzone.net/

The Mix

The Mix offers a confidential service aimed at under 25s. Open from 11am to 11pm every day you can **call 0808 808 4994** for free advice from trained supporters. Alternatively, you can use their online chat service or crisis messenger service, where you can discuss any issues via text message. To access crisis messenger, **text THEMIX to 85258**, this is free and anonymous. To find out more, go to their website:

https://www.themix.org.uk/get-support

Mind

Mind is a mental health charity aimed at anyone experiencing a mental health problem. They offer a wide array of information about mental health online and offer a helpline from 9am to 6pm Monday to Friday on **0300 123 3393**. Alternatively, you can email **info@mind.org.uk**, or find out more on their website:

https://www.mind.org.uk/

Appendix C

Fear Conditioning Task Instructions (Acquisition and Extinction)

In this experiment you will see pictures and hear sounds

Sometimes you will also experience a shock

Focus on the pattern of images, sounds and shocks

Press the SPACE BAR to continue

Between each picture there will be a fixation cross

It can seem like a long wait between pictures

But try not to let your attention wander

The task only takes around 15 minutes

Press the SPACE BAR to continue

On some trials, we would like you to rate the image/sound pair

You will see the image/sound AND be asked to rate how much you expect a shock

Answer using the keyboard numbers, on a scale of 1 to 5

1 indicates you NEVER expect a shock and 5 indicates you ALWAYS expect a shock

Press the SPACE BAR to continue

Remember, on most trials you do not need to do anything

However, pay attention to the images, sounds, and shocks

Think about when these things are presented, and any patterns you can see

When you are asked for a rating, consider the patterns you have observed

Press the SPACE BAR to start the task

Appendix D

Supplementary Analyses – Chapter 2

D1 Neuroticism Classification

Because participants were recruited on the basis of high or low neuroticism, which was not of interest for the current hypotheses, I investigated whether neuroticism classification affected agreement measures between PSG and Dreem across sleep stages. A 2 x 5 x 3 factorial ANOVA of individual recordings, regardless of night 1 or night 2, between participants scoring high (n=10) and low (n=5) in neuroticism across five sleep stages (N1, N2, SWS, REM, wake) and three scoring methods (PSG, Dreem-algorithm and Dreem-manual) indicated no significant effect of neuroticism F (1) = 2.49, p = .139, suggesting that data contributed by participants of low and high neuroticism were similar. There was also no neuroticism * sleep stage interaction, F (4) = 0.21, p = .934, nor a neuroticism * scoring method interaction, F (2) = 1.72, p = .199, suggesting that neuroticism had no significant effect on sleep measures.

D2 A Test of Scoring Differences: Personality Data

Most of the tested personality traits did not significantly correlate with each other. However, greater neuroticism was associated with lower conscientiousness and higher openness; correspondingly, conscientiousness and openness were negatively associated (**Table D1**).

Table D1 Pearson Correlation Between Measured Personality Traits

	Neuroticism	Extraversion	Agreeableness	Conscientious-ness	Openness
Neuroticism					
Extraversion	-.22				
Agreeableness	-.31	.56			
Conscientious-ness	-.92 ***	.29	.35		
Openness	.85 **	-.12	.15	-.70 *	

*$p < .050$, ** $p < .010$, *** $p < .001$

I investigated each personality trait separately as a predictor of time spent in SWS and REM (**Table D2**). Where participants contributed sleep recordings on two nights (n=5), time in SWS or REM was averaged. A longer time in SWS across night 1 was weakly associated with longer in night 2, $r = .86$, $p = .063$; there was no association in REM, $r = .10$, $p = .878$. Agreeableness was a strong predictor of time spent in SWS, but no other trait showed a significant association (**Figure D1**).

