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EEG THETA OSCILLATIONS DURING SLEEP DEPRIVATION

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ABSTRACT

Brain oscillations of different frequencies characterize the electroencephalogram (EEG) during distinct cognitive and vigilant states. Theta oscillations (4-8 Hz) are unusual because they have been found in the near-opposite conditions of sleepiness and alert cognitive control. Most neuroscience research focuses exclusively on the latter, leaving this paradox unresolved. With this thesis, I focus instead on theta during sleep deprivation (sdTheta), which has been hypothesized to reflect intrusions of local slow wave sleep on wake, based on a study in rats. The goal was to determine whether sdTheta in humans could also be considered a form of local sleep in wake, or if it was a manifestation of more typical cognition-related theta. I collected high-density EEG data from young healthy adults undergoing sleep deprivation to observe how sdTheta is affected by time awake, time of day, different tasks, and conditions. To independently track the effects of sleep deprivation, I also conducted extensive questionnaires and collected pupillometry data. I found that sdTheta can be widespread across the brain, although the specific sources depend on the ongoing task. Curiously, theta mostly originated from areas *not* critical for the task. I found that sdTheta occurs in bursts, making it unlike the isolated theta events thought to reflect local sleep. Furthermore, I found that independently from changes in the occurrences of such bursts, wake oscillation amplitudes increase with time awake, following a homeostatic trajectory. This supports the hypothesis that neuronal connectivity increases with time awake, which is what underlies sleep need. Unexpectedly, I found that the wake maintenance zone, a time before habitual bedtime when it is difficult to fall asleep, can mask these homeostatic changes in oscillation amplitudes. However, the wake maintenance zone only minimally affects the presence of sdTheta bursts. Finally, I could not find any evidence that theta bursts were the cause of behavioral lapses nor compensating for sleep loss, supporting the previous finding of sdTheta originating from task-unrelated areas. Therefore, I tentatively propose that sdTheta bursts are a manifestation of unneeded parts of the brain at rest, although not necessarily “local sleep.” If this means that sdTheta is a different type of oscillation from theta involved in cognition, then care will be needed to dissociate the two types. Regardless of what it does, theta makes for a robust marker of sleep need and can have many clinical diagnostic applications, especially when analyzed effectively.

RIASSUNTO

L’elettroencephalogramma (EEG) è caratterizzato da oscellazioni di diverse frequenze le quali distinguono stati mentali. Le oscillazioni theta (4-8 Hz) sono insolite perché sono state riscontrate in condizioni quasi opposte di sonnolenza e di elevato controllo cognitivo. La maggior parte della ricercha sulle onde theta si focalizza esclusivamente su quest'ultimo aspetto, lasciando irrisolto questo paradosso. Con questa tesi, mi concentro invece sulle onde theta che appaiano durante la deprivazione del sonno (sdTheta), le quali si ipotizza riflettano una forma di sonno localizzato durante la veglia. L’ipotesi alternativa è invece che riflettano una manifestazione più tipica di cognizione, forse contrastando gli effetti negativi della sonnolenza. Ho raccolto dati con EEG ad alta densità da giovani adulti sani sottoposti a deprivazione del sonno per osservare come sdTheta sia influenzato dalla durata di veglia, dall'orario, dall’attività e dalle condizioni. Per rintriacciare in modo indipendente gli effetti della sonnolenza, ho raccolto anche estesi questionari e dati di pupillometria. Ho scoperto che sdTheta è diffuso in tutto il cervello, anche se le fonti specifiche dipendono dall’attività in corso. Notevolmente, sdTheta ha origine principalmente da aree non critiche per il compito. Ho scoperto che sdTheta si verifica a scatti, a differenza dalle onde theta singole che si ipotizza riflettano il sonno locale. Inoltre, ho scoperto che, indipendentemente dai cambiamenti nelle quantità di tali scatti, le ampiezze delle oscillazioni aumentano con la durata di veglia, seguendo una traiettoria omeostatica. Ciò supporta l'ipotesi che la connettività neuronale aumenti con il tempo di veglia, il che sottende il bisogno di sonno. Ho scoperto anche che la "zona di mantenimento della veglia," un periodo in cui è difficile addormentarsi appena prima dell’orario abituale per dormire, può mascherare questi cambiamenti omeostatici nelle ampiezze delle oscillazioni. Tuttavia, la zona di mantenimento della veglia influenza solo minimamente la presenza di sdTheta. Infine, non sono riuscita a trovare alcuna evidenza che gli scatti theta siano la causa di mancate risposte comportamentali o altrettanto che potessero agevolare le prestazioni contrastando la sonnolenza. Ciò conferma la precedente scoperta che sdTheta ha origine da aree del cervello non correlate al compito. Perciò propongo che gli scatti sdTheta riflettano il riposo delle parti del cervello non attualmente necessarie, anche se questo non intende necessariamente "sonno locale." Se ciò significa che sdTheta è una forma diversa di oscillazione rispetto alle onde theta coinvolte nella cognizione, sarà necessario prestare attenzione su come dissociare le due tipoplogie. Nonostante non sia chiaro la loro funzione, le onde theta sono un segnale affidabile del bisogno di sonno, e potranno avere molte applicazioni diagnostiche mediche.

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1 INTRODUCTION

Being sleep deprived is a miserable experience. Your thoughts move through molasses, your eyelids are made of lead, and your emotions rival those of the Grinch at Christmas. Side effects may include headaches, nausea, and a general feeling of unwellness. All the while, you can only think about one thing: your bed. The big question is of course "why do we sleep?" but put another way: "why is it so awful staying awake too long?" What terrible things are happening to our poor neurons when we skip a night of sleep? How do we power through it, and what happens when we can no longer cope?

I'd like to think there are a couple answers to these questions in here, all thanks to theta waves. These are brain oscillations between 4 and 8 Hz that become increasingly common the more time you spend awake (Aeschbach et al., 1997; Cajochen et al., 2002; Finelli et al., 2000). Theta waves are usually measured with surface electrodes on the scalp in humans, but fortunately they also appear in rodents (Vyazovskiy et al., 2011), so we have some clue as to what neural process causes them. When measured intracortically, theta during sleep deprivation reflects local networks of neurons synchronously firing together and being silent together, exactly what happens during sleep to generate slow waves. The hypothesis is therefore that theta waves are *intrusions of local sleep during wake*. This could nicely explain why behavior deteriorates during sleep deprivation.

The idea that theta activity corresponds to local sleep is compelling but runs into difficulties when compared with almost any other study of brain electrophysiology. The problem is that theta waves are involved in *everything*, from ADHD to Zen meditation (Angelidis et al., 2016; T. Takahashi et al., 2005). But the most problematic of all is that theta is a reliable marker of intense cognition, from arithmetic to working memory (Arellano & Schwab, 1950; Brookes et al., 2011). There are a lot of possible explanations why completely opposite conditions could generate the same brain wave, and identifying the answer is an important step towards understanding the role of these waves in either scenario.

The goal of my research was therefore to better understand theta activity related to sleep deprivation, and how it could be different, if it even was different, from the theta associated with cognitive processes. Maybe they were slightly different frequencies, or came from different areas, different waveforms, or maybe they were indistinguishable, requiring some creative reinterpretation of the evidence. To answer these questions, I needed to compare the EEG of the same individuals under the cognitive conditions that generate theta waves, and then again under sleep deprivation, determine if they were different in any way, and check if these theta oscillations were a help or a hindrance.

The following introduction brings together all the major literature related to theta, with a focus on areas of research that are most in conflict with sleep deprivation theta, or most in agreement. This will be followed by the three publications I wrote on this topic. The first is *The theta paradox: 4-8 Hz EEG oscillations reflect both sleep pressure and cognitive control* (Snipes et al., 2022), which elaborates on the discrepancy and directly compares theta related to cognition with theta related to sleep deprivation. The second, *How and when EEG reflects neuronal changes in connectivity due to time awake* (Snipes et al., 2023), demonstrates that there is a dissociation between theta occurrences and theta amplitudes across time awake, which substantially complicates how to interpret changes in theta power, especially during sleep deprivation. The third, *EEG markers of sleepiness do not predict lapses in attention during sleep deprivation*, unfortunately determines that theta during sleep deprivation is not actually responsible for behavioral lapses. In the discussion, I will then attempt to resolve the theta paradox and elaborate new findings and suggest some possible future research directions on this topic.

I tried to avoid bogging down the text with too much background information; so definitions, brief descriptions, and digressions are often provided as footnotes, with more in-depth explanations and semantic hair-splitting at the end in the Glossary. At the end of each paper there is additional information that fills in some unanswered gaps between the publications. There are also colored textboxes scattered throughout the document; these are self-standing tangents which I find very interesting, but are not strictly related to the main topic of this thesis. They can be read in isolation, or not at all. It's a long thesis, essentially composed of many mini-essays, so I highly encourage selective reading based on the topics most of interest to you. To help with skimming, at the end of each chapter, there's a "tldr" (too long, didn't read) summary, so it's possible to get the main message of each section by just reading these captions.

tldr; theta oscillations characterize the EEG during sleep deprivation, but they can also be found under a variety of cognitive conditions. With this thesis, I try to learn more about theta during sleep deprivation to better understand what it could be.

1.1 Why we can't stay awake forever

There are two types of people in the world: those that want to sleep more, and those that want to sleep less. They both have the same problem: staying awake for too long gets hard. The first step towards a solution is clear: we need to figure out why we can't just stay awake forever.

The irony of sleep deprivation is that it is subjectively one of the worst things that can ethically be done to research participants, and yet it is surprisingly hard to objectively measure its effects. Consistently, sleepiness and other subjective variables have larger effect sizes than any behavioral outcome (Groeger et al., 2014; Lo et al., 2012), and somehow the more complex tasks show the smallest effects of all (Lim & Dinges, 2010). The explanation for this is that degradation *does* happen with sleep deprivation, but sufficient compensation mechanisms exist to maintain steady performance for the duration of a research experiment (Chee & Choo, 2004; Drummond et al., 2005). The implicit understanding is that if we can bypass such compensation effects and find a proper objective measure of sleep deprivation, then we can understand what is happening during wake that makes sleep necessary.

Ultimately, with enough sleep deprivation, pretty much any measurable behavior is affected (Boonstra et al., 2007; Killgore, 2010). The harder question to answer is why do we need sleep after just 16 hours of wake? Behaviorally, not much degrades within that time frame (McMahon et al., 2021; Shekleton et al., 2013). A good answer is that sleep every night performs regular maintenance, repairing stressed neural infrastructure (Vyazovskiy & Harris, 2013) and clearing metabolic by-products (Xie et al., 2013). In this case, skipping a night of sleep isn't damning, but if wake is prolonged for much longer, minor "wear and tear" could lead to real damage. Therefore, the mechanism of subjective sleepiness could have evolved to ensure regular sleep even when not strictly necessary.

Another possibility is that sleep is more urgently needed for neuronal plasticity, which is the process of strengthening connections, crticial for learning and memory. This is the basis of the *synaptic homeostasis hypothesis* (Tononi & Cirelli, 2014), which posits that during the day, neurons increase their overall synaptic strength, and sleep is necessary to "downscale" this effect in order to maintain homeostasis. Sleep is therefore needed to selectively prune synapses that are less important and consolidate those that are

worth keeping. An important assumption of synaptic homeostasis is that sleep need accumulates along a saturating exponential,[1] meaning that the most rapid changes in the brain happen early, and then increasing time awake progressively affects the brain less and less. Therefore, the brain's plasticity "saturates" sooner rather than later, which would explain why we need to go to sleep every night.

The fact that sleep is necessary for plasticity rather than just the activity of neurons is a critical distinction. This means that sleep deprivation should affect learning and memory of new content more so than well-learned behavior. In fact, memory consolidation is one of the most well-established functions of sleep (Ackermann et al., 2015; Lendner et al., 2022; Ngo et al., 2013; Nishida et al., 2009). Not sleeping results in both a reduction in memory consolidation of content learned during the day, as well as impaired ability to learn new material after sleep loss (Guttesen et al., 2023). Unfortunately, it's tricky to track the changes in plasticity and learning ability across time awake, because inevitably every repetition of the task results in improvements in performance, counteracting the detriment of time awake. The previously mentioned results come from comparing performance in one session after (and maybe one before) either a period of sleep or wake. Therefore, the catch-22 is that to track the effects of sleep deprivation with incrementally increasing time awake, you need a task that doesn't improve with repetition and therefore includes no learning, but the hypothesized reason for sleep need is a reduction in the ability to learn.

As it turns out, plasticity isn't the only function that systematically degrades with time awake; the other is sustained attention (Lim & Dinges, 2010; Lo et al., 2012). The classic paradigm is the psychomotor vigilance task (PVT), which involves monitoring a fixation point, and every 2-10 seconds, a counter starts and the participants has to push a button in response to stop it (Basner & Dinges, 2011; Dinges & Powell, 1985). The PVT is minimally affected by task repetition, so it is ideal for tracking changes in performance across extended wake (Basner et al., 2018). With increasing time awake, all responses get slower and slow responses become a *lot* slower (Doran et al., 2001); the latter are known as lapses. These lapses increase mostly linearly across wake, although with robust circadian fluctuations with time of day (Graw et al., 2004).

A compelling assumption is that these increasing lapses reflect "state instability" (Doran et al., 2001) and the intrusion of sleep on wake (Hudson et al., 2020), which would indirectly reflect the increase in sleep pressure. However, no PVT outcome measure reflects the same saturating exponential assumed to be behind synaptic sleep pressure, and the PVT is extremely sensitive to circadian and other changes in vigilance, so it is not suited to quantify changes in plasticity. Altogether, this means that there are so far no good behavioral measures of sleep need and plasticity. Therefore, neural markers are maybe the best chance we have to track the brain's changes with sleep deprivation.

tldr; to better understand why we need sleep we need reliable measures of accumulating sleep need with time awake.

1.2 Sleep deprivation theta

It took some time to narrow down, but it eventually became clear that increasing time awake results in increased theta activity (Aeschbach et al., 1999; Cajochen et al., 1995; Finelli et al., 2000; Torsvall &

[1] *See the two-process model and sleep homeostasis in section 7.3.2, page 142.*

Åkerstedt, 1987). This effect is typically measured in resting-state wake recordings, in which participants simply fixate on a point for several minutes while their EEG is recorded. Recordings are performed at regular intervals until 24, 48, or even 72h awake. The EEG is then quantified using spectral power analysis, and the resulting spectrum is subdivided into standard frequency ranges.[1] While this type of analysis results in a substantial reduction from the original signal, it allows rapid quantification that can track changes in EEG activity across time.

The increase in theta power with time awake peaks at 6.5 Hz (Finelli et al., 2000).This increase in wake was found to correlate with EEG slow wave activity during sleep (SWA; 0.5-4 Hz), with both originating primarily from frontal regions (Finelli et al., 2000).[2] SWA is the defining feature of NREM sleep,[3] decreasing exponentially across the night, and it starts off at higher amplitudes with more time previously spent awake. SWA is considered to be a marker of *sleep homeostasis*, the underlying process of sleep need building up during wake and dissipating during sleep. Together with *circadian rhythms*, this controls when and for how long any animal needs to sleep, as explained by the two-process model of sleep (Borbély, 1982). The combination of these creates *sleep pressure,* which we subjectively experience as sleepiness. The previously described *synaptic* homeostasis is hypothesized to be the reason for the increase in SWA: the more neurons are interconnected, the larger the oscillations.

The increase in theta with sleep deprivation is specific to wake, and not visible in either NREM or REM sleep (Tinguely et al., 2006), and vice-versa slow wave activity does not substantially increase during wake (Finelli et al., 2000). Nevertheless, theta in wake and slow waves in sleep reflect the same local changes in sleep homeostasis. Huber et al. (2004) found that SWA increases locally during sleep following a motor-learning task, indicating that sleep pressure was higher for the specific networks involved in the task. Vice-versa, arm-immobilization resulted in local decreases in SWA (Huber et al., 2006). Hung et al. (2013) followed up on this, showing the same effect for theta. Participants performed two sleep deprivation bouts, one in which they spent the day playing a driving simulator, the other in which they listened to audiobooks, thus involving independent brain networks. During resting EEG recorded between the tasks, theta power showed distinct local increases depending on which of the two tasks the participant had been engaged in, and these local differences matched those observed in SWA during recovery sleep. In other words, areas that underwent more plasticity while awake showed both more SWA in sleep and more theta power in wake. Therefore, the simple story is that SWA reflects sleep homeostasis during sleep, and theta power reflects sleep homeostasis during wake.

Unfortunately for the simple story, theta power also reflects circadian rhythms (Cajochen et al., 2002; Strijkstra et al., 2003). Theta power decreases following caffeine consumption (Landolt et al., 2004; Reyner & Horne, 1997) and increases with melatonin (Cajochen et al., 1996). Theta is higher during dim light compared to bright light exposure (Cajochen et al., 1998; Yokoi et al., 2003), with the effect interacting with time of day (Ahlström et al., 2018). Theta power is higher when seated compared to standing (Caldwell et al., 2000). It even increases following lunch, what Italians refer to as an “abbiocco post-pranzo” (Lowden et al., 2004; Reyner et al., 2012). Patients suffering from excessive daytime sleepiness have higher theta power, such as those with obstructive sleep apnea at night (Grenèche et al., 2008; Melia

[1] *More information on power and bands in section 7.2.1, page 135.*

[2] *I was unable to replicate this with my own data. The original study had an N = 7 but conducted 40 h of sleep deprivation, so I withhold judgement.*

[3] *More information on sleep stages in section 7.3.1, page 140.*

et al., 2015). All in all, theta power seems to be a general marker of *sleepiness* and not just homeostatic sleep pressure.

Theta correlates with subjective sleepiness, but only when measured with eyes-open (Gorgoni et al., 2014; Kaida et al., 2006; Strijkstra et al., 2003). Theta was also found to correlate with the slowing down of the fastest reaction times of the PVT (Gorgoni et al., 2014). However, when sorting participants into those who show the smallest and largest changes in performance (vulnerable vs resistant to sleep deprivation), subjective sleepiness matched the split, but theta power did not (Galliaud et al., 2008). Therefore, there is not complete agreement between subjective, behavioral, and EEG measures of sleepiness. The idea is therefore that theta more closely reflects sleep homeostasis than other factors. To disambiguate theta related to sleep deprivation from the rest, I will henceforth refer to it as sdTheta.

In general, there are very few studies about sdTheta, largely because they are almost exclusively conducted by sleep researchers, who are by definition more interested in sleep. Theta related to sleepiness barely gets mentioned in the main electroencephalography textbooks, certainly nothing related to sleep deprivation, and so the discrepancy with cognitive theta has been largely ignored (Schomer & Silva, 2011). A few older studies have tried to address the inconsistency between sdTheta and other manifestations of theta (section 1.5), but these came before the use of computer-based data analyses. Therefore, we don't have a good idea of what sdTheta actually corresponds to, what it's doing in the brain, how it's generated, why it's generated, and whether or not it interferes with normal brain functioning. We don't even really know what it looks like. Nevertheless, the current main hypothesis about sdTheta is that it may actually be a form of local sleep.

tldr; theta activity reflects sleepiness in general, but here I focused on theta that increases with sleep deprivation, "sdTheta."

1.2.1 Theta as local sleep

The idea of theta power as a generic marker of sleepiness took a backseat when it was suspected that theta waves in wake could be homologous to slow waves in sleep. Vyazovskiy et al. (2011) conducted a study in sleep-deprived rats, comparing EEG with neuronal spike firing,[1] and found that the increase in theta waves observed in the EEG corresponded to synchronized silence of local neuronal spiking, known as off-periods. This is the exact same pattern observed during slow waves in sleep, also associated with such synchronized silences (Steriade et al., 1993, 2001); the only difference is that slow waves tend to involve larger populations of neurons, and the off-periods last longer. This meant that the same firing patterns underlying sleep slow waves were behind theta during sleep deprivation, therefore suggesting that theta waves were just little slow waves.[2] Supporting this, in a sugar pellet reaching task, rats were

[1] *In research animals, it's possible to record single (or multiple) neurons' electrical signals with thin needle electrodes or grids of tiny little needles. A neuron then sends a "spike" of electric current to its interconnected neurons, and these spikes can get tallied up. Alternatively, a larger electrode is placed on the surface of the cortex in order to record the local field potential (LFP), which is slow fluctuations in the electrical field around neurons, and most closely corresponds to the human scalp EEG. But you probably knew that.*

[2] *My understanding is that other types of wake oscillations don't result in such synchronized off-periods (all neurons silent at the same time) even if individual neurons are more often silent than not.*

more likely to have an off-period just prior to a failed attempt compared to a successful one. Altogether, this paper suggested that theta events are actually a form of local sleep during wake.

Partial sleep and wake have previously been described in specialized animals like marine mammals and seabirds (Lesku et al., 2011; Mascetti, 2016), as well as pathological conditions such as sleep walking (Castelnovo et al., 2016; Terzaghi et al., 2009, 2012) or stroke (Sarasso et al., 2020). Nobili et al. (2011) also found the inverse; local wake oscillations during sleep, measured intracortically in patients. However, this result in rats suggested that some form of local sleep in wake could be found across all healthy mammals, and this could explain the behavioral deficits observed during sleep deprivation (Hudson et al., 2020; Siclari & Tononi, 2017).

Unlike with animals, it is generally not possible to measure single-neuron spiking in healthy humans, however "circumstantial evidence" suggests that off-periods could in fact underly human sdTheta as well. The previously mentioned local changes in theta power with sleep deprivation by Hung et al. are thought to reflect local sleep, anticipating the increased SWA that will occur during actual sleep. Bernardi et al. (2015) with a similar paradigm were able to show that commission errors in a go no-go task were predicted by the presence of these local theta waves. Fattinger et al. (2017) likewise found large widespread theta waves were associated with slower reaction times in children. Therefore, like in rats, performance is impaired when a theta event co-occurs.

The holy grail however was to find true off-periods intracortically during wake in humans, and Nir et al. (2017) attempted just that, looking at single-cell local field potentials of epileptic patients undergoing sleep deprivation. Unfortunately, unlike in rats, it was not possible to record as many simultaneous neurons, making it difficult to distinguish these smaller off-periods. Furthermore, epilepsy itself induces "off-periods" during wake which increase with sleep deprivation, and such pathological events would be indistinguishable from local sleep.[1] Therefore, despite best efforts, the authors were not able to find evidence of off-periods in humans during wake sleep deprivation (personal communications with Yuval Nir), like they were for slow waves in sleep (Nir et al., 2011). They did, however, find local changes in firing rates as well as in theta power, which were linked to delays in performance.

Overall, there is promising evidence to suggest that theta during sleep deprivation in humans is a form of local slow wave sleep, but no definitive proof. There are two alternative explanations for theta during sleep deprivation in humans. One is that theta related to cognition actually plays a role during sleep deprivation, maybe as some form of compensation. In this case, sdTheta is not about sleepiness pe se, but actually resisting sleep (section 1.6, page 25). The second is that sdTheta is a manifestation of sleep intruding on wake, just not slow wave sleep. Unlike in rodents, human sleep begins with an additional transition stage, NREM 1. As it happens, theta activity has also been associated with this stage (section 1.3, page 14). Therefore, it is possible that despite both rodents and humans showing sdTheta, the underlying cause may differ.

Determining if sdTheta is local sleep can only really be done with intracortical data, but the shape and distribution of theta waves can be indicative. If human sdTheta is a manifestation of local slow waves, then it should have similar properties to the first slow waves observed at sleep onset. This means single events, often with a stronger negative rather than positive deflection (Nir et al., 2011; Vyazovskiy et al.,

[1] *Sleep deprivation is a procedure done in some patients with epilepsy in order to induce epileptic activity while they are being monitored so that the epileptic source can be more carefully identified.*

2011).[1] Furthermore, they need to be sufficiently frequent and of sufficient high amplitude to emerge from the background EEG in order to conceivably explain the increase in theta spectral power observed with increasing time awake (Finelli et al., 2000). Also, it should be demonstrated that the theta power increase from the beginning of the wake period corresponds to these little slow waves; it's one thing to say sleep intrudes on wake when sleep deprived, it's more extreme to say that it does so from the beginning of a normal waking day. It's quite possible that normal waking theta activity follows some independent trajectory across the day, and only when there is high sleep need after >16 h awake do local sleep theta waves start to appear. This is the case for microsleeps, which are virtually non-existent for well-rested individuals, and only start to appear with sleep restriction, sleep deprivation, or clinical conditions (Bougard et al., 2018; Hertig-Godeschalk et al., 2020; Moller et al., 2006).[2]

tldr; there's strong evidence in rats, and weak evidence in humans, that sdTheta is actually driven by little sleep slow waves intruding on wake.

1.2.2 Fatigue theta

Independently from studies of sleepiness and sleep deprivation, increases in theta power have also been associated with "fatigue" (Tran et al., 2020). The exact definition of fatigue varies, but differs from sleep pressure in that it reflects the deterioration in performance and motivation with increasing time on a repetitive or monotonous task, rather than just with time awake. Also, an underlying assumption is that rest from the specific task is sufficient to recover from fatigue, whereas sleep pressure needs real sleep for recovery.[3] Much of the literature on this topic revolves around fatigue related to driving, flying, or similar monotonous but dangerous activities, for obvious reasons (Borghini et al., 2014; Hamann & Carstengerdes, 2023; Torsvall & Åkerstedt, 1987). Unlike sleep deprivation, fatigue has the advantage of being investigated during normal working hours.

In a meta-analysis, Tran et al. (2020) concluded that theta power, and to a lesser extent alpha power, increase with time-on-task, whereas delta power is less affected and beta power not at all affected by fatigue. Some studies have rather found increases in lower alpha power more than theta (Craig et al., 2012), which could be interpreted as a spilling-over effect or even a slowing down of alpha (Arnau et al., 2021). However, others clearly show a robust increase in frontal midline theta with time on task, spatially independent from the increase in alpha (Li et al., 2020; Trejo et al., 2015).

Fatigue researchers also noticed the discrepancy between their theta and theta during cognitive tasks. One solution to the discrepancy would be if theta during fatigue is a compensation mechanism, what Clayton et al. (2015) compare to "the revving noises of a tired motorcar trying to climb a steep hill." However, this is contradicted by the fact that the increase in theta with time on task is found both in the EEG

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[1] *Difference between "events" and "oscillations" is explained in section 7.2.2, page 136.*

[2] *Difference between "local sleep" and "microsleeps" is explained in section 7.3.4, page 142. For results, see also Figure 3.8B, page 81.*

[3] *This is not usually explicitly acknowledged, nor incorporated into the study designs (e.g. measurements after a sufficient rest period), and may not be universally considered critical to the definition of fatigue. However I think it's worth making the distinction between tiredness from which one can recover with rest, and tiredness due to plasticity (Nelson et al., 2021), which requires sleep (more details in section 7.3.5, page 143). Likely, a bit of both happens in most studies.*

during the task and in resting recordings after the task (Li et al., 2020). An alternative explanation is that theta actually reflects activity of the default mode network, and therefore deactivation of task-irrelevant areas (Trejo et al., 2015), explored more in section 1.5.1 (page 24). However, a final solution is that there are at least two manifestations of theta; a cognitive one that processes information, and one reflecting fatigue, whatever that might be. This is supported by the fact that theta power measured from the entire task recording will show a progressive increase with time awake, whereas stimulus-evoked theta actually decreases with time on task (Wascher et al., 2014). The increasing theta occurs between trials, thus doesn't interact with the task-evoked theta (Arnau et al., 2021).

Like sdTheta, the main property of fatigue-theta is an increase in theta power with passing time, so it could reasonably be the same thing. In fact, Nelson et al. (2021) specifically showed that frontal theta power increased more with a fatiguing motor-learning task rather than just a motor task, and this increased theta only decreased following a nap rather than passive rest. Therefore, fatigue theta is likely sdTheta on a shorter time scale. If sdTheta is actually local sleep, however, this assumption needs to be revisited. It's not impossible that local sleep should occur after just a few hours of wake, but it is a less likely explanation, and would require similar validation that single "mini slow waves" are driving this increase in power.

tldr; theta increases with time on task, but this is likely a manifestation of sdTheta.

1.3 NREM 1 theta

The NREM 1 sleep stage marks the transition between wake and sleep. Whether to consider it already sleep is up for debate,[1] which is why many researchers define sleep onset from the appearance of the first spindle or slow wave instead (NREM 2). According to the AASM sleep scoring guidelines, NREM 1 is defined by the disappearance of alpha oscillations, slow rolling eye movements, and an increase in low amplitude, mixed frequency activity, "predominantly 4-7 Hz" (Berry et al., 2012).

Given that sleep onset is thus characterized by theta activity, a reasonable hypothesis would be that sdTheta was the intrusion of NREM 1 on wake. The main problem with this idea is that when inspecting the spectrogram of NREM 1 (Figure 1.1), there is no characteristic "bump" in the theta range that would indicate any oscillatory component emerging from the 1/f background activity,[2] like there is for alpha during wake. Why, then, does the AASM say that NREM 1 is characterized by theta?

[1] *I vote for it being sleep; the spectral change is larger than anything I've seen during wake, sleep deprivation, or any task. The argument against NREM 1 being sleep is that it is not associated with a loss of consciousness (Ogilvie et al., 1989), but since apparently healthy individuals can still think they are conscious all the way into NREM 3 (Stephan et al., 2021), then I would rather rely on EEG changes for classification. However, it may be a gradual change.*

[2] *If the concept of "aperiodic" and "periodic" EEG is unfamiliar to you, read section 7.2.3 on page 138, it's important. Briefly, the EEG is made of an "aperiodic" signal which is a lot like noise. When plotting the spectral power of this activity on a log-log scale, it forms a straight downward sloping line.*

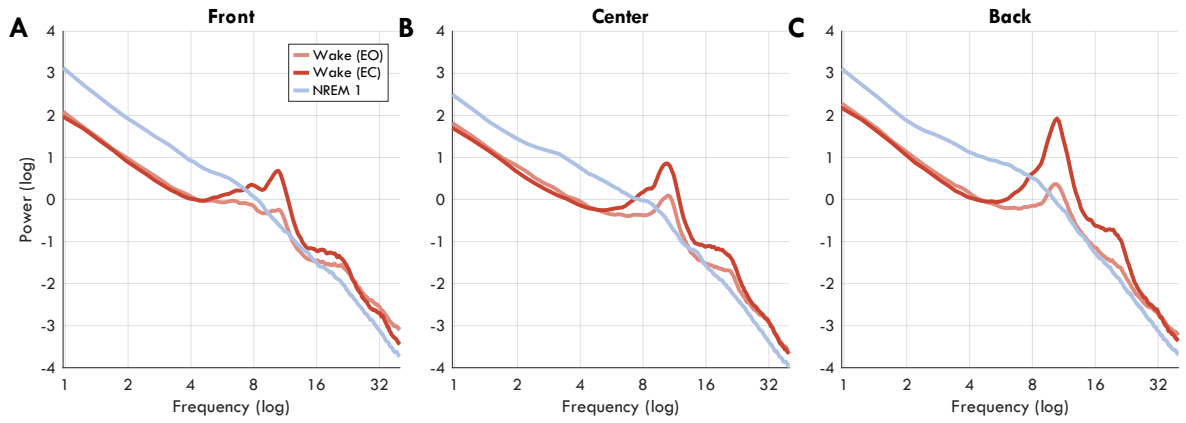

Figure 1.1: NREM 1 spectrum, log-log scale. N = 18. Eyes-open (EO) wake was taken from the Fixation Baseline Post condition, Eyes-closed (EC) wake is from Standing Baseline Post condition. NREM 1 is from the Baseline night. **A**: Front region of interest (ROI); **B**: center; **C**: back. ROI channels are depicted in Figure 2.18, page 61.

First of all, as can be seen in Figure 1.1 and Figure 7.7 (page 141) increasing sleep depth is accompanied by a steepening of the *slope* of the background activity, meaning that lower frequencies have even higher amplitudes and higher frequencies have lower amplitudes with respect to each other. In the frequency domain, the change is clearly related to the entire spectrum, however visually in the time domain the increase in slower frequencies is substantially more evident than the decrease in high frequencies. This background aperiodic activity can be easily simulated with "colored noise" (Figure 1.2A); such that by increasing the ratio of low to high frequencies, the fake signal clearly mirrors the change from wake to sleep observed in the EEG signal (Figure 1.2B). For the majority of NREM 1, for the majority of participants, this may be the only kind of "theta" present in the EEG.

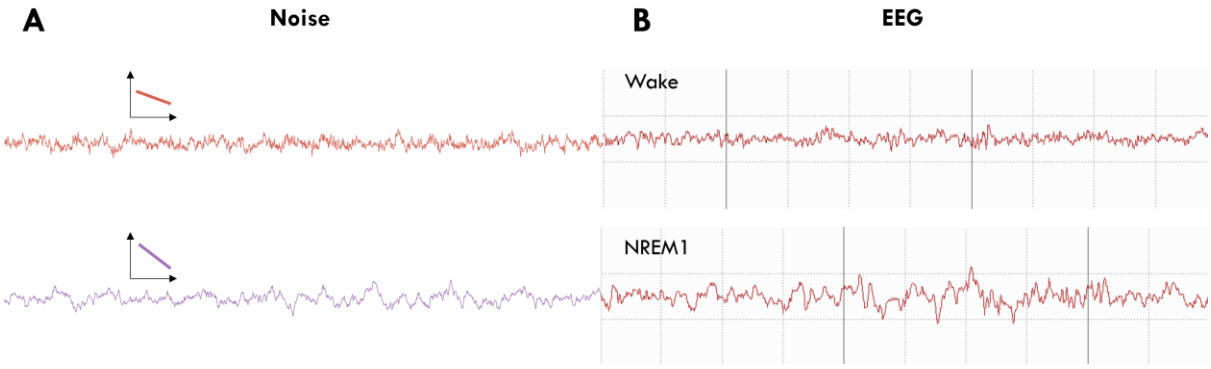

Figure 1.2: Aperiodic EEG. A: Simulated EEG data of only a 1/f spectrum with different slopes. This is done by creating a $f^{-\alpha}$ signal, randomizing the imaginary component (the "phase" of the sinusoids that make up the signal), then doing an inverse FFT. By changing the exponent α, you get different slopes. This is an extremely "dumb" simulation, just of the shape of the power spectrum, without any information about how the brain works. **B**: Screenshots of EEG from our sleep scoring program, with data classified as wake (top) and NREM 1 (bottom). Vertical lines are spaced 1 s apart, horizontal lines indicate ± 37 µV.

However, some individuals have genuine theta oscillations during NREM 1. Santamaria & Chiappa (1987) wrote a review about the EEG and EOG markers while falling asleep and found that across large datasets, a subset (from a single individual to ~30%) show some form of theta-like oscillations. The authors provide a variety of labels from "fronto-central sharp bursts," "generalized sharp bursts," "six-per-second phantom spike waves," "temporal asymmetric theta/delta," "rhythmic mid-temporal theta" and "wicket spikes," not to mention the most common "vertex sharp waves." These waves have different frequencies,

durations, amplitudes, and channel locations. Part of the plethora of categories comes from non-standardized nomenclature across studies, but even within the same authors' data, there is an incredible variety of oscillatory activity in the theta range occurring during NREM 1. Given their relative infrequency, as well as the variability across individuals, these peculiar manifestations of theta oscillations don't show up in group averages.

A few studies *have* found average increases in theta power during the transition from wake to sleep, usually at the low end of the theta range, between 1 and 3 Hz (Bódizs et al., 2005), and 3-5 Hz (Achermann et al., 2019; Wright et al., 1995). Marzano et al. (2013) did find an increase in occipital theta just after sleep onset using a different oscillation detection method. However, a common phenomenon during sleep onset is a slowing down of the alpha rhythm, which means it may sometimes enter the upper theta range (Santamaria & Chiappa, 1987), and may explain the effect. A study in cats found in-vivo alpha and theta oscillations generated by the lateral geniculate nucleus during relaxed wakefulness and drowsiness, respectively, and in-vitro they found that the same cells could generate either alpha, theta or delta by progressively decreasing doses of a glutamate receptor agonist (Hughes et al., 2004). While this would suggest that theta during NREM 1 could be explained as wake rhythms slowing down, given the heterogeneity of human theta rhythms described in the literature, this seems to me an oversimplification and may reflect some but not all of the changes observed.

In our own data, we had one participant with remarkable theta oscillations during NREM 1 (Figure 1.3). These oscillations were mu-shaped, almost exactly 6 Hz, extremely large (> 50 µV peak to peak), and curiously located around the right mastoid. For this reason, when sleep scoring, the waves appeared global due to the use of linked mastoids as reference. These bursts were also present during wake, and came to dominate the EEG during sleep deprivation (Figure 3.4, page 77).

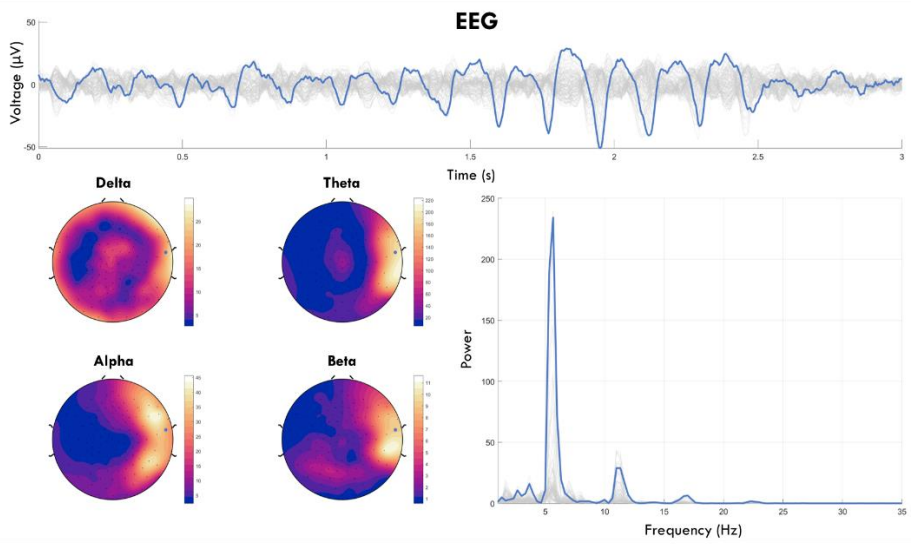

Figure 1.3: NREM 1 theta burst in P15. Top: 3 second window of EEG with a prominent theta burst during NREM 1. Bottom left: topographies of delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (15-25 Hz) power during the above theta burst. Color scale is spectral power in $\mu V^2/Hz$. Bottom right: power spectrum, untransformed, of the theta burst. N.B. the second and third peaks after theta reflect harmonics, due to the non-sinusoidal shape of the oscillation. The blue lines indicate the channel specified with the gray dot in the topographies. The gray thin lines represent all the other channels.

It may not be widely known, even among sleep scorers, that there is both a change in background activity that characterizes most of NREM 1, and occasionally actual theta bursts. Mostly, this is due to the

ambiguity with which scoring manuals describe theta in this stage, whether by accident or by design. For an inexperienced sleep scorer, the background activity of virtually all NREM 1 EEG looks like sporadic waves that are slower than alpha and faster than delta, so easily interpreted as "theta activity." Experienced scorers who may be more familiar with the rare participants with NREM 1 theta bursts will instead assume that the "4-7 Hz activity" in the manual refers to such occasional bursts. What can also happen, as I observed with our own participant, is that scorers can misinterpret NREM 1 theta bursts as alpha instead and thus score wake. This is understandable since theta and alpha are not easily distinguished visually on 20-30 s timescales (Figure 1.4), especially since theta bursts are more common in the second half of NREM 1 and not back-to-back with alpha bursts (Rechtschaffen & Kales, 1968; Santamaria & Chiappa, 1987). Therefore, even an experienced scorer, who has for sure come across an individual with genuine theta oscillations in NREM 1, may have failed to recognize them as anything but alpha.

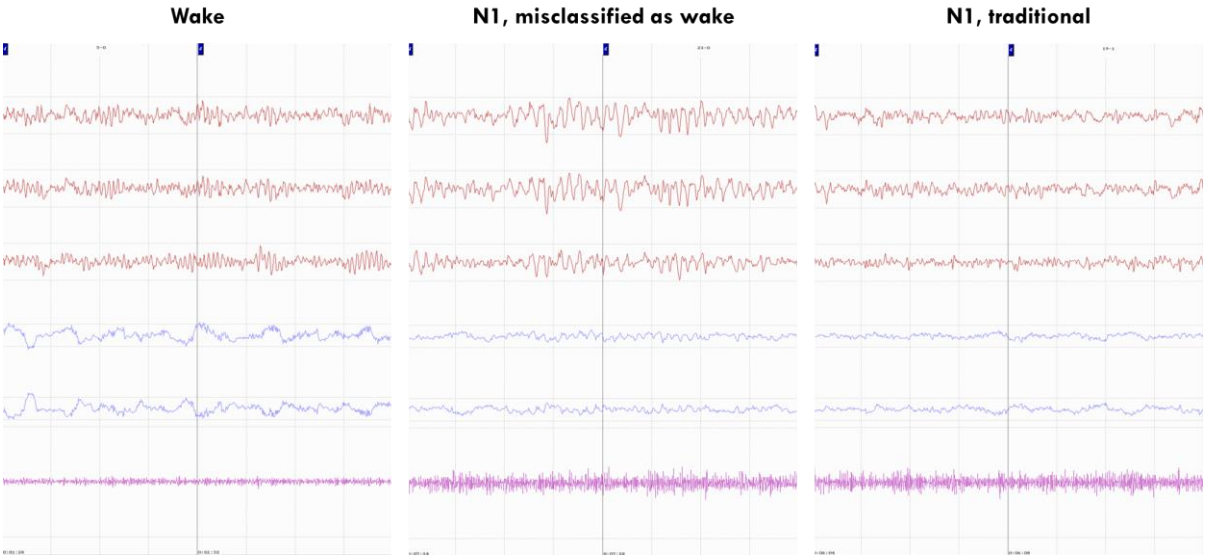

Figure 1.4: Misclassified theta bursts in NREM 1. Screenshots from the scoring software used for this study, all from the same participant (P15). Left: typical example of pre-sleep wake EEG, characterized by alpha and rapid eye movements. Middle: mu-shaped theta (~6 Hz) during NREM 1 like in Figure 1.3. It's not visible from this window, but the EOG before and after is characterized also by slow rolling eye movements, thus should have been scored NREM 1. Right: a different portion of NREM 1, without any oscillations and only displaying the background activity.

For most applications of polysomnography, it is inconsequential whether theta activity occurs in the form of a burst or as a change in background activity, so long as NREM 1 can be clearly identified. However, to understand theta oscillations during sleep deprivation, the distinction is critical. Studies looking at sdTheta clearly indicate a narrow-band effect (Finelli et al., 2000; Tinguely et al., 2006), which would mean it is unlikely to be driven by the change in slope of the aperiodic EEG. However, it is still possible that the theta bursts seen in some participants also appear during sleep deprivation. To establish whether this is the case, at least a qualitative assessment needs to happen to determine whether these NREM 1 theta bursts appear during sleep deprivation, and if they are sufficiently frequent to explain the increase in power. Given how rare and variable these individuals are, it is nevertheless unlikely that they can drive the sdTheta effect observed with group averages.

tldr; an alternative explanation for sdTheta is that it is driven by the intrusion of special NREM 1 bursts during wake, but these are quite rare.

Box 1.1: The history of confusion around NREM 1 theta

Someone less familiar with EEG might only know about theta waves in the context of NREM 1. This is because introductory neuroscience textbooks only describe oscillations related to sleep stages, and associate NREM 1 with theta (Bear et al., 2016; Kandel, 2013; Purves et al., 2018). Ironically, this is one of the least studied manifestations of this oscillation, occurring in just a fraction of the population. How then did this become the only entry for theta oscillations in textbooks?

The association between theta and sleep onset began with the first sleep EEG paper ever, Gibbs et al. (1935). At the time, they did not yet have today's canonical oscillation bands, and more importantly they had limited recording equipment. Gibbs identified 3-5 cycles per second (cps) waves appearing after a "flat period" following the disappearance of alpha. Davis et al. (1937) found something similar around 4-5 cps. These papers went on to define the first sleep stages, described by Loomis et al. (1937). Stage A was wake and stage B was when sleep began, characterized by rolling eye movements and low voltage activity. Stage B was further divided into B1 and B2, the latter of which was when low-voltage delta waves (defined as 4-5 cps) start to appear. The transition to stage C occurred when the delta waves increase in amplitude. These delta waves are close to theta. However, a contemporary article pointed out that these apparent 3-5 cps waves were in fact slow waves (0.5-3 cps); early EEG recording devices' hardware unintentionally high-pass filtered the signal in the middle of the delta range, leaving in the recording only upper delta (Blake & Gerard, 1937).

Following these early results of sleep EEG, there was the second world war. I am not a historian, but there is a telling drop in sleep research between the late 1930's and the 1950's. During this time, the main repository of knowledge about EEG oscillations was the Atlas of Electroencephalography by Gibbs & Gibbs (1941), which included an example EEG fragment of sleep onset that supposedly had 5-7 cps waves (Figure 1.5A). However, this looks suspiciously like background activity (Figure 1.2A). Walter and Dovey (1944) referred to this atlas when officially declaring the band's name "theta," which they associated with the "state just proceeded or following natural sleep." After WWII, sleep EEG research picked up again, with Roth (1961) subdividing the Loomis sleep stages even further, such that B became 2a, 2b, and 2c; with 2b showing "typical waves at 5-6/sec and amplitude of 10-40 μV." However, no data nor citation is provided to support this. Nevertheless, from this point on theta waves were associated with sleep onset.