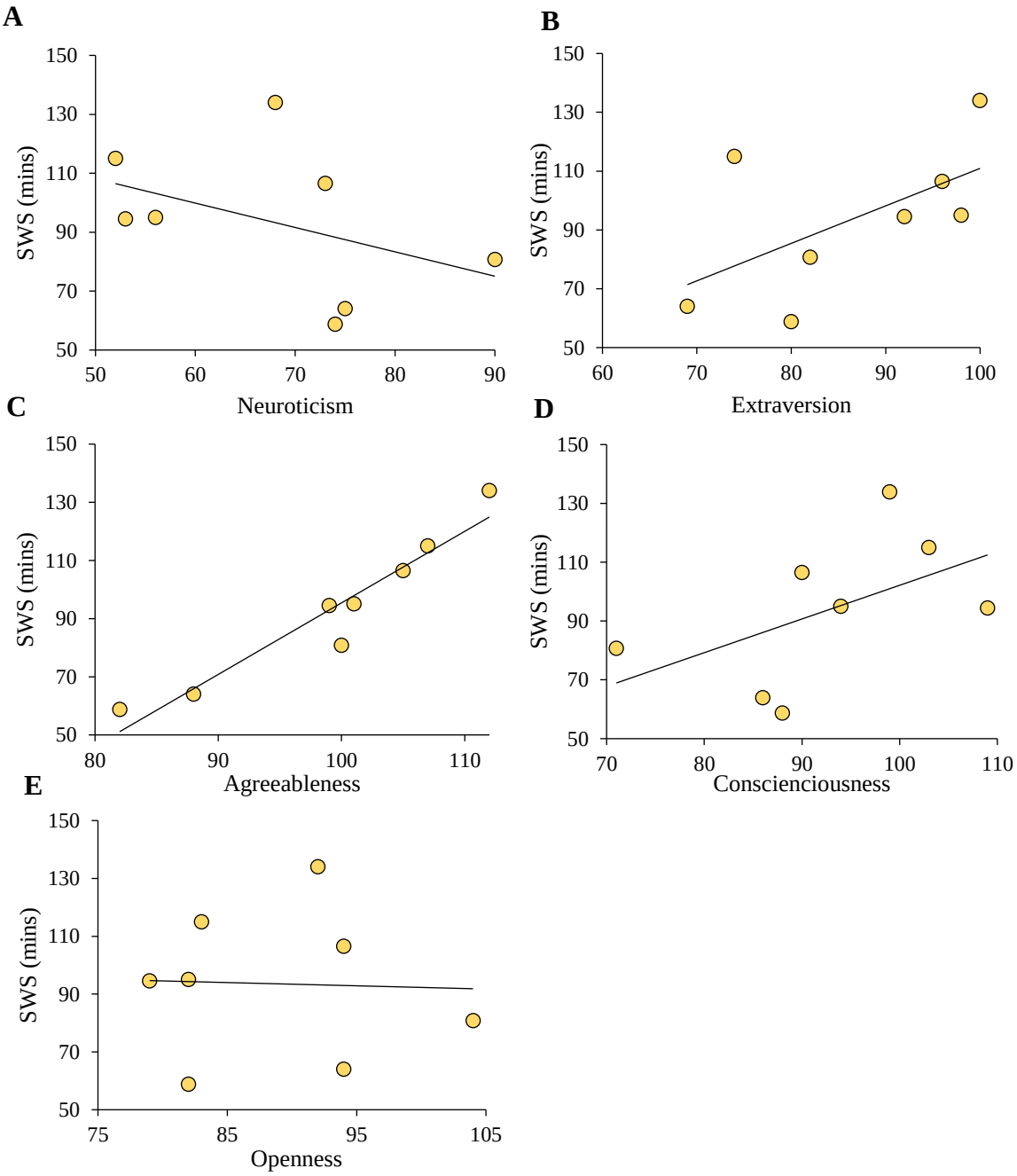


Figure D1 Personality Traits and PSG-Scored SWS

Agreeableness showed a positive association with time spent in SWS (**C**). There was no association with other personality traits: neuroticism (**A**), extraversion (**B**), conscientiousness (**D**), or openness (**E**).

Table D2 Linear Regression: SWS and Personality Traits

				Unstandardised Coefficients	
	R^2	F (1,6)	*p*	B [SE]	95% CI
Neuroticism	.19	1.36	.288	-0.83 [0.71]	-2.56, 0.91
Extraversion	.35	3.17	.125	1.28 [0.72]	-0.48, 3.03
Openness	.00	0.01	.928	-0.11 [1.21]	-3.06, 2.84
Agreeableness	.92	65.95	< .001	2.46 [0.30]	1.72, 3.20
Conscientiousness	.28	2.34	.179	1.15 [0.75]	-0.70, 2.99

No trait showed a strong association with REM (**Figure D3**). Again, each trait was considered independently as a predictor of REM (as scored by PSG) in a linear regression model (**Table D4**). No personality traits predicted time spent in REM, therefore no further analyses were conducted.