In 1968 Rechtschaffen & Kale published the first manual for sleep scoring, identifying wake, four stages of non-REM, and REM. In this manual, the description of NREM 1 managed to be both exceptionally accurate and highly misleading. "Stage 1 is defined by a relatively low voltage, mixed frequency EEG with a prominence of activity in the 2-7 cps range. [...] The highest voltage 2-7 cps activity (about 50-75 μV) tends to occur in irregularly spaced bursts mostly during the latter portion of the stage" (Rechtschaffen & Kales, 1968). In a footnote the authors argue for the term "relatively low voltage, mixed frequency EEG" instead of "low voltage, random," because "'random' means recurring at inconsistent time intervals, rather than denoting a mixture of frequencies." The authors cite Roth as a source. Throughout the manual, many examples of NREM 1 are provided (Figure 1.5B), but none are described as containing "high voltage bursts" and instead are all of low-voltage mixed frequency activity and vertex sharp waves. It is not clear whether the 50-75 μV "irregularly spaced bursts" refers to theta bursts like in Figure 1.3, or just the mixed frequency activity further increasing in amplitude. Regardless, later sleep texts began using "4-7 Hz theta activity" interchangeably with "low voltage mixed frequency EEG" as if describing the same phenomena.

The Rechtschaffen manual was the main source for popular science books on sleep (Hobson, 1989; J. Horne, 1989), that then became the main sources for the major neuroscience textbooks of today, which ended up using the exact same figures from the pop-sci books (Figure 1.5C-D). More crucially, the current AASM sleep scoring guidelines score NREM 1 if there is "low-amplitude, mixed frequency EEG activity: predominantly 4-7 Hz activity" (Berry et al., 2012).

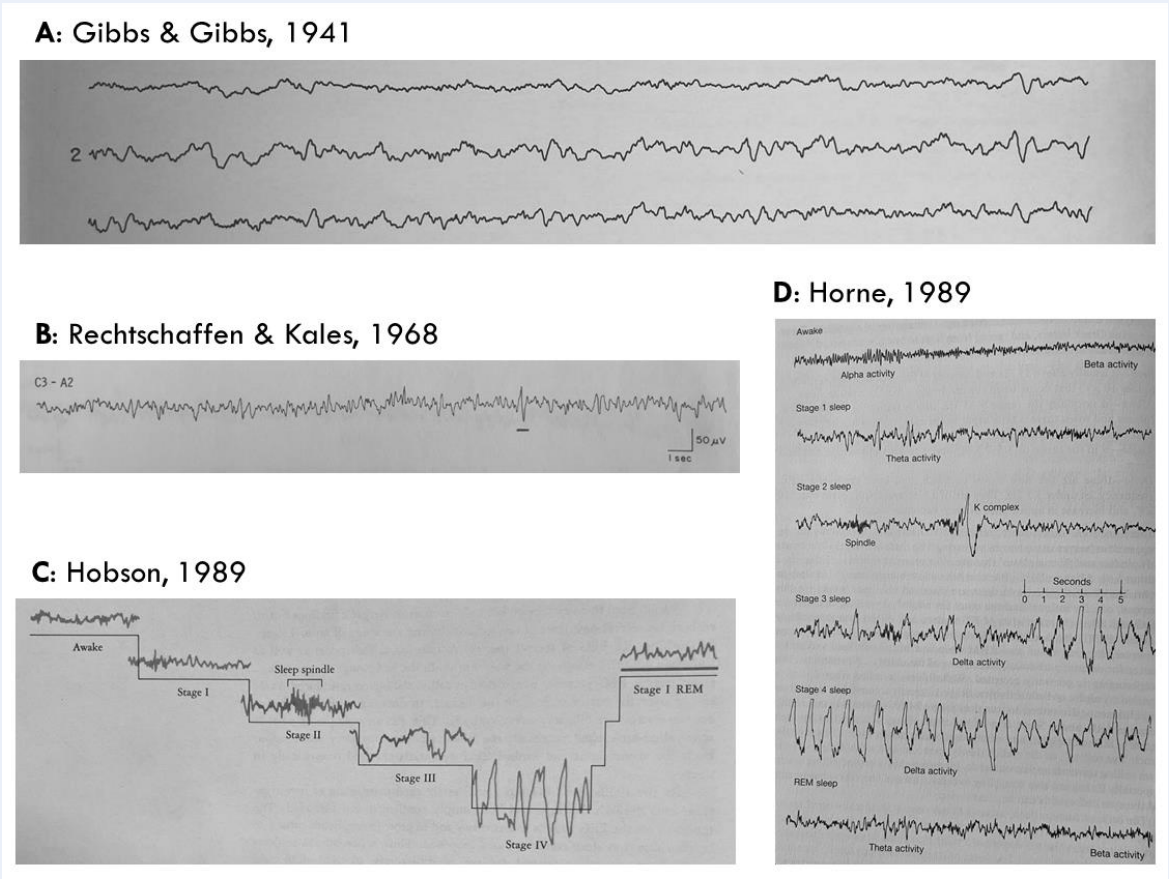

Figure 1.5: **Historic examples of "theta" during NREM 1. A:** Page 48 from Gibbs & Gibbs (1941). "Drifting: ten to twelve per second activity absent, replaced by 5-7 per second activity with 18-24 per second waves superimposed." **B:** Figure 11 from Rechtschaffen & Kales (1968). "Stage 1. This epoch is typical of the early portion of Stage 1. There are slow eye movements and a relatively low voltage, mixed frequency EEG throughout the epoch." **C:** from Hobson (1989), Chapter 1. In a separate table, Stage I is indicated as being characterized by 4-8 cycles per second, with amplitudes of 50-100 µV, called "theta waves." **D:** Figure 1.1 from Horne (1989). "Theta activity" is labeled for Stage 1 and REM. All figures copied for citation purposes. N.B. these examples of theta do not differ from the simulated data in Figure 1.2.

tldr; there's a long tradition of confusing background activity for theta oscillations.

1.4 Hippocampal theta

For anyone who has studied rodents, the mention of theta activity usually brings to mind just one thing: hippocampal theta oscillations. One of the most investigated functions of hippocampal theta is spatial exploration of an environment (Buzsáki, 1996, 2005). Hippocampal place cells fire at specific phases of ongoing theta oscillations,[1] anticipating the upcoming locations in a process known as *phase precession* (Diba & Buzsáki, 2007; Foster & Wilson, 2007; O'Keefe & Recce, 1993; Skaggs et al., 1996). Essentially, while moving across the environment, the neurons representing the current location of the animal will fire at the trough of the theta oscillation, and the neurons representing the previous and subsequent locations will discharge on the descending and ascending phases, respectively (Buzsáki & Vöröslakos,

[1] *Place cells are neurons that fire when the individual finds themselves in a specific location in space (Moser et al., 2008).*

2023). While navigation is the best understood, many other functions of the hippocampus are believed to relate to theta, especially episodic memory.

A related hypothesis to phase precession is that different theta phases are optimized for either encoding or retrieving information from memory, such that information from the external world arrives at the trough of theta oscillations, whereas information from internal memory arrives at the peak (Hasselmo et al., 2002). This is because the trough is associated with "long term potentiation," i.e. strengthening of synapses needed for encoding new memories. Siegle and Wilson (2014) found experimental support for this phase dissociation using closed-loop optogenetics,[1] targeting hippocampal inhibitory neurons selectively at each phase, either during a memory encoding or memory retrieval portion of a task. They confirmed that inhibiting the hippocampus at the theta peak (when information is retrieved) during the encoding period improved performance, and inhibiting at the trough (when information is encoded) during the retrieval period also improved performance, but no effect was present when inhibiting the opposite phases in the respective task periods. Other studies have found similar evidence of a theta phase relationship to plasticity (Hölscher et al., 1997; Huerta & Lisman, 1995).

The hippocampal theta rhythm is not limited to active wake, however. It is also the defining feature of REM sleep in rodents (Figure 1.6), so much so that it is used instead of actual "rapid eye movements" to score this sleep stage (Adamantidis et al., 2019).[2] Theta in REM and active wake are normally the same frequency, however a mice mutant was found to have slower theta during REM but not wake (Shin et al., 2005; Tafti et al., 2003), suggesting possibly different generators and functions. REM theta has also been shown to have place-cell phase precession, suggesting daytime memories are recapitulated during REM sleep (Louie & Wilson, 2001). REM sleep is also thought to be important for emotional memory processing (Hutchison & Rathore, 2015), which would again suggest that theta has a functional role as in wake.

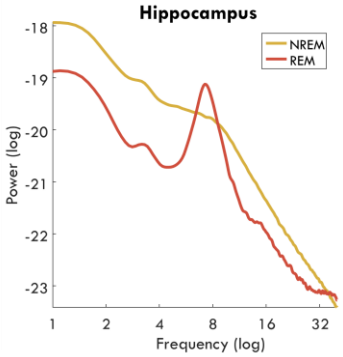

Figure 1.6: Mouse hippocampus LFP during sleep. Data from A. Osorio-Forero.

Hippocampal theta in rodents is different from sdTheta in humans, for several reasons. Most obviously, sdTheta is recorded awake and without any task, so unlikely to reflect either REM or task-related cognition.[3] Second, if it is at all possible to measure hippocampal activity on the surface of the EEG, it requires careful signal source separation because of how far the hippocampus is from the surface (Joensen et al., 2023). Hippocampal theta oscillations may or may not be synchronized with the neocortex; while studies in rodents find prefrontal theta rhythms synchronized to the hippocampus (O'Neill et al., 2013; Popa et al., 2010; Sirota et al., 2008), intracortical studies in humans have shown that theta activity can be independent across areas (Brzezicka et al., 2018; Cantero et al., 2003; Cox et al., 2019).[4]

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[1] Optogenetics is a method straight from a sci-fi novel where you trick neurons that were firing in a previous moment of interest to fire again whenever a light is shined on them. Bonkers!

[2] Apparently, there are no standardized guidelines for sleep scoring animal data. Shocking!

[3] REM sleep takes usually well over an hour of NREM sleep before it appears, otherwise it's considered pathological. Therefore, the previously discussed ideas of intrusions of sleep wouldn't extend to intrusions of REM sleep.

[4] On the one hand, theta in the hippocampus and medial prefrontal cortex in humans can change in opposite directions whereas in rodents they are synchronized in a task-dependent manner. On the other, there are substantial differences

Especially problematic is the fact that there does not seem to be a prominent theta rhythm in the human hippocampus, and it may even be at a slower frequency, around 3 Hz (Moroni et al., 2007; Watrous et al., 2013).[1] Likewise, surface EEG spectra of REM sleep find no periodic component in the theta range (Tinguely et al., 2006; von Ellenrieder et al., 2020). Like with NREM 1, any difference from wake is driven just by aperiodic activity (Figure 1.7). This doesn't exclude the presence of occasional theta oscillations in human REM sleep, but certainly indicates they are less prominent than theta in rodents (Figure 1.6). Indicatively, they must be substantially less common than spindles, which clearly leave a mark in the NREM 2 spectrum. Some studies find effects related to theta power during REM sleep in humans (Eichenlaub et al., 2018), however again from the spectra they provide, the effect is more likely driven by changes in background activity than a specific oscillation.[2] Given that theta doesn't appear in REM sleep, and if it exists it's likely slower, then hippocampal theta is unlikely to drive sdTheta.

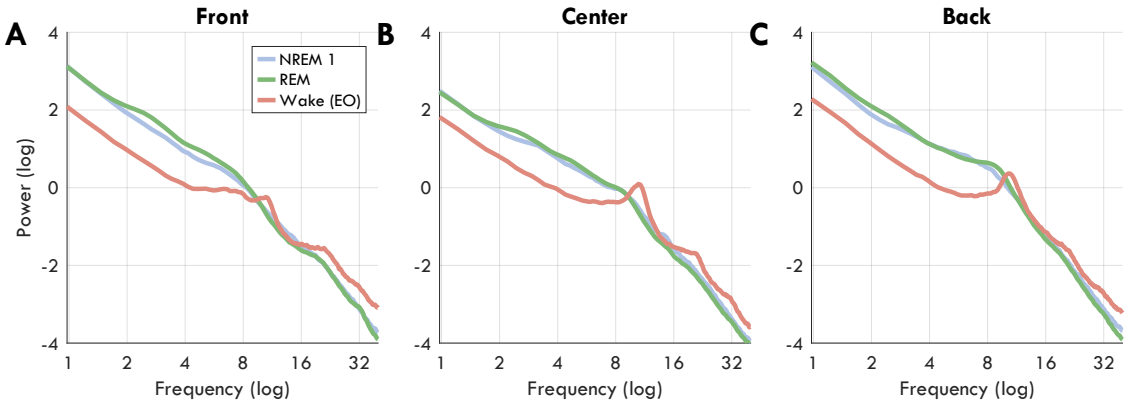

Figure 1.7: REM sleep spectrum, log-log scale**.** Average from 18 participants. NREM 1 and REM are from the baseline night, Wake is from the baseline morning Fixation recording. Similar spectra have been published elsewhere (Baird et al., 2018; Tinguely et al., 2006; von Ellenrieder et al., 2020).

Most decisively, already in rats, hippocampal theta has been shown to be distinct from sdTheta: the theta power increase during sleep deprivation actually occurs at a lower frequency than the standard hippocampal theta in rats (Vyazovskiy & Tobler, 2005). Altogether, this makes it highly unlikely that sdTheta is a direct manifestation of hippocampal theta, and instead suggests that there are two different types of oscillations that just happen to be in overlapping frequency bands.

tldr; the most understood form of theta oscillations comes from the hippocampus, proven to be functionally relevant to cognitive function, and exist independently from sdTheta.

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between human and rodent frontal cortices in terms of connectivity and function (Laubach et al., 2018; Schaeffer et al., 2020) which make it questionable to rely on rodents as a viable animal model for prefrontal activity.

[1] *More information in Box 1.2.*

[2] *Nishida et al. (2009) found a correlation between theta power differences between left and right prefrontal areas and emotional memory consolidation, with an actual peak at 5.75 Hz in right prefrontal areas, but this result was not replicated with larger sample sizes (Ackermann et al., 2015).*

Box 1.2: Do humans even have a hippocampal theta rhythm?

The presence of a hippocampal theta rhythm is so obvious in rodents, that it is the main signal used to score REM sleep, alongside muscle atonia. Other mammals also seem to have hippocampal theta, most reliably during REM sleep (Winson, 1972), so it is surprising then that theta does not unequivocally appear in the human hippocampus (with similar difficulties for other primates [Crowne et al., 1972; Stewart & Fox, 1991]). Unfortunately, the only way to properly measure hippocampal theta in humans is from intracortical recordings in epilepsy, so evidence is scarce, but there does not appear to be any consistency across individuals; some patients have a hippocampal theta, others do not (Aghajan et al., 2017; Arnolds et al., 1980; Bohbot et al., 2017; Cox et al., 2019; Kahana et al., 1999; Uchida et al., 2001). This may be due to individual differences in frequency, as suggested by Watrous et al. (2013) and Bódizs et al. (2001). They found hippocampal oscillations rather in the upper delta range during respectively spatial navigation and REM sleep. Similarly, Lega et al. (2012) argue that there are two hippocampal rhythms, one at 3 Hz, the other at 8 Hz, with the slower one more homologous to rodent theta. Alternatively, the individual differences may be due to differences in electrode locations, as suggested by Cantero et al. (2003). However, Cantero found hippocampal theta to occur in bursts around 1 s long, which were shorter than bursts appearing even during quiet wakefulness, therefore not exceptional to REM sleep.

In practice, this means that hippocampal theta rhythms in humans are much less reliable than in rodents, even if they are eventually found to exist in all individuals. The effect may be highly sensitive to location, whereas rodent cortical EEG is sufficient to detect hippocampal theta (Vyazovskiy & Tobler, 2005) for how strong the signal is. Human hippocampal oscillations seem much more variable in frequency across individuals (assuming this is not also a location-dependent effect), whereas rodent REM spectra are more similar than either wake or NREM, also across studies (Miladinović et al., 2019). Furthermore, even the best evidence of human REM theta shows that it is not a very sustained response, whereas in rodents it is nearly constant. All in all, human hippocampal theta is much less impressive than in rodents, and therefore it is unlikely to have as central a role in cognition.

tldr; there is spotty evidence for hippocampal theta in humans, making it unlike theta in rodents, which is an extremely clear signal.

1.5 Frontal-midline theta

A plausible alternative explanation is that sdTheta is a manifestation of frontal midline theta (fmTheta). fmTheta is a high-amplitude (50-75 μV) oscillation easily identifiable in the human surface EEG, around 6 Hz, occurring in bursts lasting from less than a second to over a minute, with approximately sinusoidal waves (Mitchell et al., 2008). As the name suggests, fmTheta peaks over electrode Fz (Figure 1.8), and originates from the anterior cingulate cortex (ACC) / medial prefrontal cortex (Ishii et al., 1999, 2014). fmTheta is found during cognitive tasks such as the N-back working memory task, mental calculation, and the Uchida-Kraepelin task (Arellano & Schwab, 1950; Ishihara & Yoshi, 1972; Ishii et al., 1999;

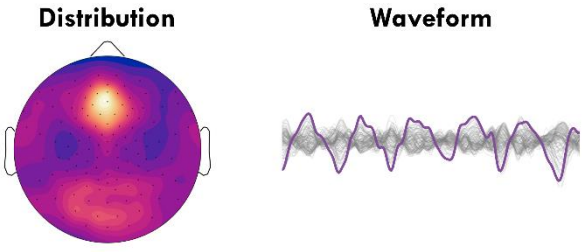

Figure 1.8: frontal midline theta. Left: topography of fmTheta for a single participant. Right: ~1 s example of a theta burst. Each gray line is a different channel, the colored line indicates the channel with the highest amplitude.

Mitchell et al., 2008; Sasaki et al., 1996). The common feature of these tasks is focused and sustained attention, or a resistance to distractions.

A critical fact about fmTheta is that it is anticorrelated to the fMRI BOLD signal from its source, a measure of brain metabolism and therefore activity (Logothetis & Wandell, 2004), so fmTheta reflects inactivity or even inhibition in these areas. This was found for fmTheta both during rest (Scheeringa et al., 2008) and during tasks (Miller et al., 2009; Ossandón et al., 2011; Scheeringa et al., 2009). Therefore, while fmTheta is commonly present during cognition, it is not strictly involved in neuronal computations, and in fact originates from task-irrelevant areas. Nevertheless, it may still be functionally relevant.

Further evidence that fmTheta is not strictly related to cognition comes from the fact that it is only found in a fraction of individuals, and it also occurs spontaneously during rest (Inanaga, 1998). Depending on the task, fmTheta has been observed between 8 and 67% of individuals (Mitchell et al., 2008), and is generally more common in children, adolescents (Ishihara & Yoshi, 1972), and young adults compared to older adults (Inanaga, 1998). In addition to age, there is some evidence that fmTheta is dependent on personality, such that low anxiety and high extroversion characterizes individuals with high fmTheta (Inanaga, 1998). It could also be that individuals with high theta are more susceptible to hypnosis, whatever that might indicate about individual differences (Sabourin et al., 1990).[1]

Investigation into fmTheta took off with Ishihara and Yoshi (1972), and from this followed a great deal of research in Japan throughout the 80's and 90's. Unlike later research, this work identified theta oscillations by visual inspection, providing unique insights. Unfortunately, many of these papers are not available online, and many of their contributions no longer circulate in the modern literature. This turned out to be the fate of a series of papers investigating frontal-midline theta during sleep (Hayashi et al., 1987; Ishihara et al., 1981; N. Takahashi et al., 1997).

Hayashi et al. (1987) found that frontal midline theta was present during sleep, especially prevalent in REM sleep and to a lesser extent in NREM 1, more so than during wake before sleep onset. This might have contributed to the pantheon of NREM 1 theta in section 1.3. Individuals with high fmTheta during wake (measured independently from the sleep EEG) were also the ones more likely to present fmTheta during sleep. Of course, "prevalent" was at most 8 bursts per 10 minutes of REM, but this nevertheless precludes considering fmTheta strictly a wake oscillation. The authors suggest this may be a form of "mentation" during sleep. These results are supported by Nishida et al. (2004) who found 2 out of 3 patients had theta during REM, measured from intracortical ACC electrodes.

Even more relevant to this thesis, fmTheta during cognitive tasks was related to theta during drowsiness.[2] Takahashi et al. (1997) conducted a study taking 39 participants who were found to have frontal-midline theta during drowsiness (out of 465 male Japanese airmen), compared to controls. They found that these participants with drowsiness theta also had fmTheta during a cognitive task, which wasn't the case for controls. Furthermore, the authors could not find any differences in frequency, origin (from a 10-20 array), or burst duration between drowsiness theta and cognition theta. They suggested that fmTheta during light drowsiness may act as some kind of inhibitory mechanism when falling asleep.

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[1] A recent study found that highly hypnotizable individuals could use hypnotic recordings to reduce sleep onset times (Cordi et al., 2020). Putting these concepts together, maybe such individuals could be screened with fmTheta.

[2] The difference between "drowsiness" and "sleepiness" is explained in section 7.3.5, page 143.

These studies would therefore suggest that fmTheta and sdTheta are the same thing. They both originate from frontal areas (Finelli et al., 2000; Mitchell et al., 2008; Tinguely et al., 2006), and when directly compared, they were not readily distinguishable (N. Takahashi et al., 1997). fmTheta being anti-correlated to BOLD activity could likewise explain sdTheta. However, all of these are quite old experiments, often with fewer than 30 electrodes, and relied on manual classification of theta bursts. An updated investigation was called for.

tldr: there's a prominent theta oscillation from frontal channels called fmTheta that is normally present during focused cognition. It is associated with less neuronal activity in the areas from which it originates, therefore sdTheta could be fmTheta.

1.5.1 Mind wandering, meditation, and the default mode network

The ACC in the medial temporal cortex is one of the most versatile brain areas, implicated in both cognition and emotion (Bush et al., 2000; Etkin et al., 2011), pain (Kwan et al., 2000), remembering (Weible, 2013), conflict monitoring (Botvinick et al., 2004), and more. Part of this hodge-podge list of functions comes from the fact that the medial cortex is quite large and there are likely subdivisions, although researchers can still disagree on how to interpret even the same results (Ebitz & Hayden, 2016).[1] For fmTheta though, the most relevant role may be the ventral ACC's association to the default mode network (DMN) (Greicius et al., 2003).

The DMN is a set of distributed brain areas whose fMRI BOLD activities are highly correlated with each other, but anti-correlated to traditional cognitive tasks and task networks (Fox et al., 2005; Raichle et al., 2001). While first discovered as areas more active during rest than during such tasks, it was later found that the DMN was even more active during *internally oriented* tasks such as those involving autobiographical memories, imagining future scenarios, and social inferences (Buckner & DiNicola, 2019).[2] During externally-oriented tasks, greater activity of the DMN was in fact associated with mind wandering, an umbrella term for task-unrelated thoughts (Mason et al., 2007; Smallwood & Schooler, 2015). Supporting this, lesions to the medial temporal cortex lead to substantially *less* mind wandering in patients (Bertossi & Ciaramelli, 2016). Since BOLD deactivations of the ACC are related to fmTheta, it is plausible that fmTheta is anticorrelated to the DMN more generally, such that when the DMN is at rest or inhibited, fmTheta is visible in the EEG.[3] This is the reason fmTheta is present in so many different conditions: because it reflects the inactivity of internally oriented networks. This may even be related, somewhat counterintuitively, to meditation.

Meditation is the practice of training to focus the mind in order to achieve a state of mental clarity, calm, and relaxation. It often involves (for beginners) focusing attention on a particular object, or breathing

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[1] *For example Parvizi et al. (2013) used electrical stimulation of the ACC in patients and concluded that the ACC was responsible for "the will to persevere," but the flip side of patients' descriptions was a feeling of dread, worry, and irritability.*

[2] *This circles back to those results relating the ACC to emotions and pain, both forms of internal monitoring. I haven't been able to properly sort through the literature, but often times the more cognition related functions of the ACC are rather from the dorsal ACC (Carter & van Veen, 2007).*

[3] *As far as I can tell, most of the link between theta and the DMN is just from the ACC, but this could be due to just how the brain is folded, or the ACC is special, I don't know.*

rhythm, mantra, etc. Prominent theta bursts were discovered during meditation already in 1973 (Banquet, 1973; Hebert & Lehmann, 1977). Later studies confirmed that this was specific to expert meditation and not merely sitting with eyes closed (Aftanas & Golocheikine, 2001). Successful meditation is characterized by a resistance to mind wandering, and in fact expert meditators have higher frontal theta power during meditative moments compared to moments of mind wandering, despite having overall less mind-wandering episodes than non-experts (Brandmeyer & Delorme, 2018).[1] It is therefore plausible that meditation consists of the willful inhibition of the DMN, and this manifests itself with more fmTheta, whereas the loss of focused attention and switch to mind wandering decreases fmTheta.

So how does this relate to sdTheta? The effects of sleep deprivation on the DMN are variable across the network (Chen et al., 2018; De Havas et al., 2012; Gujar et al., 2010) and so it is difficult to make any predictions about how these changes would affect fmTheta in particular. Furthermore, recent evidence suggests that there are at least two subnetworks of the DMN, and interindividual differences make it difficult to disentangle these more subtle effects (Buckner & DiNicola, 2019). From the behavioral side, mind wandering actually increases with sleep deprivation (Poh et al., 2016), which would predict that fmTheta should decrease. However, the increase in "task unrelated thoughts" was undetected by the participants, who reported similar levels of meta-aware mind wandering at baseline and sleep deprivation, which could indicate a different "type" of mind wandering during sleep deprivation. In fact, mind wandering and mind blanking have been related to topographically distinct manifestations of theta activity (Andrillon et al., 2021). Altogether, this means that the relationship between DMN, sleep deprivation, and surface EEG theta are hard to predict. Fortunately, given the specific source of fmTheta, it can be readily distinguished from sdTheta if the latter originates from a different source.

tldr: the areas that generate fmTheta are part of the default mode network, which is active during mind wandering and deactivated during meditation and tasks.

1.6 Cognition theta

The oscillation most at odds with sdTheta is theta evoked during cognitive tasks, cogTheta. The interpretation of cogTheta has evolved over time, from a means of short-term memory storage, to perceptual binding, and then as a form of executive control. cogTheta has been measured on the surface EEG from various locations and it is time-locked to specific task events such as stimulus presentation, memory retention windows, or behavioral responses. Changes in theta are dependent on task conditions (e.g., the more difficult condition, the more theta) and often these changes are related to task outcomes (e.g., more theta predicts success). Virtually all research into cogTheta assumes that it is functionally relevant to cognition. Most explanations draw inspiration from the hippocampal theta literature (section 1.4), and many in fact assume a synchronization between the neocortex and the hippocampus. For example, Buzsáki (2010) argues that theta generally acts as a form of "neural syntax" whereby oscillations segment neuron firing in a meaningful way.

[1] *Interestingly, they also found that in experts, as meditative depth increased with time meditating, sleepiness decreased, whereas sleepiness increased for non-experts. This suggests that meditation and fmTheta are restorative, possibly like sleep itself. *Hint hint**.

Theta activity was first associated with short term and working memory (Gevins et al., 1997; Lisman & Idiart, 1995).[1] A typical short term memory experiment involves some variant of a Sternberg task (Sternberg, 1966), in which participants are presented with a set of stimuli, then for a couple of seconds they have to hold those items in memory, until a probe then asks them if a given stimulus was part of that set (e.g. Figure 2.2A on page 38).[2] During the retention period, trials with more items to hold in memory have higher theta power than those with less items (Brookes et al., 2011; Jensen & Tesche, 2002; Maurer et al., 2015; Michels et al., 2010; Scheeringa et al., 2009). An early interpretation of this effect was that theta oscillations were responsible for holding all those items in memory (Lisman & Idiart, 1995; Roux & Uhlhaas, 2014), with each item "stored" at a different phase of the theta oscillation. However, there has been limited evidence for this (Raghavachari et al., 2001), and if anything it's an oversimplification.

A more popular interpretation is that theta is involved in "perceptual binding" across distant cortical areas, synchronizing activity in order to encode or retrieve items from memory (M. Bastiaansen & Hagoort, 2003; Benchenane et al., 2011; Herweg et al., 2020; Sauseng et al., 2010). This is like the *communication through coherence hypothesis* (Fries, 2015). This can get borderline philosophical, but at its simplest, coherence refers to how distant cortical neurons can be involved in the same mental representation of something when it is temporarily held in short-term memory, especially when different neuronal substrates are required to then act upon that information. The idea is that only phase-locked neurons can communicate effectively, because they will be receptive to inputs at the same time. Data from hippocampal theta found evidence of phase-specific effects for encoding and retrieval, which could explain similar mechanisms in the neocortex.

Intracortical studies in monkeys provide the best evidence of this long-distance theta coherence. In two similar experiments (H. Lee et al., 2005; Liebe et al., 2012), macaques were trained to perform a short term memory task, with multi-unit recordings of both visual (V4) and parietal/frontal areas. As in the hippocampus, single cell firing was found to be locked to specific phases of theta oscillations, especially during the delay window in which visual items were held in memory. These theta oscillations were synchronized between visual and prefrontal areas. Unfortunately, when a similar short term memory experiment was done in humans, despite theta reliably increasing during the retention window, there was no synchronization across distant areas (Raghavachari et al., 2006).

Instead, in human intracortical data there is rather evidence of increased synchronization being related to episodic memory, with greater medial-temporal lobe and prefrontal coherence during encoding periods predicting better memory retrieval (K. L. Anderson et al., 2010; Solomon et al., 2017). Surface EEG studies have also found correlations between theta power during encoding and subsequent successful memory retrieval (Khader et al., 2010; Osipova et al., 2006), with the effect localized to the MTL (Hanslmayr, Volberg, et al., 2011).[3] Additionally, pre-stimulus theta before recall was also associated with successful retrieval (Addante et al., 2011; Gruber et al., 2008; Herweg et al., 2016).

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[1] Short-term memory is just holding items in memory briefly (like remembering a phone number until you can write it down), and working memory involves additionally manipulating that information, like performing sums or re-ordering the items. Episodic memory is long-term memory related to specific events in time and space.

[2] The equally common task for working memory is the N-back task, in which a stream of letters is presented, and the participant has to keep track of whether there are repetitions, N-many letter back. It gets really hard after 1 back.

[3] This study also found that BOLD activity was higher for successful encoding trials in the right parahippocampus, but this did not perfectly overlap with the source of theta. Furthermore, the fluctuations of theta across trials did not correlate

Other than strictly for memory, theta has been found in many other cognitive tasks, including visual detection (Missonnier et al., 2006), error detection and action monitoring (M. X. Cohen, 2011; Luu & Tucker, 2001), goal updating (Cooper et al., 2017), planning (Domic-Siede et al., 2021), and interference resistance (Staudigl et al., 2010). This has led to the interpretation of theta as a manifestation of a-specific executive control (Cavanagh & Frank, 2014), possibly with frontal cortices exerting influence on other areas through synchronized theta oscillations (Cavanagh et al., 2009). Most of these studies identify frontal-midline sources of theta, so basically what I described before for fmTheta applies (section 1.5, page 22). These interpretations of cognitive control would seem at odds with fmTheta reflecting inhibition, however, there are two possible explanations: one is that theta as inhibition *is* a form of executive control, inhibiting task-irrelevant networks to improve performance; and the other, not mutually exclusive idea, is that there are multiple manifestations of theta.

The latter has actually been demonstrated, even within the same trials of a task (Brzezicka et al., 2018; Töllner et al., 2017). Pastötter & Bäuml (2014) for example found that there were two changes in theta related to episodic memory encoding: a slow theta (2-4 Hz) which was higher for correctly recalled memory items, located over central and right-mastoid clusters;[1] and a fast theta (5-7.5 Hz) higher for forgotten items, originating from frontal-midline areas, arriving a bit later in the trial. This slow theta could actually be hippocampal theta, given that it matches human intracortical recordings which find the same dissociation between slow and fast theta in the hippocampus (Lega et al., 2012). Therefore, cogTheta related to memory and coherence exists in addition to and independently from fmTheta, with different functions and relationship to behavior. However, it's important to remember that fmTheta is substantially larger than cogTheta.

Unlike fmTheta that can be observed in the raw EEG trace, all these results of theta during cognition emerge from time-frequency analyses involving averaging many trials time-locked to either the onset of the stimulus or response (or retention window), and identifying the changes across frequencies that emerge relative to a baseline period (M. X. Cohen, 2014). Invariably, this means that these manifestations of cogTheta would not be visible in the average recording power spectra. This makes it unlikely that cogTheta could explain the dominant presence of theta during sleep deprivation, and more likely that the two coexist, like cogTheta and fmTheta, or sdTheta and hippocampal theta in rats.

However, it's still possible for cogTheta to be behind sdTheta, in which case sdTheta would have to be some form of compensation mechanism, such as an increase in cognitive control to stay awake and on task. sdTheta could reflect some top-down signal required to stay awake, originating from the prefrontal cortex (Steenland, 2014). This explanation doesn't work so well for theta related to fatigue (section 1.2.2, page 13), given that the increase with time on task was also present when the task wasn't being performed (Li et al., 2020), but in the case of sleep deprivation, the self-control needed to stay awake is also present during passive rest. If sdTheta is a form of cognition theta, then two predictions should be met: sdTheta should be highest during more difficult cognitive tasks, especially those suspected of maintaining

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with BOLD activity across trials. Therefore, the higher BOLD activity and theta may possibly come from neighboring but not overlapping areas.

[1] *I found the right-mastoid especially noteworthy, since it matches the source of theta in my special P15 (Figure 1.3). I suspected that this unusual theta might be from the hippocampus because of its unusual source; what other notable brain structure would have a peak over the mastoids? Those channels are probably the absolute closest to the hippocampus, with the least amount of unrelated cortex in between.*

performance through compensation mechanisms (Lim & Dinges, 2010); and even more so than at baseline, theta during sleep deprivation task trials should be related to better performance.

If sdTheta and cognition are instead distinct, it begs the question of what would happen if sdTheta occurs on top of the usual cognition theta. Do the same oscillators get repurposed? Or are they completely independent, maybe even mutually exclusive oscillations? Is this what drives sleep deprivation deficits? Careful analyses would be needed to answer these questions, with a better understanding of how to distinguish the two different waveforms.

tldr; a lot of research finds theta activity related to cognition. If cogTheta is behind sdTheta, then it may be a compensation mechanism for staying awake.

1.6.1 Theta synchronization

As mentioned with regards to hippocampal phase precession and perceptual binding, an important feature of brain oscillations are phases. Even in the absence of changes in oscillation amplitudes, there is compelling evidence that information transfer across distant brain regions is facilitated by phase synchronization of oscillations like theta across distant cortical areas (Fell & Axmacher, 2011).[1] For example, Polanía et al. (2012) found in a working memory task that 0 phase differences between parietal and frontal areas resulted in improved reaction times, and then demonstrated that in-phase theta tACS stimulation improved reaction times,[2] whereas out-of-phase stimulation resulted in worsened reaction times. Other studies found that greater memory load increased theta coupling between these areas, making the case that phase synchronization is more important to cognitive function than oscillatory amplitude (Payne & Kounios, 2009; Sauseng, Klimesch, Schabus, et al., 2005).

This is all compelling evidence for the functional role of theta in cognition, but because it doesn't necessarily correspond to changes in the overall amount of theta, it doesn't explain why bursts of oscillations sometimes do or don't happen. The presence of an unrelated burst in the same frequency would theoretically disrupt this careful orchestra of synchronized oscillations. This makes the hypothesis of multiple types of theta a little problematic; it would be important to show that these different types of theta come from non-overlapping areas, and if they do co-occur in task brain areas at a critical moment in time, there should be some kind of behavioral deficit.

tldr; theta phases synchronized across the brain are functionally relevant to cognition, but theta during sleep deprivation could disrupt this function.

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[1] *Technically, any increase in an oscillation amplitude reflects a local increase in phase synchronicity; that's how the signal becomes strong enough to emerge on the surface. Changes in local phase synchronicity can only emerge as changes in amplitude, which can be tricky to interpret, but changes in synchronicity across distant areas can be quantified based on phase locking between the two signals.*

[2] *Transcranial alternating current stimulation (tACS). A relatively weak current is sent through the brain, usually at a frequency typical of the brain. It feels like a mild tingling on your skin.*

Box 1.3: Speech theta & entrainment

Like with other forms of cognition, speech processing is associated with increased theta power (M. C. M. Bastiaansen et al., 2005). However, a fancier function for theta oscillations during natural speech would be entrainment. Entrainment refers to the synchronization of endogenous EEG oscillations to external rhythmic stimuli in order to predict the timing of upcoming signals and improve detection (Thut et al., 2011).[1] As it happens, the envelope of speech (Figure 1.9) is in the delta-theta range in all languages (Ding et al., 2017). Therefore, the hypothesis is that theta oscillations during continuous speech predict the timing of subsequent syllables, thus improving detection (Giraud & Poeppel, 2012; Hyafil et al., 2015). In a noisy environment, theta entrainment should allow specific synchronization of the listener to just one stream of speech, such that incoming syllables will arrive at theta phases where neurons are highly excitable, resulting in better recognition, whereas anything out of phase would just as easily end up in theta phases of low neuronal excitability (Buzsáki & Vöröslakos, 2023; Giraud & Poeppel, 2012). Supporting this, tACS applied during speech processing in noise has been shown to improve speech comprehension (Riecke et al., 2015, 2018).

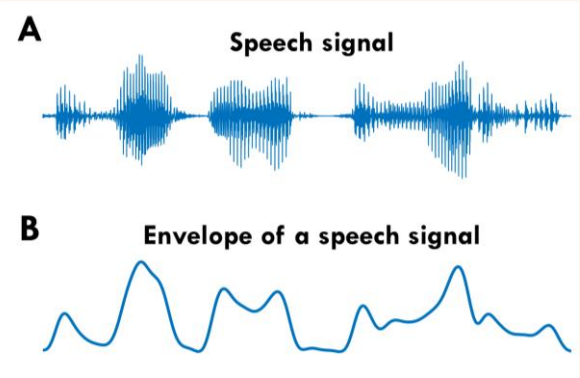

Figure 1.9: An audio speech signal in time. A: The entire speech waveform, around 1 s. **B**: The speech envelope.

The main problem with this hypothesis is that even if speech is approximately rhythmic, it is not rhythmic enough that it becomes predictable (Cauldwell, 2002; Jadoul et al., 2016); the easiest way to perceive the difference between predictable and unpredictable speech is to talk synchronized to rhythmically clapping hands. Ultimately, entrainment would help speech perception if it is rhythmic, but this is a general feature for any form of rhythmic stimulus (Hickok et al., 2015; Lakatos et al., 2013). When speech is not rhythmic, which it usually isn't, entrainment would actually be a hindrance since off-beat syllables would get suppressed.

An alternative explanation as to why some studies find theta-related EEG activity during continuous speech is that listening to speech is a form of "fuzzy" frequency tagging.[2] Because speech is an auditory stimulus which comes as a sequence of syllables more or less in the theta range, this will result in the brain responding to this incoming stream at approximately the same frequency, regardless of whether the speech is understood (Ding et al., 2015).

tldr; theta might help with speech comprehension through entrainment. However, it is more likely that the association with theta is just a by-product of the brain processing a semi-rhythmic signal.

[1] *"Synchronization" is when two or more oscillators start oscillating at the same frequency, such that the phase difference is constant. "Entrainment" is when one oscillator causes another to synchronize with it. So an external stimulus can entrain the brain, but different brain areas synchronize between each other, unless robustly proven otherwise.*

[2] *Frequency tagging is a clever paradigm in which you present a stimulus at a certain frequency, e.g. one picture per second of abstract shapes, then once every N pictures, the shapes make up a face. Then, you can see in the power spectrum of the EEG if there is both a peak at the frequency of the overall images, and then, if the difference of the oddball was detected, there should also be a second peak at a lower frequency for the faces. This can be used to determine whether new-born infants can already discriminate faces (Buiatti et al., 2019).*

1.7 What could theta during sleep deprivation be?

As you can see, there is an enormous amount of literature on theta oscillations. There is sufficient evidence to tell some types of theta apart, and merge other types together. Unfortunately, little evidence has directly compared theta during sleep deprivation to other manifestations of theta. The most popular hypothesis is that sdTheta is a form of local sleep, composed of little slow waves intruding on wake. However, evidence for this in humans is extremely limited, and this interpretation is highly incompatible with the more well-studied theta oscillations during cognition. Depending on whether these are the same or different types of oscillations, sdTheta could be a direct reflection of accumulating sleep need with time awake, or indirectly a compensation mechanism for resisting sleep. More specifically, here is the final list of hypotheses of what theta during sleep deprivation could be:

1) **A sleepiness oscillation:** sdTheta oscillations may uniquely reflect the cognitive state of sleepiness, making them completely distinct from all forms of theta observed under normal, well-rested conditions; this would be like the difference between wake alpha and sleep spindles. If sdTheta is notably distinct from other types of theta (e.g. in frequency, source, or waveform), this would make it a reliable objective biomarker. Such theta could further be:
   a) Unique to wake drowsiness: Theta could be unrelated to the underlying cause of such drowsiness and it could be as present during early morning sleep inertia as during sleep deprivation.
   b) Unique to time spent awake: It is also possible that these theta oscillations are not present for any type of drowsiness, but only high sleep homeostatic pressure.
   c) **NREM 1 theta** bursts intruding on wake.
2) **Local slow waves:** the increase in theta power could be just like that observed in rats; the intrusion of little slow waves during wake.
3) A **slowing of alpha** oscillations. This is unlikely, as alpha is primarily occipital and sdTheta primarily frontal, but it hasn't ever been directly ruled out.
4) An increase in **frontal-midline theta**: it's also possible that sdTheta in humans is just a manifestation of fmTheta, which for whatever reason increases with time awake.
5) An increase in **cognition theta:** it's also possible that the theta observed during sleep deprivation is indistinguishable from theta activity observed during cognitive tasks. In this case sdTheta would have to reflect a compensation mechanism.

To figure out which was the correct answer, I conducted an extended wake study in young healthy adults performing a variety of tasks under different conditions.[1] The main goal was to determine whether the increase in theta power could be explained by an increase in little slow waves or instead resembled theta activity during cognitive tasks.

tldr; there are a lot of possibilities as to what theta oscillations during sleep deprivation represent, so my thesis is about testing some of the most likely options.

[1] *The difference between "extended wake" and "sleep deprivation" is provided in section 7.3.3, page 142.*

2 THE THETA PARADOX: 4-8 HZ EEG OSCILLATIONS REFLECT BOTH SLEEP PRESSURE AND COGNITIVE CONTROL

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This paper was published in *The Journal of Neuroscience* in October (Snipes et al., 2022). It details the methods of my experiment, the problem of theta related to both sleep and cognition, and analyses on how fmTheta compared to sdTheta. I designed this experiment, wrote the ethics, programmed the tasks, collected the data, preprocessed and analyzed the data, and wrote the paper. Elena Krugliakova conducted the source localization analysis. Elias Meier helped prepare the experiment material, recruited participants, collected the data, and helped with some of the preprocessing. Reto Huber supervised the design and execution of the project, provided equipment and financing. All authors contributed to editing the manuscript.

2.1 Abstract

Human electroencephalographic (EEG) oscillations characterize specific behavioral and vigilance states. The frequency of these oscillations is typically sufficient to distinguish a given state, however theta oscillations (4-8 Hz) have instead been found in near-opposite conditions of drowsiness during sleep deprivation and alert cognitive control. While the latter has been extensively studied and is often referred to as "frontal midline theta,"[1] the former has been investigated far less but is considered a marker for sleep pressure during wake. In this study we investigated to what extent theta oscillations differed during cognitive tasks and sleep deprivation. We measured high-density EEG in 18 young healthy adults (9 female) performing 6 tasks under 3 levels of sleep deprivation. We found both cognitive load and sleep deprivation increased theta power in medial prefrontal cortical areas, however sleep deprivation caused additional increases in theta in many other, predominantly frontal, areas. The sources of sleep deprivation theta were task-dependent, with a visual-spatial task and short-term memory task showing the most widespread effects. Notably, theta was highest in supplementary motor areas during passive music listening, and highest in the inferior temporal cortex (responsible for object recognition) during a spatial game. Furthermore, while changes in task performance were correlated with increases in theta during sleep deprivation, this relationship was not specific to the EEG of the same task and didn't survive correction for multiple comparisons. Altogether, these results suggest that both during sleep deprivation and cognition theta oscillations may preferentially occur in cortical areas not involved in ongoing behavior.

2.1.1 Significance statement

EEG research in sleep has often remained separate from research in cognition. This has led to two incompatible interpretations of the function of theta brain oscillations (4-8 Hz): that they reflect local sleep

[1] *After publication, I realized that there was actually not much overlap between papers referring to fmTheta and to cognitive control.*

events during sleep deprivation, or that they reflect cognitive processing during tasks. With this study, we found no fundamental differences between theta oscillations during cognition and theta during sleep deprivation that would suggest different functions. Instead, our results indicate that in both cases, theta oscillations are generated by cortical areas not required for ongoing behavior. Therefore, at least in humans, theta may reflect either cortical disengagement or inhibition.