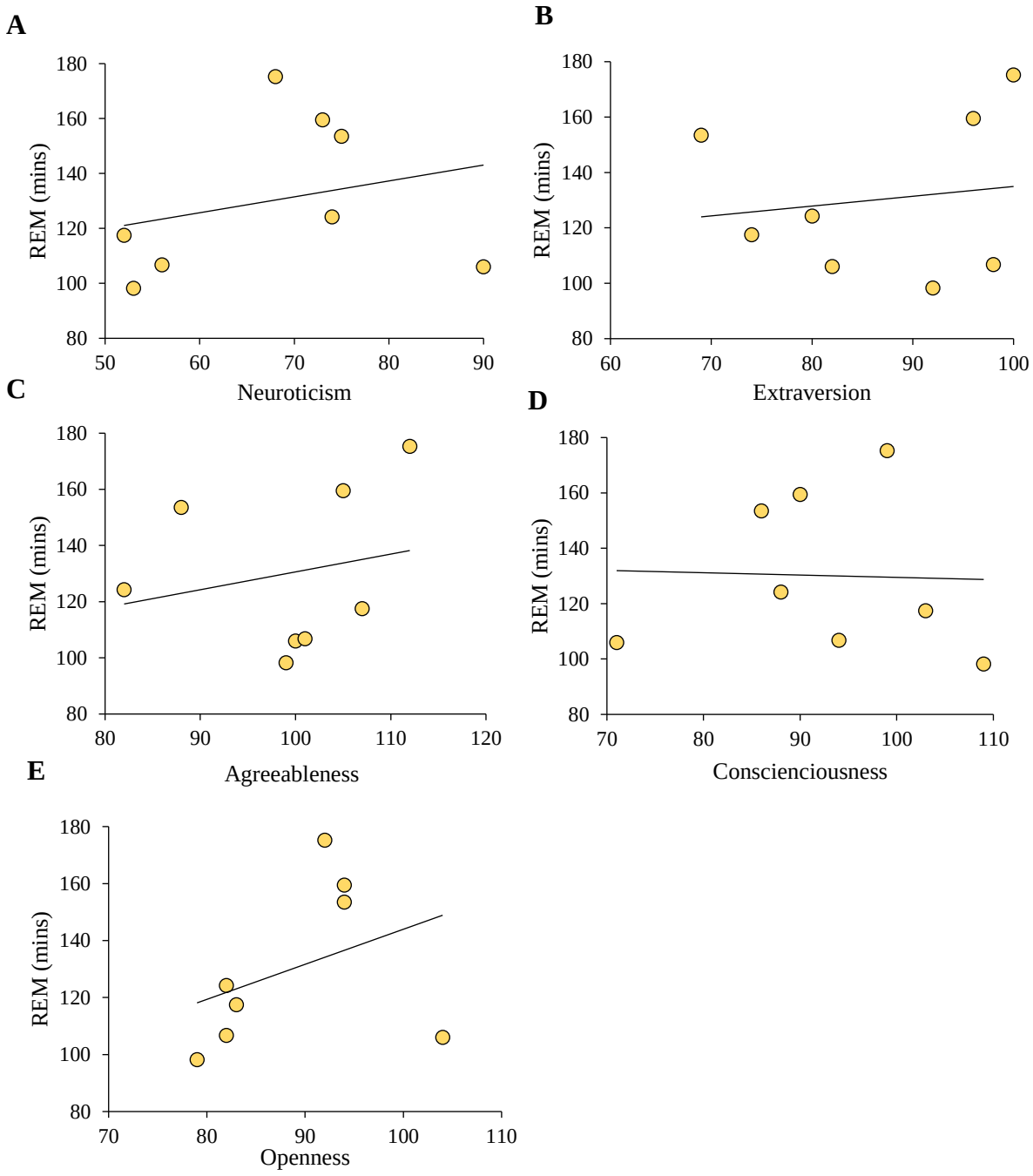


Figure D3 Personality Traits and PSG-Scored REM

There was no association between REM and the measured personality traits: neuroticism (**A**), extraversion (**B**), agreeableness (**C**), conscientiousness (**D**), or openness (**E**).

Table D4 Linear Regression: REM and Personality Traits

				Unstandardised Coefficients	
	R^2	F (1,6)	*p*	B [SE]	95% CI
Neuroticism	.07	0.46	.525	0.58 [0.86]	-1.52, 2.68
Extraversion	.02	0.13	.733	0.35 [0.99]	-2.07, 2.78
Openness	.14	0.94	.370	1.23 [1.27]	-1.88, 4.34
Agreeableness	.05	0.30	.604	0.64 [1.16]	-2.20, 3.47
Conscientiousness	.00	0.01	.936	-0.08 [1.00]	-2.54, 2.34

Appendix E

Supplementary Analyses – Chapter 3

E1 Algorithmic and Manual Scoring in Fear Conditioning Dreem Data

I calculated agreement between algorithmic and manual scoring of Dreem-recorded sleep in my fear conditioning study, as an indication that my manual scoring performed similarly to the data from my validation of Dreem against PSG (Chapter 2). In addition, the six-month delay between data collection may also have affected sleep: sample 2 was close to the summer exam period, summer daylight hours may have meant earlier wake times/more disrupted mornings, or Dreem may have updated their software.

Therefore, I compared total agreement across the night for sample 1 (fear conditioning), sample 2 (fear conditioning) and Chapter 2, testing algorithmic scoring against manual scoring as the ground truth. Kappa values from Chapter 2 scored manually and algorithmically were closer to that of Sample 2, consistent with the fact these data were collected around the same time. However, values did not significantly differ from either sample: sample 1, t (27) = 1.40, p = .172; sample 2, t (26) = -0.31, p = .761, without correction for multiple comparisons (**Figure E1**).

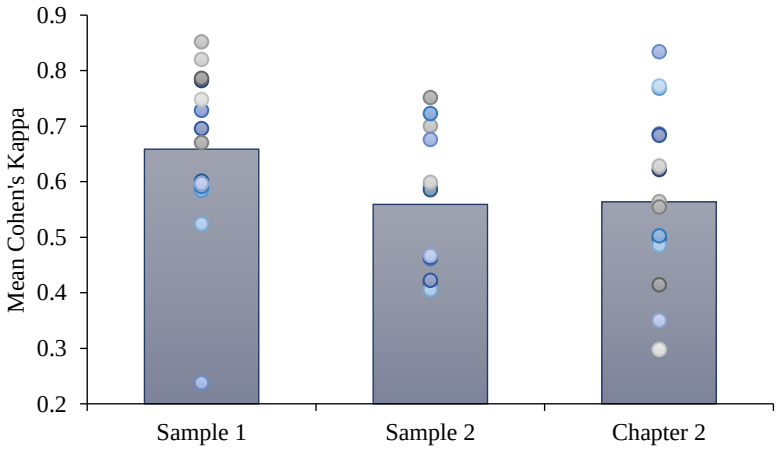


Figure E1 Cohen's Kappa Agreement Between Fear Conditioning Samples 1 and 2, and the Dreem Validation Data from Chapter 2

Sample 1 showed greater agreement between algorithmic and manual scoring of Dreem data than sample 2 and Chapter 2, though this difference was not significant. Scatter shows individual Dreem recordings.

Per sleep stage, there was a difference in sensitivity for N1, REM and wake, and in specificity for N1, SWS, and wake (**Figure E2**).

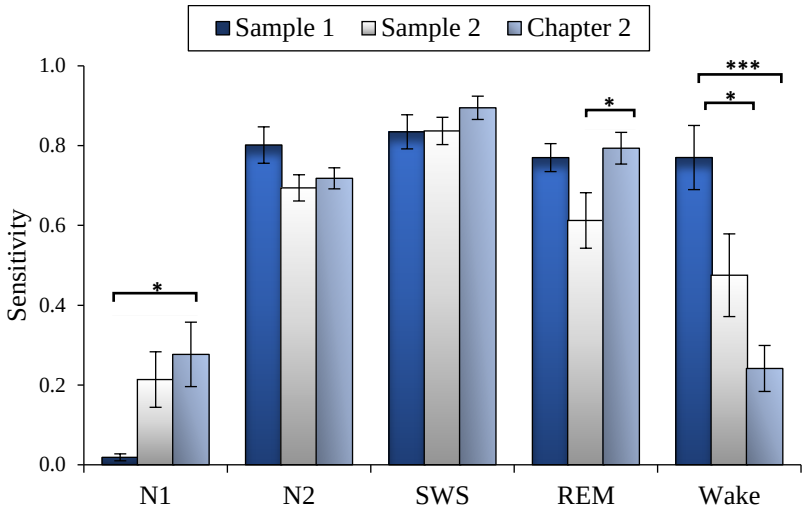


Figure E2 Sensitivity per Sleep Stage Between Fear Conditioning Samples 1 and 2, and the Dreem Validation Data from Chapter 2

Sensitivity in N1 was significantly greater in Chapter 2 compared to sample 1, sensitivity in REM was significantly greater in Chapter 2 compared to sample 2, and finally sensitivity in wake was significantly greater in sample 1 compared to sample 2 and Chapter 2. There were no significant differences in N2 or SWS.

Three-way between-subjects ANOVAs indicated no differences in N2, $F(2,41) = 2.35$, $p = .109$, or SWS, $F(2,41) = 0.99$, $p = .382$, but significant differences in N1, $F(2,41) = 4.66$, $p = .015$, REM, $F(2,41) = 3.92$, $p = .028$, and wake, $F(2,41) = 13.72$, $p < .001$. Subsequent post-hoc tests indicated which comparisons significantly differed within these stages (**Table E1**).

Table E1 Algorithmic and Manual Scoring Agreement: Sensitivity per Sleep Stage

Sleep Stage	Comparison	*p*
N1	Sample 1 against Sample 2	.114
	Sample 1 against Chapter 2	.016
	Sample 2 against Chapter 2	1.000
REM	Sample 1 against Sample 2	.097
	Sample 1 against Chapter 2	1.000
	Sample 2 against Chapter 2	.037
Wake	Sample 1 against Sample 2	.045
	Sample 1 against Chapter 2	< .001
	Sample 2 against Chapter 2	.077

Chapter 2 = Dreem validation study.

E2 Shock Expectancy Ratings: Reaction Times

Reaction times greater than 10 seconds (n=3), all of which occurred on the first rating of day 2, were excluded. Unlike ratings, these data were normally distributed.

Reaction times decreased across acquisition training, although there was some divergence between CS+ and CS- responses (**Figure E2**). A 2 x 7 repeated measures ANOVA indicated a significant difference in CS, F (1) = 5.41, p = .026, and across blocks, F (3.74) = 21.42, p < .001, but no significant interaction, F (3.77) = 1.02, p = .398.

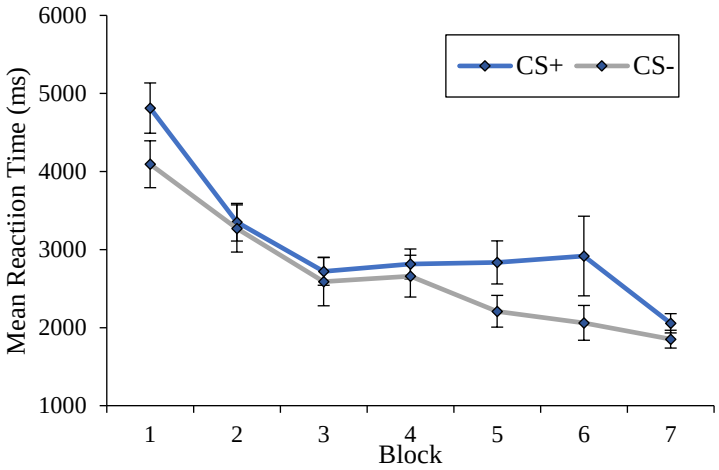


Figure E2 Reaction Time Across Trials on Day 1

Reaction times decreased similarly for CS+ and CS- across acquisition. Error bars show ± SEM.

Reaction times decreased during extinction, but all post-reinstatement trials were similar (**Figure E3**). A 2 x 4 repeated measures ANOVA indicated no significant difference in CS, F (1) = 0.04, p = .853, a significant difference across blocks, F (2.09) = 6.49, p = .002, but no significant interaction, F (2.06) = 0.28, p = .764. Likewise, for trials after reinstatement, a 2 x 4 repeated measures ANOVA indicated no significant difference in CS, F (1) = 1.66, p = .206, a significant difference across blocks, F (2.48) = 7.45, p < .001, but no significant interaction, F (2.44) = 1.52, p = .223.

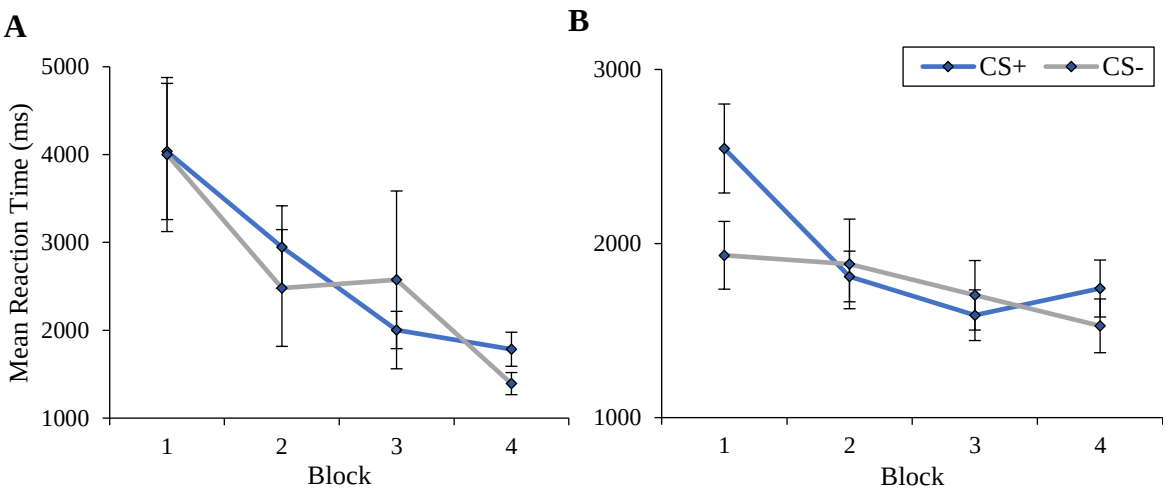


Figure E3 Reaction Time Across Trials on Day 2

There were no significant differences between CS+ and CS-, or across trials during extinction (**A**) or after reinstatement (**B**). Error bars show ± SEM.