2.2 Introduction

Oscillations in the EEG have been associated with behavioral states such as alertness, drowsiness, and sleep. This typically allows oscillations to be used as objective markers for vigilance. The exception are theta oscillations (4-8 Hz), which have been separately identified as indicators of drowsiness and intense cognition.

Theta oscillations increase during sleep deprivation in animals (Vyazovskiy & Tobler, 2005) and humans (Aeschbach et al., 1997). Theta is considered to reflect sleep pressure, i.e. the interaction between circadian rhythm and time spent awake determining when an individual feels the need to sleep (Borbély, 1982; Cajochen et al., 2001). Given the presence of theta oscillations when and where sleep pressure is highest (Finelli et al., 2000), they have been hypothesized to be a form of local sleep during wake (Siclari & Tononi, 2017; Vyazovskiy et al., 2011). During sleep, slow waves (0.5-4 Hz) in the surface EEG correspond to synchronized silencing of neuronal spiking, known as “off periods” (Steriade et al., 2001). Vyazovskiy et al. (2011) found these off periods to also occur during sleep deprived awake rats, corresponding to theta oscillations in local field potentials.

Equally robust research has separately linked theta activity to cognition. Theta has been associated with a variety of functions (Buzsáki, 2005), most notably hippocampal theta during spatial navigation in rats (Buzsáki, 1996; O’Keefe & Recce, 1993) and frontal-midline theta during cognitive tasks in humans. Frontal-midline theta (fmTheta) has been associated with arithmetic (Ishihara & Yoshii, 1967; Ishii et al., 2014), working memory (Gevins et al., 1998; Jensen & Tesche, 2002), and even meditation (Banquet, 1973; D. J. Lee et al., 2018). fmTheta has been source-localized to the anterior cingulate cortex and medial prefrontal cortex (Ishii et al., 2014; Michels et al., 2010; Onton et al., 2005), where it has been anti-correlated to fMRI BOLD (functional magnetic resonance imaging, blood-oxygen level dependent) activity in these areas (Scheeringa et al., 2008, 2009). The exact function of fmTheta oscillations in cognition is still unresolved although various explanations have been proposed (Hsieh & Ranganath, 2014; Klimesch et al., 2005; Sauseng et al., 2010). One of the most well-elaborated hypotheses is that theta is responsible for synchronizing neuronal firing across cortical regions (Lisman & Jensen, 2013). This has been supported by intracortical recordings in macaques for short-term memory tasks (H. Lee et al., 2005; Liebe et al., 2012). Evidence in humans has been mixed (Brzezicka et al., 2018), however given the strong association with tasks, theta is generally hypothesized to be functionally relevant for cognitive processing.

Currently, research in theta oscillations increasing with sleep deprivation (sdTheta) (Finelli et al., 2000; Vyazovskiy et al., 2011) has remained largely independent from research in cognition and fmTheta (Ishii et al., 2014; Jensen & Tesche, 2002; Maurer et al., 2015). It is therefore unknown if these represent either two distinct oscillations in the theta range or the same, as has been suggested by Takahashi et al. (1997) and Mitchell et al. (2008). If sdTheta and fmTheta are distinct, this would resolve the apparent paradox of an oscillation reflecting both drowsiness and cognition. If sdTheta is instead a manifestation of fmTheta, then its interpretation as local sleep should be reconsidered.

We conducted this exploratory sleep deprivation study in young healthy adults to disentangle the changes in theta related to both drowsiness and cognition using high-density EEG. Six tasks were performed under three levels of sleep pressure (Figure 2.1). To determine whether sdTheta and fmTheta could be considered the same oscillation, we first looked at their topography within a short-term memory task and source-localized their neural substrates. We also inspected their spectrograms to determine if they could be differentiated by peak frequency. To explore more generally if sdTheta is affected by behavioral state, we compared its topography and source localization in all 6 tasks. Lastly, to determine what impact sdTheta and fmTheta might have, we correlated changes in theta with changes in behavioral performance.

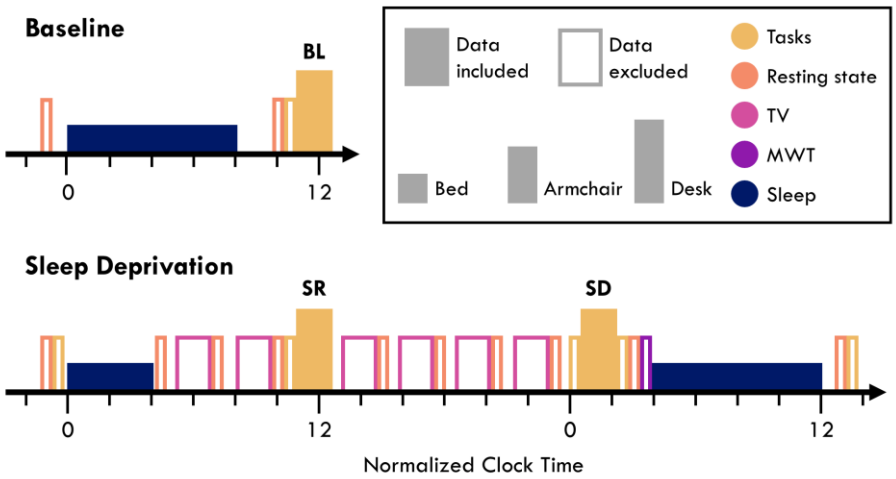

Figure 2.1: Experiment timeline. Each block indicates an EEG recording session. Filled blocks indicate data analyzed in this paper. Color indicates the activity participants engaged in: sleep (dark blue), the maintenance of wakefulness test (MWT, purple), TV watching (pink), resting state recordings (orange), and tasks (yellow). The height of each block indicates the condition in which data was collected: lying in bed (short), seated in a comfortable armchair with foot and backrest (medium), and seated at a desk (tall). The desk task block included the six tasks of this paper (STM, LAT, PVT, Speech, Game, Music) in randomized counterbalanced order, repeated three times during baseline (BL), sleep restriction (SR) and sleep deprivation (SD). The armchair task blocks included the PVT and LAT, in the same order for each participant as in the desk task block. These were counterbalanced to either come before or after the desk task block. Two additional armchair LAT recordings were performed after the SD session. Brief empty spaces indicate transition periods allowing for delays. Six longer breaks were included prior to each TV block in which participants were provided with meals. The exact timing was adjusted to individual habitual bedtimes, with the above diagram depicting the schedule for a bedtime of 00:00. Participants were free to wake up when they wished at baseline and during the recovery night and were woken up after 4 h during the first sleep deprivation night.

2.3 Materials & methods

2.3.1 Participants

Participants were recruited from Swiss universities through online advertisements and word of mouth and screened for eligibility with an online questionnaire. Out of 75 applicants, one was recruited for technical pilots (data not included), 31 passed but did not initiate contact or were unable to meet the scheduling requirements, 19 participants were recruited, and one dropped out midway and so was not included in further analyses. Of the 18 participants who completed the experiment, 9 were female and 3 were left-handed. Mean age (± standard deviation) was 23 ± 1 years old. All participants self-reported above-average English fluency (68% ± 13% on a scale from *terrible* to *native speaker*), with 1 participant a native English speaker. All had corrected-to-normal vision and self-reported no hearing impairments.

Applicants were screened prior to participating in order to: A) have a uniform, neurotypical population; B) avoid potential drop-outs due to adverse reactions to the experimental conditions; C) ensure participants' lifestyles were similar enough to the requirements of the control week (the week prior to each recording session) so as not to cause major disruptions; D) avoid any health or life conditions that could interact negatively with sleep deprivation or other experimental conditions; E) ensure participants were at least somewhat vulnerable to sleep deprivation in order to avoid floor effects.

Inclusion criteria were:

- Age between 18 and 25 (A)
- Good sleepers, with a PSQI ≤ 5 (Pittsburgh Sleep Quality Index; [Buysse et al., 1989]), few nighttime awakenings, and resistance to adverse environmental conditions such as background noise or dim lights (B)
- A regular sleep-wake rhythm, with an MCTQ score between 2 and 6.5 (Munich Chronotype Questionnaire; [Roenneberg et al., 2015]), sleep duration between 6 and 11 h, a preferred bedtime between 21:00-01:00 and wakeup time between 06:00-11:00 (A, C)
- A BMI (body mass index) between 18 and 30 (A, D)

Exclusion criteria were:

- Habitual napping (C)
- Sleep-related disturbances or disorders such as insomnia or daytime sleepiness (D)
- Pregnancy or currently experiencing a difficult period in life (stress, loss, etc.) (D)
- Any medical, psychological, or psychiatric conditions (B, D)
- Any physical impairment at the time of recording or recent use of a long-term cast/bandage (D)
- Sensitive skin (B)
- Currently or recently taking prescription medication, excluding contraceptives (A, D)
- Regular recreational drug consumption, use of prescription stimulants, heavy consumers of alcohol (either daily consumption or occasional binge drinking), or smokers (A, C)
- Habitual consumption of more than 3 cups of coffee per day (C)
- Prior experience with shift work, regular experience with changing time zones, or spending > 20 h awake (E)
- Resilience to sleep deprivation (E)

Data collection and interaction with participants was conducted according to Swiss law (Ordinance on Human Research with the Exception of Clinical Trials) and the principles of the Declaration of Helsinki, with Zurich cantonal ethics approval BASEC-Nr. 2019-01193. All participants signed informed consent prior to participation and were made aware that they could terminate the experiment at any time. Due to scheduling restraints caused by the COVID-19 pandemic, some leniency was allowed for edge cases of the screening criteria (e.g. one participant was 26 at the time of recording, another had early morning work experience as a baker).

2.3.2 Experiment design

Participants came to the laboratory twice, first for the baseline then the sleep deprivation bout, separated by at least 4 days. Experiments were typically conducted on weekends. The baseline was scheduled first to determine whether participants could in fact sleep in the laboratory and tolerate the EEG net before attempting the substantially longer sleep deprivation protocol. Data was collected between February and

December 2020, overlapping with the COVID-19 pandemic and consequent lockdowns. Due to scheduling restraints, 4 participants conducted the baseline after the sleep deprivation recording, so the experimental session orders were not balanced, nor uniform.

During the week prior to each session, participants were asked to maintain a regular sleep wake cycle, going to bed and waking up within 1 h of a pre-determined sleep and wakeup time based on their personal preference. These individualized sleep and wake times were then used during the experiment. During the control week, participants wore a wrist accelerometer (GENEActiv, Activinsights Ltd.) and filled out regular sleep reports to ensure compliance. Participants were further asked to abstain from alcohol in the 3 days prior to the measurement, and limit caffeine consumption to no more than the equivalent of 2 cups of coffee, and never after 16:00. They were asked to avoid time-zone travel and any activities they knew could affect their sleep (e.g. parties, skiing, sauna).

Baseline: Participants first prepared for bed, then the EEG net was set up. After impedances were checked, participants were given careful instructions on how to perform the different tasks (with brief practice demonstrations), and to avoid touching the net or other movements during recordings. Afterwards, participants went to bed at the agreed-upon time (21:55-00:47) and were left to sleep for as long as they wished (6.2-10.3 h). In the morning, participants first filled out a sleep quality questionnaire (data not included). Then, participants were provided breakfast and given time to wake up. Finally, participants performed the baseline (BL) task block (8:10-11:17), 1.8 ± 0.6 h from wake onset. Additionally, a brief resting wake recording was conducted in the evening and in the morning, however the data was not included in this manuscript. The complete schedule is depicted in Figure 2.1.

Sleep deprivation: Participants went to bed at the same time as the baseline. They were woken up 4 hours later. Throughout the day, participants repeated 6 cycles, each consisting of a break, 2 TV episodes from a series of their choice, and a brief rest recording. During the breaks, participants were provided a small home-cooked meal (selecting items from a menu beforehand), thus eating the same plate during every break. They repeated 2 of these cycles in the early morning, then conducted the morning sleep restriction (SR) task block after 6.4 ± 0.2 h from wake onset (within 7.7 ± 39.5 min of the BL block). The SR block was included to identify the effects of time spent awake and asleep while controlling for circadian clock time. Participants went through 4 more cycles before conducting the sleep deprivation (SD) task block, after 20.0 ± 0.1 h from wake onset and within 2.6 ± 10.5 min of the prior night's bedtime. Following the tasks, participants preformed a final rest test, then a maintenance of wakefulness test (MWT) in which they had to try and stay awake in a dark room for as long as possible (data not included).[1] After 23.6 ± 0.5 h of wake, participants went to bed and slept for as long as they wished. As with the baseline bout, additional rest recordings were conducted before and after each night (data not included).

During wake recordings, participants were monitored by an experimenter to ensure they did not fall asleep. From the evening before the first night to the day after the recovery night, participants remained in the sleep laboratory and did not have access to clocks or external time cues. Two participants reported nausea with increasing sleep deprivation and were therefore provided a break outside just prior to the SD block (in complete nocturnal darkness).

[1] *Unfortunately, I never got to use this data. It was recorded in case resisting sleep really did seem to be what generated sdTheta, in which case theta during the MWT should have been higher than during actual sleep onset a few minutes later.*

2.3.2.1 Tasks

Each task block lasted approximately 2 hours. The six tasks were performed seated upright at a desk in a well-lit room (~100 lux at eye level), on a laptop. The order of tasks was randomized and counterbalanced across participants. For each participant, tasks were conducted in the same order for all three blocks. In addition to the main task block, two tasks (LAT, PVT, see below) were performed under soporific conditions (comfortable armchair, 10 lux lighting), counterbalanced either before or after the main desk task block, as well as after the first evening and last morning rest recordings of the sleep deprivation bout (see Figure 2.1). This condition is not included in this manuscript. Each task began and ended with a 1 min rest period allowing participants to adjust and get comfortable. After each task, participants answered a task battery questionnaire asking how they experienced the task.

Short-Term Memory Task (STM): Participants performed a ~25 min delayed match-to-sample / short-term memory task, adapted from Habeck et al. (2004) and Maurer et al. (2015). The task consisted of 120 trials divided in 4 blocks, with 3 memory load levels randomized across trials for a total of 40 trials per level. Stimuli are depicted in Figure 2.2A. Each trial was separated by a 1-2 s pause with a black screen. The *encoding* window began when a red fixation square appeared in the center of the screen for 1 s. Then 1, 3, or 6 symbols (selected from a pool of 30 "letters" of the Aurebesh fictional alphabet) were displayed around the fixation point in 8 possible locations for 2 s. Participants were instructed to maintain fixation on the red square while memorizing these symbols. This was followed by a 4 s *retention* window in which only the fixation point was displayed, and participants had to hold in memory the symbols. The trial ended with the *probe* window, in which a probe symbol replaced the central fixation point and participants had to indicate with left or right arrow keys whether the probe symbol was contained in the encoding set or not, within 3 s. The probe was from the encoding set in 50% of trials. No feedback on performance was provided. Accuracy was the primary outcome measure of the STM task, calculated as the percentage of correct rejections + correct acceptances to the probe relative to the total number of trials.

Psychomotor Vigilance Task (PVT): This is a standard reaction-time task used in sleep deprivation paradigms, based on Basner and Dinges (Basner & Dinges, 2011). The total task duration was 10 min. Participants were presented with a red fixation rectangle on a gray background (Figure 2.2B). Every 2-10 s, the rectangle was replaced with a millisecond countdown and participants had to press a button as fast as possible to stop it. The response time would then freeze for 1 s and be colored in yellow if less than 0.1 s (false alarm), green if between 0.1 and 0.5 s (correct response), and red if later than 0.5 s (lapse). If participants did not respond within 5 seconds, an alarm would sound to wake them up. The following performance outcome measures were evaluated: mean, median, and standard deviation of reaction times (RTs); mean RTs of the fastest 10% of trials and the slowest 10%; and the total number of lapses (RT > 0.5 s).

Lateralized Attention Task (LAT): This was a 12 min visual-spatial reaction time task, modelled after the PVT. 6 blocks (2 min each) alternated between having the left or right visual hemifield in white, and the other in black (Figure 2.2C). Participants had to maintain fixation on a red rectangle in the center of the screen, and covertly attend to the white half of the screen. Every 2-10 s a feint grey circle (1 cm radius, #F7F7F7) would appear randomly in any location of the illuminated hemifield and shrink away completely within 0.5 s. Participants were instructed to press a button before the circle disappeared, in which case the circle would freeze and flash green. Responses up to 0.5 s after the circle completely disappeared were considered late, no response within this time was a lapse, and a response at any other time a false alarm. If 5 stimuli were missed consecutively, an alarm would sound to wake up the

participant. During the delay periods, 50 ms pink noise tones were presented every 1.5-5 s at ~50dB. Participants were instructed to ignore these tones. Performance outcome was measured as: mean, median, and standard deviation of RTs; mean RTs of the fastest 10% of trials and the slowest 10%; percentage of correct responses (0.1 s < RT < 0.5 s), late responses (0.5 s < RT < 1 s), and lapses (no response). Unlike the PVT, the LAT allows the distinction between slower RTs and complete lapses of attention.

Speech Fluency Task: Participants performed a tongue-twister reading task in English for 5-10 min. This consisted of 20 trials, one per sentence. Each sentence was repeated during each task block. A trial began with the sentence written on the screen (Figure 2.2D). Participants were instructed to read it in their head once or twice to get familiar with it, but not practice speaking. When they were ready, they could press a button, and a green bar would appear below, steadily shrinking to count down a 10 s reading window. In this time, participants had to read out loud the sentence as many times as possible, as clearly as possible, and as correctly as possible, while their speech was being recorded. This was the only task in which the researcher was not in the room in order to reduce participants' self-consciousness. Performance outcome was measured as the number of correctly spoken words per second, and the number of mistaken words per second. Speech scoring was conducted manually by author SS, blinded to session and participant. A mistake was whenever a word was unfinished, not in the prompt, skipped, repeated (even partially, e.g. "se-seashells"), switched with a synonym (or any other unrelated word), or interrupted (e.g. by giggling). Switching two syllables of two words was counted as two mistakes (e.g. Yew Nork), whereas switching the order of two words was counted as one mistake.

Game: Participants played the mobile game BBTAN (based on the 1986 game *Arkanoid* by Taito) for 10 minutes (Figure 2.2E). They started each session from level 1. The game involved a robot with a ball at the bottom of the screen, and a row of 1-6 bricks at the top. By tapping and dragging on the screen, participants could orient an arrow from the robot, and the ball would be launched from the robot in the indicated direction. The goal was to bounce the ball against the walls and hit as many bricks as possible, such that every time the ball hit a brick, the brick lost a point, and when the brick had no more points, it disappeared. At each round, after the ball was launched, hit the bricks, and bounced back to the bottom, the remaining set of bricks descended by 1 row, and a new row of bricks appeared at the top. When the bottom-most row of bricks reached the robot, the player lost the game. There were additional game features to help remove bricks faster. This was a "simple but addictive" game, requiring a minimum amount of spatial strategy to win, without any time pressure. No outcome measure was recorded for this task.

Music: Participants listened to two songs for 2.5 min each: the beginning of the instrumental soundtrack *Light of the Seven* composed by Ramin Djawadi from *Game of Thrones: Season 6*, and the beginning of the soundtrack *Finale (William Tell Overture)* composed by Hans Zimmer from *The Lone Ranger*.

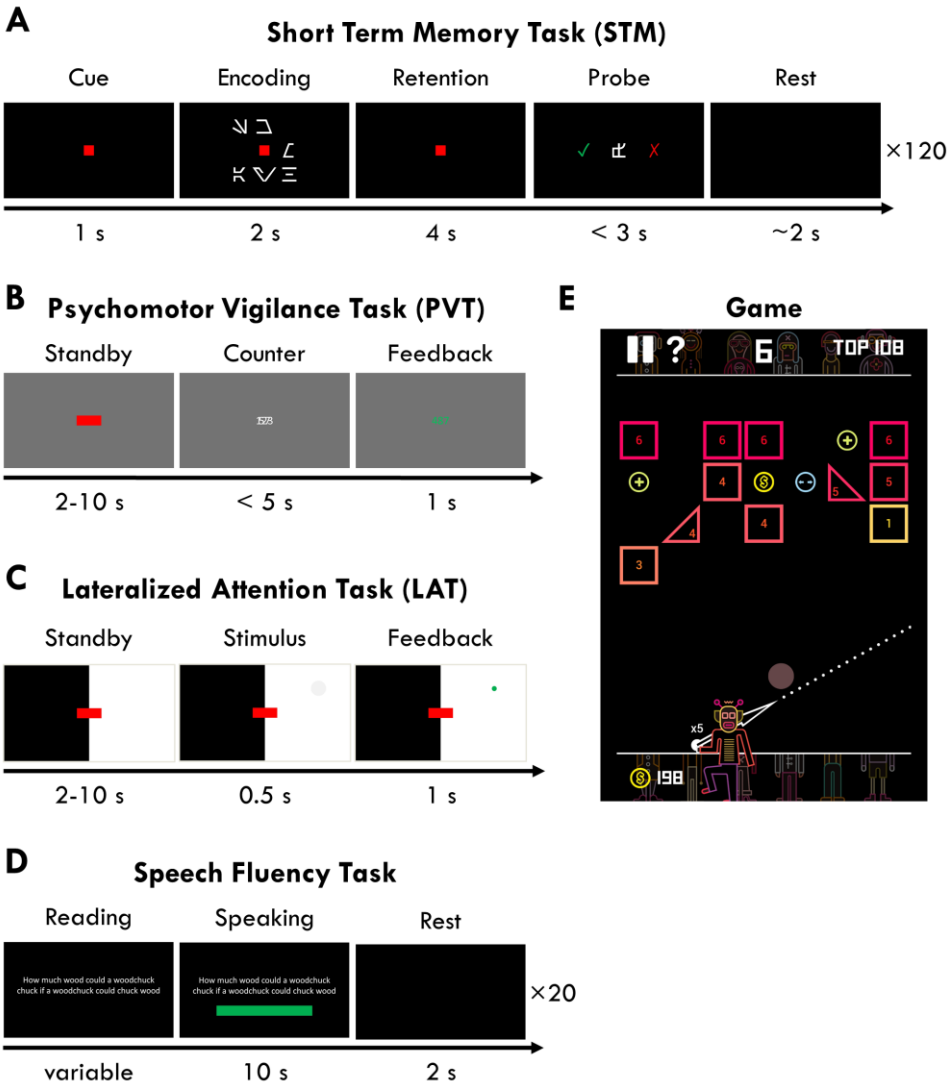

Figure 2.2: Task stimuli. A-D: Tasks were performed on a Lenovo ThinkPad P53 laptop (15.6" FHD, Intel Core i7-9750H) with Windows 10. The computer was kept at 50% volume and 100% brightness for all tasks. The tasks were programmed in Python v3.6.5 using the PsychoPy v3.2.4 toolbox. Digital triggers were sent from the task computer to the EEG recording system via USB. Responses for the PVT and LAT were recorded with the USB-connected MilliKey™ button box. **E**: The Game was played on a 10.1" Huawei MediaPad T5, running Android Oreo.

2.3.3 Questionnaires

A custom-built online survey tool, the Experiment Web Organizer for Questionnaires (EWOQ), was created for collecting questionnaire data through a web browser, written in React/typescript and hosted on Netlify and Google Cloud Platform. During the laboratory experiments, all questionnaires were filled out on a tablet, whereas the screening questionnaire and daily sleep reports were filled out on the participants' personal devices. Only the PSQI, MCTQ and KSS are external, validated questionnaires. All others were created for this experiment and have not been tested on a broader population. The task questionnaires were conducted to evaluate subjective experiences during each task. Answers were given on a ~10 cm continuous slider with labels, which are indicated on the y axes in Figure 2.16.

2.3.4 EEG recording and analysis

High-density EEG was recorded using HydroCel Geodesic Sensor Nets™ with 128 channels, connected to DC BrainAmp Amplifiers and recording software Brainvision Recorder (Vers. 1.23.0003, Brain Products GmbH, Gilching, Germany). Data was recorded with a sampling rate of 1000 Hz with Cz reference. Impedances were set to be < 5 kOhm for ground, reference, and external electrodes, and < 25 kOhm for all other electrodes. After re-checking impedances, gel was refreshed every 4-6 hours during the sleep deprivation bout, and in the morning after each night of sleep.

All data preprocessing, analysis, and statistics was done with custom scripts in MATLAB (R2019b) based on the EEGLAB toolbox v2019.1 (Delorme & Makeig, 2004). All further analyses involving source localization were performed with the FieldTrip toolbox v20210606 (Oostenveld et al., 2011).

Preprocessing: EEG data was filtered between 0.5-40 Hz and downsampled to 250 Hz. Visual detection of major artifacts and bad channels was conducted by author SS, blind to participant, task, and session. Overall, 4 ± 3 channels were removed on average per recording, out of 120 (Figure 2.20A). ICA was then used to remove physiological artifacts, mainly eye movements, heartbeat, and muscle activity (Dimigen, 2020). On average, 39 ± 12 components were removed from each recording (out of 106-122, Figure 2.20B). The Speech task had significantly more components removed, and the Music task the least. The majority of components removed were related to muscle artifacts. Bad channels were interpolated, and only the first 4 min of clean data were used, with average reference. The full pipeline is described in detail in Figure 2.19.

Channel space power calculation: The power spectral density (PSD) estimate was calculated using MATLAB's pwelch function, with 8 s windows, Hanning tapered, and 75% overlap. To account for large interindividual differences in theta power (Figure 2.22) and the 1/f power amplitude distribution across frequencies, PSD for each frequency was z-scored. For theta topographies (e.g. Figure 2.7), z-scored PSD values between 4-8 Hz were averaged. For power spectrums (e.g. Figure 2.11), z-scored PSD values were averaged into 3 pre-selected regions of interest (ROIs): Front, Center, and Back. Exact channels are indicated in Figure 2.18. For mean theta values (e.g. Figure 2.5B), these ROI spectrum averages were further averaged between 4-8 Hz.

Source localization: Beamformer source localization was done with the dynamic imaging of coherent sources (DICS) algorithm from FieldTrip (Gross et al., 2001; Westner et al., 2022). A finite-element head model was implemented with the SimBio toolbox (Vorwerk et al., 2018) based on the segmentation of a standard MRI template brain. A 3D grid with 10 mm resolution (3294 voxels) was used as a source model. After being projected into the source space, power was z-scored for each frequency. For visualization, t-tests were conducted for all gray-matter voxels, cluster corrected for multiple comparisons (Maris, 2012; Maris & Oostenveld, 2007), and significant clusters projected onto the inflated brain. To determine the main anatomical sources, z-scored data was parcellated based on the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The median value of all voxels within each area was then averaged across frequencies. For both pipelines, only cortical areas were included, as there is currently little evidence that activity from deep brain structures reaches the scalp. The exact pipeline is provided in Figure 2.21.

Trial analysis: Data from the STM task was separately analyzed by trial type, using data from the entire 25 min recording. Each trial was first divided into 2 s epochs for each window (encoding, first retention, second retention, and probe), and power was calculated with *pwelch* using a Hanning tapering window.

The retention window was divided into 2 epochs in order to have the same duration as the encoding and probe epochs. Trials with more than 25% of samples marked as noise (during preprocessing step B in Figure 2.19) were excluded. The minimum number of trials for each memory load level for each session was 25. These remaining trials were then split by level and averaged. For each participant and each frequency, power values were then z-scored across epochs, trial types, channels, and sessions. The exact pipeline is provided in Figure 2.18.

2.3.5 Statistics

All parametric statistics were based on $\alpha = 5\%$. One PVT BL recording is missing, otherwise there were always 18 EEG datasets per task, per session.

ANOVAs: each two-way repeated measures analysis of variance (rmANOVA) was calculated using MATLAB's Statistics and Machine Learning Toolbox. Greenhouse-Geisser corrected p-values were always used due to occasional violations of sphericity. Eta-squared (η^2) effect sizes were calculated using the Measures of Effect Size (MES) Toolbox based on Hentschke & Stüttgen (2011).

T-tests: whenever only two conditions were being compared, paired t-tests were calculated. Hedge's g effect sizes are reported when t-values are described in the text. These were calculated using the MES toolbox.

Correlations: Spearman's rank correlations were conducted between behavioral outcome measures and untransformed EEG theta power in pre-selected regions of interest. Untransformed power values were used in order to better capture inter-individual differences.

FDR correction: Corrections for multiple comparisons were done by controlling for the *false discovery rate*, according to the procedure by Benjamini and Hochberg (1995). This was done using the Mass Univariate ERP Toolbox. FDR was chosen over other methods because it required the fewest a-priori assumptions and thresholds (Groppe et al., 2011).

2.4 Results

2.4.1 Changes in sleep architecture and subjective sleepiness confirm the effectiveness of the sleep deprivation protocol

To determine whether the sleep deprivation protocol was successful in increasing sleep pressure, we evaluated changes in sleep architecture between the baseline night and recovery night following sleep deprivation (Table 2.1). We found shorter sleep onset latencies and more deep sleep (NREM3), key indicators of increased sleep pressure.

All sleep stages except REM sleep showed a significant change between baseline and recovery, with NREM3 increasing 30% at the expense of wake (-30%), NREM1 (-47%), and NREM2 (-16%). Sleep onset latency (SOL) significantly decreased from 16.8 minutes to 5.6 minutes. Overall sleep duration was shorter during the recovery night, although this was not statistically significant (p-value = .108), and sleep efficiency increased from 92% to 96%. Together, these results indicate that sleep pressure, specifically for slow wave sleep, increased over the 24 h wake period.

	BASELINE	PRIOR NIGHT	RECOVERY NIGHT	PRIOR NIGHT VS BASELINE	RECOVERY NIGHT VS BASELINE	RECOVERY VS PRIOR NIGHT
Wake	40.6 ± 30.1	18.1 ± 17.2	20.7 ± 9.3	.001	.008	.544
NREM 1	22.3 ± 12.3	10.8 ± 8.8	10.6 ± 4.8	< .001	< .001	.919
NREM 2	257.6 ± 34.2	115.1 ± 22.3	214.3 ± 51.6	< .001	.001	< .001
NREM 3	89.7 ± 40.1	64.6 ± 23.8	109.6 ± 37.0	< .001	.027	< .001
REM	111.8 ± 32.0	33.4 ± 13.2	118.2 ± 29.8	< .001	.450	< .001
SOL	16.8 ± 7.8	16.9 ± 13.2	5.6 ± 2.1	.986	< .001	.002
SDu	481.8 ± 31.1	224.2 ± 16.8	453.0 ± 76.2	< .001	.108	< .001
WASO	28.1 ± 26.0	5.7 ± 8.4	17.1 ± 9.0	.001	.076	.001
SE (%)	92.5 ± 5.2	92.6 ± 7.0	95.6 ± 1.8	.950	.018	.080
ROL	103.5 ± 47.5	98.7 ± 41.2	60.9 ± 19.4	.458	< .001	< .001

Table 2.1: Sleep architecture. All values in the first three columns are in mean minutes ± standard deviations, except SE which is in percentages (100 * SDU / Total time in bed). The last three columns indicate p-values from paired t-tests between the different nights. PRIOR NIGHT refers to the 4 h night that begins the sleep deprivation session, and RECOVERY NIGHT refers to the night after. Acronyms: REM (rapid eye movements), SOL (sleep onset latency), SDU (sleep duration), WASO (wake after sleep onset), SE (sleep efficiency), ROL (REM onset latency).

To determine the degree of sleep deprivation experienced by the participants, a two-way rmANOVA was conducted on KSS subjective sleepiness scores (Figure 2.3A) with factors *session*, *task*, and their interaction (all other questionnaire data in Figure 2.16). There was a highly significant and very large effect of session ($F_{(2, 30)} = 35.42$, $p < .001$, $\eta^2 = .355$), a significant medium effect of task ($F_{(5, 75)} = 14.7$, $p < .001$, $\eta^2 = .073$) and a non-significant interaction ($F_{(10, 150)} = 0.96$, $p = .440$, $\eta^2 = .008$). This was the only subjective rating with a large effect of session, followed next by motivation ($\eta^2 = .07$, all statistics in Figure 2.16). During sleep deprivation, participants felt less sleepy during the Game and most sleepy during the STM task (Figure 2.3B).

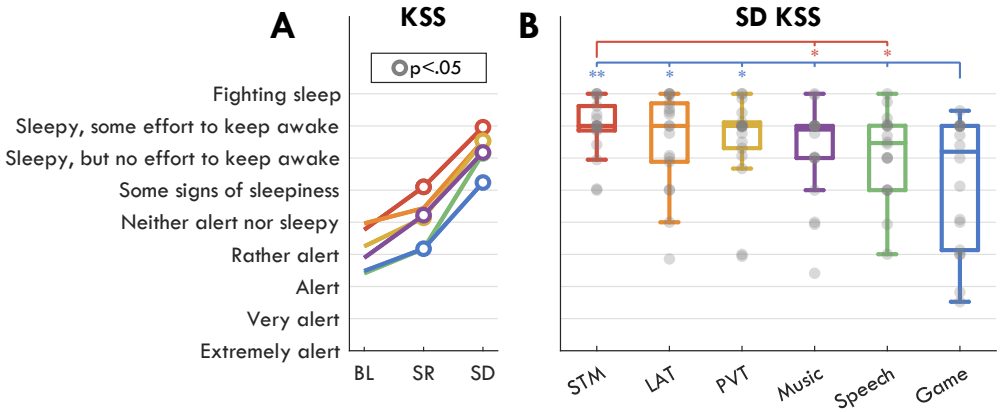

Figure 2.3: Subjective sleepiness ratings. Based on an adapted visual-analogue Karolinska Sleepiness Scale (KSS) collected after each task. The labels were those of the original categorical KSS, but participants could choose intermediate values on the continuous scale. **A**: Average scores for each task and each session. Each colored line represents a task (STM: red, LAT: orange, PVT: yellow, Speech: green, Game: blue, Music: purple). White-filled circles indicate a significant change from BL, FDR corrected for multiple comparisons. Figure 2.16 provides the results for all other

questions. **B**: KSS scores during the SD task block. Gray circles represent each participant, the boxplot indicates median and interquartile range for each task. Stars indicate significant differences in paired t-tests (the color indicates one task, the location of the star the other), FDR corrected for multiple comparisons, such that: * p-value < .05, ** p-value < .01, *** p-value < .001. The empty tick mark indicates a trend (p-value < .1).

2.4.2 fmTheta is more localized than sdTheta

For fmTheta and sdTheta to be considered the same oscillation, they should originate from the same brain areas. To determine if this was the case, we analyzed changes in theta from the short-term memory task (STM) during the retention window.

fmTheta was calculated by comparing z-scored power spectral density (PSD) changes between 4-8 Hz from L1 trials (1 symbol to hold in memory) to L3 trials (3 symbols to hold in memory), at BL during both the first and second retention epochs (Figure 2.17). Only the first epoch resulted in a significant increase in theta in any channel, therefore all further analyses were conducted on this epoch. L6 trials were also compared to L1 (Figure 2.17) but this did not yield different results from L3 vs L1. Because of the higher memory load, we had originally expected L6 to have more theta than L3. Given that performance for L6 trials was barely above chance level (Figure 2.14A), we interpret this result as L6 being too difficult, causing participants to not engage in at least some of the trials. Therefore, we focused on L1 vs L3.

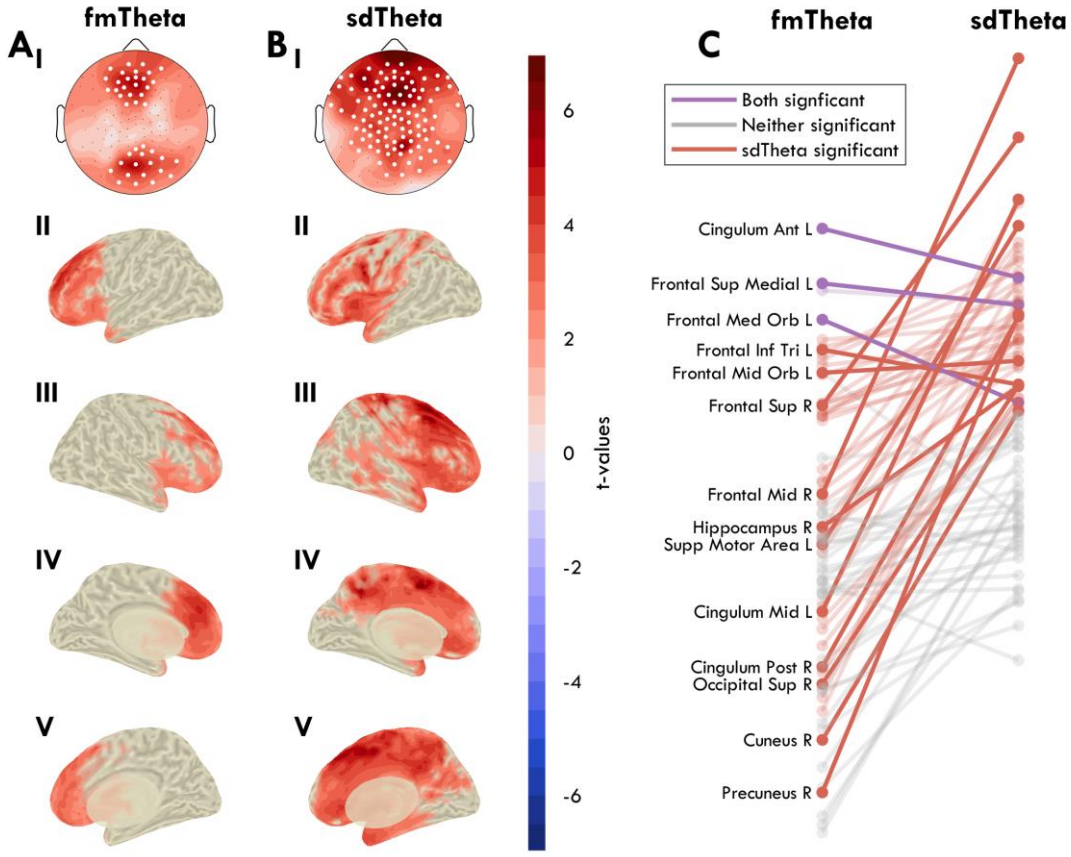

Figure 2.4: Sources of fmTheta and sdTheta. Theta is measured as average z-scored power between 4-8 Hz during the first retention epoch of the STM task. **A**: Frontal-midline theta, calculated as the difference between trials with 3 items vs 1 item to hold in memory, from the BL session. **B**: Sleep deprivation theta, calculated as the difference between SD trials and BL trials with 1 item to hold in memory. **I**: Theta changes represented in a 2D topography of EEG channels, as a head seen from above (nose on top). Black dots indicate all channels, white dots indicate channels

in which the change was statistically significant (p-value < .05) based on paired t-tests, FDR corrected for multiple comparisons. Source localization is presented in II-V as inflated brains. T-values are plotted with the same color scale in the channel and source space, such that red indicates a positive increase in theta from L1 to L3 in A, and from BL to SD in B. In the source space, voxel-wise cluster correction was implemented to mask non-significant effects. Figure 2.17 provides the topographies also for the second retention window and L1 vs L6 trials. **II**: Left hemisphere, lateral view. **III**: Right hemisphere, lateral view. **IV:** Left hemisphere, medial view. **V**: Right hemisphere, medial view. **C**: Change in t-values for all areas between the fmTheta (A) and the sdTheta (B) comparisons, based on the AAL atlas. Lines in gray depict areas that showed no significant effects in either comparison, after FDR correction. Lines in red indicate areas showing a significant change in sdTheta, and lines in purple both in sdTheta and fmTheta. No area was only significant for fmTheta. Exact t-values can be seen in Figure 2.9.

In the channel space, two significant channel groups emerged (Figure 2.4A I): the frontal peaking over ch11 (Fz; $t_{(17)}$ = 5.61, p = .002, Hedge's g = 0.76); the posterior peaking over ch75 (Oz; $t_{(17)}$ = 5.61, p = .002, g = 0.76). Source localization identified the left medial frontal cortex as the main source (Figure 2.4A IV), especially the anterior cingulate cortex (t = 4.76) and the superior frontal gyrus, medial (t = 4.06) as well as orbital part (t = 3.59; t-values for anatomical areas provided in Figure 2.9). These results replicate previous findings (Ishii et al., 2014; Maurer et al., 2015; Michels et al., 2010; Onton et al., 2005; Scheeringa et al., 2009). The right medial cortex also showed increases in theta, however these areas did not survive correction for multiple comparisons.

sdTheta was calculated using the same first retention epochs but comparing L1 trials from BL to L1 trials from SD (Figure 2.4B). Unlike for fmTheta, this necessitates a between-session comparison. sdTheta was more widespread across the cortex than fmTheta, showing cluster-corrected increases in 38% of gray matter voxels relative to 21%, respectively. All areas showing load-effects of fmTheta were also significant for sdTheta (Figure 2.4C), and the areas showing highest sdTheta were not among those significantly increasing in fmTheta. Specifically, the peak location of sdTheta was different in both the channel space (ch5) and source space: right middle frontal gyrus (t = 6.95) and superior frontal gyrus (t = 5.94; Figure 2.4B III). sdTheta extended along the medial cortex up to the cuneus (maximum t-value t_{max} = 5.15) and was additionally present around the left insula (t_{max} = 4.58), and the temporal poles (t_{max} = 3.67). Therefore, sdTheta and fmTheta have different primary sources, and different spread throughout the cortex.

2.4.3 fmTheta fades with increasing sleep deprivation

If sdTheta and fmTheta are independent oscillations, they should both be present during sleep deprivation when performing the STM task. fmTheta was therefore calculated at every session, for both L3 vs L1 and L6 vs L1 (Figure 2.5A). Surprisingly, fmTheta decreased in amplitude with increasing sleep deprivation, until no channel showed statistically significant differences with memory load during SD.

A two-way rmANOVA was conducted with factors *session*, *load,* and their interaction, separately for three regions of interest (ROIs). In the Front ROI there was both a significant and large effect of session ($F_{(2, 34)}$ = 17.17, p < .001, η^2 = .287), a significant but small effect of load ($F_{(2, 34)}$ = 5.92, p = .008, η^2 = .030), and a small significant interaction ($F_{(4, 68)}$ = 3.74, p = .017, η^2 = .016). In the Center ROI there was a significant effect of session ($F_{(2, 34)}$ = 10.16, p < .001, η^2 = 0.198), no effect of load ($F_{(2, 34)}$ = 1.35, p = .271, η^2 = .006), and a trending interaction ($F_{(4, 68)}$ = 2.37, p = .095, η^2 = .022). In the Back ROI there was a significant effect of session ($F_{(2, 34)}$ = 4.64, p = .028, η^2 = .072), a small trending effect of load ($F_{(2, 34)}$ = 2.63, p = .096, η^2 = .013), and a significant interaction ($F_{(4, 68)}$ = 3.88, p = .019, η^2 = .014).

The interaction between load and session was driven by a larger increase in theta for low memory load trials during sleep deprivation (Figure 2.5B). To better understand this, we compared sdTheta topographies (BL vs SD) for each memory load level (Figure 2.5C). L1 showed the largest and most widespread

increase in theta (t_{max} = 7.28, p < .001, g = 1.57), L3 the lowest and most local increase (t_{max} = 4.32, p = .024, g = 0.87), and L6 was intermediate (t_{max} = 4.93, p = .007, g = 1.45). As a result of sdTheta increasing more in low memory load trials, fmTheta effectively disappeared. However, given that for most of the participants these three sessions were performed in order, it is also possible that this disappearing fmTheta is driven by a repetition effect, although previous studies (Habeck et al., 2004) have not found repetition effects of behavior in this task design.

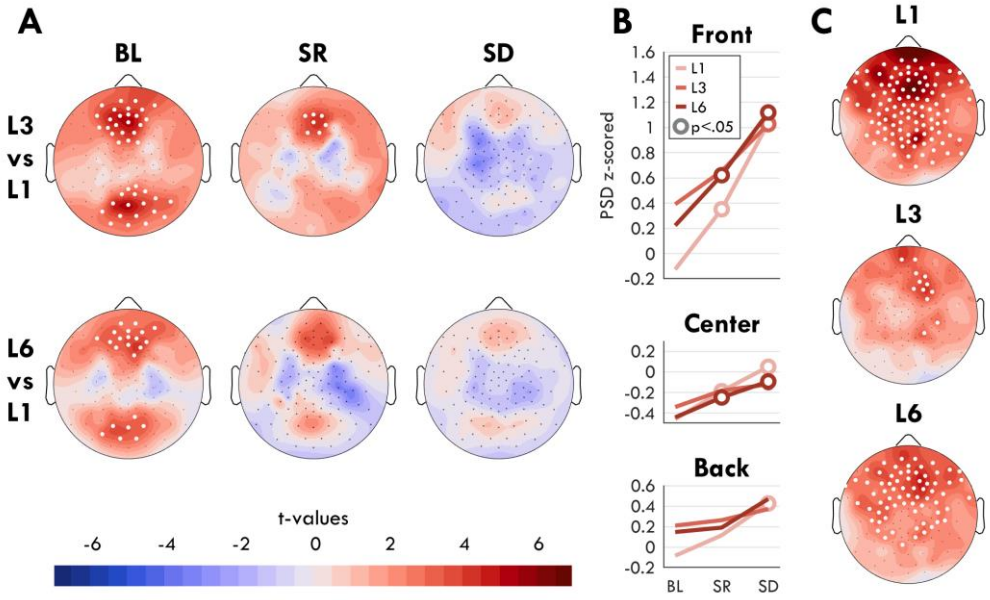

Figure 2.5: Interaction between STM task level and sleep deprivation theta power. **A**: Difference in theta power for the first half of the retention period during the STM task between level 3 (top row) and level 6 (bottom row) relative to level 1 for every session. Color represents t-values such that red indicates greater theta power in L3/L6 relative to L1. White dots indicate a significant effect, FDR corrected for multiple comparisons. **B**: Mean z-scored theta power across sessions for each load level at each region of interest (ROI). White circles indicate a significant change from BL, filled circles a trend, FDR corrected for multiple comparisons. **C**: Change in theta power topographies during the first retention epochs between SD and BL, split by memory load. Same color scale as A, with red indicating more theta in SD relative to BL. Figure 2.18 illustrates the analysis pipeline.