Day 8 reaction times showed a similar pattern to day 2 (**Figure E4**)**.** A 2 x 4 repeated measures ANOVA indicated no significant difference in CS, F (1) = 2.41, *p* = .142, a significant difference across blocks, F (1.44) = 10.59, *p* = .002, but no significant interaction, F (1.67) = 1.75, *p* = .198. After reinstatement, a 2 x 4 repeated measures ANOVA indicated no significant differences in CS, F (1) = 1.83, *p* = .197, across blocks, F (3) = 0.27, *p* = .847, or a significant interaction, F (1.45) = .26, *p* = .856.

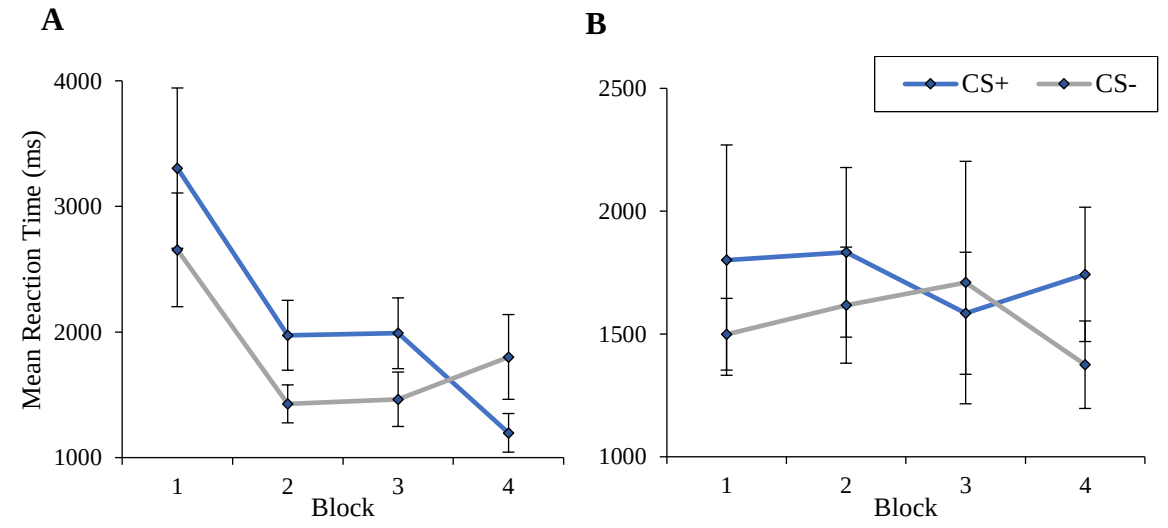


Figure E4 Reaction Time Across Trials on Day 8

Reaction times decreased across extinction (**A**). There were no significant differences after reinstatement (**B**). Error bars show ± SEM.

E3 Associations Between Reinstatement Effects and Sleep

Linear regression indicated no significant associations between REM % or SWS % with CS discrimination at the first trial after cued reinstatement on day 2 or day 8, or any spontaneous reinstatement at the first trial of day 8 after the 7-day period between sessions.

Table E2 Associations Between Sleep and Reinstatement

						Unstandardised Coefficients	
			R^2	F (df)	*p*	B [SE]	95% CI
Cued Reinstatement Day 2		REM %	.00	0.01 (1,24)	.931	0.00 [0.02]	-0.03, 0.03
		SWS %	.06	1.64 (1,24)	.213	-0.02 [0.02]	-0.05, 0.01
Cued Reinstatement Day 8		REM %	.03	0.35 (1,11)	.566	-0.01 [0.02]	-0.07, 0.04
		SWS %	.00	0.00 (1,11)	.993	0.00 [0.03]	-0.05, 0.05
Spontaneous Reinstatement Day 8		REM %	.22	3.14 (1,11)	.104	-0.01 [0.00]	-0.01, 0.00
		SWS %	.00	0.00 (1,11)	.927	0.00 [0.00]	-0.01, 0.01

E4 Associations Between Subjective Shock Expectancy Ratings and Sleep

Linear regression indicated no significant associations between REM % or SWS % with shock expectancy ratings change overnight, or after extinction learning on day 2 or day 8.

Table E4 Associations Between Sleep and Subjective Shock Expectancy Ratings After Reinstatement

						Unstandardised Coefficients	
			R^2	F (*df*)	*p*	B [SE]	95% CI
Overnight Change		REM %	.00	0.01 (1,24)	.913	0.00 [0.03]	-0.06, 0.06
		SWS %	.00	0.04 (1,24)	.851	-0.01 [0.03]	-0.07, 0.06
Extinction Learning Day 2		REM %	.00	0.03 (1,25)	.876	0.00 [0.02]	-0.03, 0.03
		SWS %	.07	1.91 (1,25)	.180	0.02 [0.01]	-0.01, 0.05
Extinction Learning Day 8		REM %	.07	0.04 (1,10)	.841	-0.01 [0.03]	-0.07, 0.06
		SWS %	.01	0.08 (1,10)	.788	0.01 [0.03]	-0.06, 0.08

E5 Heart Rate Variability as an Indicator of Discriminatory Fear Learning

I investigated differences between CS+ and CS- responses across the fear conditioning experiment, with HRV as the dependent variable, to explore whether it showed markers of discriminatory fear learning as I found in SCRs. I found no significant CS differences, there was a significant reduction in variability across extinction on day 2, but no significant interaction with CS.