2.4.4 Sources of sdTheta are task dependent

The results from Figure 2.4 show distinct topographies for fmTheta and sdTheta. The literature has identified fmTheta to consistently originate from the same medial region, however similar source localization has never been done for sdTheta. To determine whether sdTheta is consistent or task-dependent, we compared theta changes from BL in 6 different tasks. Mean theta values for all tasks in regions of interest are provided in Figure 2.6. Figure 2.7 depicts the sdTheta changes for both SR and SD relative to BL in the channel space, and Figure 2.8 provides the source localization for SD relative to BL displayed on inflated brains. Figure 2.9 provides the t-values for all anatomical regions found to be significant in at least one comparison of SD relative to BL.

A two-way rmANOVA was conducted for each ROI with factors *session*, *task,* and their interaction (mean values in Figure 2.6A-C). The Front ROI had a significant effect of session ($F_{(2, 32)}$ = 28.02, p < .001, η^2 = .224), a trending effect of task ($F_{(5, 80)}$ = 22.51, p < .001, η^2 = .249), and a significant interaction ($F_{(2, 160)}$ = 1.88, p = .090, η^2 = .010). The Center ROI also had a significant effect of session ($F_{(2, 32)}$ = 13.09, p < .001, η^2 =

.105), a significant effect of task ($F_{(5, 80)} = 14.05$, $p < .001$, $\eta^2 = .239$), and a significant interaction ($F_{(2, 160)} = 2.53$, $p = .035$, $\eta^2 = .021$). The Back ROI did not have a significant effect of session ($F_{(2, 32)} = 2.41$, $p = .111$, $\eta^2 = .021$), but a strong effect of task ($F_{(5, 80)} = 21.67$, $p < .001$, $\eta^2 = .305$), and no interaction ($F_{(2, 160)} = 0.79$, $p = .549$, $\eta^2 = .007$). Therefore, although the effects were small, sdTheta was significantly task dependent. While the Game had the overall highest frontal theta (Figure 2.6D), the increase with sleep deprivation was more pronounced in the STM, PVT, and LAT (Figure 2.6E).

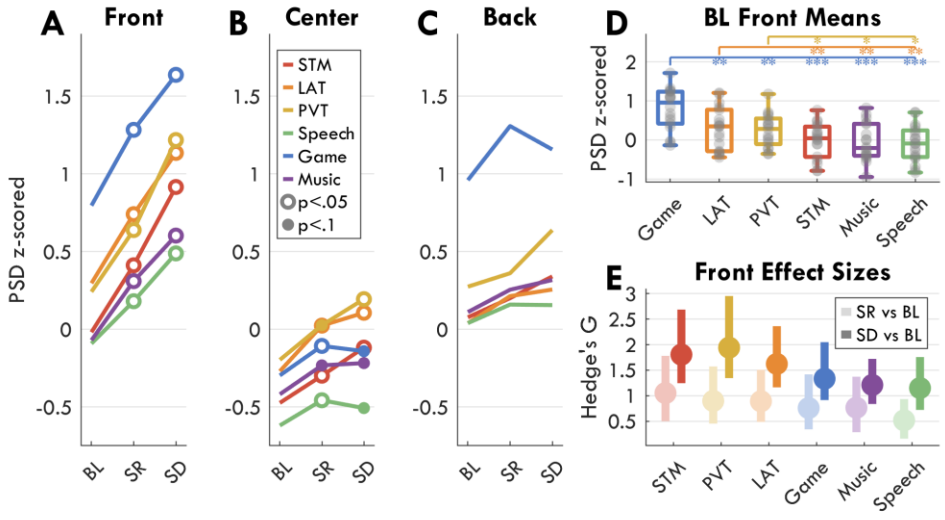

Figure 2.6: Change in theta across sessions for all tasks by region of interest (ROI). Mean z-scored theta power for 3 ROIs: Front (**A**), Center (**B**), and Back (**C**). Open circles indicate within each task a significant change in theta relative to BL, filled circles indicate a trend, based on paired t-tests, FDR corrected for multiple comparisons within each plot. **D**: Mean theta power for all tasks at baseline in the front ROI. Gray circles represent each participant, the boxplot indicates median and interquartile range. Stars indicate significant differences between tasks (the color indicates one task, the location of the stars the other) such that: * p-value < .05, ** p-value < .01, *** p-value < .001. E: Hedge's g effect sizes of the changes in theta in the front ROI from BL to SR (light colors) and SD (dark colors). The disk indicates Hedge's g, the bars indicate 95% confidence intervals. Figure 2.19 illustrates the preprocessing pipeline. Figure 2.20 indicates the channels and components removed during the preprocessing.

When comparing theta changes across the whole topography, all tasks showed increases in theta between BL and SR in most channels, however no channel was significant for the Speech and Music conditions after FDR correction (Figure 2.7, center). The highest overall increase was seen for the LAT over ch109 ($t_{max} = 5.74$, $p = .002$, $g = 1.33$), accompanied by widespread increases. Due to the otherwise medium-low effect sizes, the comparison between BL and SR was not further investigated with source localization. However, these results demonstrate already in the channel space how task-specific changes are present also when controlling for circadian time.

From BL to SD, the task-specific sdTheta topographies become even more evident (Figure 2.7, right). The LAT, STM, and PVT showed the most widespread increases, as well as the highest amplitude (PVT: $t_{max} = 7.52$, $p < .001$, $g = 1.85$; LAT: $t_{max} = 7.10$, $p < .001$, $g = 1.24$; STM: $t_{max} = 6.31$, $p = .001$, $g = 1.80$). The Speech task showed the lowest and most local increase in theta ($t_{max} = 5.50$, $p = .005$, $g = 1.51$).

The source space allowed further anatomical localization of the origin of theta. All tasks except the Game showed a predominantly right, frontal increase in theta (Figure 2.8),[1] although no anatomical area survived FDR correction for the Speech task (Figure 2.9). One of the primary sources of sdTheta across all tasks was the right superior frontal gyrus. All tasks (except Speech) also had significant theta originating from the right hippocampus, parahippocampus, anterior and middle cingulate cortex. The STM and LAT had further extensive increases across both dorsal and medial frontal areas, with the STM showing high theta activity along the left lateral sulcus (Rolandic operculum, insula), and the LAT in the right lateral sulcus (Heschl's gyrus, Rolandic operculum, insula). Unfortunately, source localization along this sulcus is challenging due to how gray matter is folded and may require subject-specific MRI structural scans for accurate results.

The overall strongest source of sdTheta was the left supplementary motor area during the Music task (Figure 2.9, t_L = 6.54), extending contralaterally (t_R = 4.77) as well as into the middle cingulate cortex. Bilateral supplementary motor areas were also the main sources of theta for the PVT (t_L = 4.70, t_R = 4.96). The supplementary motor area showed significant increases in the LAT and STM but to a lesser extent (STM: t_L = 3.13; LAT: t_R = 4.17) and were not significant in the Game.

Finally, the most atypical distribution of sdTheta came from the Game (Figure 2.8), which showed minimal increases in frontal cortices and primary sdTheta originating from the right inferior temporal cortex (inferior temporal gyrus, mid temporal gyrus, fusiform gyrus; t_{max} = 5.65). The only other task to show significant sdTheta in these regions, to a lesser extent, was the LAT (inferior temporal gyrus, t = 2.99).

Overall, the majority of sdTheta occurred in medial and superior frontal cortices, with a right lateralization. LAT and STM were the most widespread in the source space (Figure 2.8; 39% and 35% of significant voxels, respectively), the Game, Music, and PVT intermediate (28%, 27%, 25%), and Speech the least (9%). While most sdTheta sources were frontal, there were substantial differences between tasks. The high theta from the supplementary motor area in the Music task and in the inferior temporal cortex in the Game suggests a preference of sdTheta for cortical areas not critical for the ongoing behavioral task.

[1] *In hindsight, this higher frontal gyrus theta might reflect changes in oscillation amplitude (and synaptic strength with sleep pressure) more than task-specific changes in the quantities of oscillations, since it's in common across tasks (next paper).*

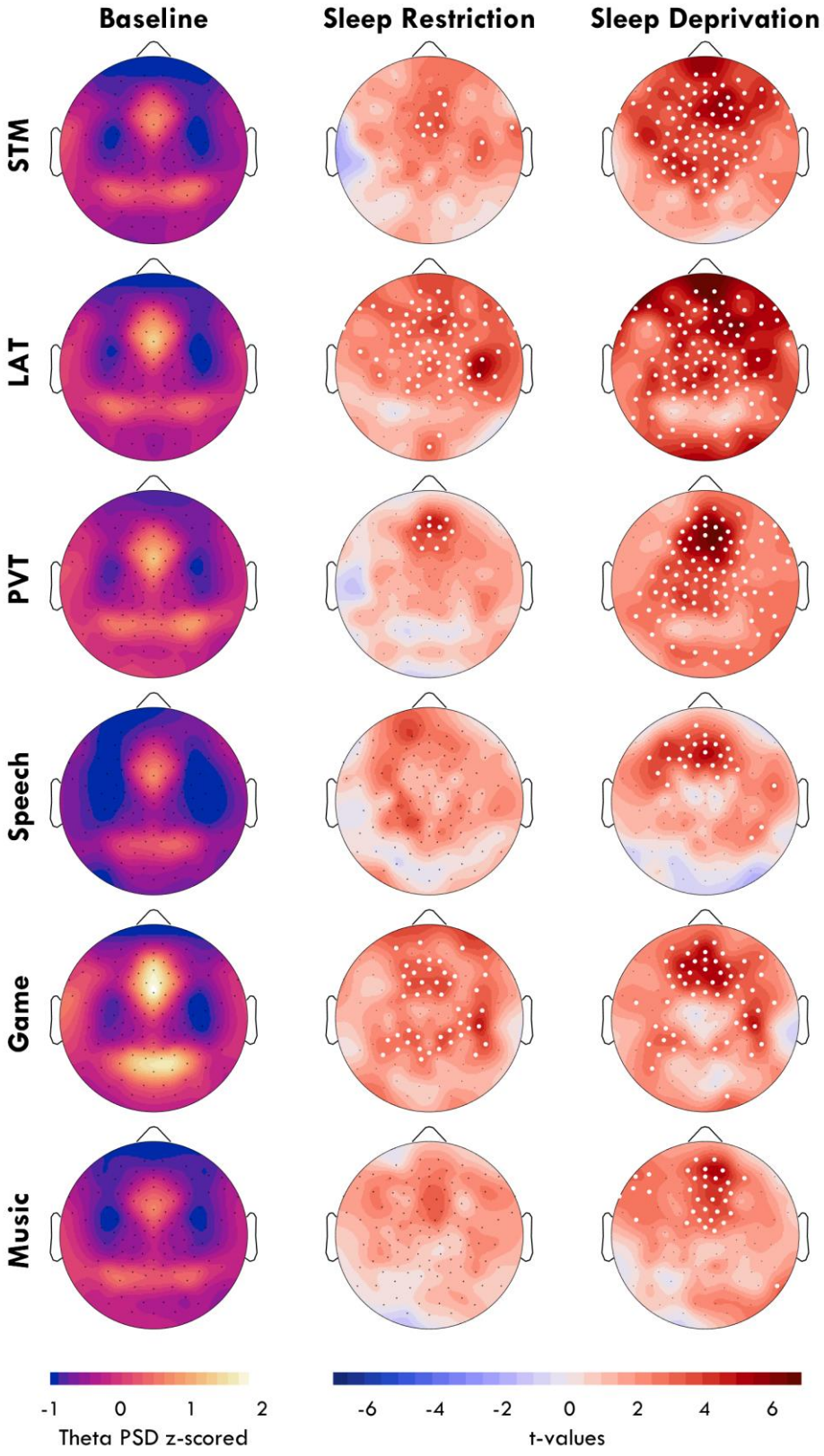

Figure 2.7: Theta sleep deprivation topographies by task. First column: mean z-scored theta power topographies at BL. Second & third column: the change in theta power from BL to SR and SD, respectively. Color indicates t-values, with red indicating an increase relative to BL. Black dots indicate all channels, white dots indicate channels in which the change was statistically significant (p-value < .05), FDR corrected for multiple comparisons.

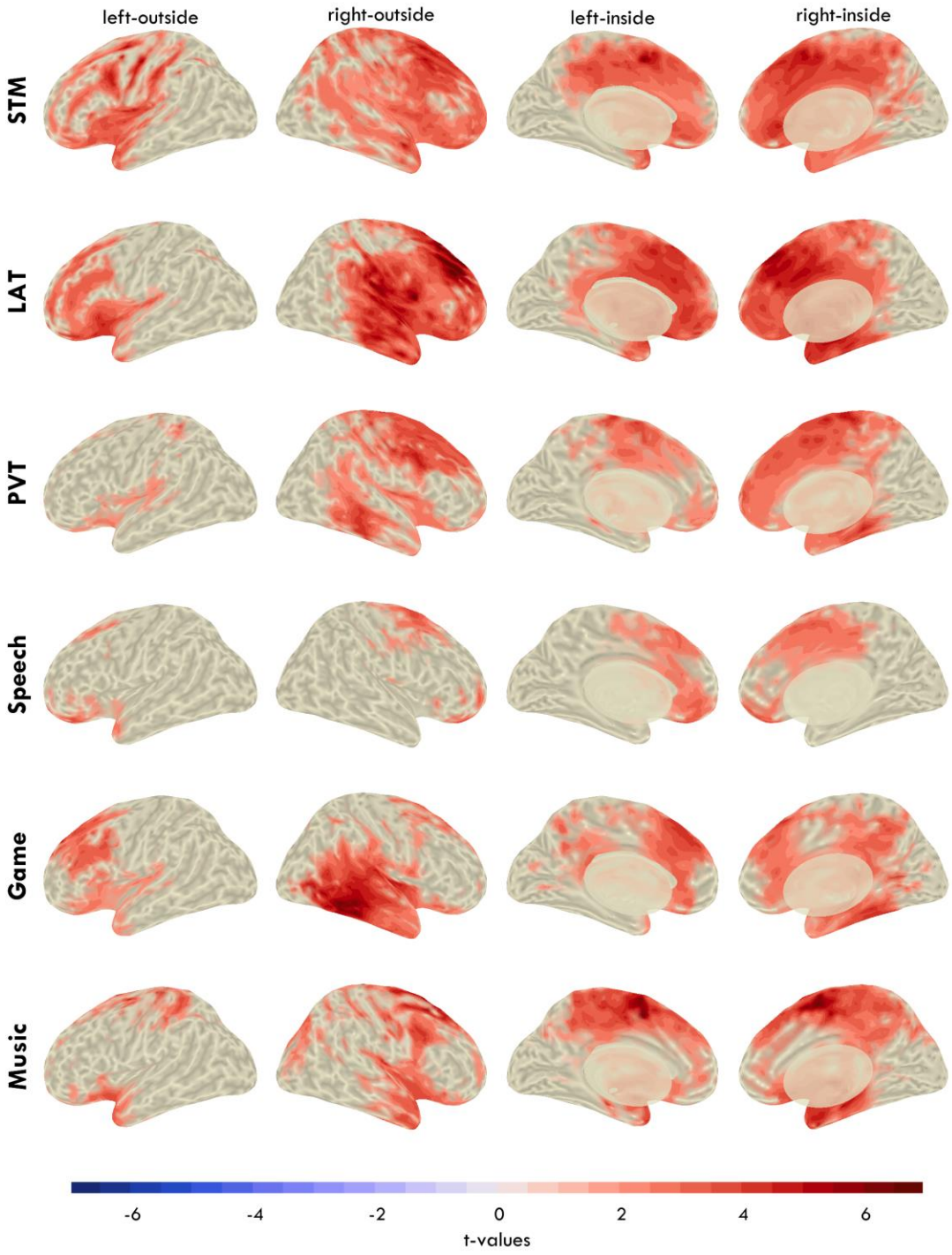

Figure 2.8: Change in theta from BL to SD in the source space projected on inflated brains. Color indicates t-values, such that red indicates an increase in power from BL to SD. Voxel-wise cluster correction was implemented to mask non-significant effects. Figure 2.21 illustrates the analysis pipeline for the source localization.

	STM	LAT	PVT	Speech	Game	Music	fmTheta	sdTheta
Precentral L	2.55	0.55	0.32	-0.11	0.07	2.35	-2.17	1.51
Frontal Sup R	5.45	6.07	4.34	3.53	3.19	4.91	2.48	5.94
Frontal Sup Orb L	2.96	4.50	1.99	2.65	2.45	2.20	3.97	3.80
Frontal Sup Orb R	3.35	5.00	2.77	3.03	2.87	2.70	2.88	3.53
Frontal Mid R	5.99	4.80	3.66	1.61	1.48	2.79	1.34	6.95
Frontal Mid Orb L	2.20	3.17	1.11	1.46	1.72	0.68	2.90	3.06
Frontal Mid Orb R	3.29	2.87	1.86	1.62	0.48	2.10	2.29	3.12
Frontal Inf Oper L	3.21	1.88	0.70	1.14	2.23	0.11	0.77	3.35
Frontal Inf Oper R	4.36	4.06	3.49	1.72	1.79	3.40	0.91	4.41
Frontal Inf Tri L	2.42	2.61	1.67	0.99	2.22	-0.23	3.20	2.75
Frontal Inf Tri R	2.71	3.64	2.00	0.99	1.02	1.15	1.39	3.33
Frontal Inf Orb L	2.99	3.23	1.84	2.07	2.37	1.21	2.51	3.16
Frontal Inf Orb R	3.44	3.78	2.23	2.31	2.04	2.33	2.35	4.00
Rolandic Oper L	4.68	0.93	1.75	0.35	0.74	0.99	-0.11	4.12
Rolandic Oper R	2.71	5.56	1.93	2.08	2.90	2.03	0.81	2.76
Supp Motor Area L	3.13	3.96	4.70	2.35	2.20	6.54	0.69	4.80
Supp Motor Area R	2.72	4.17	4.96	2.75	2.74	4.77	0.59	4.51
Olfactory L	3.43	4.06	2.52	1.69	2.22	4.01	3.23	3.84
Olfactory R	3.71	4.60	2.55	1.68	2.61	3.78	2.35	3.70
Frontal Sup Medial L	2.85	4.70	2.15	2.27	3.89	3.71	4.06	3.78
Frontal Sup Medial R	2.22	4.90	2.71	1.65	3.72	3.70	3.33	3.51
Frontal Med Orb L	1.92	3.16	2.18	1.47	1.47	1.79	3.59	2.52
Frontal Med Orb R	3.02	3.76	2.92	1.75	2.32	2.52	3.00	3.29
Rectus L	4.15	4.42	2.14	3.14	3.34	2.75	3.15	4.35
Rectus R	4.12	4.16	2.57	2.18	2.57	3.24	2.51	4.09
Insula L	4.42	3.18	2.63	1.51	2.59	1.36	1.49	4.58
Insula R	3.14	4.96	2.66	2.03	3.03	3.32	2.42	3.33
Cingulum Ant L	3.45	5.15	2.56	3.05	4.29	3.03	4.76	4.13
Cingulum Ant R	3.66	5.56	3.36	2.01	3.21	3.23	3.07	4.21
Cingulum Mid L	3.92	3.72	3.40	2.10	2.48	5.57	-0.17	5.14
Cingulum Mid R	3.70	3.72	3.70	3.05	3.05	5.30	0.72	5.08
Cingulum Post L	2.45	2.05	1.67	0.80	2.91	2.34	-1.28	3.89
Cingulum Post R	3.04	1.82	1.73	1.46	2.97	3.53	-0.88	3.63
Hippocampus R	3.30	4.02	3.42	1.08	4.00	3.48	0.92	2.73
ParaHippocampal R	2.98	5.06	3.45	0.74	3.44	4.50	1.24	2.98
Cuneus R	0.85	-0.10	-0.04	0.79	0.95	2.34	-1.82	2.42
Occipital Sup R	1.46	0.46	0.12	1.33	1.67	2.52	-1.10	2.74
Occipital Mid R	1.56	-0.66	-0.28	0.78	1.59	3.05	0.23	0.80
Fusiform R	2.02	2.91	2.75	1.89	4.75	2.02	0.24	2.18
Postcentral L	1.23	-0.14	0.68	-0.33	0.54	3.12	-3.02	1.33
SupraMarginal R	2.92	3.28	2.23	1.22	2.06	0.76	-1.60	1.78
Precuneus L	2.41	0.84	1.07	0.51	1.84	1.72	-1.45	3.80
Precuneus R	2.82	1.05	1.54	0.94	1.90	2.67	-2.50	3.65
Paracentral Lobule L	1.75	3.37	2.89	1.74	1.39	4.37	-0.26	2.40
Paracentral Lobule R	1.54	2.14	1.93	1.21	1.07	3.15	-0.95	2.58
Heschl L	2.81	2.99	2.73	0.93	2.09	2.04	-0.40	2.48
Heschl R	2.34	6.01	2.08	1.60	3.65	2.59	0.59	1.95
Temporal Sup L	2.59	1.90	2.06	0.69	1.67	1.63	-0.61	2.57
Temporal Sup R	2.77	4.85	1.86	1.74	4.08	1.61	0.48	2.35
Temporal Pole Sup L	3.89	3.62	2.09	2.72	2.25	3.35	2.49	3.46
Temporal Pole Sup R	3.12	3.95	2.00	0.89	2.73	3.58	1.66	3.35
Temporal Mid R	2.24	2.89	2.78	1.96	4.93	1.11	1.11	2.36
Temporal Pole Mid L	3.88	3.31	1.50	1.99	2.64	3.51	2.36	3.00
Temporal Pole Mid R	3.25	4.38	2.67	1.16	2.94	3.43	1.51	3.67
Temporal Inf R	1.74	2.99	2.97	2.20	5.65	1.40	1.81	1.96

Figure 2.9: T-values of the change in theta by anatomical source. Only areas with at least one significant test (BL vs SD in all tasks; L3 vs L1 from fmTheta and L1 BL vs L1 SD for sdTheta in the STM) are included. Text in gray indicates areas not significant after FDR correcting for multiple comparisons. Text in white indicates the top 10% of t-values in the whole table.

Figure 2.7, left column, illustrates how the average theta power at baseline more resembles fmTheta (Figure 2.4A I), especially for the Game, than it does sdTheta within tasks. This suggests that sdTheta occurs in addition to task-related fmTheta found at BL. In order to determine whether sdTheta could be further distinguished from this baseline fmTheta, we inspected the spectrograms of the different tasks for all participants. In particular, we were interested in whether tasks with high frontal BL theta showed an additional distinct peak in the theta range following sleep deprivation. This would support the hypothesis of theta during sleep deprivation as a separate oscillation from task-related, baseline fmTheta.

Paired t-tests between BL and SR/SD z-scored power spectrums confirmed that the effect of sleep deprivation was specific to the theta range, resulting in a prominent peak in the average SD Front ROI spectrum for all tasks (Figure 2.10). However when inspecting individual participants' spectrums, sdTheta often did not occupy a single consistent peak within or across individuals (Figure 2.11). Instead, individuals' peaks were spread over the entire theta range, often with multiple smaller peaks within the same participant. Furthermore, the maximum peak frequency for a given participant was not consistent across tasks (Figure 2.12A-B).

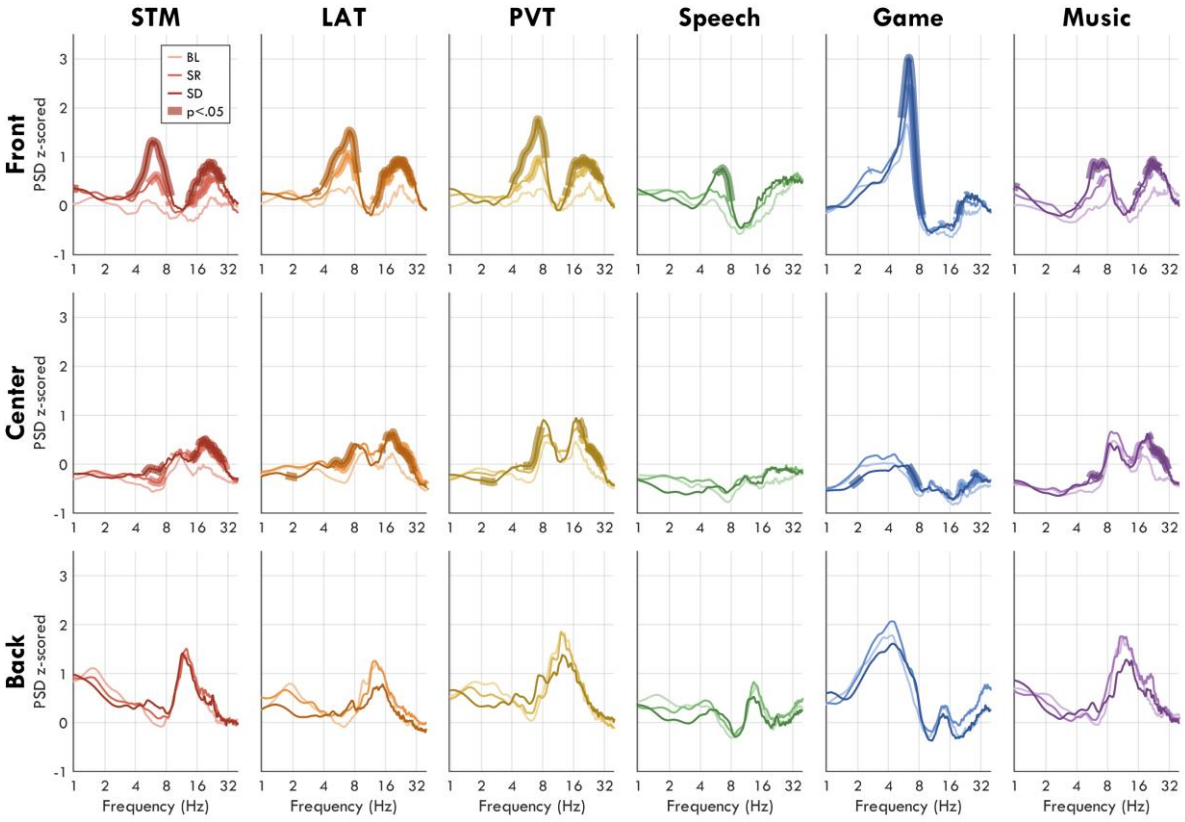

Figure 2.10: Average z-scored power spectrums from each ROI for each task. Thin lines indicate the spectrum at each session, averaged across participants. Thick lines indicate statistically significant changes (paired t-tests, p-value < .05, FDR corrected) for a given frequency relative to BL. The frequency axis is log-transformed. The y-axis represents power spectral density, z-scored. N.B.: while there is an increase of both theta and beta (15-25 Hz) with sleep deprivation, the lack of increase in the delta (1-4 Hz) and alpha (8-12 Hz) ranges indicate that the spectral changes are not due to broadband increases.

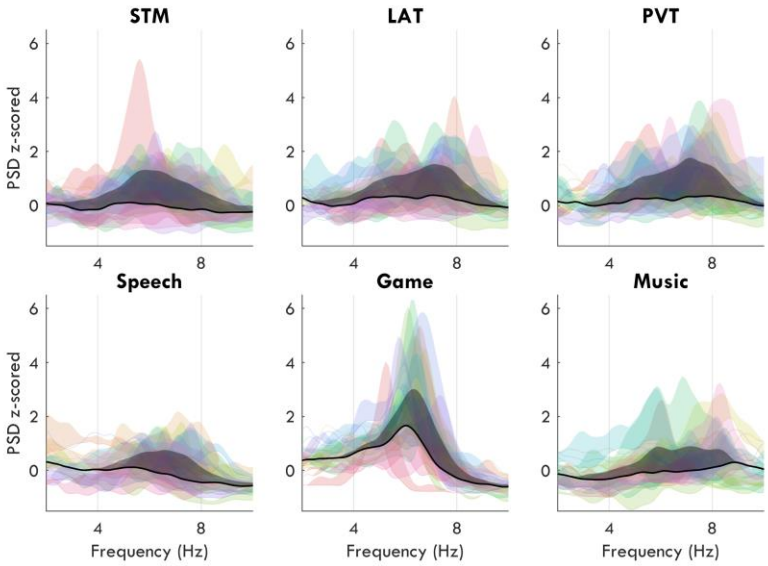

Figure 2.11: Z-scored power spectrums from the front ROI for each task. Overlapping spectrums from the Front ROI of each task for every participant. The base curve of each colored patch represents the BL spectrum, the upper curve the SD spectrum, and the filled-in area reflects the increase in power. The average power change across participants is the final patch in black. Figure 2.22 provides the uncorrected spectrums.

The exception was the Game, which showed the overall highest amplitude frontal theta as well as the most clearly defined peak both during BL and SD (Figure 2.12C-D), with prominence values (calculated as the difference in z-scores between the maximum theta amplitude and the closest trough in the spectrum) of 1.72 ± 1.14 (MEAN ± STD) at BL and 2.94 ± 1.88 at SD. By contrast, the STM task had a prominence of 0.33 ± 0.27 at BL, and 0.71 ± 0.94 at SD. Unexpectedly, the STM task had low BL frontal theta, similar to Speech and Music (Figure 2.6D).

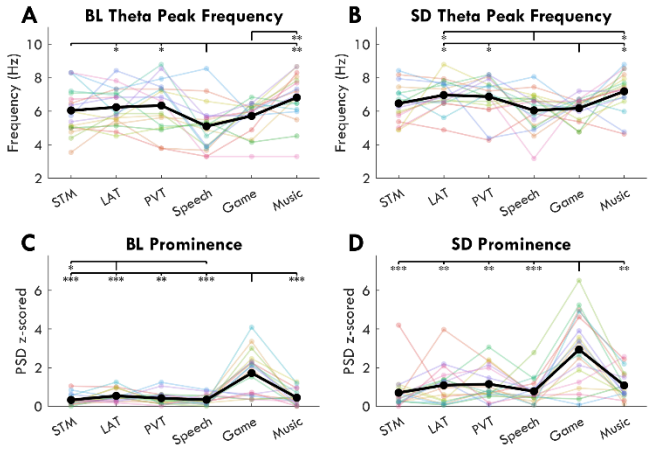

Figure 2.12: Prominence and peak frequency of z-scored power spectrums from the Front ROI. Each color represents a different participant, the black line indicates the average. Asterisks indicate significant differences from paired t-tests between tasks, FDR corrected, such that: * p-value < .05, ** p-value < .01, *** p-value < .001. **A-B**: The highest amplitude peak in the 3-9 Hz range. **C-D**: Prominence refers to the amplitude difference between the highest peak and the closest trough to that peak within a 3-9 Hz range.

Due to the clear presence of fmTheta at BL in the Game, we considered this task to be the most likely to show both an fmTheta peak and an sdTheta peak during SD. The BL peak frequency was significantly different from the SD peak frequency, increasing from 5.7 ± 1.0 Hz to 6.4 ± 0.5 Hz ($t_{(17)}$ = 2.62, p = .018, g = 0.84). For reference, the STM peak was 6.0 ± 1.4 Hz at BL, and 6.4 ± 0.7 Hz at SD, but the increase was not statistically significant ($t_{(17)}$ = 0.87, p = .397, g = 0.30). However, as can be seen in the individual Game spectrums in Figure 2.11, only a single peak is present for most participants, with the baseline theta peak merely shifted in frequency and increased in amplitude during SD. Multiple peaks were instead found in

all other tasks during SD, which may indicate a multitude of different theta oscillations not found in the Game.

Visual inspection of the EEG data provided further insight into task-related theta differences. At BL, fmTheta bursts as described by Mitchell et al. (2008) were visible primarily in the Game task (Figure 2.13A) in 11 individuals. These were frontal midline bursts that lasted 1-5 s with amplitudes around 15-20 µV. No other types of prominent theta oscillations were similarly detectable by visual inspection in any task at BL (best example, Figure 2.13C). During SD, fmTheta became even more prominent in the Game EEG (Figure 2.13B), with higher amplitudes and longer bursts, appearing for 13 participants and increasing in other tasks as well. In addition to fmTheta, widespread bursts often with frontal peaks appeared during sleep deprivation especially in the LAT and STM (Figure 2.13D). These had a much shorter duration (2-3 oscillations), but with a higher peak amplitude (> 40 µV). As can be seen from the spectrums (Figure 2.13 II), Game theta bursts yielded narrow-band theta power, whereas the LAT bursts had more widespread spectrums. These examples support an interpretation of at least 2 types of oscillations in the theta range that increase with sleep deprivation.

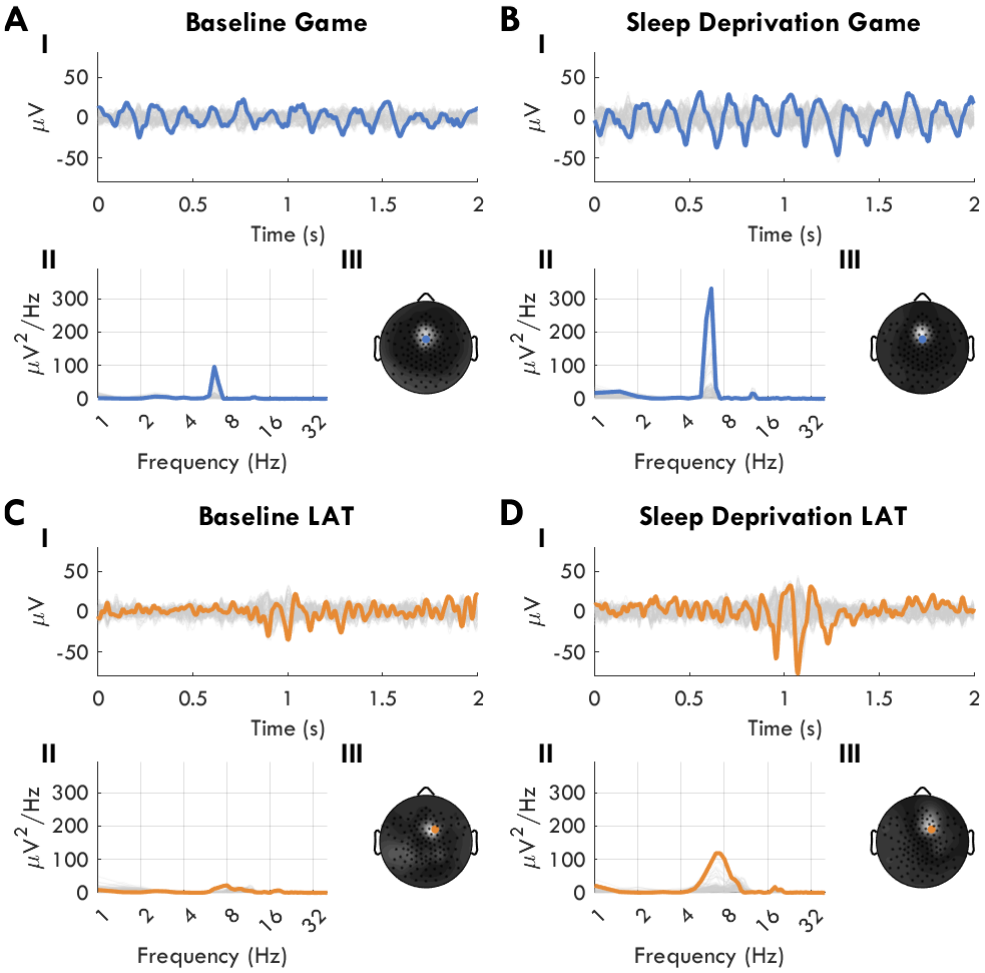

Figure 2.13: Examples of theta bursts. Taken from the same participant during BL (**A, C**) and SD (**B, D**), and from the Game (A, B) and the LAT (C, D). **I**: EEG data in time, amplitude in microvolts. All channels are represented in gray, and the channel expressing the highest theta in color. **II**: Power spectrums of all channels in gray, and peak theta channel in color. X-axis is log-transformed. **III**: Average theta power mapped across all channels from the 2 s shown in I. The scale is normalized for each plot separately to the min-max. Colored dot indicates the same channel highlighted in I and II (ch6 for Game, ch118 for LAT).

2.4.5 Short-term memory performance does not relate to either fmTheta or sdTheta

Given that the presence of sdTheta and fmTheta are dependent on the ongoing task, we wished to explore whether there was a relationship between theta and behavioral outcomes. If fmTheta is functionally relevant, or if sdTheta is a form of local sleep, then the changes in theta across individuals should correlate with the extent of behavioral deficits.

Maurer et al. (2015) found that the increase in fmTheta with short-term memory load was negatively correlated with the change in accuracy, such that the more fmTheta, the worse participants performed with increasing load. We did not replicate this correlation for either the first retention epoch ($r_{(16)}$ = -.05, p = .850) nor the second ($r_{(16)}$ = -.30, p = .233).

Before determining whether there was any correlation between STM performance and sdTheta, we evaluated whether there was an effect of sleep deprivation on performance using a 2-way rmANOVA with factors *session*, *level*, and their interaction. We found no effect of session ($F_{(2, 34)}$ = 0.45, p = .636, η^2 = .002), a very large effect of level ($F_{(2, 34)}$ = 275.68, p < .001, η^2 = .717), and no significant interaction ($F_{(4, 68)}$ = 0.43, p = .717, η^2 = .001). Performance accuracy across sessions is provided in Figure 2.14A.

Despite the lack of an effect of sleep deprivation on STM accuracy, we still performed correlations between the change in performance for each memory load level and the change in theta power from BL to SD for the three ROIs. Neither the Front (L1: $r_{(16)}$ = -.04, p = .862; L3: $r_{(16)}$ = -.02, p = .935; L6: $r_{(16)}$ = -.13, p = .605), Center (L1: $r_{(16)}$ = -.06, p = .810; L3: $r_{(16)}$ = -.14, p = .585; L6 $r_{(16)}$ = -.08, p = .749) nor Back ROI (L1: $r_{(16)}$ = -.15, p = .542; L3: $r_{(16)}$ = -.37, p = .128; L6: $r_{(16)}$ = -.30, p = .231) showed significant correlations between the difference in theta and the difference in behavior. Therefore, short-term memory performance accuracy was not related to either fmTheta or sdTheta.

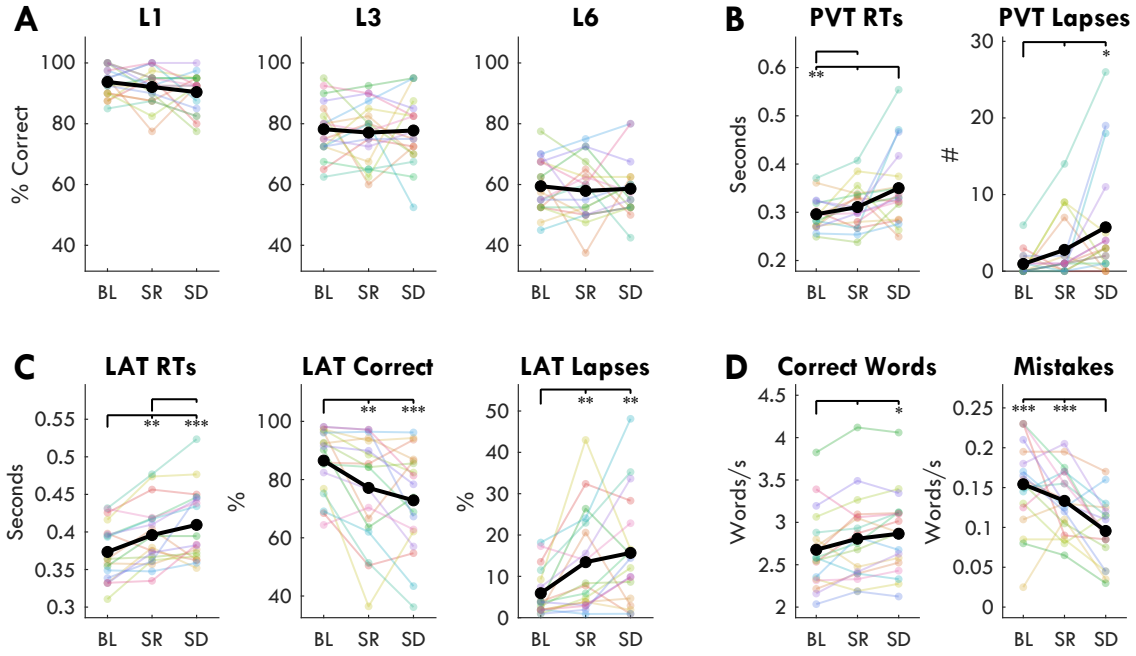

Figure 2.14: Task performance. A: STM recall accuracy for every memory load level (1, 3, 6) at every session. The y-axis indicates percentage of correctly identified probes (both true positives and correct rejections). Thin lines indicate individual participants, thick lines indicate the mean. Chance level was 50%. No level showed a significant change

from BL. **B**: PVT performance. Left: mean reaction times (RT) in seconds. Right: number of trials for which the RT > 0.5 s. **C**: LAT performance. Left: mean RTs. Middle: percentage of trials for which the RT was between 0.1 s and 0.5 s (i.e., while the stimulus was still visible). Right: percentage of trials for which no response was given. **D**: Speech Fluency Task performance. Left: rate of correct words per second across sessions. Right: rate of mistaken words per second across sessions. Asterisks indicate significant differences from paired t-tests between sessions, FDR corrected, such that: * p-value < .05, ** p-value < .01, *** p-value < .001. Figure 2.23 highlights the performance for the 4 participants who conducted the baseline after the sleep deprivation bout.

2.4.6 Behavioral performance is not directly related to the increase in sdTheta

In rats, local sleep events were found to result in behavioral lapses in a reaching task (Vyazovskiy et al., 2011). Therefore, we expected that an increase in response lapses in the PVT and LAT would correlate with increases in theta. More generally, to determine whether the occurrence of sdTheta could affect any behavioral measure, we first established which outcome measures changed significantly with sleep deprivation (Figure 2.14, Figure 2.15A), and then correlated the change from BL to SD for each performance measure with the change in theta from BL to SD for each ROI.

STM performance accuracy for all three memory load levels were the only measures which did not show a statistically significant change with sleep deprivation (as anticipated by the previously described 2-way ANOVA). The PVT (Figure 2.14B) and LAT (Figure 2.14C) showed a worsening of performance with increased reaction times (PVT: $t_{(16)} = -3.45$, $p = .003$, $g = 0.84$; LAT: $t_{(17)} = -4.51$, $p < .001$, $g = 0.80$) and increased number of lapses (PVT: $t_{(16)} = -2.94$, $p = .010$, $g = 0.84$; LAT: $t_{(17)} = -4.44$, $p < .001$, $g = 0.93$), consistent with the literature (Basner & Dinges, 2011). The Speech task (Figure 2.14D) unexpectedly showed a significant reduction in the number of mistakes ($t_{(17)} = 4.81$, $p < .001$, $g = -1.17$) and an increase in words per minute ($t_{(17)} = -3.16$, $p = .006$, $g = 0.39$). N.B. these two variables were not significantly correlated between each other ($r_{(16)} = -.37$, $p = .129$) although they both showed improvement with sleep deprivation.

The PVT has previously been shown to be unaffected by task repetition (Basner et al., 2018), and the outcome measures of both the PVT and LAT performed under soporific conditions in this experiment all returned to baseline following recovery sleep (data not shown). Similarly, the STM task has also been shown to be unaffected by task repetition (Habeck et al., 2004), albeit with two repetitions instead of three. Therefore, the behavioral changes in the Speech task are the only ones that may have been affected by learning.[1]

To determine whether any of these behavioral changes in performance (both positive and negative) were related to sdTheta, we correlated each measure with the change in untransformed theta power for each ROI during the first 4 minutes of the respective tasks. A significant correlation was found between the decrease in number of Speech mistakes per minute and the increase in frontal theta ($r_{(16)} = -.53$, $p = .025$), as well as number of correct words per minute ($r_{(16)} = .54$, $p = .023$), such that the more participants improved, the more theta they had. The increase in mean reaction times (RTs) of the fastest 10% of responses of the PVT was positively correlated with the increase in theta over the Back ROI ($r_{(15)} = .54$, $p = .027$). No other performance measure showed a significant correlation with sdTheta of the same task.

In a previous sleep deprivation study, Gorgoni et al. (Gorgoni et al., 2014) also found a positive correlation between the increase in the mean of the fastest 10% of PVT RTs with increases in centro-posterior theta power. However, theta was measured during a separate resting EEG, recorded just prior to the task.

[1] *This is a good example of why tasks with a learning component doesn't work for repeated measures.*

Inspired by this, we then correlated all of our behavioral outcome measures with sdTheta in *all* tasks, for each ROI (Figure 2.15B). No correlation between behavioral outcome measure and sdTheta survived FDR correction for multiple comparisons, including the within-task ones previously described. We therefore provide the correlations with uncorrected p-values and limit ourselves to cautious interpretations.