Table E4 HRV as a Marker for Acquisition and Extinction Learning

		F (*df*)	*p*
Acquisition	CS	0.10 (1)	.754
	Trial	0.75 (6)	.612
	CS*Trial	1.65 (6)	.135
Extinction Day 2	CS	0.07 (1)	.792
	Trial	2.99 (7)	.005
	CS*Trial	1.26 (4.38)	.285
Extinction Day 8	CS	0.17 (1)	.685
	Trial	0.37 (3.86)	.820
	CS*Trial	0.39 (3.04)	.761

Values calculated via 2 x 7 (acquisition) or 2 x 8 (extinction) repeated measures ANOVAs. The Greenhouse-Geisser correction was used when the assumption of sphericity was violated.

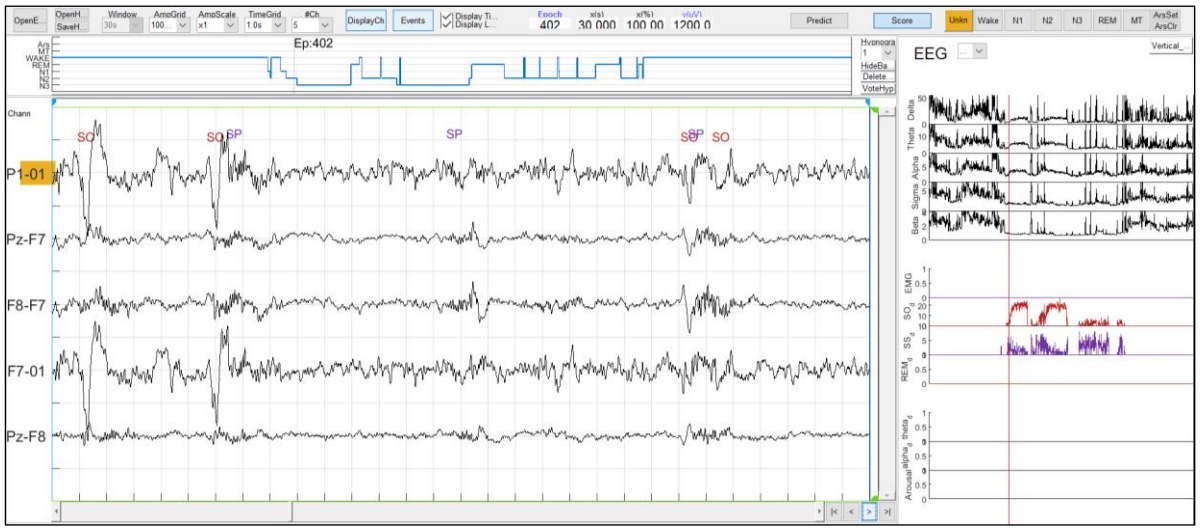
Appendix F

Supplementary Analyses – Chapter 4

F1 Slow Oscillation and Spindle Event Detection

I show an example epoch of detected slow oscillations and spindles in **Figure F1**.

A



B

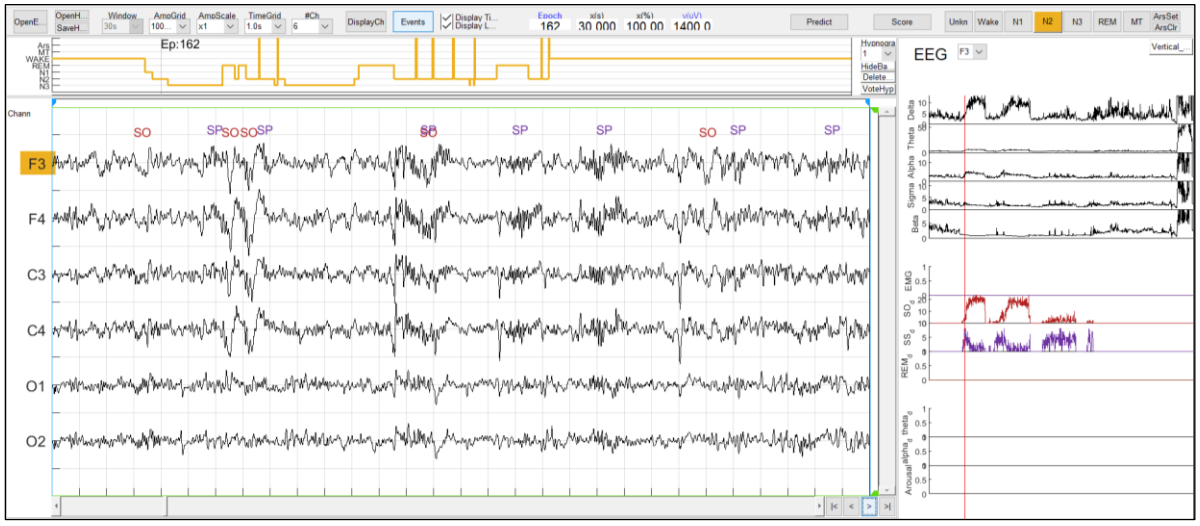


Figure F1 Slow Oscillation and Spindle Detection

A recently developed detection algorithm uses EEG input to determine adaptive noise-signal thresholds. Detection is not necessarily consistent between Dreem (**A**) and the same epoch as recorded by PSG (**B**). The algorithm plots detected slow oscillations and spindles onto the inputted EEG signal, per channel. On the left, histograms plot the frequency of these events (red = slow oscillations, purple = spindles). Power in the delta, theta, alpha, sigma, and beta frequency bands is also shown. Note that Dreem has an extra 240 epochs extraneous wake as described in Chapter 2.

F2 Power and Overnight Fear Consolidation

In Chapter 4 I show differences and associations between slow oscillation and spindle event detection count. To add strength to this finding, I show that event density (the average event count in each scored epoch) indicates very similar results (**Table F1**).

Table F1 Differences and Associations in Slow Oscillation and Spindle Detection Density

		Paired-Samples t-test		*Linear Regression (Unstandardised Coefficients)*				
		t (*12*)	*p*	R^2	F (*1,11*)	*p*	B [SE]	95% CI
Slow Oscillations (100s)	N2	-3.65	.003	.08	0.89	.365	0.15 [0.16]	-0.20, 0.51
	SWS	1.05	.312	.55	13.62	.004	0.79 [0.21]	0.32, 1.26
Spindles (100s)	N2	6.67	< .001	.41	7.77	.018	0.85 [0.31]	0.18, 1.52
	SWS	1.46	.171	.13	0.18	.683	0.10 [0.24]	-0.42, 0.62

Appendix G

Supplementary Analyses – Chapter 5

G1 Bad Dream Criteria

I used the criteria from Robert and Zadra (2014) to classify dream reports. I classified an entry as a 'bad dream' if it met one of the criteria in **Figure G1**.

Themes	Description
Being chased	Dreamer being chased by another character but not physically attacked.
Physical aggression	Threat or direct attack to one's physical integrity by another character, including sexual aggression, murder, being kidnapped or sequestered.
Interpersonal conflicts	Conflict-based interaction between two characters involving hostility, opposition, insults, humiliation, rejection, infidelity, lying, etc.
Environmental abnormality	Bizarre or implausible events appearing in the dream's environment.
Evil presence	Seeing or feeling the presence of or being possessed by an evil force, including monsters, aliens, vampires, spirits, creatures, ghosts, etc.
Accidents	The dreamer or another character is involved in an accident, including vehicle accidents, drowning, slipping, falling, etc.
Disaster/calamity	Plausible events ranging from relatively small-scale anomalies such as a fire or flood in one's house or neighborhood to larger scale disasters such as earthquakes, war, the end of the world, etc.
Failure or helplessness	Difficulty or incapacity of the dreamer to attain a goal, including being late, lost, unable to talk, losing or forgetting something, and making mistakes.
Insects/vermin	Presence of or infestation, bites or stings from insects, rats, snakes, etc.
Health-related concerns and death	Presence of physical illness, disease, health-related concerns, or death of a character or of the dreamer.
Apprehension/ worry	Dreamer is afraid or worried about someone or something, without an objective threat being present.
Others	Includes idiosyncratic as well as infrequent themes such as being naked, being self-critical, being in an insalubrious environment, and being unable to find/embarrassed to use a toilet.

Figure G1 Bad Dream Criteria

Image reproduced from (Robert & Zadra, 2014). The criteria were used as shown.

G2 Anxiety and Overnight Changes in Fear Responses

I investigated whether overnight changes in CS+ or CS- responses (SCRs) were associated with anxiety. Linear regression indicated no significant effects (**Table G1**).

Table G1 Associations Between Anxiety and SCR Change Overnight

					Unstandardised Coefficients	
	Anxiety Type	R^2	F (1,34)	*p*	B [SE]	95% CI
CS+	Trait	.01	0.18	.672	0.00 [0.01]	-0.02, 0.02
	State	.03	1.04	.315	0.01 [0.01]	-0.01, 0.04
	IU	.01	0.25	.624	0.01 [0.01]	-0.02, 0.03
CS-	Trait	.01	0.01	.890	0.00 [0.01]	-0.02, 0.02
	State	.01	0.41	.528	0.01 [0.01]	-0.01, 0.03
	IU	.00	0.04	.836	0.00 [0.01]	-0.02, 0.03

G3 Sleep and Anxiety Associations

I also investigated whether sleep was associated with anxiety. Again, linear regression indicated no significant effects (**Table G2**).

Table G2 Associations Between Anxiety and SCR Change Overnight

					Unstandardised Coefficients	
	Anxiety Type	R^2	F (1,34)	*p*	B [SE]	95% CI
REM %	Trait	.00	0.00	.969	0.01 [0.17]	-0.35, 0.37
	State	.01	0.14	.717	0.08 [0.21]	-0.36, 0.52
	IU	.04	0.91	.349	-0.27 [0.24]	-0.72, 0.26
SWS %	Trait	.01	0.16	.693	-0.01 [0.18]	-0.43, 0.29
	State	.00	0.01	.929	0.02 [0.22]	-0.43, 0.47
	IU	.00	0.08	.771	0.07 [0.24]	-0.43, 0.57

G4 Differences Between Male and Female Anxiety

Comparing reinstatement effects between males (n = 10 on Day 2, n = 7 on Day 8) and females (n = 28 on Day 2, n = 10 on Day 8), females showed a tendency towards more negative reinstatement on day 2 and lower (SCR) responses to both stimuli on day 8 but there were no significant differences (**Figure G1, Table G3**).