Similar to Gorgoni et al. for the PVT, we found significant positive correlations for the increase in fastest 10% RTs also with the LAT sdTheta (Front: $r_{(15)} = .65$, $p = .006$, Center: $r_{(15)} = .69$, $p = .003$, Back: $r_{(15)} = .58$, $p = .016$) and Music sdTheta (Back: $r_{(15)} = .55$, $p = .025$). Significant correlations were additionally found with the LAT sdTheta and mean PVT RTs (Center: $r_{(15)} = .52$, $p = .034$, Back: $r_{(15)} = .54$, $p = .027$) and median RTs (Center: $r_{(15)} = .61$, $p = .010$, Back: $r_{(15)} = .50$, $p = .041$), as well as with Back Music sdTheta and mean RTs ($r_{(15)} = .57$, $p = .019$), median RTs ($r_{(15)} = .51$, $p = .038$), and lapses (Back: $r_{(15)} = .50$, $p = .043$).

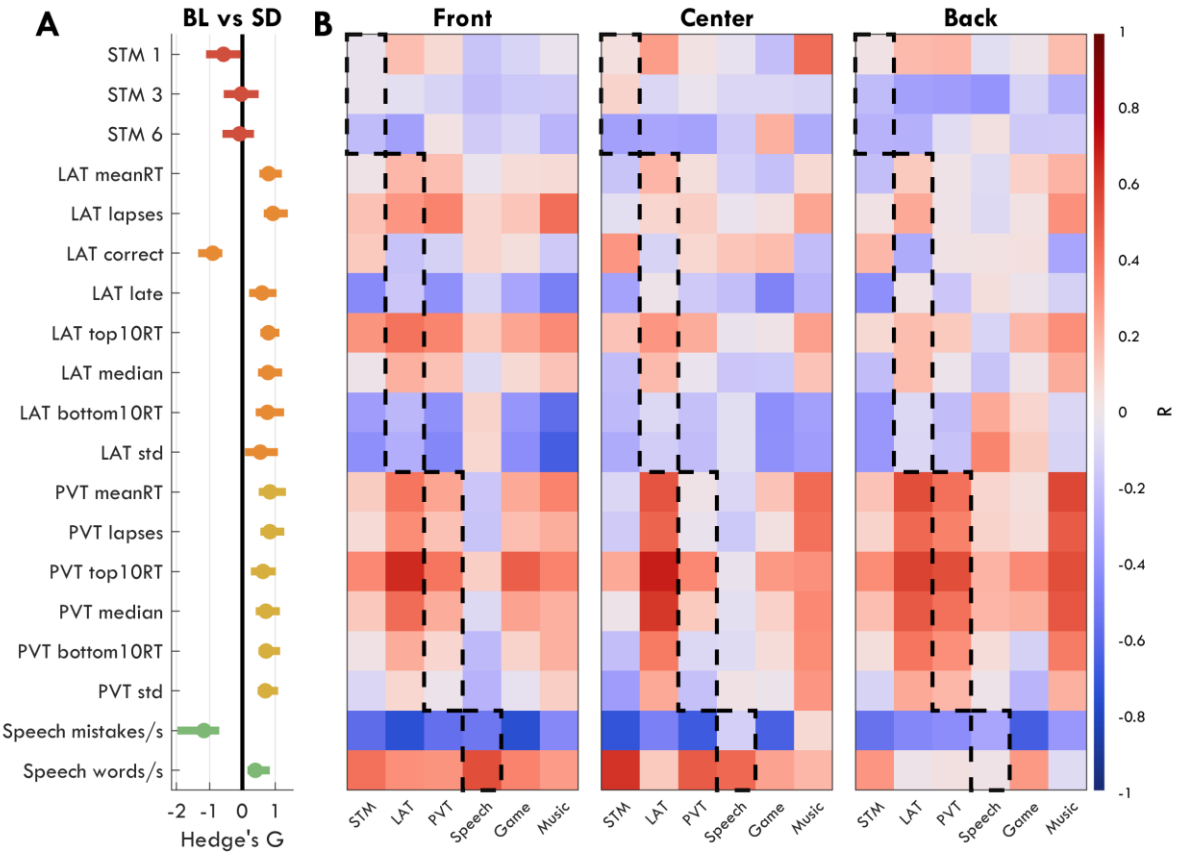

Figure 2.15: Correlations between changes in behavioral performance and changes in theta for each ROI. **A**: Hedge's g effect sizes for paired t-tests comparing BL to SD for each behavioral outcome measure. Bars indicate 95% confidence intervals. Positive values indicate an increase in that outcome measure from BL to SD. **B**: R-values for each pairwise correlation between behavioral measure and theta power for each task for each ROI. Comparisons within the same task are outlined with a dotted edge. Red in-dicates positive correlations, blue indicates negative. N.B. the R values within the dotted line are not higher than outside it.

Notably, despite robust decreases in LAT performance with sleep deprivation (Figure 2.15A), no outcome measure was significantly correlated with LAT sdTheta. Instead, significant negative correlations were found between Front Music and LAT late responses ($r_{(16)} = -.49$, $p = .041$), the slowest 10% of RTs ($r_{(16)} = -.57$, $p = .015$), and the standard deviation of RTs ($r_{(16)} = -.66$, $p = .004$).

Finally, the reduction in mistakes in the Speech task was significantly negatively correlated with Front sdTheta in all tasks except trending in Music (STM: $r_{(16)} = -.58$, $p = .012$; LAT: $r_{(16)} = -.73$, $p = .001$; PVT: $r_{(15)} = -.57$, $p = .017$, Speech: $r_{(16)} = -.53$, $p = .025$; Game: $r_{(16)} = -.74$, $p < .001$; Music: $r_{(16)} = -.44$, $p = .067$), and to a lesser extent significant in the Center ROI for sdTheta in the STM, LAT, and Game, and Back sdTheta in the STM and Game. Notably, the correlations between mistakes and theta were higher for the STM, PVT and Game than for the Speech sdTheta itself. The increase in Speech words per minute was positively correlated with sdTheta in the Speech (Front: $r_{(16)} = .54$, $p = .023$), STM (Center: $r_{(16)} = .63$, $p = .007$), and PVT (Center: $r_{(15)} = .50$, $p = .045$).

Overall, these results show that behavior and sdTheta can correlate but not necessarily, nor even especially, within the same task. While none of these correlations survive correction for multiple comparisons, the absence of a clear preference for within-task correlations is indicative.

2.5 Discussion

In the literature, there exists two opposing interpretations of theta oscillations: one posits that they reflect cognition, the other that they reflect sleep pressure and possibly even local sleep. With this study, we investigated whether this paradox could be resolved by the existence of separate oscillations in the theta band. Our results clearly indicate that theta caused by sleep deprivation is not strictly a manifestation of classic fmTheta because: A) their primary sources are in different cortices, namely the right superior frontal gyrus for sdTheta and the left anterior cingulate cortex for fmTheta; and B) sdTheta is present in a broader subset of areas (Figure 2.4).

Despite these differences in sources, we did not find evidence of the simultaneous occurrence of sdTheta and fmTheta during the short-term memory task performed under sleep deprivation (Figure 2.5), nor distinct theta peaks in EEG power spectrums (Figure 2.11) which would have further supported an interpretation of two independent oscillations. In Vyazovskiy and Tobler (2005), sdTheta in rats was at a lower frequency than the wake hippocampal theta rhythm (5.5 Hz vs 7.5 Hz), with both peaks present during sleep deprivation. This was not replicated in our Game condition where only a single theta peak was present during sleep deprivation, despite a strong, slower, baseline fmTheta (Figure 2.6D). Rather than a separate, additional spectral peak, it appears that fmTheta itself increased in amplitude with sleep deprivation.

For all other tasks, sdTheta occupied a broad range with multiple peaks (Figure 2.11). This can be explained by the different waveforms visually identified (Figure 2.13): long steady trains of theta in the Game, and high amplitude irregular short bursts in other tasks. These morphological differences make the theta trains comparable to occipital alpha bursts, and the short bursts more comparable to isolated slow waves in sleep. This could mean that sleep deprivation in humans induces two types of changes in theta: an increase in fmTheta when already present at baseline, and the appearance of local sleep.

An alternative, simpler explanation is that theta may reflect the same mechanism during both cognition and sleep deprivation, regardless of waveform. Simultaneous EEG-fMRI studies previously found that fmTheta originating from the medial prefrontal cortex corresponds to BOLD deactivations in these areas (Scheeringa et al., 2008, 2009). Our source localization of sdTheta across the different tasks also suggests that these oscillations may be a marker for cortical areas *not in use*.

First, we found high sdTheta activity in the bilateral (but especially left) supplementary motor area in the Music listening condition. It is compelling that the one task not requiring movement showed such strong

theta activity in brain areas involved in complex motor planning (Goldberg, 1985). The PVT also showed strong activity in bilateral supplementary motor areas, which may seem contradictory. However, the PVT required simply pushing a button after a very obvious stimulus appeared; this is a reflexive response with little need for deliberative action. By contrast the LAT, which had identical motor requirements but difficult to detect stimuli, despite otherwise widespread high-amplitude theta, showed less activity in the supplementary motor areas than the PVT (Figure 2.9). Supporting this distinction between reflexive and deliberative action, mean reaction times of the LAT were ~20% slower than during the PVT (Figure 2.14B-C), despite identical task requirements (respond within 0.5 s). Vice versa, supplementary motor area activity did not significantly increase in the Speech or Game, two tasks characterized by deliberative motor control.

Second, high sdTheta was found in the right inferior temporal cortex in the Game, extending all the way to the fusiform gyrus. These areas collectively form the *ventral visual pathway* responsible for object recognition (Ishai et al., 1999). This is in opposition to the *dorsal visual pathway* running from the occipital cortex to dorsal parietal areas such as the supramarginal gyrus and parietal sulcus, where object location is processed (Freud et al., 2016). The Game was almost exclusively a spatial task, requiring participants to map out a target path for a bouncing ball. The only other task to show significant theta activity in the inferior temporal cortex was the LAT, a spatial attention task. Instead the STM, in essence an object recognition task, showed no significant increase in these areas (Figure 2.9).

One possible interpretation for theta in unused areas is that it has a role in *active* inhibition. Such a hypothesis has already been proposed for theta during cognition. Buzsáki in 1996 suggested that theta in the hippocampus could act as a low-energy solution to selective inhibition (Buzsáki, 1996; Thompson & Best, 1989), such that only neurons synchronized to fire at the correct phase of an ongoing oscillation would successfully transmit action potentials. The role of theta phases in inhibition was supported by phase-targeted closed loop stimulation in mice (Siegle & Wilson, 2014). It may therefore be the case that fmTheta and sdTheta in humans also reflect a low-energy active inhibitory state that conflicting brain networks enter to compensate for cognitive load and sleep deprivation, respectively.

Alternatively, theta could reflect *passive* cortical disengagement. In this scenario, an entire network or brain area ceases to receive inputs, and essentially goes in "standby." This is comparable to alpha oscillations in visual areas during eyes closed (Kirschfeld, 2005). An interpretation of theta as disengagement, more so than inhibition, would also explain theta activity occasionally found in NREM 1 (Santamaria & Chiappa, 1987), at the transition between wake and sleep. In essence, theta as inhibition would be a compensation mechanism for sleep deprivation, whereas theta as disengagement would be a consequence of sleep deprivation, bringing the brain closer to true sleep.

Regardless of whether theta reflects inhibition or disengagement, our behavioral results support the source localization finding that sdTheta occurs primarily in task-irrelevant areas. Despite large changes in performance with sleep deprivation across most outcome measures in the LAT, PVT, and Speech tasks (Figure 2.15A), these changes were not especially correlated with sdTheta in their respective tasks (Figure 2.15B). Equal or even larger correlations were found between changes in performance and sdTheta in *different* tasks (although without surviving FDR correction). Therefore, it is unlikely that the changes in behavior can be attributed to the occurrence of theta oscillations. As it is, these results suggest only a general relationship between the impact of sleep deprivation on performance and on theta.

The most unexpected finding was the decrease in mistakes during the Speech task, and subsequent anti-correlation with sdTheta in almost all tasks and all ROIs. To our knowledge, there is no prior study with

tongue twisters during sleep deprivation, however a study by Tucker et al. (2010) used a verbal fluency task in which participants had to come up with as many words as possible starting with a specific letter. The authors found both a practice effect and a sleep deprivation effect, such that *both improved* performance. While we cannot dissociate these effects in our data, we do see that of the four participants who did the baseline session after the sleep deprivation, two still showed notably higher performance during SD compared to BL, and two showed no change (Figure 2.23D). It is therefore possible that this speech task also improves with both repetition and sleep deprivation. A possible explanation could be that the more "sleep deprived" prefrontal control areas are, the less inhibited participants, especially non-native speakers, become. Alternatively, given that sdTheta is hypothesized to reflect plasticity and therefore ability to learn, the same interindividual differences in changes in theta with time awake could be reflected as individual differences in tongue-twister learning ability. More studies investigating the link between sdTheta and learning are needed to resolve this problem.

While our study offers unique insight into theta under different conditions, it also suffers limitations. First, the sessions were not conducted in counterbalanced order. While previous studies (Bernardi et al., 2015; Hung et al., 2013) have demonstrated sdTheta returns to baseline following recovery sleep, it is still possible that some of the effects we observe (e.g. disappearance of fmTheta with sleep deprivation) are a consequence or at least an interaction with task repetition. Furthermore, caution is needed when interpreting the source localization data, given the lack of structural MRIs and digitization of electrode positions. Finally, there are many other factors that can influence theta (fatigue, age, etc.), and fmTheta is not even the only manifestation of theta during cognition within a single task (Brzezicka et al., 2018; Pastötter & Bäuml, 2014). These results therefore cannot be generalized beyond classic frontal-midline theta as recorded from surface EEG. It is imperative to verify and expand these results with other experiments, analyses, and participant populations.

In conclusion, we do not provide a definitive resolution to the theta paradox but suggest three possible explanations for our results: 1) fmTheta and sdTheta are separate oscillations, but both can occur during sleep deprivation, maybe one as a compensation mechanism, the other as local sleep; 2) sdTheta is merely a more widespread form of fmTheta, and both reflect active cortical inhibition of task-irrelevant networks; 3) or both reflect passive cortical disengagement.

2.6 Supplementary material

2.6.1 Published supplementary figures

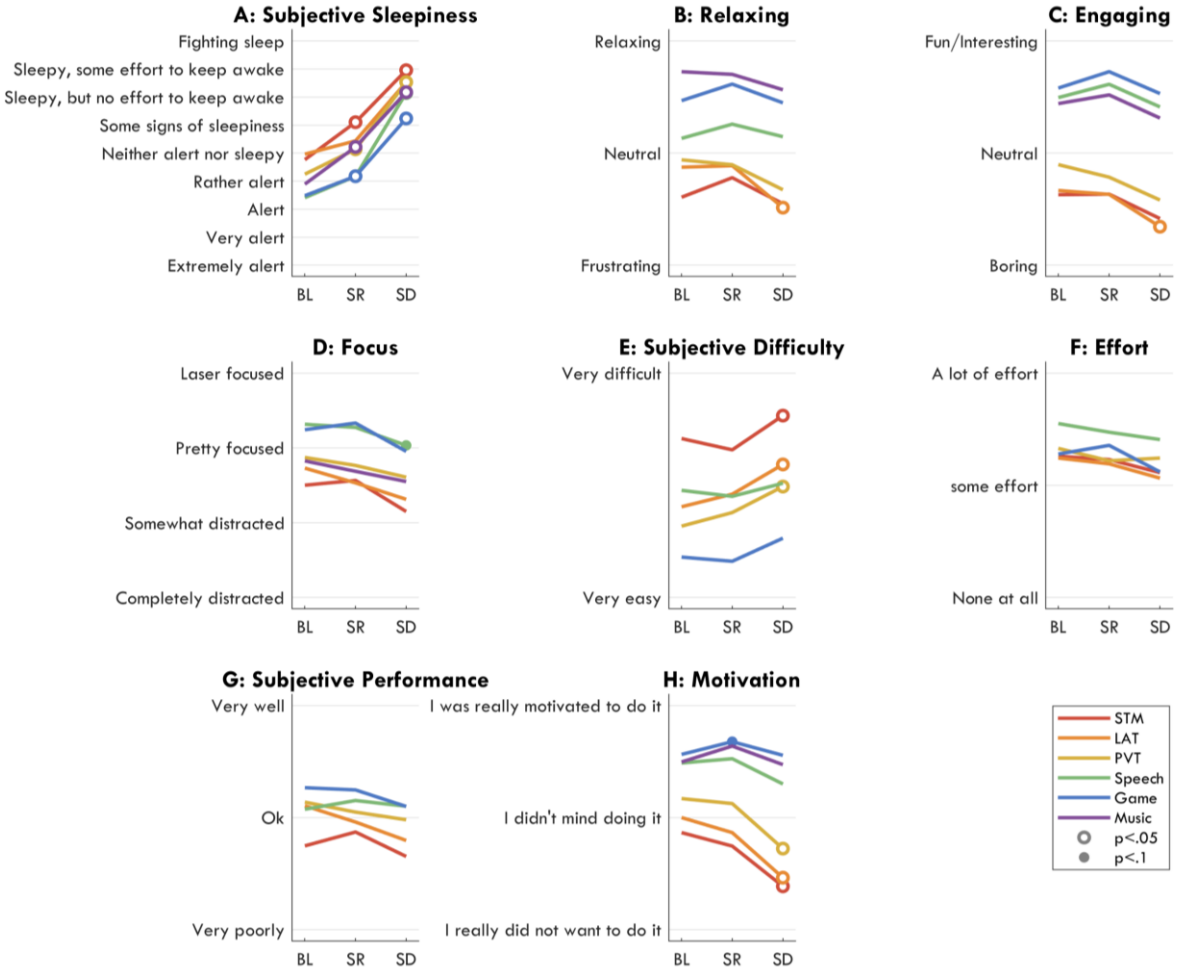

Figure 2.16: Questionnaire answers for each task. All answers were given on a ~10 cm slider with labels at specific intervals (indicated on the y-axis). White-filled circles indicate a significant change from BL, small colored circles a trend, FDR corrected. Each question was asked in this order. A 2-way rmANOVA was conducted for each question with factors session, task, and their interaction. Due to occasional missing data, not all analyses included every participant, therefore for each statistic, the degrees of freedom (subscript in $F_{(A, B)}$) indicate the sample size (N= B/A+1). No analysis had fewer than 16 participants, and the majority had all 18. **A**: "Please indicate your sleepiness right now." (Session: $F_{(2, 30)} = 35.42$, $p < .001$, $\eta^2 = .35$; Task: $F_{(5, 75)} = 14.7$, $p < .001$, $\eta^2 = .073$; Interaction: $F_{(10, 150)} = 0.96$, $p = .440$, $\eta^2 = .008$) **B**: "How did you experience this task? [Relaxing]" (Session: $F_{(2, 30)} = 5.13$, $p = .012$, $\eta^2 = .019$; Task: $F_{(5, 75)} = 41.97$, $p < .001$, $\eta^2 = .530$; Interaction: $F_{(10, 150)} = 1.11$, $p = .365$, $\eta^2 = .010$) **C**: "How did you experience this task? [Engaging]" (Session: $F_{(2, 30)} = 6.42$, $p = .015$, $\eta 2 = .027$; Task: $F_{(5, 75)} = 43.63$, $p < .001$, $\eta^2 = .548$; Interaction: $F_{(10, 150)} = 1.52$, $p = .191$, $\eta^2 = .010$) **D**: "How focused on the task were you?" (Session: $F_{(2, 30)} = 5.25$, $p = .016$, $\eta^2 = .039$; Task: $F_{(5, 75)} = 13.63$, $p < .001$, $\eta^2 = .235$; Interaction: $F_{(10, 150)} = 0.39$, $p = .853$, $\eta 2 = .006$) **E**: "How hard was it to perform this task?" (Session: $F_{(2, 30)} = 7.02$, $p = .006$, $\eta^2 = .038$; Task: $F_{(4, 60)} = 31.67$, $p < .001$, $\eta^2 = .426$; Interaction: $F_{(8, 120)} = 0.71$, $p = .585$, $\eta^2 = .008$) **F**: "How much effort did you put into performing this task? (Think about how much you tried to do well, and how much more you could have done)." (Session: $F_{(2, 28)} = 2.17$, $p = .139$, $\eta^2 = .022$; Task: $F_{(4, 56)} = 4.84$, $p = .015$, $\eta^2 = .114$; Interaction: $F_{(8, 120)} = 0.37$, $p = .838$, $\eta^2 = .006$) **G**: "How well do you think you did the task?" (Session: $F_{(2, 30)} = 2.02$, $p = .156$, $\eta^2 = .025$; Task: $F_{(4, 60)} = 8.96$, $p < .001$, $\eta^2 = .134$; Interaction: $F_{(8, 120)} = 1.04$, $p = .401$, $\eta^2 = .023$) **H**: "How motivated were you during the task?" (Session: $F_{(2, 20)} = 6.93$, $p = .021$, $\eta^2 = .070$; Task: $F_{(5, 50)} = 19.61$, $p < .001$, $\eta^2 = .381$; Interaction: $F_{(10, 100)} = 3.33$, $p = .020$, $\eta^2 = .04$).

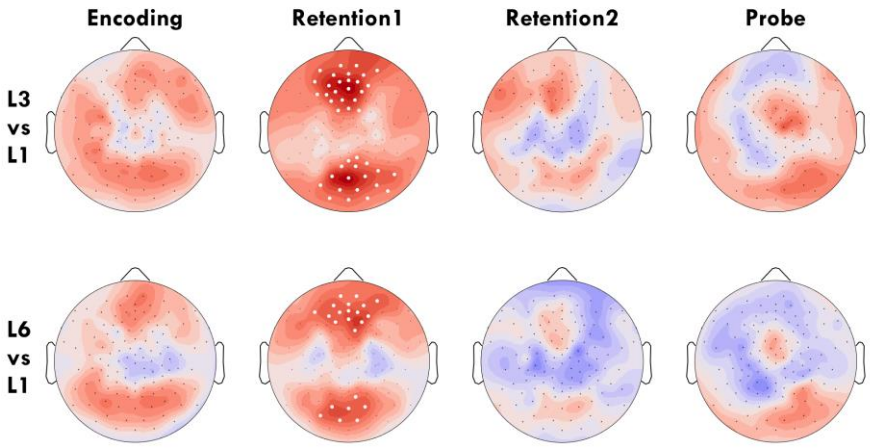

Figure 2.17: Difference in theta power topographies between levels at BL for every epoch of the STM task. Level 1 is compared to Level 3 (top row) and level 6 (bottom row) for each 2 s epoch. Encoding was when participants were viewing the items to memorize. Retention1 is the first half of the window in which participants had to hold the items in memory. Retention2 is the second half. Probe is when participants had to indicate whether a probe symbol was part of the original set. Participants' answers ended the probe window, therefore this 2 s epoch could also encompass some of the rest window that followed. The color scale is the same as in Figure 2.4, with red indicating an increase in theta relative to L1.

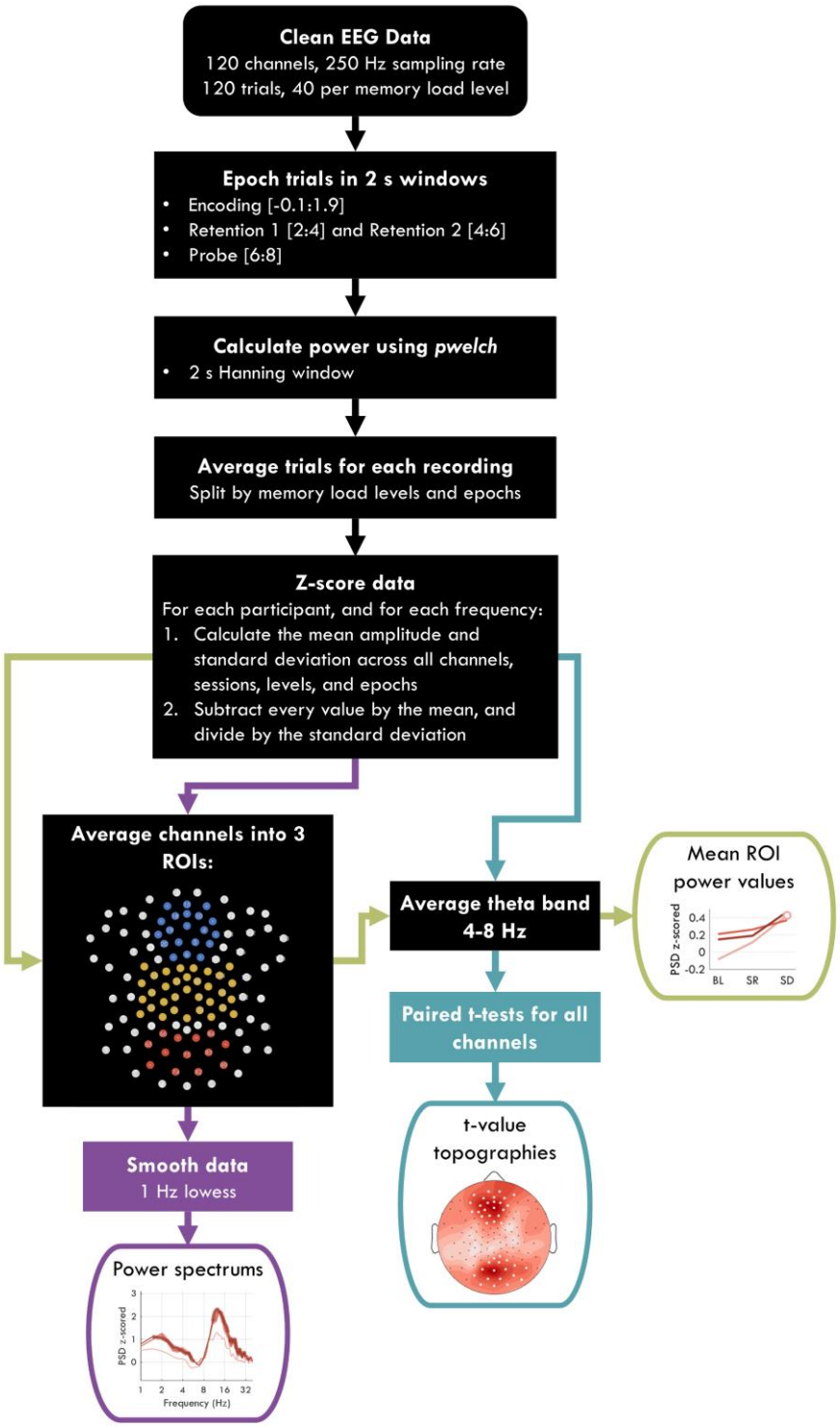

Figure 2.18: STM EEG analysis pipeline. Starting data was preprocessed as described in Figure 2.19. Sections in black indicate steps in common between more than one analysis. Purple indicates steps for calculating power spectrums, teal indicates steps specific to topographies, and green steps for average region of interest (ROI) power. The ROI channels were pre-selected, and in the diagram the Front ROI is in blue (3, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, 18, 19, 20, 22, 23, 24, 112, 118, 124), Center in yellow (7, 30, 31, 35, 36, 37, 41, 42, 47, 51, 52, 53, 54, 55, 60, 61, 62, 78, 79, 80, 85, 86, 87, 92, 93, 97, 98, 103, 104, 105, 106, 110, 129), and Back in red (65, 66, 69, 70, 71, 74, 75, 76, 82, 83, 84, 89, 90). STM epochs were all of 2 s duration, however the encoding epoch was shifted 0.1 s earlier to avoid initial retention EEG responses. The pipeline for all other task EEG analyses (e.g. Figure 2.7) is identical, except without trials or epoching, and using 8 s windows with 75% overlap across the first 4 minutes of data.

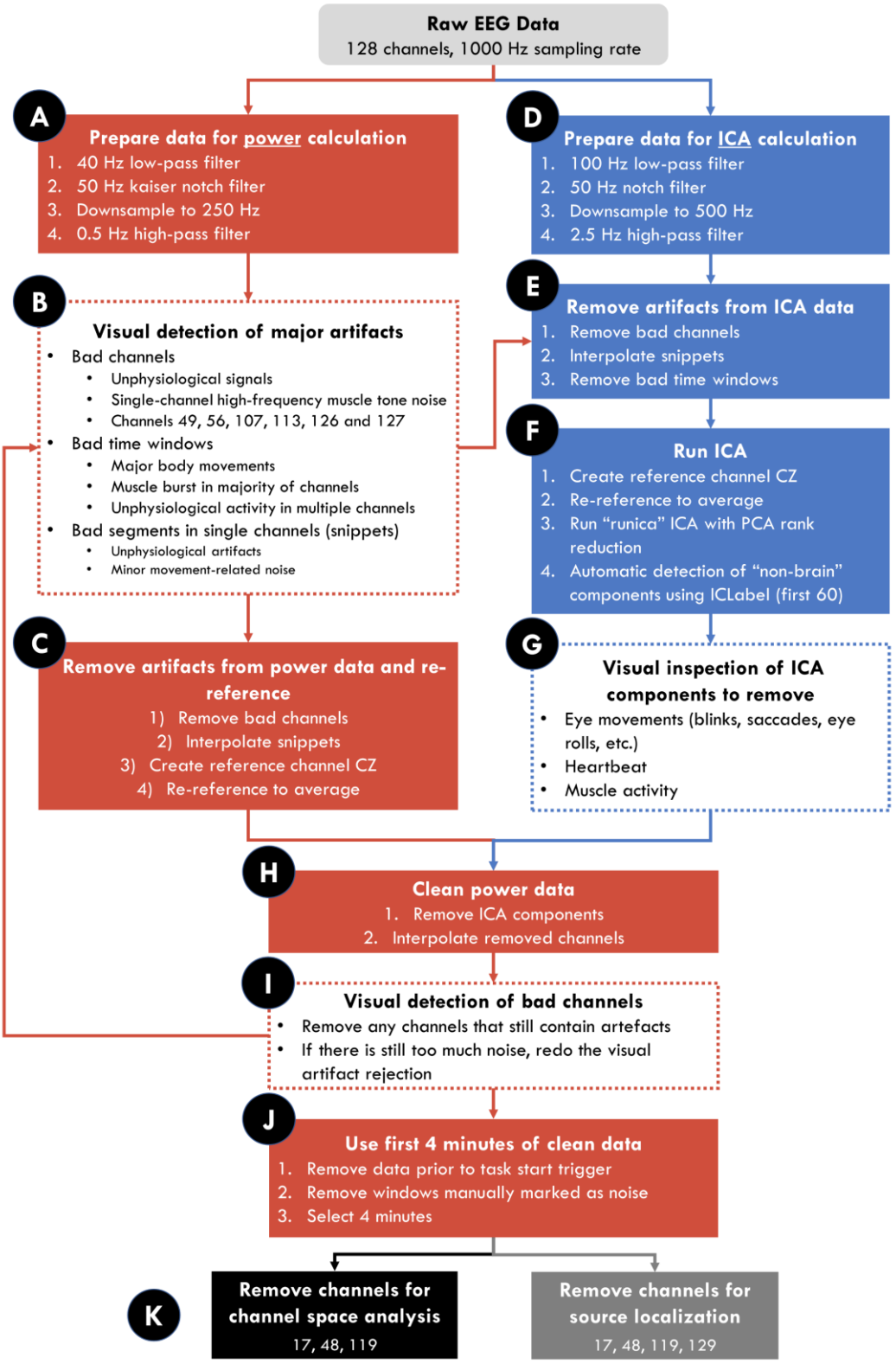

Figure 2.19: Pipeline for data preprocessing. Red steps were conducted on the data used for the power analysis (250 Hz sampling rate, 0.5-40 Hz). Blue steps were conducted on the data used for the independent component analysis (ICA; 500 Hz sampling rate, 2.5-100 Hz). White-filled steps (B, G, I) involved manual work. **A**: First, data was low-pass filtered at 40 Hz using EEGLAB's default filter. A Kaiser notch filter was then applied to remove 50 Hz line noise and subsequent harmonics. Data was then down-sampled to 250 Hz. A 0.5 Hz high-pass Kaiser-window based FIR filter was then applied (0.25 Hz stopband, 60 dB stopband attenuation, 0.05 passband ripple). **B**: The data was visually

inspected to identify bad channels (Figure 2.20A), bad time windows, and bad single-channel segments (i.e. snippets). Bad channels were considered as such that if they contained any non-physiological signals (anything not from the brain, muscles, or eyes) that occurred either continuously or repeatedly throughout the recording. Furthermore, external channels outside the EGI net were automatically removed (49, 56, 104, 113), as well as the face channels (126, 127). Bad time windows were any segments in time in which an artifact affected multiple channels at once, often due to body movements or brief muscle clenching. Bad snippets were non-physiological artifacts affecting only a few channels. **C**: Prior to removing artifacts with ICA, bad channels were removed, snippets interpolated, and the data re-referenced to the average. However, bad time windows were not removed. These are removed later (J). **D**: Data used for calculating the ICA was filtered and downsampled differently from A to maximize the detection of eye-movement artifacts. **E-F**: For ICA, only clean data was used, Cz was restored, and all channels re-referenced to the average. EEGLAB's "runica" ICA algorithm was applied, with principal component analysis (PCA) rank reduction. Using EEGLAB's ICLabel function (v1.2.4), the first 60 components were automatically classified as either brain data or artifacts. Components were marked for removal if they had a "brain" classification value lower than .1 but restored if they had a classification as "other" larger than .6 (i.e. an unknown component). **G**: Visual inspection was then conducted to correct any misclassifications, or mark for removal additional bad components outside the first 60 (total components removed in Figure 2.20B). **H-I**: After the components were removed, one final visual inspection of the data was done to remove any additional bad channels, and possibly repeat the preprocessing if notable artifacts remained in the data. **J**: To have the same amount of data for each task, the first 4 minutes of clean data was used to calculate power. **K**: Channels 17, 48 and 119 were further removed from all datasets, as these were often removed due to poor signal quality in steps B and I. Channel 129 was removed for the source localization as its coordinates were not available.

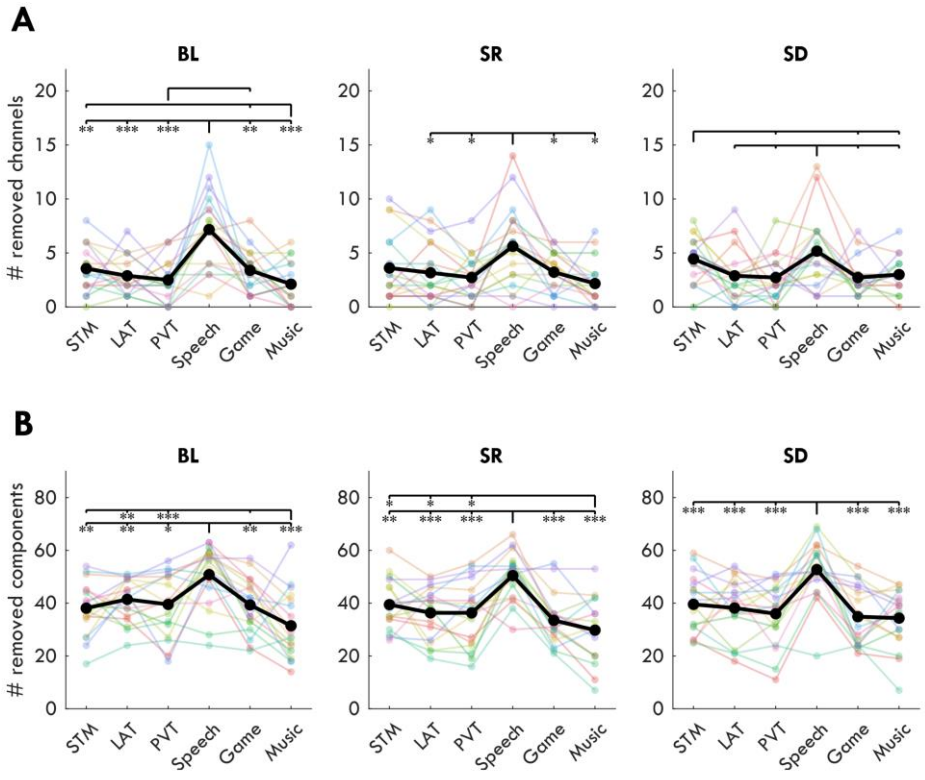

Figure 2.20: Removed channels and components for each recording and each session. **A**: Number of channels removed (out of 120). Each colored line represents a participant. The black line is the group average. **B**: Number of removed components after ICA (max 120). Asterisks indicate significant differences from paired t-tests between sessions, FDR corrected, such that: * p-value < .05, ** p-value < .01, *** p-value < .001.

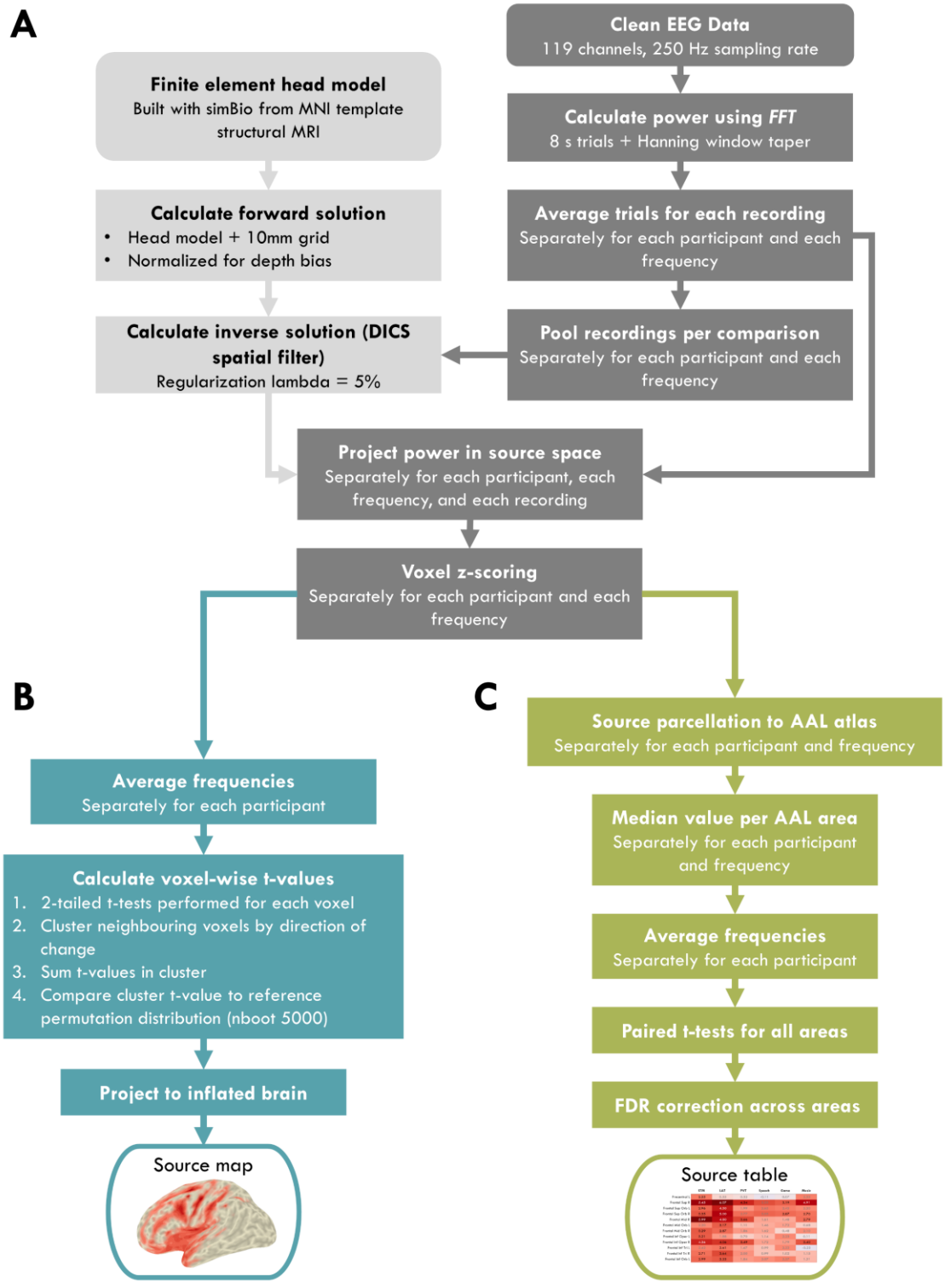

Figure 2.21: Pipeline for source localization analysis. A: To compute theta power for the source localization, we used a fast Fourier transform (FFT) with a Hanning taper, applied to each 8 s window. To construct the forward model, we obtained a finite-element head model, implemented with the SimBio toolbox based on the segmentation of the template T1 MRI image from the Montreal Neurological Institute into gray matter, white matter, cerebrospinal fluid, scalp and skull. Subsequently, a standard 3D grid (10 mm spacing, 3294 voxels inside the head) and the head model were used to compute the leadfield matrix. To avoid depth bias, the leadfield was normalized. As an inverse solution, we used the DICS beamformer technique. We first computed common spatial filters based on a cross-spectral density

matrix obtained from pooled conditions, with a regularization parameter lambda set to 5%. The pre-computed common spatial filters were then applied independently to each condition. After projecting each recording to the source space, each frequency was z-scored for each participant (as done in the channel space). **B**: 3D brain source maps. Non-parametric cluster correction was implemented instead of FDR because it was only intended as a mask for the inflated brains plots, and not as hypothesis testing. First, independent samples t-tests for all voxels was done for the contrast of interest (2-tailed, $p < .05$). Next, significant neighboring voxels were clustered if they showed the same direction of effect. To assess the statistical significance of each cluster, a cluster-level test statistic was calculated by computing the sum of all t-values in the cluster. The significance of each cluster was estimated by comparing the cluster-level test statistic to a reference permutation distribution derived from the data. The reference distribution was obtained by randomly permuting the data 5000 times. The cluster p-value was estimated as the proportion of the elements in the reference distribution exceeding the cluster-level test statistic. For the visual representation of results, significant clusters of t-values were projected on the inflated brain surface. Due to uncertainty regarding the ability of surface EEG to detect deep brain structures' electrophysiological activity (thalamus, amygdala, etc.) these areas were covered in a patch and not included in the next analysis. **C**: We additionally performed parcellation of the grid into 80 regions of interest (parcels), in accordance with the AAL atlas. Regions of the basal ganglia and cerebellum were excluded from further analysis. The median power for each frequency across voxels was used for each anatomical area. Power for all theta frequencies was then averaged, and paired t-tests were conducted for each parcel, FDR correcting for multiple comparisons.

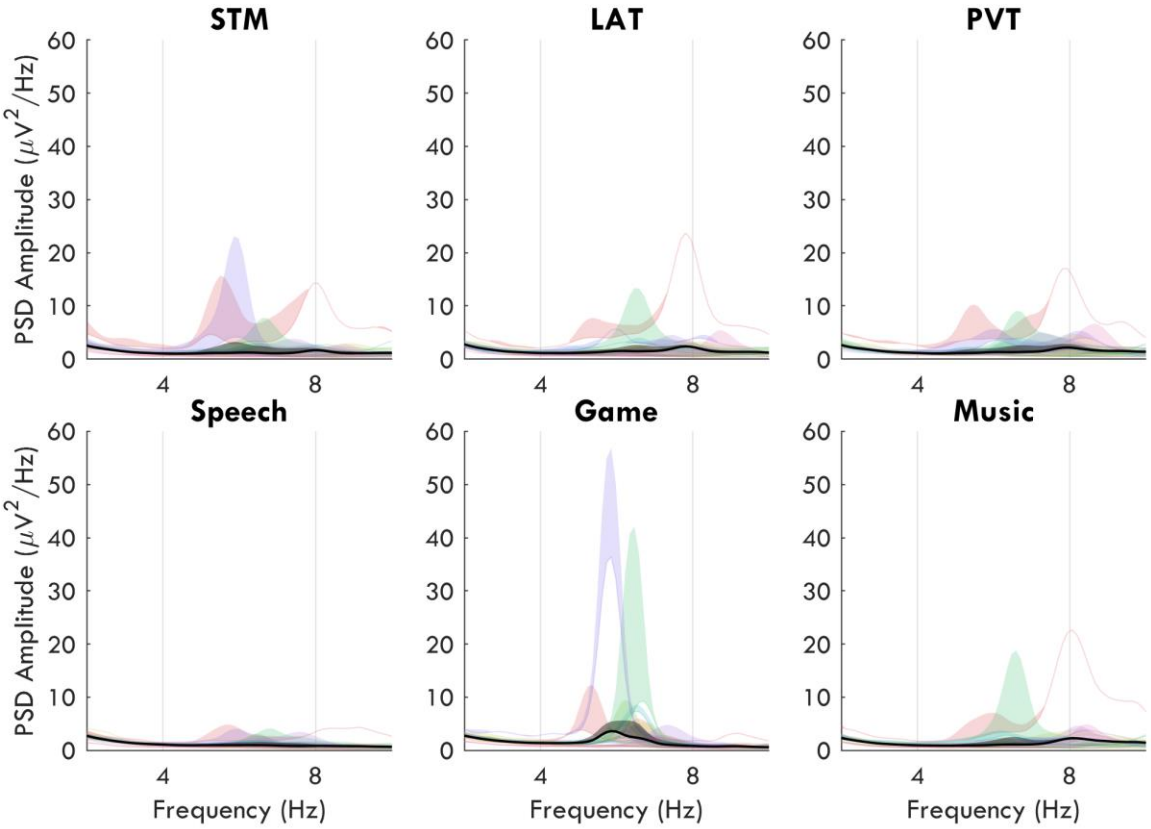

Figure 2.22: Uncorrected power spectrums from the front ROI for each task. Overlapping EEG power spectrums, untransformed, from the Front ROI of each task for every participant. The base curve of each colored patch represents the BL spectrum, the upper curve represents the SD spectrum, and the filled-in area reflects the increase in power. The average power change is the final patch in black.

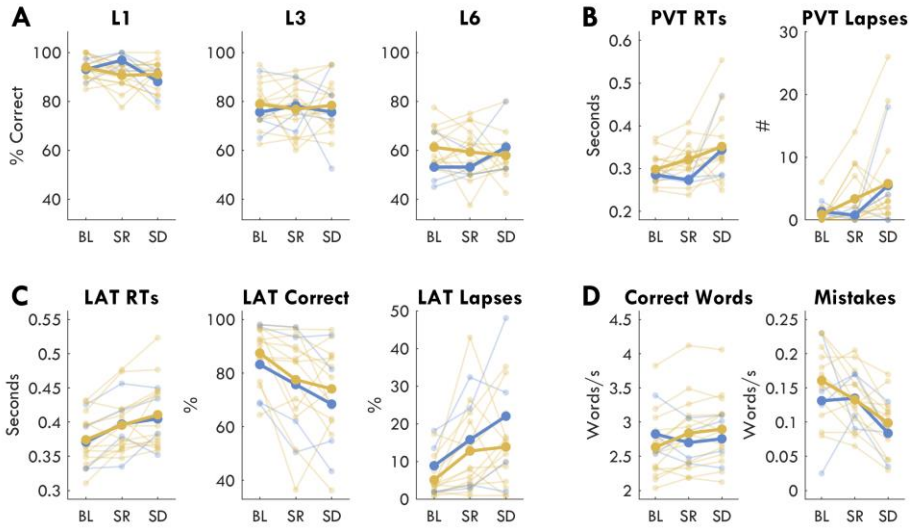

Figure 2.23: Task performance by experiment order. Same data as Figure 2.14. Participants who conducted the baseline night after the sleep deprivation session are highlighted in blue (N = 4), the remainder are in yellow (N = 14).

2.6.2 Spectrums for the short-term memory retention period

Figure 2.24 provides the z-scored average spectrums for the three ROIs (front, center, back) for the first 2 s retention period of the short-term memory (STM) task, highlighting the differences across memory load for each session. Notably, L3 theta has a double peak at BL in the 4-8 Hz range, whereas all levels have comparable frontal spectrums during SD. Given the low frequency resolution for 2 s windows (0.5 Hz), these spectra were not used in the manuscript to determine whether fmTheta had a different peak frequency than sdTheta.

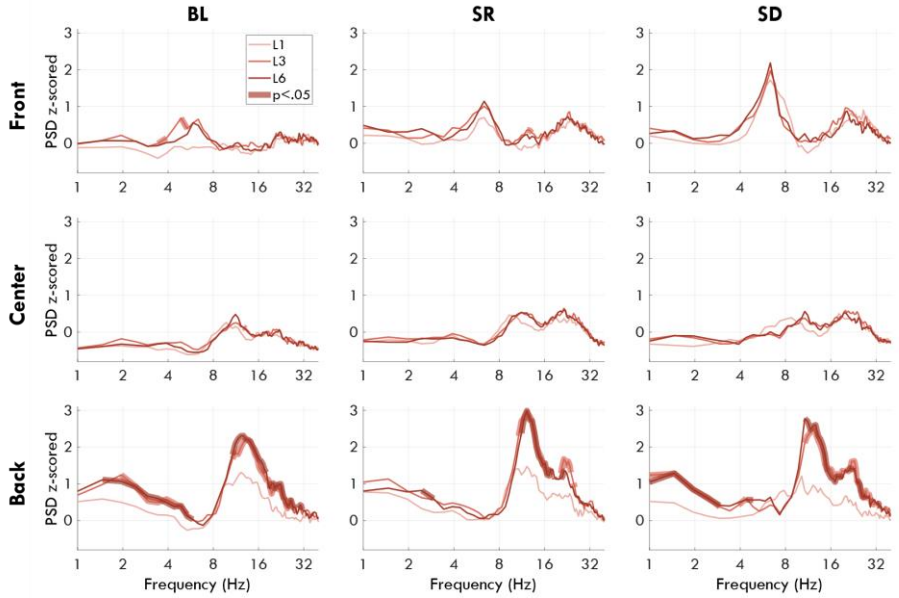

Figure 2.24: Spectrum of the first half of the retention period (2 s) of the STM task. Each row represents a different ROI, each column a different session. The thin lines represent the spectrums for the three memory loads (1, 3 and 6 items). Thick lines represent frequencies that were significantly different from L1, FDR corrected. The x-axis is log-transformed. Acronyms: PSD (power spectral density), STM (short term memory task), BL (baseline), SR (sleep restriction), SR (sleep restriction), SD (sleep deprivation), FDR (false discovery rate), ROI (region of interest).

2.6.3 Reading increased sdTheta more than speaking

The speech task had the lowest overall theta power, and the lowest and least widespread sdTheta. This task also had the most artifacts and was consequently the most preprocessed (i.e., it had the highest amount of artifact components removed using ICA). Therefore, results from this task should be taken with caution. It is however plausible that physical activity results in less theta; a study by Caldwell et al. (2000) found theta power was reduced when participants were standing compared to seated. To evaluate whether the reduced amount of theta was due to the preprocessing, or whether speech results in less theta activity, we compared theta power during epochs in which participants were reading and silently practicing the tongue twisters (between 2-30s) relative to when they were speaking (10 s).

We calculated a two-way rmANOVA with factors Session (BL, SR, SD) and Epoch (Reading, Speaking) in the three ROIs. In the front ROI there was a significant effect of session ($F_{(2, 30)} = 18.145$, $p < .000$, $\eta^2 = .372$), a trending effect of epoch ($F_{(1, 15)} = 3.45$, $p = .083$, $\eta^2 = .012$), and a significant interaction ($F_{(2, 30)} = 6.78$, $p = .015$, $\eta^2 = .022$). In the center ROI there was a significant effect of session ($F_{(2, 30)} = 3.82$, $p = .034$, $\eta^2 = .100$), no effect of epoch ($F_{(1, 15)} = 0.08$, $p = .785$, $\eta^2 < .000$), and a significant interaction ($F_{(2, 30)} = 3.65$, $p = .047$, $\eta^2 = .018$). In the back ROI there no effect of session ($F_{(2, 30)} = 1.73$, $p = .197$, $\eta^2 = .032$), no effect of epoch ($F_{(1, 15)} = 0.39$, $p = .541$, $\eta^2 = .001$), and no interaction ($F_{(2, 30)} = 1.50$, $p = .240$, $\eta^2 = .003$).

The interaction in frontal theta was driven by a steeper increase in theta with sleep deprivation during reading epochs, such that theta was higher when reading compared to speaking, but only during SD (Figure 2.25A). We compared theta topographies of SD and BL for the reading and speaking epochs separately, and the speaking and reading epochs during SD (Figure 2.25B). The reading epochs had a larger and more widespread (max g = 2.16, N significant channels= 24) theta increase than speaking epochs (max g = 1.62, N chs = 8). When directly comparing SD Speaking and SD Reading, there was a decrease in theta in frontal channels, but no channel survived FDR correction. Overall, while it may still be the case that the preprocessing of the Speech EEG removed more data than in other tasks, the act of speaking results in slightly less theta than the act of reading in frontal channels. This supports the idea that the more engaging an activity, the less overall theta.

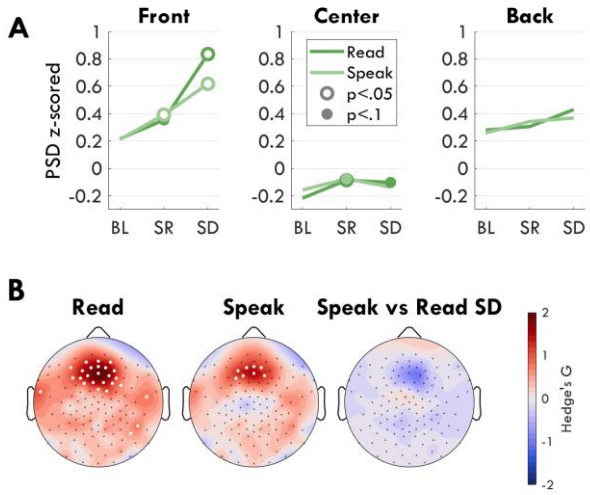

Figure 2.25: A: Mean theta power during the Speech task for reading (dark green) and speaking epochs (pale green) across sessions for the three ROIs. White circles indicate a significant change from BL, filled circles a trend, FDR corrected. **B**: Difference in theta power (as Hedge's g) between Speaking and Reading epochs from BL to SD, such that red indicates more theta during SD, and then Speaking and Reading during SD, with red indicating more theta during Speaking. White dots indicate a significant change, FDR corrected.

2.6.4 Innovations

2.6.4.1 EWOQ

Simone Accascina and I created the Experiment Web Organizer for Questionnaires (EWOQ). This allowed us to first conduct anonymized online screening, in full compliance with Swiss Ethics. Then, throughout the experiment, we were able to easily collect digital questionnaires involving over 2000 questions throughout both the control week (on participants personal devices) and during the experiment (on standardized tablets). These questionnaires were reactive, such that depending on the answers given, there would be either further follow-up questions or not. In the case of the screening questionnaire, it also provided an immediate judgement on whether the applicant was qualified to participate or not. This was a robust system that maintained full anonymity while carefully organizing the questionnaires of all the individuals, with no data loss. It was easy to use for both sleep-deprived participants and experimenters.

A key feature of EWOQ questionnaires that was not available on current commercial survey platforms was the option of visual analogue scales (Figure 2.26) that would not start with a default answer. This was important to avoid anchoring,[1] as well as avoid defaulting to the same answer. We also implemented a feature that allowed participants to click on the provided labels so that they could easily give a precise answer if they preferred. Incidentally, this revealed that despite having a generous 9 options in the KSS, participants still preferred to give intermediate values. As demonstrated in section 3.6.2, page 94, these values could mean the difference between measuring the wake maintenance zone, or not.

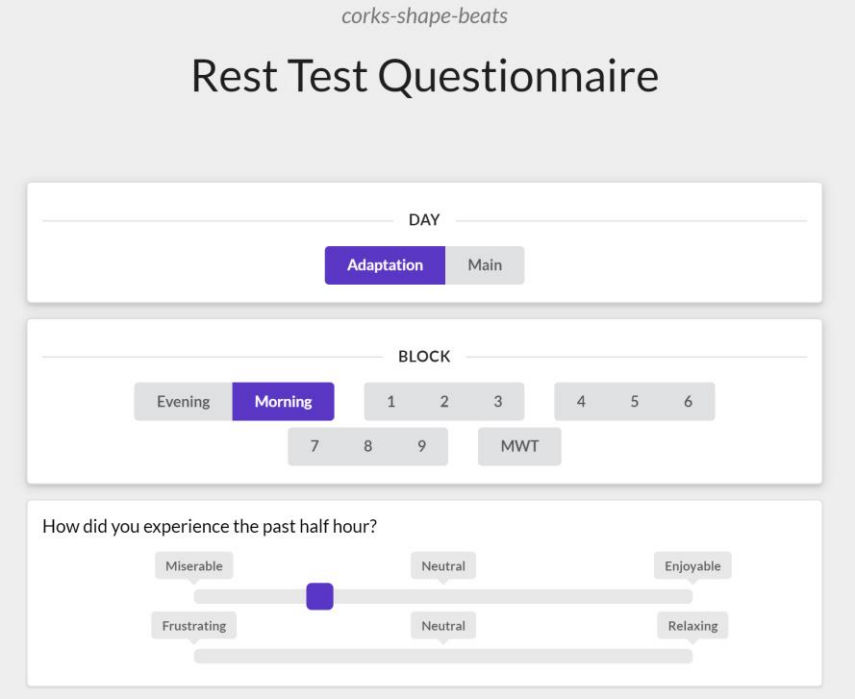

Figure 2.26: EWOQ questionnaire interface. Experimenter first selected the session information (Day, Block), then the participant continued the questionnaire, with each question appearing incrementally. The three-word code for

[1] *Anchoring is when a participant's answer is biased by some previously displayed information, usually a number (Furnham & Boo, 2011).*

each participant was written at the top; this code linked all the questionnaires for a single participant together on the online server, fully anonymized.

In addition to this project, EWOQ was used for two other studies in our lab, the Rebound closed-loop auditory stimulation project (Krugliakova et al., 2022), and the epilepsy project (Leach et al. in prep).

2.6.4.2 4/24 extended wake paradigm

Sleep deprivation studies are difficult and resource intensive. For this study, only me and one master student were involved in data collection, so we could not afford to conduct the ideal 40 h of sleep deprivation. Furthermore, it felt a bit "wasteful" to have a 24 h sleep deprivation paradigm, in which the only time participants were truly sleep deprived was the last 6 hours. Not only that, but the point of maximal homeostatic sleep pressure would then coincide with a compensatory circadian wake pressure in the morning, thus minimizing the effect.

The solution was to shift the 24 h wake period during a single day. This meant two people could supervise the entire experiment taking shifts; a morning shift who woke the participant up in the middle of the night and kept them awake and entertained until midafternoon, and an evening shift that kept them awake until the end. This meant that all sleep deprivation recordings were done at elevated levels of homeostatic sleep pressure, which incidentally revealed the WMZ (section 3, page 70).

2.6.4.3 Net mats

EGI high-density nets are one of the most comfortable options available for sleep research, while maintaining decent signal quality across the night, however they can still be quite painful. As my participants had to wear the nets for over 36 h, I decided to include an additional mat to place on the pillows of participants (Figure 2.27). I knitted some spongy covers that eased the pressure points of the electrodes, although an acceptable alternative is IKEA TOFTBO bathroom mats, which have the advantage of being standardized, although not as comfortable.

Figure 2.27: Hand-knit pillow cover. Eases pressure points of the EGI nets during sleep.

3 HOW AND WHEN EEG REFLECTS NEURONAL CHANGES IN CONNECTIVITY DUE TO TIME AWAKE

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This paper will be published in *iScience* any day now, but is already available on *BioRxiv* (Snipes et al., 2023). The experiment was designed as a replication of Finelli et al. (2000). Here, I determine to what extent the changes in power observed in the wake EEG are due to changes in the quantity of oscillations, or their amplitudes.

I designed the experiment, collected the data, analyzed the data, and wrote the paper. Elias Meier helped me collect the data, created the preprocessing and analysis pipeline for the pupil data and helped write the relevant portions of the manuscript. His master's thesis was on pupillometry during sleep deprivation. I only lightly adjusted the pipeline, and normalize pupil sizes across multiple measurements using irises. Sarah Meissner and Marc Bächinger provided supervision for this pupillometry work, designed the Oddball task, and provided recording equipment. Sarah continued to follow the project until the end, offering advice on preprocessing, analysis, and interpretation. Hans-Peter Landolt provided advice at the beginning of the project for the experiment design, but most importantly provided access to the climate controlled sleep laboratory in which we conducted our experiments. All authors contributed to editing the manuscript.

3.1 Summary

Being awake means forming new memories, primarily by strengthening neuronal synapses. The increase in synaptic strength results in increasing neuronal synchronicity, which should result in higher amplitude electroencephalography (EEG) oscillations. This is observed for slow waves during sleep but has not been found for wake oscillations. We hypothesized that this was due to a limitation of spectral power analysis, which does not distinguish between changes in amplitudes from changes in number of occurrences of oscillations. By using cycle-by-cycle analysis instead, we found that theta and alpha oscillation amplitudes increase as much as 30% following 24 h of extended wake. These increases were interrupted during the wake maintenance zone (WMZ), a window just before bedtime when it is difficult to fall asleep. We found that pupil diameter increased during this window, suggesting the ascending arousal system is responsible. In conclusion, wake oscillation amplitudes reflect increased synaptic strength, except during the WMZ.

3.2 Introduction

Good sleep is essential for daily functioning and overall quality of life. The reason we need sleep is so that physiological systems used during the day have a dedicated period to rest and conduct structural maintenance (Vyazovskiy & Harris, 2013), clear metabolic by-products (Hauglund et al., 2020; Xie et al., 2013), restore overall functioning to baseline levels (Killgore, 2010; Van Dongen et al., 2003), and more. This

means that we accumulate sleep need with time awake and can only restore balance following sleep, a process referred to as *sleep homeostasis.* Also important is the timing of sleep, controlled by a 24-h *circadian rhythm* which allows independent systems across the body and brain to synchronize their recovery to the external world's day/night cycle and thus optimize overall performance (Hastings et al., 2007; Patke et al., 2020). These homeostatic and circadian fluctuations make up the two-process model of sleep (Borbély, 1982).

The homeostatic process of the two process model in particular was designed to explain the notable changes in sleep slow waves, electroencephalographic (EEG) oscillations between 0.5 and 4 Hz that characterize NREM sleep (Achermann & Borbély, 2003). Slow wave activity decreases exponentially during NREM sleep, reflecting homeostatic sleep pressure dissipation. Vice versa, slow wave activity at the beginning of sleep depends on the duration of prior wake, following an increasing saturating exponential function (Dijk et al., 1987, 1990). This means that the buildup in sleep need is steepest during the initial hours of wake, then gradually saturates with additional time awake (Figure 3.1A).

A possible explanation for this increase in slow wave activity with prior wake is that wakefulness progressively increases neuronal synaptic strength when forming new memories, which then requires sleep to restore overall synaptic balance. This is referred to as *synaptic homeostasis*, as described by the synaptic homeostasis hypothesis (Tononi & Cirelli, 2003). In essence, learning and acquiring memories requires changes to the brain in the form of strengthened synaptic connections between utilized neurons. Increased synaptic strength increases overall connectivity which leads to increased synchronicity across the brain. This increased synchronicity between neurons will result in more synchronized oscillations in the surface EEG, detected as oscillations with larger amplitudes and steeper slopes as time awake increases. The hypothesis then predicts that sleep, when inputs cease and new memories are no longer acquired, is the only time when synaptic balance can be re-normalized to baseline levels (Tononi & Cirelli, 2003, 2014). Using computational models (Esser et al., 2007), animal sleep data (Vyazovskiy et al., 2007), and human sleep data (Riedner et al., 2007), the proponents of the synaptic homeostasis hypothesis demonstrated how decreasing synaptic strength across sleep results in the decrease of slow wave amplitudes and slopes.

While the combined models of sleep homeostasis and synaptic homeostasis can explain changes in slow wave activity across sleep, they do not likewise explain changes in wake oscillations. Human wake EEG is predominantly characterized by alpha oscillations (8-12 Hz) and to a lesser extent theta oscillations (4-8 Hz), often measured as power in the frequency domain. Theoretically, the increased connectivity with time spent awake should affect these oscillations along a similar increasing saturating exponential function as for slow waves in sleep. However, while theta power does increase with sleep deprivation, the effect is rather linear (Finelli et al., 2000). Furthermore alpha power actually decreases (Cajochen et al., 2002; Strijkstra et al., 2003).

In addition to neither oscillation following a homeostatic trajectory, both are also affected by circadian rhythmicity (Aeschbach et al., 1997; Cajochen et al., 2002; Finelli et al., 2000; Strijkstra et al., 2003), further masking potential homeostatic effects. Alpha activity fluctuates in phase with core body temperature, a reliable circadian marker peaking in the middle of the day and lowest in the middle of the night (Åkerstedt et al., 1979; Cajochen et al., 2002). Instead, theta activity is lowest in the evening (Cajochen et al., 2002), corresponding to the wake maintenance zone (WMZ; Strogatz et al., 1987; Zeeuw et al., 2018). The WMZ, more dramatically known as the "forbidden sleep zone," is a circadian window of 2-4 hours just prior to melatonin onset in which sleep becomes exceptionally difficult (Lavie, 1997). During the WMZ,

sleep onset latencies substantially increase even during extensive sleep deprivation (Dijk & Czeisler, 1995; Lavie, 1986), subjective sleepiness decreases, and behavioral performance improves (McMahon et al., 2018, 2021; Shekleton et al., 2013; Zeeuw et al., 2018). The timing of the WMZ is not reflected in traditional circadian markers such as melatonin levels or core body temperature, it has not been reported in any animal models to our knowledge, and is not represented in the classic two-process model of sleep.

Therefore, while increasing synaptic strength would have predicted an increase in both theta and alpha power with time spent awake, in practice neither oscillation strictly reflects this buildup in homeostatic pressure, and they are further synchronized to different circadian phases. However, the fact that wake oscillations do not reflect sleep homeostasis may be due to a limitation of spectral power analyses. "Power" refers to the amount of energy in a frequency band, and is typically calculated using some variant of the Fast Fourier Transform (M. X. Cohen, 2014). Once a time-series signal has been transformed into the frequency domain, power values are averaged or summed within a frequency range of interest, and this is the power for that band. While this is a simple and generally effective measure for quantifying oscillatory activity, it is simultaneously affected by the *quantity* of oscillations present in the signal and their *amplitude,* as well as broad-band changes in the entire spectrum (Donoghue et al., 2020).

The synaptic homeostasis hypothesis predicts that an increase in synaptic connectivity results in an increase in oscillatory amplitudes; this does not need to have any bearing on the number of oscillations that actually occur. It is therefore possible that non-homeostatic factors such as the WMZ could independently affect the quantity of oscillations, whereas time spent awake more specifically affects their amplitude. When both oscillation amplitudes and quantities change independently across wake recordings, the resulting power values will reflect some undifferentiated mix between the two. By separating these contributions, we may have a specific marker of homeostatic sleep pressure during wake. Not only would this provide supporting evidence for the hypothesis that sleep homeostasis is linked to synaptic plasticity, but also provide a marker for sleep pressure more easily acquired than slow wave activity during sleep.

We therefore wished to determine whether the circadian and homeostatic influences on theta and alpha oscillations could be dissociated in resting wake EEG by separately measuring changes in amplitude and changes in quantities of oscillations. Eighteen young healthy adults participated in a 4/24 extended wake paradigm (Figure 3.1A), in which they slept the first 4 hours of the night and were then kept awake for 24 hours with repeated resting state recordings (Figure 3.1B), while measuring high-density EEG. We conducted cycle-by-cycle analysis (Cole & Voytek, 2019) to identify bursts of oscillations in the theta and alpha range, a method which identifies oscillations based on the morphology of the EEG signal rather than relying on power and amplitude thresholds (for an in-depth explanation, see *STAR Methods: Method details: EEG burst detection*). We then looked at changes in the mean amplitude of bursts and the average number of cycles (i.e., oscillations present in a burst) per minute for each band. Our prediction was that both theta and alpha amplitudes would follow an increasing saturating exponential across extended wake and show decreases following sleep. At the same time, the decrease in alpha power with time awake should be explained by a decrease in the overall number of alpha oscillations. Likewise, circadian changes such as the decrease in theta during the WMZ should be reflected in decreases in the number of bursts.

To independently monitor changes in alertness across the extended wake period, we also recorded pupillometry with infrared cameras. Pupil diameter and pupil responses to salient stimuli have been linked to alertness-promoting activity in the locus coeruleus (Aston-Jones & Cohen, 2005; Joshi et al., 2016; P. R. Murphy et al., 2014), as well as other interconnected nuclei in the brainstem and forebrain that make

up the ascending arousal system (AAS; Lloyd et al., 2022; Reimer et al., 2016). While there are still many open questions about the link between pupil size and sleep/wake promoting nuclei, the relationship between any of these signals and EEG could help better explore the underlying mechanisms driving the changes in oscillatory activity across extended wake. In short, while the two-process model and the synaptic homeostasis hypothesis provide specific predictions about wake EEG amplitudes, with pupillometry we hoped to provide possible explanations for changes in oscillatory occurrences.

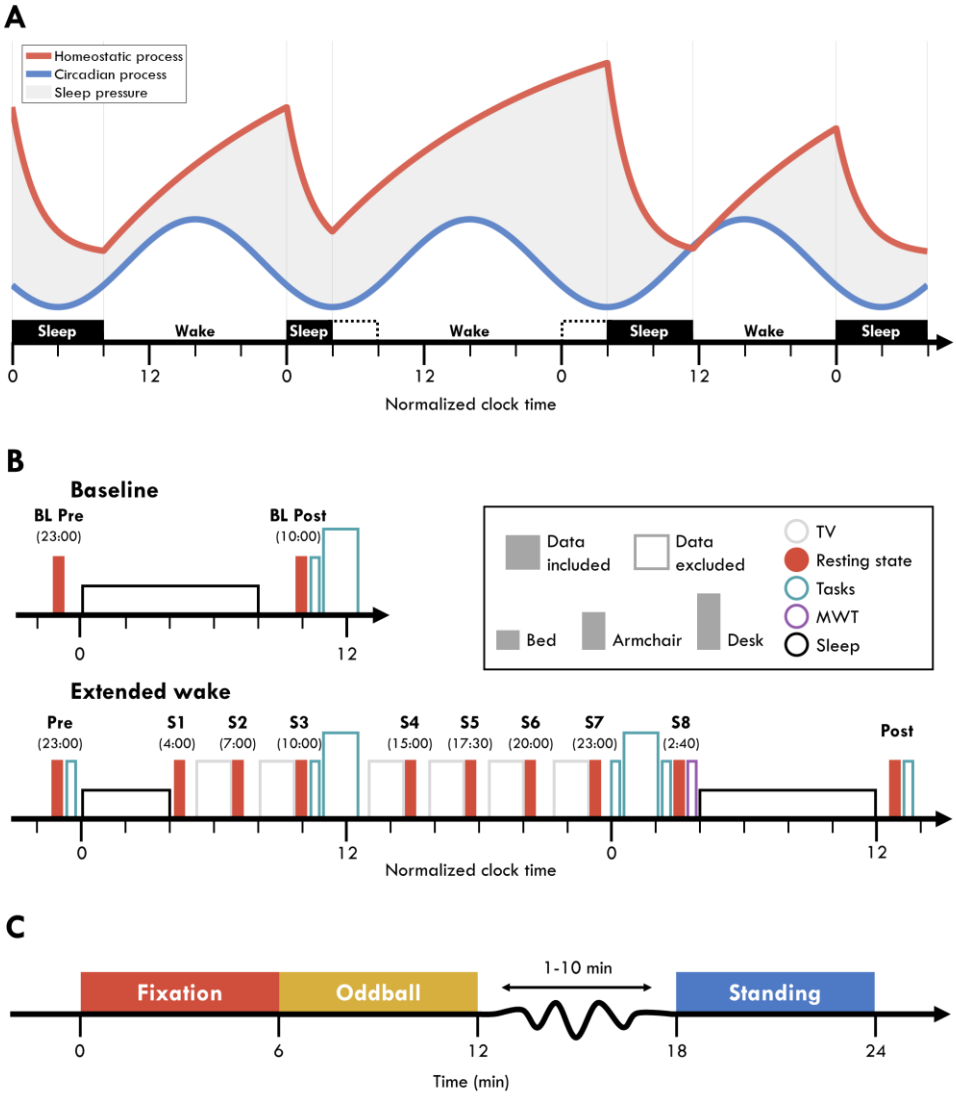

Figure 3.1: Experiment design. **A**: The two-process model during a 4/24 extended wake schedule. The red line reflects the homeostatic process, building sleep pressure monotonically with wake and dissipating during sleep. The blue line reflects the circadian process, peaking in the middle of the day and at its lowest in the middle of the night, independent of actual sleep and wake behavior. The shaded area reflects the resulting sleep pressure from combining these two processes. Black filled blocks indicate when participants actually slept, whereas the outline indicates the window in which they would have slept according to their circadian rhythm. **B**: Experiment schedule. Each block indicates an EEG recording session. Filled blocks indicate data analyzed in this paper. Color indicates the activity participants engaged in: gray, watching TV; red, the resting state recordings in C; teal, task blocks analyzed in Snipes et al. (2022); purple, the MWT; black, sleep. The height of each block indicates the condition in which data was collected: short, lying in bed; medium, seated in a comfortable armchair with foot and backrest / standing; tall, seated at a desk. Brief empty spaces indicate transition periods allowing for delays. Six longer breaks were included prior to each TV block in which participants were provided with meals. Circadian time was normalized across participants to their habitual bedtime. Participants at baseline and during the recovery night were free to wake up when they wished, and at the beginning of the extended wake period they were woken up after 4 h of sleep. **C**: Timeline for the resting state

recordings. Each condition was 6 minutes, and always done in the depicted order. Between the Oddball and Standing, a questionnaire was conducted which took a variable amount of time, followed by moving the participant from the armchair to standing.

3.3 Results

We recorded EEG, pupillometry, and questionnaire data from participants performing 3 wake resting state recordings for 6 minutes each (Figure 3.1C). The first was a standard condition, *Fixation*, in which participants were seated in a comfortable armchair and had to gaze at a fixation point ~3 m away. The second was an active auditory *Oddball*, in which tones were presented randomly and participants had to push a button after "oddball" (i.e. deviant) tones. Afterwards, participants filled out a questionnaire and then got up for the final recording of *Standing* with eyes closed. They were asked to stand for this condition because during sleep deprivation participants quickly fall asleep with eyes closed. These rest recordings were conducted 12 times: before and after each of the 3 nights of sleep, and 6 more times throughout the extended wake period approximately 3 hours apart, for a total of 8 recordings across extended wake (Figure 3.1B). The primary focus of this study was the Fixation condition, used in previous studies. The auditory Oddball was included as an exploratory condition to evaluate changes in pupillometry with time awake, especially responses to target tones which are thought to reflect activity in the locus coeruleus (P. R. Murphy et al., 2014). The EEG of both the Oddball and the Standing with eyes closed conditions were investigated in order to establish the sensitivity to homeostatic effects of other conditions.

For every outcome measure, we conducted paired t-tests on the overnight changes of the baseline night (BL Pre vs BL Post), the extended wake changes (S1 vs S8) and the changes during the WMZ (S5/S8 vs S6/S7), the timing of which could be independently determined through changes in subjective sleepiness (Figure 3.2). All t-values, degrees of freedom, p-values, and Hedge's g effect sizes are provided together in Table 3.1. Throughout the text, only the corresponding t-values will be reported, unless either effect sizes or p-values are specifically of interest (e.g. when trending).

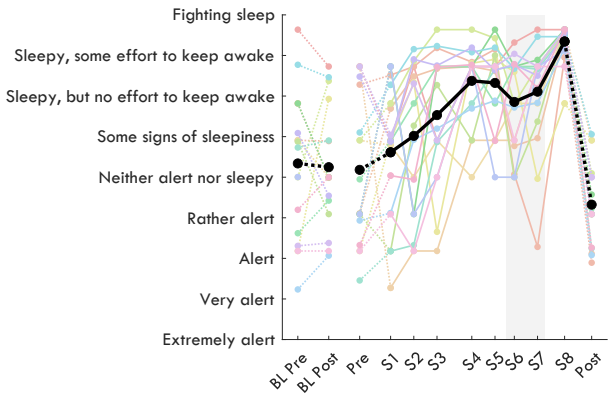

Figure 3.2: Subjective sleepiness. Sleepiness was measured on a continuous visual-analog adaptation of the KSS, using the original labels as markers (y-axis). The thick black line indicates the group average, and thin colored lines are datapoints of individual participants. Solid lines connect sessions during the same-day extended wake period, and dashed lines indicate changes across sleep. S1-S8 are spaced out relative to the time they occurred within the 24 h wake period (Figure 3.1B). The shaded gray area indicates the WMZ.

	Condition	Overnight baseline	Extended wake	WMZ
Sleepiness	–	$t_{(15)} = -0.21$, $p = .833$, $g = -0.06$	$t_{(16)} = 7.36$, $\mathbf{p < .001}$, $g = 2.61$	$t_{(16)} = -3.36$, $\mathbf{p = .004}$, $g = -1.13$
Theta power	Fixation	$t_{(17)} = -4.80$, $\mathbf{p < .001}$, $g = -0.83$	$t_{(16)} = 9.66$, $\mathbf{p < .001}$, $g = 2.99$	$t_{(16)} = -5.96$, $\mathbf{p < .001}$, $g = -1.78$
	Oddball	$t_{(17)} = -3.19$, $\mathbf{p = .005}$, $g = -0.70$	$t_{(16)} = 10.41$, $\mathbf{p < .001}$, $g = 3.76$	$t_{(16)} = -6.92$, $\mathbf{p < .001}$, $g = -2.17$
	Standing	$t_{(16)} = -0.57$, $p = .574$, $g = -0.14$	$t_{(16)} = 5.97$, $\mathbf{p < .001}$, $g = 2.26$	$t_{(16)} = -5.19$, $\mathbf{p < .001}$, $g = -1.21$
Alpha power	Fixation	$t_{(17)} = 1.75$, $p = .098$, $g = 0.26$	$t_{(16)} = 3.03$, $\mathbf{p = .008}$, $g = 1.07$	$t_{(16)} = -2.86$, $\mathbf{p = .011}$, $g = -0.63$
	Oddball	$t_{(17)} = 0.82$, $p = .421$, $g = 0.13$	$t_{(16)} = 3.89$, $\mathbf{p = .001}$, $g = 1.32$	$t_{(16)} = -3.61$, $\mathbf{p = .002}$, $g = -0.89$
	Standing	$t_{(16)} = 2.57$, $\mathbf{p = .020}$, $g = 0.71$	$t_{(16)} = -1.44$, $p = .168$, $g = -0.49$	$t_{(16)} = -1.13$, $p = .276$, $g = -0.16$
Theta burst amplitude	Fixation	$t_{(15)} = -2.06$, $p = .057$, $g = -0.74$	$t_{(16)} = 6.71$, $\mathbf{p < .001}$, $g = 2.40$	$t_{(16)} = -3.19$, $\mathbf{p = .006}$, $g = -0.70$
	Oddball	$t_{(16)} = -1.99$, $p = .064$, $g = -0.47$	$t_{(15)} = 6.92$, $\mathbf{p < .001}$, $g = 2.51$	$t_{(16)} = -4.78$, $\mathbf{p < .001}$, $g = -1.50$
	Standing	$t_{(16)} = -2.55$, $\mathbf{p = .022}$, $g = -0.55$	$t_{(16)} = 2.15$, $\mathbf{p = .047}$, $g = 0.80$	$t_{(16)} = -0.46$, $p = .655$, $g = -0.10$
Alpha burst amplitude	Fixation	$t_{(17)} = -5.55$, $\mathbf{p < .001}$, $g = -0.75$	$t_{(16)} = 4.49$, $\mathbf{p < .001}$, $g = 1.65$	$t_{(16)} = -3.71$, $\mathbf{p = .002}$, $g = -0.97$
	Oddball	$t_{(17)} = -2.00$, $p = .061$, $g = -0.43$	$t_{(16)} = 7.52$, $\mathbf{p < .001}$, $g = 2.18$	$t_{(16)} = -6.47$, $\mathbf{p < .001}$, $g = -1.58$
	Standing	$t_{(16)} = 0.14$, $p = .889$, $g = 0.04$	$t_{(16)} = 0.17$, $p = .870$, $g = 0.06$	$t_{(16)} = -2.22$, $\mathbf{p = .041}$, $g = -0.32$
Theta burst cycles/min	Fixation	$t_{(17)} = 1.08$, $p = .295$, $g = 0.34$	$t_{(16)} = 5.57$, $\mathbf{p < .001}$, $g = 2.00$	$t_{(16)} = -1.77$, $p = .095$, $g = -0.58$
	Oddball	$t_{(17)} = 1.25$, $p = .227$, $g = 0.30$	$t_{(16)} = 7.80$, $\mathbf{p < .001}$, $g = 2.52$	$t_{(16)} = -4.03$, $\mathbf{p = .001}$, $g = -1.24$
	Standing	$t_{(16)} = 0.67$, $p = .513$, $g = 0.24$	$t_{(16)} = 4.68$, $\mathbf{p < .001}$, $g = 1.70$	$t_{(16)} = -5.02$, $\mathbf{p < .001}$, $g = -1.66$
Alpha burst cycles/min	Fixation	$t_{(17)} = 3.32$, $\mathbf{p = .004}$, $g = 0.96$	$t_{(16)} = -2.87$, $\mathbf{p = .011}$, $g = -1.13$	$t_{(16)} = 1.98$, $p = .065$, $g = 0.67$
	Oddball	$t_{(17)} = 2.63$, $\mathbf{p = .017}$, $g = 0.77$	$t_{(16)} = -3.31$, $\mathbf{p = .004}$, $g = -1.37$	$t_{(16)} = 2.51$, $\mathbf{p = .023}$, $g = 0.48$
	Standing	$t_{(16)} = 3.63$, $\mathbf{p = .002}$, $g = 0.89$	$t_{(16)} = -6.17$, $\mathbf{p < .001}$, $g = -1.73$	$t_{(16)} = 2.91$, $\mathbf{p = .010}$, $g = 0.56$
Pupil diameter (mean)	Fixation	$t_{(13)} = 0.39$, $p = .699$, $g = 0.13$	$t_{(16)} = -3.78$, $\mathbf{p = .002}$, $g = -1.22$	$t_{(15)} = 4.65$, $\mathbf{p < .001}$, $g = 1.26$
	Oddball	$t_{(12)} = -1.79$, $p = .099$, $g = -0.47$	$t_{(12)} = -1.39$, $p = .189$, $g = -0.59$	$t_{(12)} = 2.17$, $p = .051$, $g = 0.64$
Pupil diameter (STD)	Fixation	$t_{(13)} = -3.76$, $\mathbf{p = .002}$, $g = -0.98$	$t_{(16)} = 3.52$, $\mathbf{p = .003}$, $g = 1.25$	$t_{(15)} = -1.69$, $p = .111$, $g = -0.65$
	Oddball	$t_{(12)} = -3.66$, $\mathbf{p = .003}$, $g = -1.22$	$t_{(12)} = 4.74$, $\mathbf{p < .001}$, $g = 1.56$	$t_{(12)} = -2.58$, $\mathbf{p = .024}$, $g = -0.90$
Pupil oddball response	Oddball	$t_{(9)} = 0.26$, $p = .802$, $g = 0.07$	$t_{(11)} = -1.58$, $p = .143$, $g = -0.55$	$t_{(9)} = 2.08$, $p = .067$, $g = 0.74$
Blink rate	Fixation	$t_{(13)} = -1.32$, $p = .209$, $g = -0.39$	$t_{(16)} = 0.62$, $p = .545$, $g = 0.22$	$t_{(15)} = -1.25$, $p = .229$, $g = -0.42$
	Oddball	$t_{(13)} = -0.02$, $p = .987$, $g = -0.01$	$t_{(13)} = 4.37$, $\mathbf{p = .001}$, $g = 1.44$	$t_{(15)} = -0.21$, $p = .839$, $g = -0.08$
Ocular microsleeps (%)	Fixation	$t_{(13)} = -0.97$, $p = .350$, $g = -0.32$	$t_{(16)} = 4.81$, $\mathbf{p < .001}$, $g = 1.56$	$t_{(15)} = -4.85$, $\mathbf{p < .001}$, $g = -1.68$
	Oddball	$t_{(13)} = -1.32$, $p = .210$, $g = -0.47$	$t_{(13)} = 4.18$, $\mathbf{p = .001}$, $g = 1.41$	$t_{(15)} = -6.28$, $\mathbf{p < .001}$, $g = -2.16$

Table 3.1: Statistics results. Paired t-tests were conducted to determine overnight changes at baseline (BL Pre vs BL Post), changes across 24 h of extended wake (S1 vs S8), and deviations from the wake trajectories during the WMZ (S5&S8 vs S6&S7). All values were z-scored for each participant, pooling sessions, and conditions. Power values were z-scored separately for each frequency prior to being averaged into bands, and pupil oddball responses were z-scored also across timepoints prior to measuring the average response. Degrees of freedom are specified in the subscript of t-values and reflect the sample size for each comparison (N = DF + 1). Effect sizes are provided as Hedge's g values. All statistics are with α = 5%, significant p-values are in bold. There is no correction for multiple comparisons, given that the hypothesis being tested only applied to extended wake changes in the Fixation condition, and all other tests were either exploratory or confirmatory (see STAR methods).

3.3.1 Changes in theta power but not alpha power replicate previous results

Before investigating oscillatory burst activity, we first determined whether our novel experimental paradigm replicated findings of previous studies showing both circadian and homeostatic changes in theta and alpha power. We expected an increase in theta and a decrease in alpha with increasing time awake,

as well as a dip in theta during the WMZ, and a peak in alpha in the middle of the day (Cajochen et al., 2002). Power spectral density was calculated using Welch's method for every channel during each recording. These values were z-scored separately for each frequency, pooling channels, conditions, and sessions. Z-scored power values were then averaged across channels, and then averaged within the theta and alpha bands.

Changes in theta power are plotted in Figure 3.3A. After the baseline night, there was a significant decrease in theta power for the Fixation ($t_{(17)}$ = −4.80) and Oddball recordings ($t_{(17)}$ = −3.19), but no change during Standing with eyes closed ($t_{(16)}$ = −0.57). Across extended wake there was a substantial increase in theta power in all conditions (Fixation, $t_{(16)}$ = 9.66; Oddball, $t_{(16)}$ = 10.41; Standing, $t_{(16)}$ = 5.97). During the WMZ, all conditions showed very large and significant decreases in theta power (Fixation, $t_{(16)}$ = −5.96; Oddball, $t_{(16)}$ = −6.92; Standing, $t_{(16)}$ = −5.19).

Changes in alpha power are plotted in Figure 3.3B. After the baseline night, alpha power showed a trend increase for Fixation ($t_{(17)}$ = 1.75, p = .098), no change for Oddball ($t_{(17)}$ = 0.82), and a significant increase during Standing ($t_{(16)}$ = 2.57). Across extended wake, alpha actually increased for Fixation ($t_{(16)}$ = 3.03) and Oddball ($t_{(16)}$ = 3.89) and showed no significant change during Standing, although on average decreased ($t_{(16)}$ = −1.44). A significant dip in alpha was present during the WMZ in the Fixation condition ($t_{(16)}$ = −2.86) and even more prominent in the Oddball ($t_{(16)}$ = −3.61).

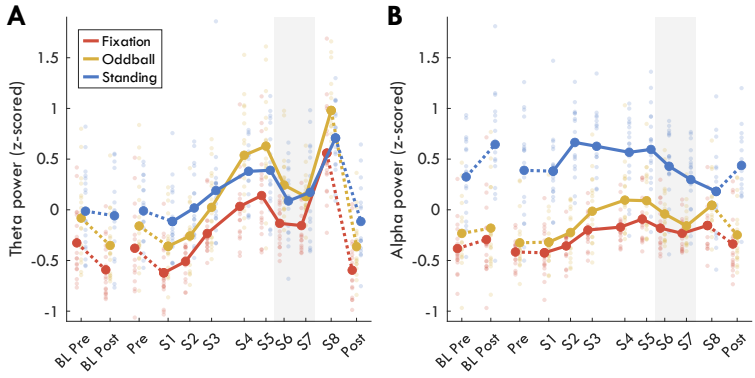

Figure 3.3: Z-scored power band changes. A: Theta power (4-8 Hz) and **B:** alpha power (8-12 Hz). Thick lines indicate group averages for each condition (as different colors) across sessions (x-axis). Solid lines connect sessions during the same-day extended wake period, and dashed lines indicate changes across sleep. S1-S8 are spaced out relative to the time they occurred within the 24 h wake period (Figure 3.1B). Dots reflect individual participants' datapoints. The shaded gray area indicates the WMZ. Power spectral density values were first z-scored for each frequency pooling channels, sessions, and conditions. All channels were included in the average except edge channels: 48, 63, 68, 73, 81, 88, 94, 99, 119. Finally, z-scored values within each band range were averaged.

Given the discrepancy with previous results that found decreases in alpha with sleep deprivation (Cajochen et al., 2002; Strijkstra et al., 2003), we inspected the spectrograms of z-scored power to determine whether some other factor was contributing to the increase in alpha in our data (Figure 3.11). We found broadband increases in power with time awake, as well as increases in theta and beta power extending into the alpha range. Furthermore, unlike previous experiments, our 4/24 design is such that S1 and S8 were during the lowest circadian points for alpha power. The broadband and neighboring band effects may have had a stronger influence on final alpha power compared to previous studies, thus explaining the discrepancy.

3.3.2 Oscillation amplitudes increase with extended wake independently from quantities, but decrease during the WMZ

Cycle-by-cycle analysis was used to identify bursts between 2 and 14 Hz (a schematic of the algorithm is provided in Figure 3.9). Figure 3.4 provides an example of the EEG and burst detection during S8. The detected bursts were then split into theta (mean frequency between 4 and 8 Hz), and alpha (8 and 12 Hz). Oscillation amplitudes were quantified as the average negative-to-positive peak voltage for all the cycles involved in a burst. The "number" of oscillations were quantified as the number of cycles per minute.