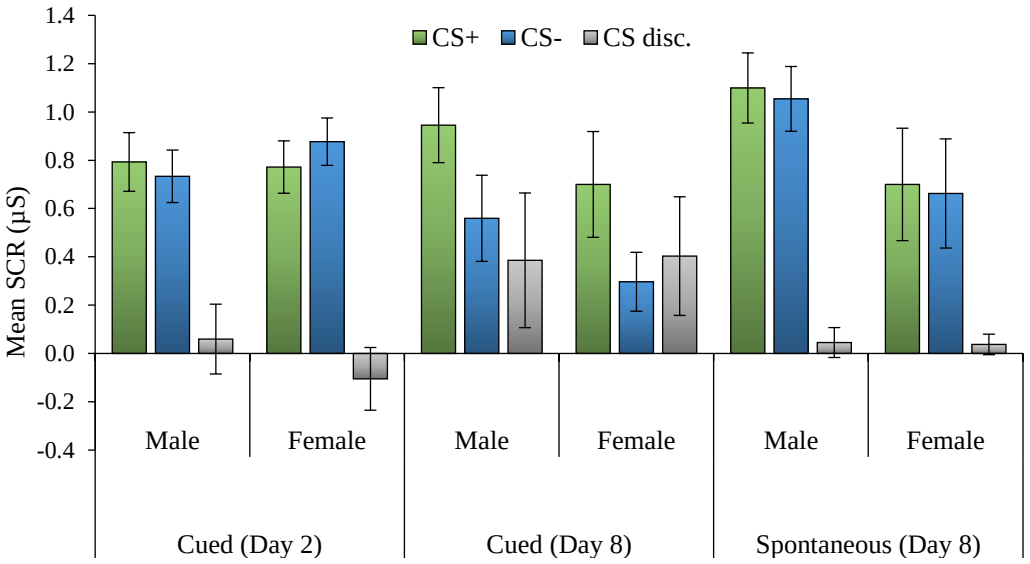


Figure G2 Male and Female Reinstatement

After cued reinstatement on day 2, males showed positive reinstatement where females showed negative reinstatement, but this difference was not significant. On day 8, female responses tended to be lower, but there were no significant differences. Error bars show ± SEM.

Table G3 Differences Between Male and Female Reinstatement Responses

		t (*df*)	*p*
Day 2 Cued Reinstatement	CS+	-0.10 (35)	.918
	CS-	0.77 (35)	.445
	CS disc.	-0.68 (35)	.504
Day 8 Cued Reinstatement	CS+	-0.84 (15)	.413
	CS-	-1.26 (15)	.226
	CS disc.	0.05 (15)	.963
Day 8 Spontaneous Reinstatement	CS+	-1.31 (15)	.211
	CS-	-1.33 (15)	.203
	CS disc.	-0.09 (15)	.927

Independent-samples t-tests.

There were also no differences between females and males in reported anxiety levels (**Table G4**).

Table G4 Differences Between Female and Male Anxiety Measures

Anxiety	Gender	Mean ± SD	t (*36*) [a]	*p*
Intolerance of Uncertainty	Female	26.68 ± 6.93	0.41	.830
	Male	26.30 ± 7.18		
State	Female	32.18 ± 7.63	0.91	.697
	Male	31.10 ± 6.97		
Trait	Female	37.57 ± 6.60	1.03	.367
	Male	34.50 ± 7.53		

Independent-samples t-tests.

Appendix H

Differences Between Fear Conditioning Samples 1 and 2

I investigated potential differences between the fear conditioning results between the two rounds of data collection. These groups (sample 1 and sample 2) were recruited and tested approximately six months apart.

Independent-samples t-tests indicated no significant differences between CS discrimination measured at the start, t (35) = 0.12, p = .905, or end of acquisition training on Day 1, t (35) = 0.10, p = .923. This suggests that the conditioning task was highly consistent in promoting acquired fear.

Furthermore, there were no significant differences between sample 1 and sample 2 on day 2: at the first trial, t (35) = 1.82, p = .077, at the last trial of extinction, t (35) = 1.65, p = .109, or the first trial after reinstatement, t (35) = 1.79, p = .083. There were also no differences between SWS, REM, or any anxiety measure between the samples (**Table H1**).

Table H1 Sleep and Anxiety Differences Between Sample 1 and Sample 2

	Mean ± SD			
	Sample 1	Sample 2	t (*df*)	*p*
SWS %	21.99 ± 7.65	21.79 ± 9.54	0.06 (25)	.951
REM %	26.48 ± 6.66	21.27 ± 9.73	1.64 (25)	.114
Trait Anxiety	36.18 ± 9.79	37.08 ± 8.70	-0.30 (36)	.767
State Anxiety	30.55 ± 7.32	32.93 ± 7.53	-0.99 (36)	.329
IU Anxiety	26.65 ± 8.21	26.78 ± 5.33	-0.99 (32.90)	.955

Both samples showed similar inclinations towards the associations between SWS and overnight change, REM and extinction, and anxiety and reinstatement (**Table H2**).

Table H2 Associations Between Sleep and CS Discrimination per Sample

		R^2	F (*df*)	*p*	Unstandardised Coefficients	
					B [SE]	95% CI
SWS % and Overnight Change	Sample 1	.18	2.65 (1,12)	.129	0.03 [0.02]	-0.01, 0.06
	Sample 2	.29	3.72 (1,9)	.086	0.06 [0.03]	-0.01, 0.13
REM % and Extinction Learning Day 2	Sample 1	.19	2.81 (1,12)	.120	0.04 [0.02]	-0.01, 0.08
	Sample 2	.18	2.13 (1,10)	.175	0.01 [0.01]	-0.01, 0.02
Anxiety[a] and CS-Reinstatement Day 2	Sample 1	.21–.32	4.83–8.64 (1,18)	.009–.041	0.03–0.03 [0.01–0.01]	0.00–0.01, 0.05-0.06
	Sample 2	.07–.18	1.08–3.32 (1,15)	.088–. 315	0.02–0.03 [0.01–0.02]	-0.03–0.01, 0.05–0.08

[a] range across trait, state, and IU anxiety measures.

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