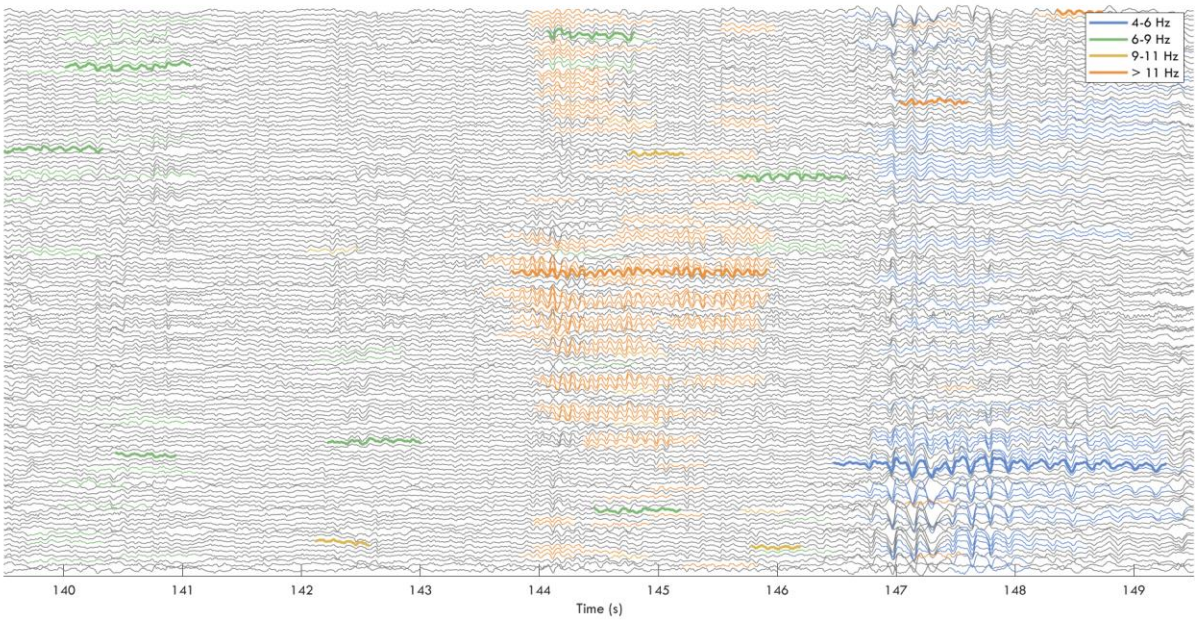

Figure 3.4: Example of detected bursts. 10 seconds of data from P15 Fixation (see Figure 3.13A). EEG data traces are in gray. Thick colored lines indicate the "reference" burst, the longest among temporally overlapping bursts in the same channel. Thin colored lines indicate overlapping bursts across channels considered to be the "same" burst as the reference. These were associated with the reference because mean frequencies were within 1 Hz of each other. Different colors represent different frequency bands.

Figure 3.5 plots the change in theta and alpha bursts by average amplitude (Figure 3.5A-B), and cycles per minute (Figure 3.5C-D). Amplitudes tended to decrease after baseline sleep for theta (Fixation: $t_{(15)}$ = −2.06, p = .057; Oddball: $t_{(16)}$ = −1.99, p = .064; Standing: $t_{(16)}$ = −2.55, p = .022). Amplitudes significantly decreased after sleep for alpha Fixation ($t_{(17)}$ = −5.55), were trending for Oddball ($t_{(17)}$ = −2.00, p = .061), and showed no change during Standing ($t_{(16)}$ = 0.14). During extended wake, amplitudes increased substantially for both theta and alpha in the Fixation (theta $t_{(16)}$ = 6.71; alpha $t_{(16)}$ = 4.49) and Oddball conditions (theta $t_{(15)}$ = 6.92; alpha $t_{(16)}$ = 7.52). Theta amplitudes increased during wake in Standing ($t_{(16)}$ = 2.15, p = .047) but no change was observed in alpha amplitudes during Standing ($t_{(16)}$ = 0.17). The trajectory of the increase in amplitudes for both theta and alpha, and Fixation and Oddball, approximated that of an increasing saturating exponential function, with steeper increases at the beginning (S1 to S3 theta Fixation increased by 19% [interquartile range (IQR): 7, 27], theta Oddball 19% [10, 26]; alpha Fixation 14% [5, 19], alpha Oddball 14% [7, 20]) compared to end of the wake period (S1 to S8 theta Fixation 31% [10, 42], theta Oddball 29% [20, 35]; alpha Fixation 20% [9, 28]; alpha Oddball 27% [13, 34]). Theta Standing amplitudes only increased across the first six hours (S1 to S3: Standing 11% [0, 16]; S1 to S8: Standing 11% [-2, 22]), and alpha increased from S1 to S2, then decreased from S5 to S6. Against our expectations,

however, both theta and alpha showed a robust decrease in amplitude during the WMZ for both Fixation (theta $t_{(16)} = -3.19$; alpha $t_{(16)} = -3.71$) and Oddball (theta $t_{(16)} = -4.78$; alpha $t_{(16)} = -6.47$).

Changes across baseline sleep in cycles per minute went in the opposite direction from amplitudes: theta quantities on average increased although this was not significant (Fixation $t_{(17)} = 1.08$; Oddball $t_{(17)} = 1.25$; Standing $t_{(16)} = 0.67$) and alpha significantly increased (Fixation $t_{(17)} = 3.32$; Oddball $t_{(17)} = 2.63$; Standing $t_{(16)} = 3.63$). During extended wake, theta quantities significantly increased in all conditions along a mostly linear trajectory (Fixation $t_{(16)} = 5.57$; Oddball $t_{(16)} = 7.80$; Standing $t_{(16)} = 4.68$), whereas alpha quantities decreased (Fixation $t_{(16)} = -2.87$; Oddball $t_{(16)} = -3.31$; Standing $t_{(16)} = -6.17$), primarily during S8. During S1, theta occupied on average 8% [IQR: 1, 8] of the Fixation recording (Oddball: 10% [1, 13]; Standing: 12% [2, 16]) and this more than doubled to 22% [4, 34] during S8 (Oddball: 25% [7, 37]; Standing: 27% [8, 33]). Instead, alpha occupied 54% [24, 78] of the Fixation recording during S1 (Oddball: 54% [27, 72]; Standing: 80% [59, 96]), which decreased to 42% [26, 58] during S8 (Oddball: 41% [26, 57]; Standing: 56% [35, 78]).

Theta and alpha cycles per minute were significantly affected by the WMZ in opposite directions during the Standing (theta $t_{(16)} = -5.02$; alpha $t_{(16)} = 2.51$) and Oddball conditions (theta $t_{(16)} = -4.03$; alpha $t_{(16)} = 2.91$) but trending in Fixation (theta $t_{(16)} = -1.77$, $p = .095$; alpha $t_{(16)} = 1.98$, $p = .065$), such that theta quantities decreased relative to the overall trajectory, and alpha increased (or did not decrease along the expected trajectory).

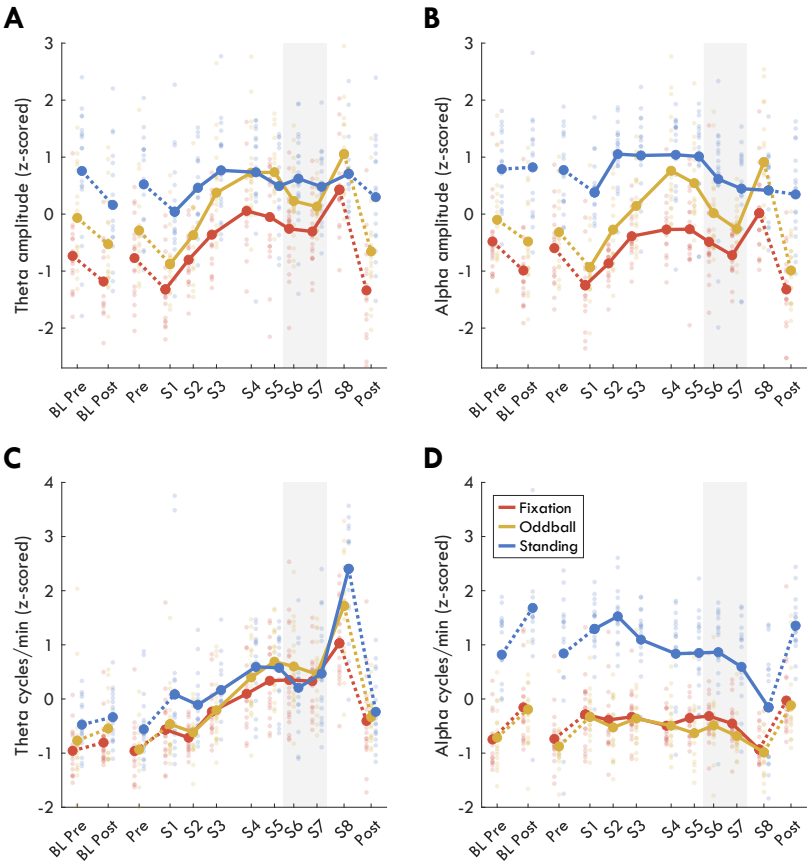

Figure 3.5: Z-scored burst changes in amplitude and quantity. **A**: Average theta burst amplitudes, **B:** alpha burst amplitudes, **C**: number of theta cycles per minute, **D**: alpha cycles per minute. Thick lines indicate group averages for each condition across sessions (x-axis), with color indicating condition. Solid lines connect sessions during the same-

day extended wake period, and dashed lines indicate changes across sleep. S1-S8 are spaced out relative to the time they occurred within the 24 h wake period (Figure 3.1B). Dots reflect individual participants' datapoints. The shaded gray area indicates the WMZ. All values are z-scored within each figure, such that sessions and conditions were pooled.

To determine whether oscillation amplitudes and quantities originated from the same areas, we inspected the mean distribution of amplitudes and cycles per minute for theta and alpha bursts across the 123 channels, pooling sessions (Figure 3.6A-B). To determine whether the changes observed in Figure 3.5 were spatially dependent, we performed paired t-tests between S1 and S8 for each channel, with false-discovery rate (FDR) correction (Figure 3.6C-D).

For all three conditions, theta bursts were located primarily in frontal-midline channels, which also generated the largest amplitudes (Figure 3.6A). The increases observed with extended wake were widespread although somewhat patchy for both amplitudes and cycles per minute (Figure 3.6C) and were not limited to the main frontal-midline sources of theta. Alpha amplitudes and cycles per minute were instead spatially dissociated (Figure 3.6B), with high amplitudes originating more occipitally, and high quantities originating more centro-parietally. While the increase in alpha amplitudes in the Fixation and Oddball were similarly widespread as in theta, during the Standing condition the increase was only frontal (Figure 3.6D, top row). Instead, the decrease in alpha quantities was localized to the centro-parietal regions in Fixation and Oddball, with more widespread decreases in Standing (Figure 3.6D, bottom row).

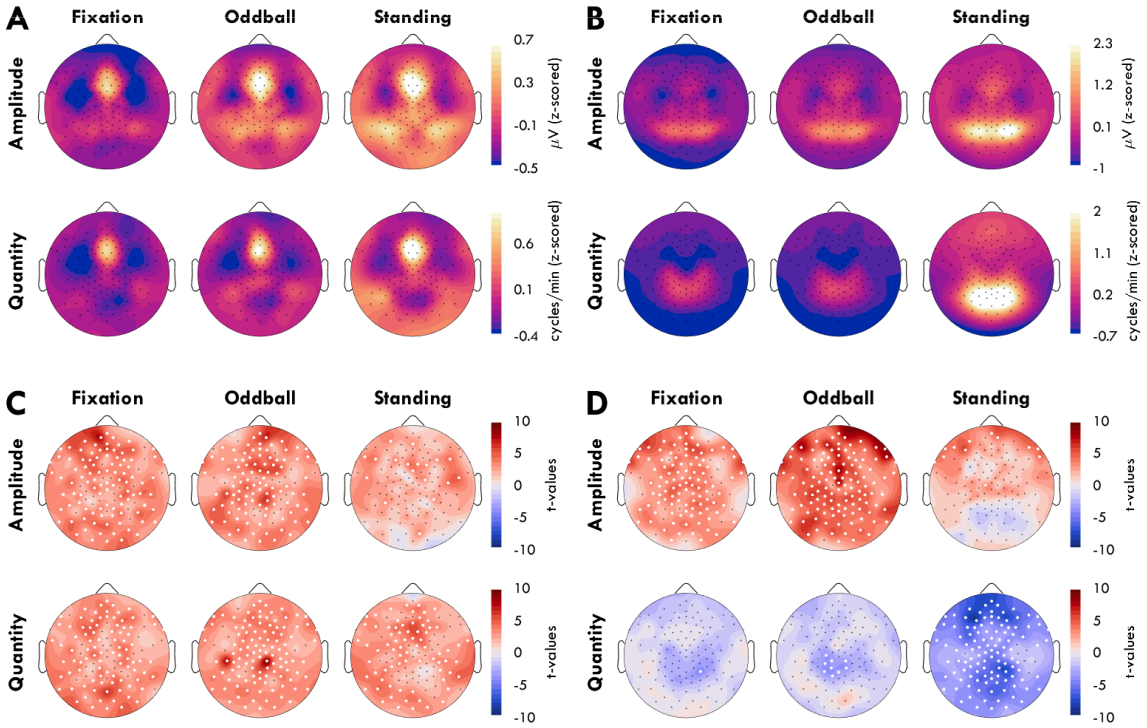

Figure 3.6: Topographic distribution of burst amplitudes and cycles per second. A-B: Amplitudes (top row) and cycles per minute (bottom row) for theta (A) and alpha bursts (B) across 123 channels for each condition, z-scored and averaged across all sessions. Warmer colors indicate higher amplitudes/quantities. **C-D**: Change in amplitudes and cycles/min from S1 to S8 for theta (C) and alpha bursts (D) represented as t-values, such that red indicates an increase with time awake. White dots indicate channels for which the difference was significant ($p<.05$, $N = 17$) based on paired t-tests, with false discovery rate correction.

3.3.3 Pupil diameter means and standard deviations change during the WMZ, while pupil responses to oddball tones do not

To explore further what drives the different trajectories observed in the EEG data across wake, and in particular the changes in the WMZ, we analyzed pupillometry data from the Fixation and Oddball conditions. In both, mean pupil diameter after an initial decrease remained largely constant during the extended wake period (Figure 3.7A), with a specific increase during the two WMZ timepoints (Fixation $t_{(15)}$ = 4.65; Oddball $t_{(12)}$ = 2.17, p = .051). There was also a significant drop in pupil diameter from S1 to S8 during Fixation ($t_{(16)}$ = −3.78, p = .002) but not Oddball ($t_{(12)}$ = −1.39, p = .189). Interestingly, the two baseline recordings done in the evening an hour before bedtime (BL Pre, Pre) showed larger diameters during Oddball than during Fixation (BL Pre: $t_{(12)}$ = 2.18, p = .050, g = 0.62; Pre: $t_{(16)}$ = 3.22, p = .005, g = 0.63), but not during the same recording of extended wake (S7 $t_{(14)}$ = -0.77, p = .453, g = -0.16). This indicates an interaction, at least within the WMZ, between recording condition, pupil diameter, and prior sleep restriction.

Standard deviations of pupil diameter were also assessed (Figure 3.7B). Across sleep, there was a large significant decrease in standard deviations for both conditions (Fixation $t_{(13)}$ = -3.76; Oddball $t_{(12)}$ = -3.66). During extended wake, standard deviations increased to maximum values in the afternoon (S4, 15:00). Standard deviations then tended to decrease during the WMZ, although the effect was only significant in the Oddball ($t_{(12)}$ = −2.58, p = .024) and not Fixation ($t_{(15)}$ = −1.69, p = .111). Across wake there was a significant increase in standard deviations from S1 to S8 (Fixation $t_{(16)}$ = 3.52; Oddball $t_{(12)}$ = 4.74), although S8 Oddball values returned to those of S3-S5 after the WMZ, whereas S8 Fixation remained lower.

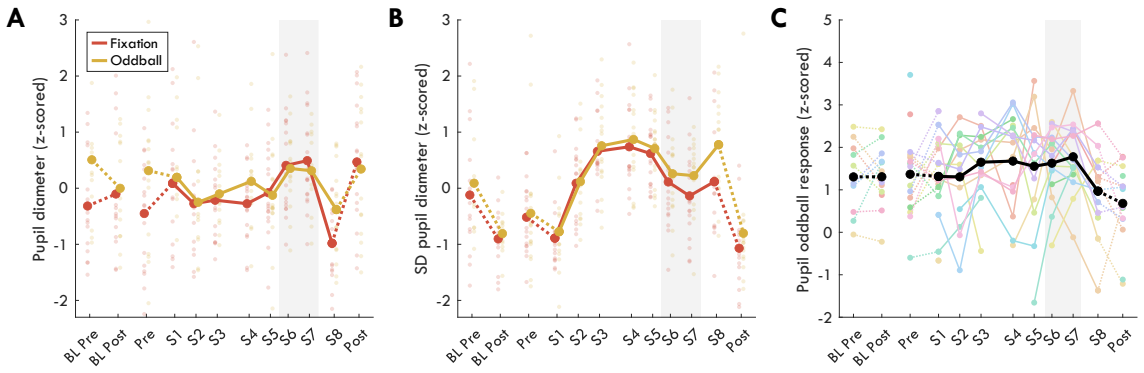

Figure 3.7: Pupil diameter. **A**: Mean diameter and **B**: standard deviations. **C**: Oddball pupil diameter response to target tones relative to standard tones from 0.5 to 2 s after tone onset. Colored lines indicate data from individual participants. Timecourses are provided in Figure 3.12.

Finally, we investigated the pupil response to target tones during the auditory Oddball condition (Figure 3.7C, Figure 3.12). Unfortunately, there was substantial data loss due to increased eye-closure with extended wake (Figure 3.8B) combined with equipment malfunctions during measurements, so power for this analysis is reduced. Pupil response to oddball tones was quantified as the area under the curve between the pupil response to targets relative to standard tones, from 0.5 to 2 s after tone onset. There was no change in response to targets from evening to morning around a baseline night of sleep ($t_{(9)}$ = 0.26), nor was there a significant change from beginning to end of the extended wake period, although there was on average a decrease in pupil oddball response ($t_{(11)}$ = -1.58). There was trending effect of the WMZ ($t_{(9)}$ = 2.08, p = .067). However, as can be seen from Figure 3.7C, this was almost entirely due to a drop in the oddball response for S8 relative to previous sessions (e.g. S5 vs S8: $t_{(10)}$ = 2.77, p = .020, g = -

1.07). Furthermore, there was never a return to baseline values of pupil oddball response following recovery sleep (Pre vs Post: $t_{(13)}$ = 2.43, p = .030, g = -0.62), complicating any potential interpretation.

3.3.4 Ocular microsleeps are sensitive to the WMZ, blink rates are not

In addition to actual pupil diameters, the same eye-tracking cameras were sensitive to ocular behavior such as blinking and microsleeps, both of which increase with sleepiness (Crevits et al., 2003; Moller et al., 2006) and can potentially affect measures of pupillometry. We therefore wished to determine whether the changes in pupillometry could be explained by ocular behavior, based on whether they followed similar trajectories across time. We measured all eye-closures and split them into blinks when less than 1 s (Fatt & Weissman, 2013; Kwon et al., 2013), and as ocular microsleeps when longer than 1 s (Hertig-Godeschalk et al., 2020). We specify "ocular" to distinguish from microsleeps properly classified with the EEG (Hertig-Godeschalk et al., 2020), and we label them as "microsleeps" rather than merely eye-closures because prolonged eye-closures during sleep deprivation are predictive of behavioral lapses in auditory tasks (Ong et al., 2013).

Blink rates (Figure 3.8A) gradually increased across wake in the Oddball ($t_{(13)}$ = 4.37) but not Fixation condition ($t_{(16)}$ = 0.62), and there was no change during the WMZ (Fixation $t_{(15)}$ = −1.25; Oddball $t_{(15)}$ = −0.21). Therefore, blinking could not explain changes in pupillometry. At the same time, the amount of ocular microsleeps was extremely sensitive to the WMZ (Fixation $t_{(15)}$ = −4.85; Oddball $t_{(15)}$ = −6.28), returning almost entirely to baseline levels. However, across extended wake, ocular microsleeps otherwise increased linearly, starting from near zero and reaching 10-15% of the recordings by S8 (Fixation $t_{(16)}$ = 4.81; Oddball $t_{(13)}$ = 4.18). Like with blinking, this trajectory was not reflected in the various measures of pupillometry, and therefore cannot explain the results.

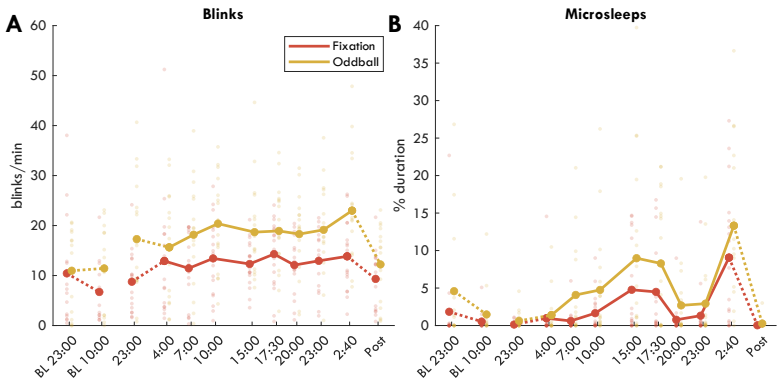

Figure 3.8: Eye-closures. **A:** Number of blinks per minute. A blink is defined as any eye-closure less than 1 s long. **B**: Percent of recording with ocular microsleeps (eyes closed longer than 1 s). N.B. here raw values are provided, although the statistics described in the text are with z-scored values.

3.4 Discussion

The two-process model of sleep has been the backbone of sleep research for the past 40 years, and has withstood the test of time (Borbély et al., 2016). Not only is sleep homeostasis uncontroversial, it is now used to prove whether a given organism sleeps at all (Tobler, 1985, 1995). The synaptic homeostasis hypothesis has been more contentious, especially in the details of the underlying mechanisms behind "synaptic strengthening" (Cary & Turrigiano, 2021; Frank, 2011, 2013), however the general idea is compelling: that synaptic changes during the day requires sleep to restore synaptic balance. Both of these models were based primarily on observations during sleep, and while they made testable predictions of what should occur during wake, measurements of EEG power did not conform to expectations. The two-process model of sleep postulated that sleep need accumulates along an increasing saturating exponential function with time awake (Figure 1A), and the synaptic homeostasis hypothesis proposed that this process is driven by increasing synaptic strength, which results in increased neuronal synchrony (Borbély, 1982; Tononi & Cirelli, 2003). By separately analyzing oscillation amplitudes and quantities, we were able to validate these predictions.

Our results reveal that indeed both theta and alpha amplitudes follow an increasing saturating exponential trajectory across extended wake, following the predicted trajectory of sleep homeostasis (Figure 3.5A-B vs Figure 3.1A). Furthermore, both theta and alpha amplitudes returned to baseline levels following recovery sleep, with trending decreases for theta and highly significant decreases for alpha around baseline sleep. These results therefore match the predictions of the two-process model and the synaptic homeostasis hypothesis. It is still possible that synaptic strength does not drive this increase in amplitudes, but at the very least, changes in wake oscillation amplitudes correspond to the changes observed in slow wave activity (Borbély, 1982; Dijk et al., 1987).

In particular, the fact that the number of alpha oscillations decreased at the same time as amplitudes increased, and the former was widespread and the latter was localized (Figure 3.7D), clearly indicates a dissociation between these homeostatic changes in amplitude from whatever process causes oscillations to occur in the first place. More subtly, while both theta amplitudes and quantities increased during extended wake, the trajectories were different, suggesting again distinct mechanisms. In both cases, spectral power was insufficient to capture these trends with time, as it cannot differentiate between simultaneous and comparably large changes in amplitudes and quantities.

These results invite re-analysis of many previous findings showing differences in power between conditions and populations. Efforts are already underway to distinguish the effects of periodic and aperiodic components of the EEG spectrum (Donoghue et al., 2020). Therefore, in cases in which the effect is largely periodic, further investigation should determine whether it is the amplitude or quantities of oscillations that change; this can then provide more interpretable results. In the context of understanding synaptic plasticity for example, it would be beneficial to re-analyze data from the studies of Hung et al. (2013) and Bernardi et al. (2015). These two landmark studies found that theta power in resting state EEG increased locally depending on prior daytime activity. Re-analysis of these datasets may reveal whether this effect was specific to oscillation amplitudes, even in the alpha band, which would further support the interpretation that such local effects are driven by spatial differences in synaptic strengthening.

Sensitivity of different conditions to sleep homeostasis. Beyond demonstrating whether the standard eyes-open resting EEG would be sensitive to sleep and synaptic homeostasis, we were interested in establishing whether this generalized to other conditions. We indeed found that the EEG of the Oddball

followed the same trajectories as Fixation, but the Standing condition did not. Theta Standing amplitudes did not increase past S3 during the extended wake period, and alpha Standing amplitudes neither decreased following sleep, nor did they increase during extended wake past S2. Given the overall larger amplitudes in this condition, this may be at least partially due to a ceiling effect. At the same time, given the eyes-closed condition, it's also possible that participants were closer to "true sleep" during S8 Standing. This is supported by the complete change in spectrogram in the Standing Back ROI (Figure 3.11). Altogether, our results indicate that oscillation amplitudes tend to reflect sleep homeostasis, however this is not the only factor contributing to these amplitudes. In practice, this means that different recording conditions will be more or less sensitive to changes in sleep homeostasis.

Cortical desynchronization during the WMZ. What did not match our predictions at all were oscillatory amplitudes during the WMZ. In both Fixation and Oddball, theta and alpha oscillation amplitudes decreased during the WMZ, then returned to their previous trajectories during S8. The effect sizes of the WMZ were actually larger for amplitudes compared to the number of oscillations (Table 3.1). The fact that oscillation amplitudes decreased implies that whatever mechanism drives the WMZ, it results in overall desynchronized cortical activity. Supporting this finding of cortical desynchrony, Ly et al. found that transcranial-magnetic stimulation (TMS) evoked potentials, reflecting cortical excitability, had lower amplitudes during the WMZ compared to earlier in the day (Ly et al., 2016). Except for such circadian changes, TMS evoked potentials across the day reflect sleep homeostasis, increasing with time awake and decreasing following sleep (Huber et al., 2013). However more generally, increased cortical synchronization reflects decreasing levels of consciousness, with deeper sleep stages and comatose states producing the largest evoked potentials (Casali et al., 2013; Massimini et al., 2005; Sarasso et al., 2014). Therefore it's possible that the WMZ may even reflect a qualitatively distinct state of alertness.

In practice, this means that oscillation amplitudes can usually be used as a marker for homeostatic sleep pressure, except during the hours before habitual sleep. We don't consider this dip in amplitudes during the WMZ (and the difference in Standing oscillation amplitudes described above) to indicate that the two-process model and synaptic homeostasis hypothesis are inaccurate, just that amplitudes of oscillations are no longer accurately reflecting the wake-related changes in neuronal connectivity and sleep homeostasis.

Timing and duration of the WMZ. It is noteworthy how the WMZ briefly interrupts both the linear increase in theta quantities and the saturating exponentials of theta and alpha amplitudes. This highlights how the WMZ is limited in time, unlike the gradual circadian component of the two-process model (Figure 3.1A). The model was established based on measures of alertness, core body temperature, and melatonin concentration, all of which changed approximately sinusoidally across 24 h (Åkerstedt et al., 1979). While none of our outcome measures were paralleling these sinusoidal fluctuations, almost all of them were clearly affected by the brief WMZ. We therefore suspect that a specific pathway is responsible for the WMZ, distinct from melatonin concentration and core body temperature, although still synchronized to the suprachiasmatic nucleus (SCN), the brain's timekeeper (Aston-Jones et al., 2001).

The timing of the WMZ in our study diverges slightly from some previous studies which find the WMZ to occur 3-6 h before bedtime (McMahon et al., 2018; Shekleton et al., 2013; Zeeuw et al., 2018), but is in agreement with others that find the WMZ 1-4 h before bedtime (Dijk & Czeisler, 1995; Lavie, 1997). Studies like ours with later WMZ times were conducted under normal office lighting conditions (~150 lux, or no manipulation reported), whereas studies with earlier WMZ times were recorded under dim lighting conditions (<10 lux). As demonstrated by Gooley et al. (2011), brighter light shifts melatonin

onset to around 2 hours later, likely explaining the difference in results. This therefore means that whatever light-induced mechanism delays melatonin onset, it also delays WMZ onset.

Neural pathways of the WMZ. Given that both the mean and standard deviation of pupil diameters were also strongly affected by the WMZ (Figure 3.8), it is likely that the ascending arousal system (AAS) is involved. The AAS includes the locus coeruleus (LC), the ventral tegmental area and substantia nigra, the dorsal and median raphe nuclei, and the basal forebrain (Lloyd et al., 2022). All these areas have been linked to changes in pupil diameter (Joshi & Gold, 2020; Lloyd et al., 2022; Reimer et al., 2016), and have widespread connections to the rest of the cortex. The LC in particular has been linked to transitory pupil responses such as the increases observed during oddball tasks (Aston-Jones & Cohen, 2005; Joshi et al., 2016; P. R. Murphy et al., 2014). Since we do not find an increase in pupil responses to oddball target tones in the WMZ (Figure 3.7), this may suggest that of all the AAS, the LC is actually not involved in the WMZ. Alternatively, this may merely indicate that pupil oddball responses are not a reliable indicator of LC activity across time. Unfortunately, due to reduced power, these results are suggestive at best, and furthermore the link between LC and pupil diameters has not been unambiguously established. Hopefully future studies will be able to determine which nuclei are involved in the WMZ.

The role of the WMZ in humans. The WMZ has, to our knowledge, only been investigated in humans. It's possible the WMZ may even be human-specific, but this can be difficult to validate because it bears a close resemblance to crepuscular behavior observed in some animal species, especially rodents (Ackermann et al., 2020; García-Allegue et al., 1999). Crepuscular rhythms manifest as increases in activity at dawn and dusk, usually accompanied by corresponding increases in core body temperature (Refinetti, 1996, 2020). By contrast, the WMZ in humans occurs in the absence of either increases in activity (Lieberman et al., 1989; Samson et al., 2017) or core body temperature (Dijk & Czeisler, 1995), suggesting differences in underlying physiological pathways, as well as different functions.

The fact that the WMZ primarily affects sleepiness and sleep latencies suggests that the main function of the WMZ is to resist sleep rather than promote activity. This may be a human-specific adaptation because we have long consolidated wake and sleep, unlike most other species who have more fragmented and polyphasic sleep (Campbell & Tobler, 1984; Samson & Nunn, 2015). By ensuring that individuals do not initiate sleep too early, the WMZ largely guarantees that the subsequent 8 hours of sleep are *completed* within the correct circadian window, thus maintaining continued synchronization with the overall circadian rhythm and environmental light-dark cycles. During normal wake, the WMZ may not be apparent or even necessary, however when homeostatic sleep pressure is unusually high (for example from insufficient sleep the night before), such a mechanism would be critical to maintain wakefulness until the onset of the correct sleep window. In polyphasic-sleep species such as mice and rats, the timing of sleep onset for any given sleep episode is less critical. An alternative hypothesis is that the WMZ is a vestige of primate nest-building, which also occurs in the evening. However, such an activity takes around 7 minutes (Fruth et al., 2018) so this does not explain why the WMZ would last several hours.

The WMZ needs to be investigated more. As speculated by Strogatz et al. (1987), such a mechanism may be behind sleep disorders such as insomnia; if the WMZ never "shuts off," this will result in substantially delayed sleep onset; if it is not present at all, this could result in circadian desynchrony. Taking this one step further, control over the WMZ could improve general wellbeing; being able to selectively shut it off could help with jetlag. Alternatively, activating the WMZ during night shifts could improve performance in critical industries such as emergency medicine or airline pilots. Our 4/24 extended wake paradigm, measuring both EEG and pupillometry, consists of a comparatively easier and equally effective approach

to investigating the WMZ relative to the standard >40 h sleep deprivation, and may therefore be better suited for large-scale studies also involving patients.

3.4.1 Limitations of the study

While we are satisfied with many of the design choices for this experiment, there is room for improvement. Given the unexpected importance of the WMZ, we would have benefitted from a traditional circadian marker such as melatonin concentration, which would have allowed more precise synchronization across participants to circadian phase. Additionally, more frequent recordings (e.g. every hour) would have provided a better temporal resolution to delineate the start and end of the WMZ for each participant. Regarding the wake recordings, given that the Oddball condition produced the largest effect sizes, it's possible more controlled tasks provide better results than Fixation. Regarding the analyses, we implemented a relatively basic cycle-by-cycle burst detection algorithm, and there is ample room for improvement following more systematic development of this approach.

Regarding the interpretation of the EEG results, it is important that they are replicated with datasets using much longer bouts of sleep deprivation, spanning more than 24 h and with more than a single recording after the WMZ; it's possible that slower circadian changes are still present in oscillation amplitudes, which cannot be disentangled within a single period. Likewise, data exists using the forced desynchrony protocol (Cajochen et al., 2002) which can properly dissociate circadian from homeostatic changes, as well as a constant routine protocol to control for homeostatic pressure (Cajochen et al., 2001). It would be important to see to what further extent amplitudes and number of bursts differently reflect circadian and homeostatic changes. Regarding the pupillometry results, it is important that they are replicated with larger sample sizes, and possibly comparing circadian changes with and without sleep restriction, as our results suggest an unexpected interaction.

3.4.2 Conclusions

In summary, we found that wake EEG oscillations reflect the increase in neuronal connectivity that builds up with time awake, through increased amplitudes, which change independently across time from oscillation quantities. We demonstrated that both theta and alpha amplitudes follow the same increasing saturating trajectories of sleep homeostasis previously identified with slow waves during sleep. However, the wake maintenance zone proved to be such a potent contributor to wakefulness as to temporarily counteract these effects, impacting both the amplitudes and number of occurrences of oscillations. In addition to the EEG, we have identified mean pupil diameter as specifically sensitive to this window. This specificity strongly suggests that the WMZ is caused by a wakefulness driver distinct from the gradual sinusoidal 24 h circadian fluctuations in alertness. Finally, we speculate that the ascending arousal system may be crucially involved, and that the WMZ may be human-specific.

3.5 STAR Methods

3.5.1 Experimental model and study participant details

18 participants completed the experiment. University student applicants were screened for good health, good sleep quality, and at least some sleep deprivation vulnerability. 19 participants were recruited, and one participant dropped out midway. Of the 18 participants who completed the experiment, 9 were

female and 3 were left-handed, all of European ancestry. Between-sex comparisons were not considered due to the small sample size and consequent low power. Participants were required to be between the ages of 18 and 26 in order to reduce interindividual age-effects of sleep homeostasis; consequently, mean age (± standard deviation) was 23 ± 1 years old. This limits generalizability, but the outcomes for specific populations can be anticipated from homeostatic changes in slow wave activity. All participants self-reported no hearing impairments. Data collection and interaction with participants was conducted according to Swiss law (Ordinance on Human Research with the Exception of Clinical Trials) and the principles of the Declaration of Helsinki, with Zurich cantonal ethics approval BASEC-Nr. 2019-01193. Participants signed informed consent before the study.

3.5.2 Method details

3.5.2.1 Experiment design

Participants conducted a 4/24 extended wake paradigm, depicted in Figure 3.1. This involved habituation to a regular sleep-wake schedule prior to the experiment (minimum 4 nights), with bedtimes and wakeup times selected to match the participant's preferred window and daily schedule. During the experiment, participants went to bed at their habitual bedtime, and were woken up 4 hours later. They were then kept awake for 24 h, followed by a recovery night. In addition to the extended wake bout, participants conducted a baseline night in which they slept during their habitual sleep window. The baseline was conducted before the extended wake bout in all but four participants.

The experiment schedule is in Figure 3.1B. Resting wake EEG recordings were measured before and after each night of sleep, and an additional 6 times during the 24 h wake period, for a total of 12 recordings. Prior to each recording S2-S7, participants were seated in the same position, watching 2 TV episodes around 40 minutes each, from a series of their choice. After each rest recording, participants were free to move around, and were provided with a home-cooked meal which they had selected from a list of vegetarian options (each meal during each break was the same). 6 of these breaks were included, each around 40 minutes (adjusting for delays in the schedule).

During the rest recordings, participants were seated in a comfortable armchair with a footrest (IKEA strandmon) in a well-lit room (~150 lux at eye level) and had to maintain fixation on a 20 cm red cross placed ~3 m from their head, ~30 cm below eye-level. The timing of the three rest recording conditions is depicted in Figure 3.1C. Each session began with a Fixation period, in which their only instructions were to maintain fixation on the cross and stay awake. This was immediately followed by an active auditory Oddball. As the focus was on pupillometry for this task, the stimuli were tones rather than visual inputs in order to avoid any spurious changes in light. Two types of tone were presented: standards (160 tones), and targets (40 tones). Participants had to press a button whenever a target tone occurred, while maintaining fixation and staying awake. Each tone lasted 60 ms, and for each participant the tone was either 660 Hz or 440 Hz for the targets, and vice versa for the standard tones. The interstimulus interval ranged randomly from 1.8 to 2.4 s, with a minimum of 3 standard tones between targets. After the Oddball, participants were provided a questionnaire to fill out, including the Karolinska Sleepiness Scale (KSS, Figure 3.2) (Åkerstedt & Gillberg, 1990). Finally, participants stood up from the chair and moved to lean against the wall and had a Standing period with eyes closed. The purpose of this condition was to have a long recording with eyes-closed, the most typical condition for alpha activity (Kirschfeld, 2005), without participants falling asleep. Caldwell et al. (2000) previously found that there was no effect on alpha activity when comparing seated to standing recordings across sleep deprivation during eyes closed.

Participants maintained a regular sleep-wake schedule the week prior to each experiment bout, and the timing of the experimental nights was adapted to each individual's preferred circadian time. Therefore the 24 h circadian rhythm could be inferred from previous studies (Åkerstedt et al., 1979; Dijk & Czeisler, 1995; Wyatt et al., 1999). Changes synchronized to melatonin would be high during night recordings (S1, S2, S8), and low during day recordings. Vice versa, circadian changes synchronized to core body temperature would peak in the middle of the day (S4, S5), and be low in the middle of the night (S1, S8). Because the focus was on homeostatic changes, these comparisons were not statistically analyzed, but can be inferred from the outcome measures' trajectories.

3.5.2.2 EEG preprocessing & power analysis

EEG data was recorded at 1000 Hz, with 129 electrodes including the Cz reference, using EGI HydroCel Geodesic Sensor nets. Four electrodes were external to the net, and were positioned on the mastoids and under the chin for sleep scoring (sleep architecture is available in Snipes et al. [2022]). Two electrodes (126, 127) were located on the cheeks and excluded, leaving 123 channels for EEG data analysis after re-referencing to the average. Preprocessing and data analyses were done using EEGLAB (Delorme & Makeig, 2004) and custom MATLAB scripts. Data was downsampled to 250 Hz and filtered between 0.5-40 Hz. Major artifacts were identified visually, and physiological artifacts (eye movements, heartbeat, muscle activity) were removed with independent component analysis (ICA). The process is depicted in Figure 2.19.

Power was calculated as power spectral density using Welch's method with 8 s windows, Hanning tapered, 75% overlap. Power values for each participant and each frequency were z-scored pooling across sessions, conditions, and channels. Z-scored values were then averaged across all channels excluding the outer-edge electrodes (Figure 3.3). When plotting spectrograms, a 1 Hz lowess filter was used to smooth the signal (Figure 3.11).

3.5.2.3 EEG burst detection

There were two main reasons for analyzing EEG oscillations as bursts using cycle-by-cycle analysis. First, when visually inspecting the EEG during extended wake, the most prominent features are in fact bursts rather than single isolated events, as can be seen in the example of Figure 3.4. Second, any method trying to investigate independent changes in oscillation amplitude and quantity must ensure that the detection method does not rely on either. Previous studies investigating plasticity-dependent effects and local sleep in wake identified waves based on either fixed or relative voltage thresholds (Andrillon et al., 2021; Bernardi et al., 2015; Fattinger et al., 2017; Hung et al., 2013; Quercia et al., 2018). The problem with fixed thresholds when trying to answer our research question is that when oscillations increase in amplitude without changing in quantity, they will still *appear* to increase in quantity since more waves are now above-threshold. The additional problem with relative thresholds, such as taking the top N% of all waves recorded for a given participant, is that it constrains the number of detected oscillations independently of how prevalent they are in the signal. Therefore, if a given participant has no oscillations, this method will identify false positives from the 1/f aperiodic background activity. Vice-versa, if a participant has a recording completely dominated by oscillations (such as with eyes-closed), this method will miss most of them. The problem of dependency between quantity and amplitude, as well as the problem of both over- and underestimating oscillations, persists for all oscillation-detection methods that require amplitude cutoffs, including wavelets and Hilbert (M. X. Cohen, 2014). Cycle-by-cycle analysis avoids this by relying

entirely on the shape and regularity of the signal; the tradeoff is that it is not suited to detecting single isolated waves such as local sleep events (Vyazovskiy et al., 2011).

For our analysis, burst detection was conducted with custom MATLAB scripts adapted from Cole and Voytek's Python *bycycle* package (Cole & Voytek, 2019). The pipeline described below is also provided schematically in Figure 3.9. First, clean EEG data was filtered into narrow overlapping bands (2-6, 4-8, 6-10, 8-12, 10-14 Hz) using a minimum order high-pass then low-pass equiripple FIR filter (stopband frequency = passfrequency ± 1 Hz, passband ripple 0.04 dB, stopband attenuation 40 dB). Zero-crossings were identified in the narrow-band filtered data. Then between descending zero-crossings and rising zero-crossings, negative peaks were identified as the minimum value in the "unfiltered" data (minimally filtered during pre-processing between 0.5 and 40 Hz). Positive peaks were also identified as the maximum values in the unfiltered data between rising and descending zero-crossings, and these were used as the start and end of each cycle around the negative peak.

Once all the peaks were identified, 4 consecutive cycles had to meet the following properties in order to qualify as an oscillation burst: A) the cycle's negative peak had to correspond to a local minimum; B) the mean distance to the neighboring peaks had to be within the range of the period of the filter (e.g. between 0.1 – 0.17 s when filtering between 6-10 Hz); C) the minimum ratio between the distance in time of the current peak to its neighbors had to be above 0.6 (i.e. similar consecutive periods); D) the rise amplitude, measured as the voltage difference between the prior positive peak to current negative peak, and decay amplitude of the cycle had to have a ratio of at least 0.5 (i.e. one flank was not less than half the amplitude of the other); E) the minimum ratio between the cycle amplitude (negative peak to positive peak voltage, averaging both neighboring positive peaks) and neighboring cycles had to be more than 0.6 (i.e. similar consecutive amplitudes); F) the proportion of timepoints decreasing in amplitude between previous positive peak and current negative peak, and timepoints increasing in amplitude between current peak and following positive peak, had to be above 0.6 (i.e. how much *time* during the cycle the signal went in the wrong direction); and G) the proportion of the voltage increasing from positive to negative peak, and decreasing from negative to positive peak, had to be above 0.6 (i.e. how much *amplitude* went in the wrong direction). The criteria B, E, and F are from Cole and Voytek, whereas A, C, D, and G are our additional optimizations. The parameters and burst-detection criteria were chosen through trial-and-error on an independent subset of data recorded during this experiment (the Game and PVT conditions of the SD task block reported in Snipes et al. [2022]). The procedure involved iteratively adjusting thresholds and introducing cycle exclusion criteria until the theta and alpha burst detection was largely consistent with visual inspection.

Bursts were detected for all frequency bands, using both the EEG signal and the inverse of the EEG signal (because for mu-shaped rhythms, the sharper peaks resulted in better burst detection). Within each channel, overlapping bursts were compared, and the largest was retained intact. Smaller partially overlapping bursts were cut, and if the non-overlapping segment still retained 4 cycles, it was considered a new burst. Then, bursts were aggregated across channels based on temporal overlap (at least 50%) and if the mean frequency was within 1 Hz for the overlapping cycles.

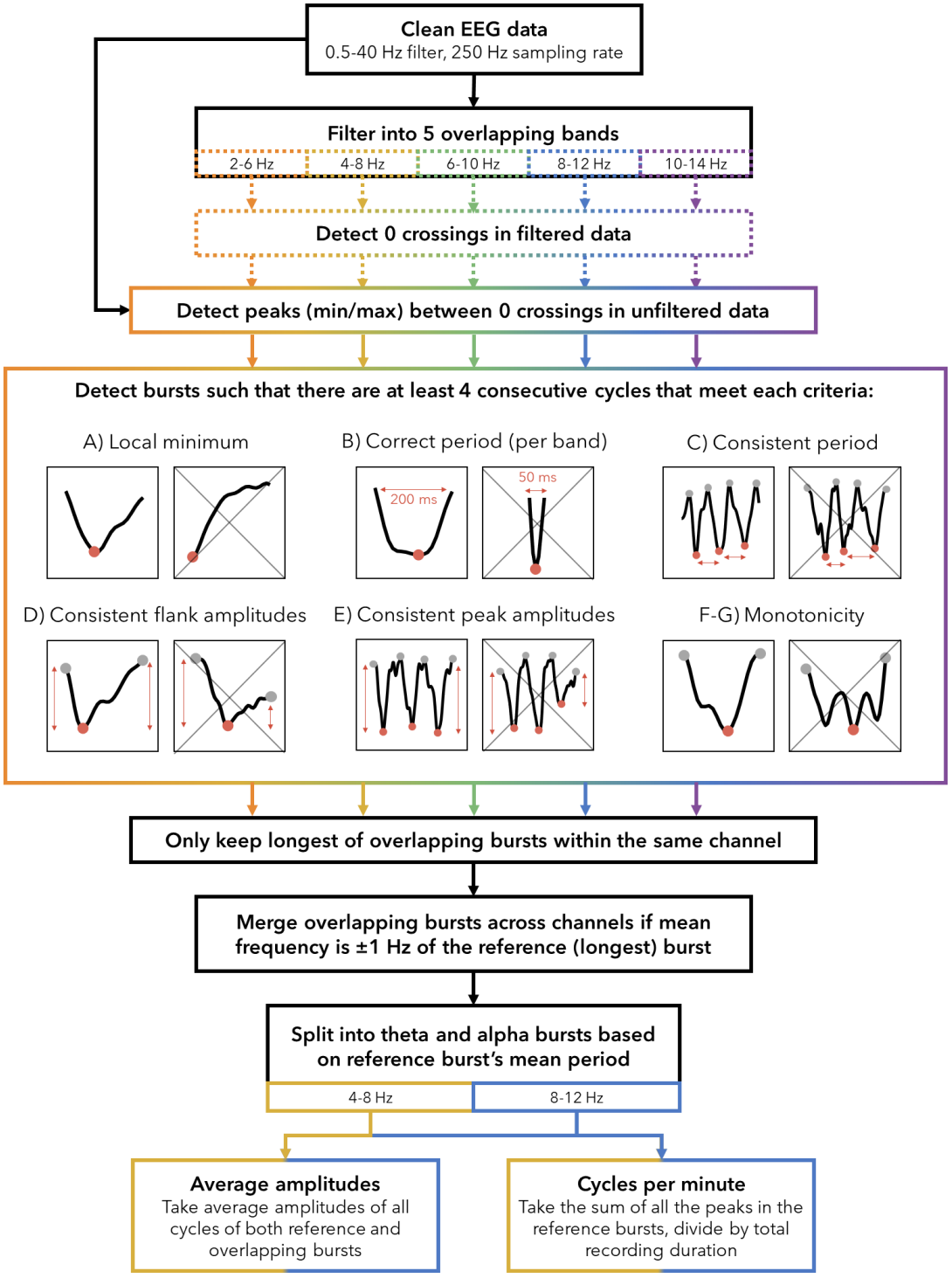

Figure 3.9: Burst detection algorithm. Solid outline indicates processes conducted on "unfiltered" data (only filtered between 0.5 and 40 Hz), dotted lines indicate processes conducted on filtered data (in 4 Hz bands). Colors indicate data processed separately for each band, black indicates processes done on pooled/undifferentiated data. A-G are examples of cycles that do or do not meet the criteria (crossed out). A and B depict half-cycles, from zero-crossing to zero-crossing. D and F/G indicate a whole cycle, from positive peak to positive peak. C and E indicate 3 consecutive cycles. In cycle-examples, red circles indicate the negative peaks, and gray circles positive peaks.

Burst frequencies were defined as the reciprocal of the mean distances between negative peaks. Burst amplitudes were calculated by first averaging the rise and decay amplitudes of each cycle, then the average of these across all cycles in the aggregated bursts in different channels, then averaging the amplitude of all bursts within the band of interest. Burst quantities were calculated as the sum of all the cycles in

the reference burst (the longest of all the overlapping bursts), divided by the duration of the recording, resulting in cycles per minute. This was chosen instead of the total number of bursts per minute because in extreme cases, bursts could become so long that their quantity decreased, and this was no longer representative of their occurrence in the data.

Figure 3.13A-B plots the distribution of the number of bursts by frequency for two example participants. Cycle-by-cycle analysis allowed clear differentiation between clusters of bursts by frequency. However, many individuals did not have two (theta/alpha), but in fact three or more clusters, and these distributions changed with time awake (best example: Figure 3.13A, Fixation). At the same time, other participants showed more classical bimodal distributions (Figure 3.13B). Ideally, we would have used individualized bands to delineate theta and alpha, however these shifting distributions complicate such an approach. Therefore, we limited ourselves to group average results using traditional frequency bands. Furthermore, rather than quantifying the occurrence of a given oscillation by the number of bursts as shown in Figure 3.13A-C, we used instead the number of cycles per minute (Figure 3.13G), as this also captures changes in burst duration (Figure 3.13E).

3.5.2.4 Eye tracking & pupillometry

Eye tracking was done with Pupil Core "glasses" (Pupil Labs, Berlin, Germany). These were eyeglass frames with two rear-facing infra-red cameras. Pupil diameter was estimated from the video recorded with a sampling rate of on average 120 Hz. Data was exported using Pupil Player. All analyses were then conducted with a sampling rate of 50 Hz. During measurements, the eye tracker failed multiple times, resulting in substantial data loss. Sleep loss further resulted in noisier data (more eye-closure, less fixed gaze, half-closed eyelids).

The eye tracking variables blink rate and ocular microsleeps were measured using the confidence values of the pupil diameter estimates (from 0 to 1): when model confidence fell below 0.5, this was considered an eye-closure. This approach was chosen based on our observation of the video relative to the model confidence. Consecutive timepoints with confidence values over 0.5 that lasted less than 50 ms were still considered eyes-closed, and consecutive timepoints under 0.5 and less than 50 ms long were considered eyes open. The cutoff to split blinks and microsleeps was based on previous research identifying microsleeps as short as 1 s (Hertig-Godeschalk et al., 2020).

2D pupil diameter was estimated from the eye videos offline with Pupil Player, measured in pixels. Between the recordings, the eye tracking glasses were removed and readjusted. Therefore, in order to compare mean pupil diameter across sessions, the diameters in pixels had to be re-scaled. For every video, a frame was selected (192 x 192 pixels, 4.5 x 4.5 cm), and the eye's iris diameter was measured in centimeters (when viewed at an angle, a disk becomes an ellipse, and the largest diameter of the ellipse is the diameter of the disk; Figure 3.10). By using the human mean iris diameter (12 mm), a conversion factor was calculated between pixels and millimeters, and this was applied to all 2D pupil diameter measurements:

$$pupil\ (mm) = \frac{pupil\ (px) \times video\ width\ (cm) \times standard\ iris\ (mm)}{iris\ (cm) \times video\ width\ (px)}$$

While this does not preserve individual differences in eye-size, it is sufficient for comparing across-session changes in diameter within participants (reasonably assuming irises do not change in size with sleep pressure). Furthermore, it allows the exclusion of unphysiological outliers of diameter estimates.

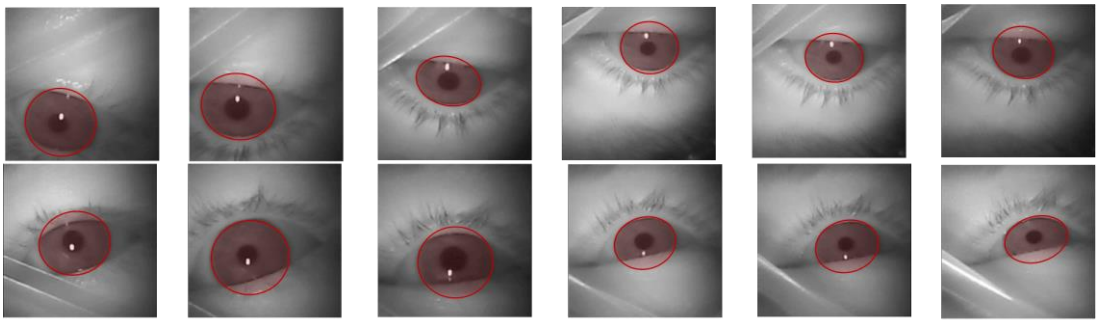

Figure 3.10: Collection of videoframes from the eye-tracking for a single participant. Red circles were used to measure make a fit of the iris, then identify the maximum radius; done manually with PowerPoint. The upside-down eyes are all the right eyes. The diagonal thing in the video is part of the EGI nets. Not included in the iScience publication.

Pupil preprocessing was done with the PhysioData toolbox (Kret & Sjak-Shie, 2019). Finally, removed datapoints less than 0.5 s were linearly interpolated, and then isolated chunks of datapoints less than 0.5 s were removed. Only data from one eye was used for each participant. The eye was chosen based on which had the most data after preprocessing.

To measure pupillary response to deviant tones during the Oddball, pupil diameters were epoched between -0.5 and 2 s relative to tone onset. All 40 targets were used, with 40 standards taken from the trial just prior to each target. Trials with less than 2/3 of clean timepoints were excluded. Recordings with less than 15 trials for either targets or standards were excluded. Furthermore, if any *timepoint* for a given tone type was derived by averaging fewer than 10 trials, this session was also excluded.

For each trial, the pupil response to tones was first baseline corrected (the mean between -0.5-0 s was subtracted from all datapoints in the trial), then all trials were averaged for each recording, split by target and standard tones. Participants with fewer than 6 recordings out of the 12 were excluded. Finally, average pupil responses for all timepoints, both targets and standards, and all sessions were z-scored within each participant. Pupillary response was calculated as the area under the curve between 0.5 and 2 s between target and standard.

3.5.3 Quantification and statistical analysis

To quantify the effects of extended wake, sleep, and the WMZ, for each outcome measure we conducted the same three paired t-tests. For wake-dependent changes, we compared values from the start and end of the 24 h extended wake period, S1 and S8. These were within 2 h of the same circadian phase, therefore any differences should largely be due to sleep homeostasis. To quantify sleep-dependent changes, we compared values from the wake recordings before and after the baseline night, BL Pre and BL Post. Unlike for wake changes, these were conducted at different circadian times and the difference in sleep homeostatic pressure was lower, however these are typical recordings during sleep studies.

To statistically quantify any deviation during the WMZ from the underlying trajectory of a given outcome measure, we linearly interpolated values from S5 (17:30) to S8 (2:40) for timepoint 21:30 and compared it to the average of S6 (20:00) and S7 (23:00). The timepoints of the WMZ were determined based on the converging results of subjective sleepiness (Figure 3.2) and theta power (Figure 3.3A), both of which showed a decrease in an otherwise monotonic increase during recordings S6 and S7, corresponding to 1-4 h before habitual bedtime.

All statistics were paired t-tests, such that $p < .05$ was considered statistically significant. All t-tests were conducted on z-scored values (pooling sessions and conditions for each participant) to better account for interindividual differences, provide more normally distributed datapoints, and more fair comparison of effect sizes across outcome measures. Due to occasional data loss for different outcome measures, the degrees of freedom are always provided, from which the sample size can be inferred (N = DF+1).

Tests were selected a-priori for BL Pre vs BL Post to quantify overnight changes, and S1 vs S8 to quantify wake changes. To quantify the WMZ, a single value based on the average of the two recordings systematically showing effects (S6 and S7) were used. These were compared to an "expected" value based on S5 and S8, linearly interpolated. While previous studies quantified the effect by comparing WMZ values with measurements just prior, we considered this an under-estimate of the effect, as it doesn't take into account the overall trajectory of the data, i.e. what values those timepoints would have had without the presence of the WMZ. However, our method can also overestimate the WMZ, if either S5 or S8 deviated substantially from the rest of the recordings. Therefore, results were interpreted in the context of the trajectories observed in the figures.

Hedge's g effect sizes were reported for each test in Table 3.1, calculated with the Measures of Effect Size Toolbox (Hentschke & Stüttgen, 2011). Effect sizes are typically evaluated with Cohen's rule-of-thumb such that g values <.2 are "small," around 0.5 "medium," and >.8 "large" (J. Cohen, 1988). To determine what effect sizes we had enough power for, we conducted a post-hoc statistical power analysis using standard values of $\alpha = .05$ and $1-\beta = .8$. For an N = 18, we had power for effect sizes of Hedge's $g \geq 0.68$, and N = 10 had power for Hedge's $g \geq 0.95$. While this is generally a limitation, both sleep deprivation effects and WMZ effects tend to be quite large (Zeeuw et al., 2018).

No correction for multiple comparisons was done for these statistical tests as the majority were exploratory (e.g., Oddball/Standing conditions, pupil measures) or confirmatory (e.g., if amplitudes increase across wake, they should also decrease after sleep). Furthermore, there was a mixture of dependent and independent comparisons (e.g., power = amplitudes + quantities). All these t-tests were calculated in order to quantify the changes across outcome measures and thus compare effect sizes and relative robustness. The main hypothesis of whether both theta and alpha oscillation amplitudes increased with extended wake was a-priori selected for the Fixation condition. False-discovery rate correction (Benjamini & Hochberg, 1995) was however conducted for the 123 t-tests in each of the topographies of Figure 3.6C-D.

Throughout the text, the changes in average oscillation amplitude across extended wake are provided as average percent change from S1, with interquartile range (25% and 75% of the individuals) provided in brackets. This was used instead of standard deviation to better represent potentially skewed distributions. Likewise, the change in quantities of oscillations are described in the text as percentage of the entire recording, with corresponding interquartile ranges.

3.6 Supplementary material

3.6.1 Published supplementary figures

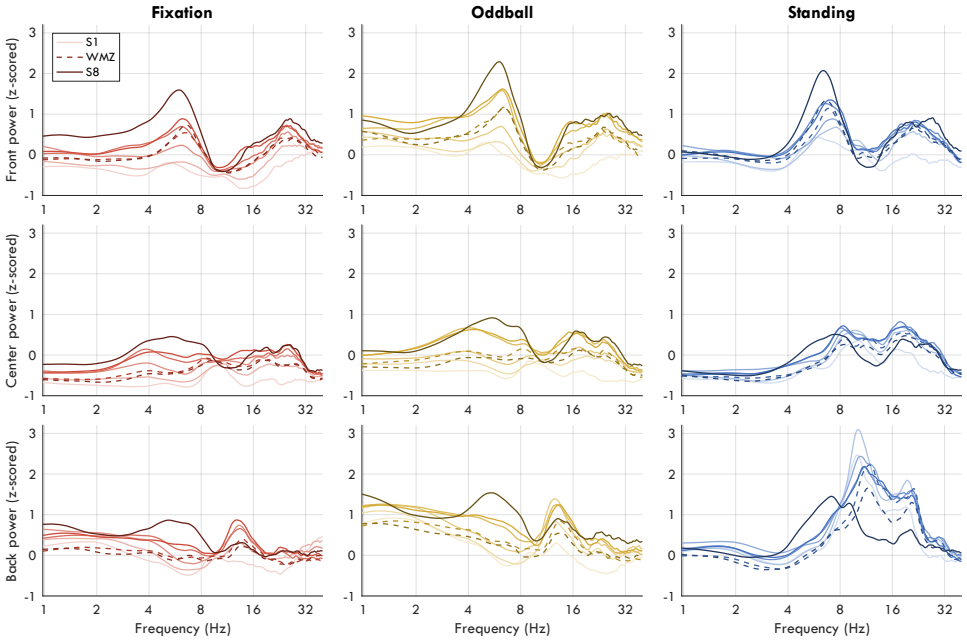

Figure 3.11: Z-scored power spectrums across extended wake, related to Figure 3.3. Each row plots an ROI (Front, Center, Back), each column a different condition. Color darkness indicates session, from S1 to S8, such that darker lines indicate more time awake. Dashed lines are the WMZ recordings (S6, S7). The x-axis indicates frequency on a log scale.

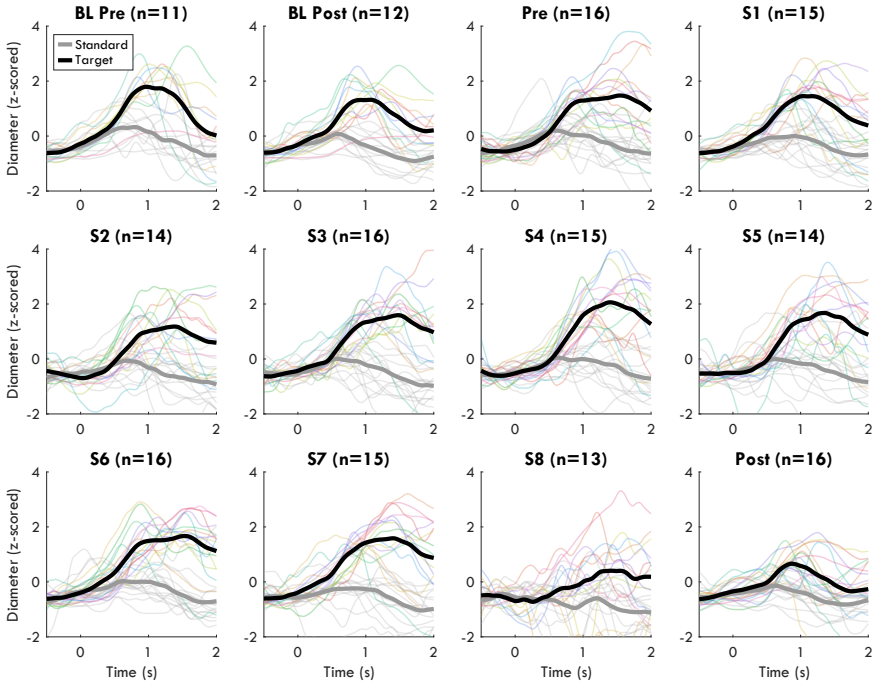

Figure 3.12: Pupil response to tones in the Oddball, related to Figure 3.7C. Pupil diameters were locked to tone onset, baseline corrected (-.5 to 0 s from tone onset), and then z-scored pooling timepoints, tone type (target and

standard), and session. Group average standards are in gray, oddball targets in black. Individuals' average pupil response to standard tones are thin gray lines, and individuals' target responses are thin colored lines. Timecourses were smoothed over 2 s for visualization. Due to data loss and increasing noise, multiple recording sessions were lost, and so the sample size for each session is indicated in the figure titles.

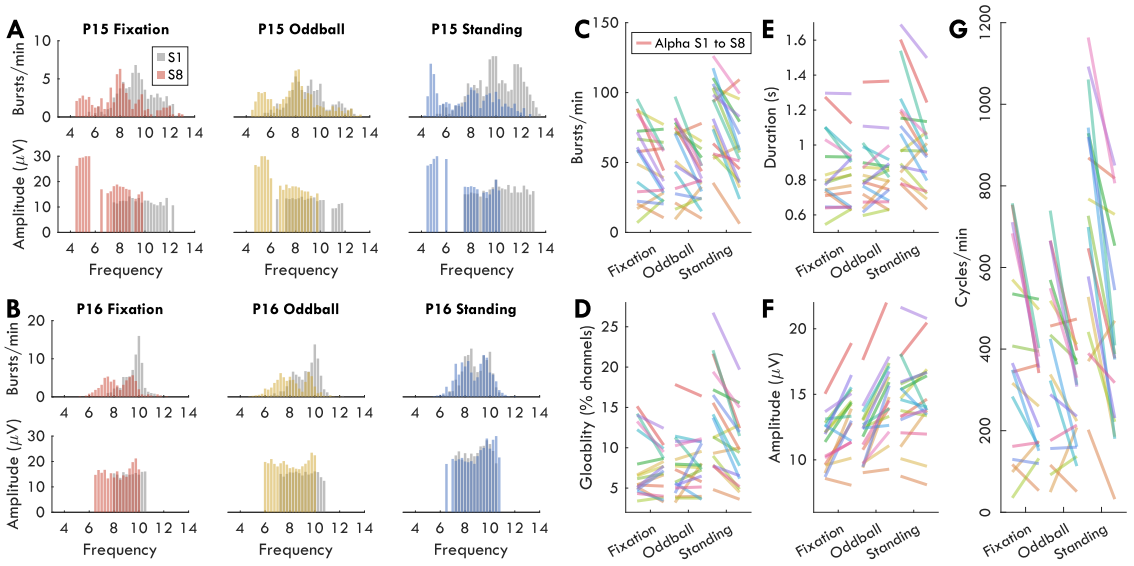

Figure 3.13: Burst properties, related to STAR Methods. **A-B**: Distribution of number of bursts per minute for each frequency (top plot) and average amplitudes (bottom plot) for two participants. Gray histogram depicts data from the first extended wake recording (S1), and colored histograms the last (S8). Missing values in the amplitude plot correspond to bins for which there were fewer than 10 bursts across the 6 min recording. **C**: Alpha bursts per minute for all participants from S1 (left point of each colored line) to S8 (right point) for each condition. Each participant is a different color. **D**: Average alpha globality, measured as the percentage of channels with an overlapping burst within ±1 Hz of the reference burst. **E**: Average alpha burst duration in seconds. **F**: Average alpha amplitudes, in microvolts. **G**: Average cycles per minute.

3.6.2 Questionnaire sensitivity

As part of the EBRS 2022 conference, I presented a poster with preliminary results from this study. I included more information about the different questionnaire questions included during the multiple recordings (Figure 3.14).

Participants were asked in four different ways how tired they felt during the Fixation condition: how much they wanted to sleep on a 7 point Likert scale (Figure 3.14A), how alert they felt on a visual-analog scale (VAS; Figure 3.14B), the KSS with options to provide intermediate answers (Figure 3.14C), and how difficult it was to stay awake on a visual analog scale (Figure 3.14C).

I found that the Likert scale managed to completely miss the WMZ, indicating it was extremely insensitive, whereas both the KSS and especially the VAS were highly sensitive to the WMZ. Furthermore, the VAS also reflected the homeostatic buildup, being steeper at the beginning. Interestingly, the question on alertness, despite also being a VAS, was also largely insensitive to the WMZ.

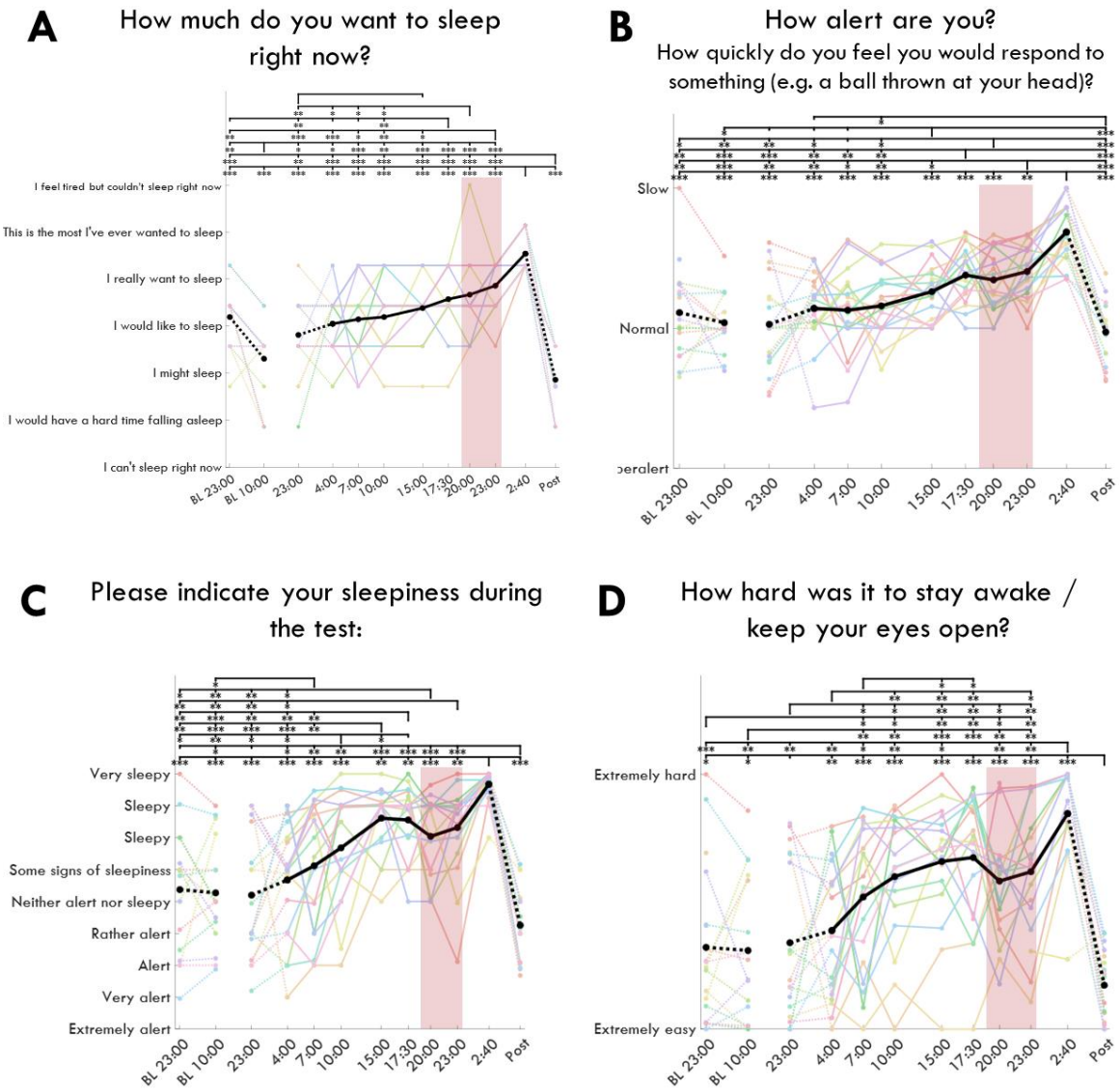

Figure 3.14: Subjective sleepiness ratings. Presented at the EBRS conference, 2022. **A**: Discrete Likert scale on sleepiness. Question on top is the text participants were presented with, labels on the y axis were the mutually exclusive options. Stars and bars at the top connect significant pairwise comparisons such that: * p < .05, ** p < .01, *** p < .001. **B**: VAS on alertness. Labels on the y-axis were the labels on the scale (see Figure 2.26). **C**: KSS. **D**: VAS on difficulty staying awake.

Therefore, subjective sleepiness measures are highly dependent both on the answer options provided (and their format) as well as the question itself. Of all the standardized questionnaires for asking about subjective sleepiness, The KSS was best based on first principles; it had a wide range of options that were clearly well defined, and all in a single question, making it easy to repeat over and over again. However, during sleep deprivation, results hit ceiling. Therefore, I would recommend either adding options to the scale (e.g. “this is the most I’ve ever wanted to go to sleep”), or using an open-ended VAS (Figure 3.14D).

tldr; visual analogue scales with continuous answer options are more sensitive to changes in sleep pressure.

3.6.3 The problem with single-theta-peak detection methods

Previous studies investigating theta and sleep deprivation identified theta as single events, which is what local sleep is assumed to be (Andrillon et al., 2021; Bernardi et al., 2015; Fattinger et al., 2017). Why not use their theta detection methods? First, these methods rely on amplitude thresholds to define an event, and this makes the number of bursts dependent on the amplitudes. Then, from visual inspection of the EEG, there were a lot of examples of theta bursts, but few notable single theta events. More importantly, these algorithms don't take into account the 1/f background and they bias the total amount of waves that can be detected.

To prove this point, I implemented the algorithms used in Bernardi et al. and Fattinger et al. and compared it with my implementation of cycle by cycle analysis. I took one channel from four different recordings: a channel with a lot of theta activity, a channel with low theta activity, a channel with no oscillatory activity, and a channel with high alpha activity (Figure 3.15A). I then compared the number of theta peaks per minute identified by each algorithm (Figure 3.15B).

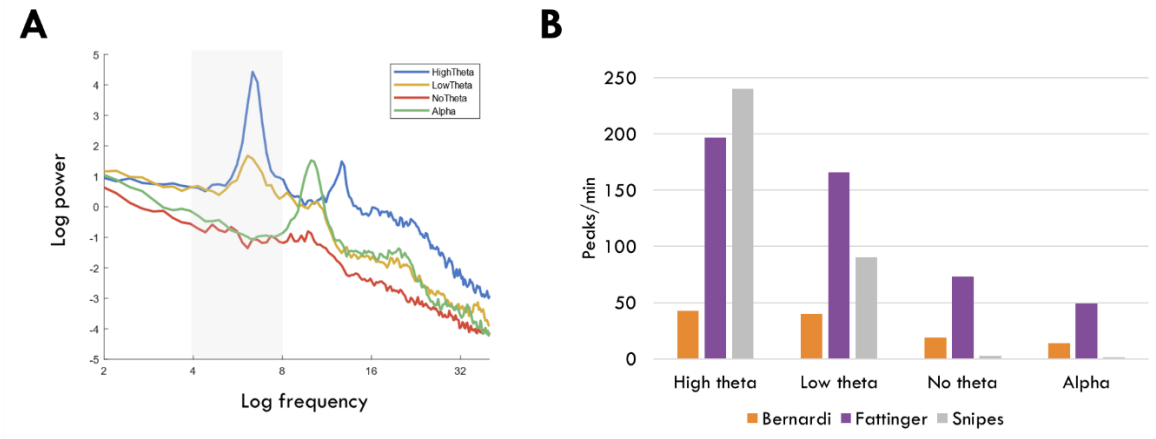

Figure 3.15: comparison of theta detection algorithms. **A**: log-log scale of power spectra for 4 6-minute channels from different participants based on visual identification of oscillatory activity. **B**: Number of peaks per minute identified by each algorithm. Orange was from Bernardi et al. (2015), purple from Fattinger et al. (2017), and gray from Snipes et al. (2023).

Bernardi et al. used an algorithm that took the 20% of theta peaks with the highest amplitudes. This results in comparable number of peaks whether there is a lot of oscillatory activity, or none. Because the 1/f background activity randomly produces theta events, these will be the majority of captured theta when there are no "real" theta waves, and vice-versa, when the entire channel is dominated by theta, only 20% of the actual theta oscillations will make the cut. Only with the optimal proportion of oscillatory theta in the signal will the algorithm correctly balance between true positives and true negatives. Fattinger et al., based on Massimini et al. (2004), set instead a fixed amplitude threshold based on the standard deviation of the overall signal amplitude. This found substantially more theta oscillations than the Bernardi algorithm, but still identified high amounts of theta in the channels where no oscillatory theta activity was present. A different approach is needed to detect single waves that aren't aperiodic background activity. For now, I focused on bursts instead.

tldr; amplitude-based detection methods both over and underestimate the amount of oscillatory activity.

4 EEG MARKERS OF SLEEPINESS DO NOT PREDICT LAPSES IN ATTENTION DURING SLEEP DEPRIVATION

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This paper will be submitted to Scientific Reports imminently. Here, I address the issue of whether the theta bursts discovered in the previous paper have any behavioral consequences. The Lateralized Attention Task (LAT) was designed in order to maximize the chances of identifying local sleep in wake; this task was the main focus of the whole LSM experiment. It needed to result in a sufficient number of behavioral lapses on which proper analyses could be conducted, and these lapses needed to not be attributed to eye-closures or other confounding factors.

I designed the experiment, collected the data, analyzed the data, and wrote the paper. Elias Meier helped collect the data. Reto Huber supervised the project.

4.1 Abstract

Sleepiness is associated with bursts of theta oscillations in the wake electroencephalogram (EEG); however, the behavioral relevance of these bursts has not been established. Given that increased sleepiness is associated with increased behavioral impairments, we wished to determine whether theta bursts could be the cause. 18 young healthy adults performed the lateralized attention task (LAT) when well rested (BL) and after >20 h awake (SD), both times under soporific conditions. High-density EEG and video of eye-closures were measured, and the timing of eyes-open EEG bursts were related to trial outcomes: fast responses, slow responses, and lapses. We found no relationship between theta bursts at any timepoint nor channel around lapses, either during BL or SD. Instead, we found a higher likelihood of theta bursts during the stimulus window of fast trials at BL, suggesting a "theta boost" to performance. Furthermore, alpha bursts were found to anticipate fast trials rather than slow or lapse trials, contrary to previous findings which find the opposite. Because we measured the LAT under soporific conditions, this may suggest that the relationship between vigilance and alpha follows an inverted U, with both extremely low and extremely high vigilance associated with less alpha activity. Overall, neither theta nor alpha bursts were found to predict lapses in behavior during sleep deprivation, and instead predicted better performance under soporific but well-rested conditions. These results therefore support the finding that theta during sleep deprivation preferentially occurs in task-unrelated areas.

4.2 Introduction

Sleepiness can be deadly. Up to 20% of road traffic accidents are attributed to insufficient sleep, with only 17 h of extended wake being equivalent to mild alcohol intoxication (Dawson & Reid, 1997; Gibbings et al., 2022; J. A. Horne & Reyner, 1995). While multiple cognitive systems are likely compromised during sleep deprivation, the most affected seems to be sustained attention (Lo et al., 2012). Laboratory tests of sustained attention such as the psychomotor vigilance task (PVT) reliably capture increasing behavioral lapses with time spent awake, circadian rhythm, and even cumulative sleep restriction (Basner & Dinges, 2011; Dinges & Powell, 1985; Graw et al., 2004; Van Dongen et al., 2003). Given the role sleepiness

can have on health and safety, there has been a justifiable interest in trying to identify the neural mechanisms leading to these behavioral lapses.

One of the most notable features of brain activity are bursts of oscillations in the EEG, reflecting different states of vigilance (Schomer & Silva, 2011). Since the first EEG recordings, sleepiness has been associated with theta oscillations (4-8 Hz) (Smith, 1938), and is typically quantified using spectral power (Aeschbach et al., 1997; Cajochen et al., 2002; Finelli et al., 2000; Snipes et al., 2022) or as single theta waves (Andrillon et al., 2021; Bernardi et al., 2015; Fattinger et al., 2017; Hung et al., 2013). However, recently we have been able to quantify the changes in bursts specifically, which had previously only been described qualitatively (Ebersole & Pedley, 2003). In resting wake EEG we found a near-linear increase in theta bursts with time awake (Snipes et al., 2023), so we wished to determine whether these theta bursts were predictive of the comparable increase in behavioral lapses.

We collected high-density EEG data from 18 young healthy adults undergoing a 4/24 extended wake paradigm (4 h of sleep, 24 h of wake; full schedule in Figure 4.1A). To capture attentional lapses, we used an adaptation of the PVT, the Lateralized Attention Task (LAT). Like the PVT, this involved fixating on a rectangle in the center of the screen, with stimuli appearing every 2-10 seconds. However, the stimuli were faint circles that would shrink within 0.5 s (Figure 4.1B). Participants had to push a button whenever they saw the stimulus, and it would flash green if caught in time. A lapse was defined as any trial for which no response was given. To further increase the proportion of lapses, the task was performed under soporific conditions with lights off and seated in a comfortable armchair with foot and headrest. The LAT was performed three times when well-rested (baseline, BL), and three times following 20 h of extended wake (sleep deprivation, SD).

To test the hypothesis of whether theta bursts could contribute to lapses, we investigated both the occurrences of bursts in time (pooling channels) and the occurrences in space (averaging time windows) around stimulus onset. We expected theta bursts could be associated to lapses in two ways: theta could be more likely when the stimulus was present, indicating that theta disrupted processing and responding to the stimulus; or theta could be uniformly more common in the seconds around the trial, indicating a general marker for a non-vigilant state (Makeig & Jung, 1996) even if the bursts themselves do not directly cause the lapse. By analyzing the changes in theta with high-temporal resolution, we could determine the direction of causality. By analyzing changes in topography, we had greater sensitivity to local effects.

To establish the specificity of these results to the theta range, we conducted the same analyses on alpha bursts (8-12 Hz), which have previously been shown to anticipate behavioral impairment in well-rested conditions, reflecting the above-mentioned within-session fluctuations in vigilance (Huang et al., 2007; Makeig & Jung, 1996). To provide a comparison with a reliable lapse-causing event, we also applied the same analysis to eye-closures, which during sleep deprivation likely reflects microsleeps (Hertig-Godeschalk et al., 2020; Ong et al., 2013). To determine whether the relationship between a given event and lapses was specific to sleep deprivation, we also conducted the same analyses for BL sessions.

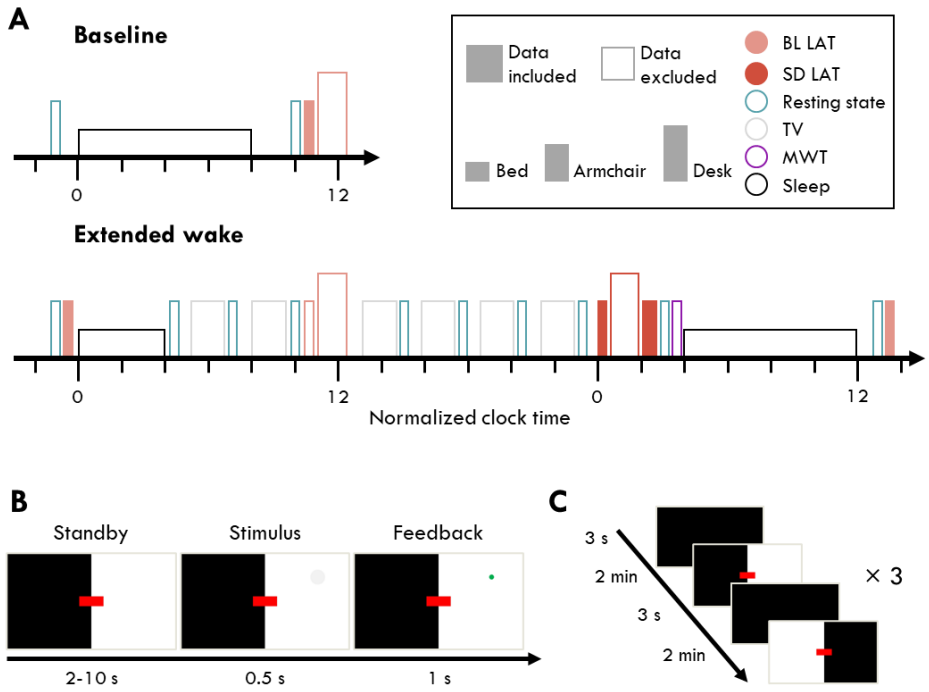

Figure 4.1: Study design. **A**: Experiment schedule. Each block indicates an EEG recording session. Filled blocks indicate data analyzed in this paper. Color indicates the activity participants engaged in: gray, watching TV; teal, the resting state recordings (analyzed in Snipes et al. (2023)); peach, baseline task blocks; red, sleep deprivation task blocks; purple, the MWT; black, sleep. The height of each block indicates the experimental condition in which data was collected: short, lying in bed; medium, seated in a comfortable armchair with foot and backrest; tall, seated at a desk, analyzed in Snipes et al. (2022). Brief empty spaces indicate transition periods allowing for delays. Six longer breaks were included prior to each TV block in which participants were provided with meals. Circadian time was normalized across participants to their habitual bedtime. Participants at baseline and during the recovery night were free to wake up when they wished, and at the beginning of the extended wake period they were woken up after 4 h of sleep. **B**: LAT trial. Participants had to fixate on the red rectangle, and every 2-10 seconds, a gray circle would appear somewhere in the white area. If they pressed a button before the stimulus completely shrunk away, it would flash green as positive feedback. **C**: The 12 minute LAT consisted of 6 blocks, alternating between the left and right screen being illuminated. Brief pauses separated the switch.

4.3 Results

4.3.1 The LAT is sensitive to eyes-open lapses

We first wished to determine whether the LAT was an appropriate task for measuring lapses following extended wake, and whether the adaptations from the PVT effectively increased eyes-open lapses. Participants performed one BL PVT session the morning after the baseline night of sleep, and one SD PVT session after 20 h of wake, counterbalanced with the first LAT. The PVT defines lapses as trials with reaction times (RT) > 0.5 s. This means that lapses include both sluggish responses (Figure 4.2A) and "true" lapses in attention, when the participant misses the stimulus onset, then recovers later and eventually presses the button. Capturing both is what makes the PVT a sensitive and robust measure of sleepiness, however this is suboptimal for investigating whether a given event can cause an attention lapse. Shifting the lapse threshold to higher RT values avoids these sluggish responses, but this also increases the proportion of lapses with eyes closed (Figure 4.2C). Therefore, for lower RTs the PVT cannot distinguish between slow responses and lapses, and for higher RTs lapses mostly reflect microsleeps.

The main difference between the LAT and PVT is that LAT stimuli appeared only briefly and were difficult to detect, minimizing the orienting response (Pavlov, 1927). This meant that even a brief lapse in attention would result in missing the stimulus entirely. Therefore, with the LAT it is possible to separate slow responses from complete lapses in attention (Figure 4.2D-E). The average percentage of LAT trials classified as a lapse was 12% [interquartile range: 5, 19] at BL, and 33% [22, 44] at SD. By comparison, PVT lapses were 3% [1, 4] of BL trials, and 10% [2, 14] of SD trials (Figure 4.2B). The proportion of eyes-open lapses during SD was 58% [32, 83] of PVT lapses and 71% [65, 80] of LAT lapses. More importantly, this corresponds to 4% [1, 7] of PVT trials that are eyes-open lapses, and 22% [13, 30] of LAT trials. At BL, only 10% [5, 16] of LAT trials were eyes-open lapses, which corresponds to a highly significant increase with time awake (N = 17, t = 6.32, p < .001, g = 1.48). Therefore, the LAT captured substantially more eyes-open lapses in attention than the PVT, making it the more appropriate task to evaluate the potential detrimental effects of a given biomarker.

Because stimuli appeared at any distance from the fixation point during the LAT, it could be that most lapses occurred at the edge of participants' visual field. To check if this was the case, trials were divided into 6 quantiles based on radial distance from the fixation point (Figure 4.2F). At BL, considering only EO trials, the closest quantile had 1.3% [0.0, 1.8] of trials as lapses and the furthest had 26.0% [10.4, 37.3]. Therefore, while distance was clearly a major contributor of lapses at BL, there was no distance after which stimuli were completely missed and were thus outside of the field of view. In other words, distance from fixation increased the chances of a lapse but didn't determine one.

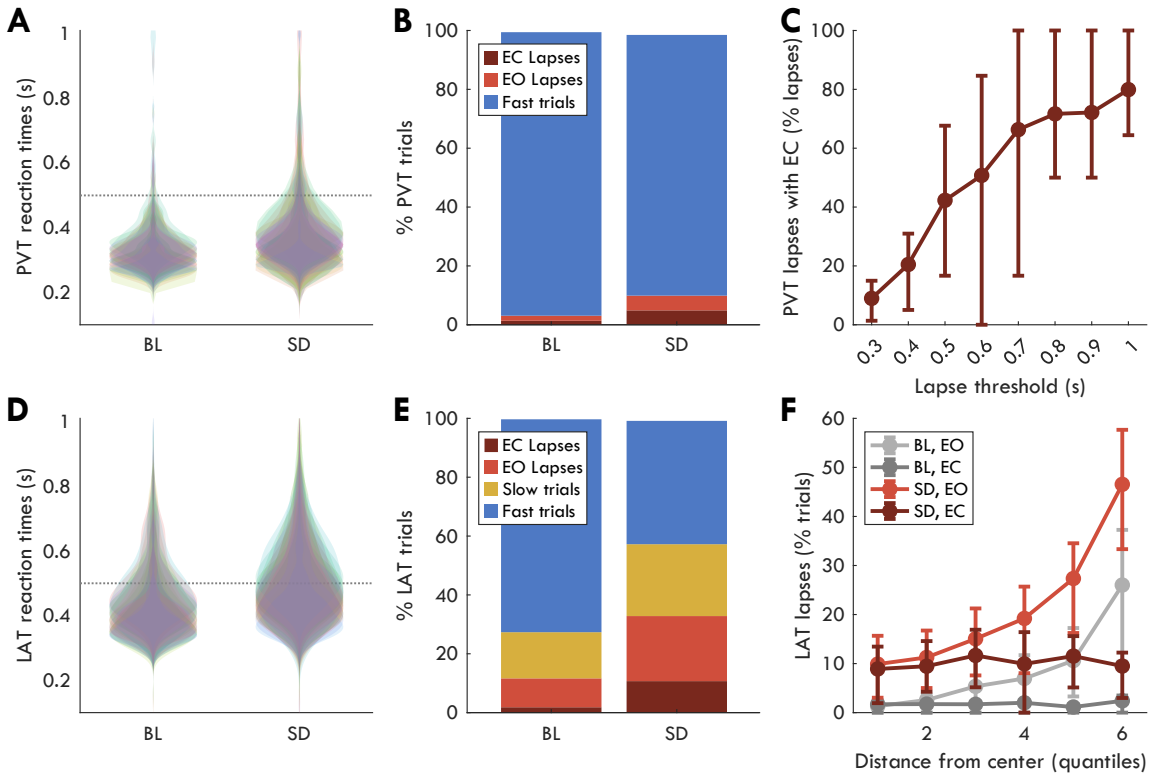

Figure 4.2: LAT versus PVT behavioral outcome measures. A: Reaction times during the PVT. Each colored "violin" represents the distribution of an individual participant (N=18). The dotted horizontal line at 0.5 s marks the threshold over which the trial was considered a lapse. **B**: Average distribution of PVT trials based on response outcome (fast responses: RT < 0.5 s; lapses: RT > 0.5 s) with lapses split by whether eyes were open or closed (N=13; due to eye-tracking data loss. Only includes participants with data in both session blocks). EC fast trials are not included in the bar graph (they are the sliver of whitespace at the top). **C:** Percentage of PVT lapses that are with EC, depending on

the RT threshold used to define lapses. Error bars indicate interquartile range around the average. The higher the RT threshold, the more lapses are due to EC. Anderson et al. (2010) performed a similar analysis, although they found 10% of lapses were with EC at 0.5 s cutoff, which only increased to 90% after ~2 s. This difference may be due to our soporific conditions. **D**: Same as A for LAT (N=18), although the LAT was performed 3 times for each session block instead of just once. N.B: BL recordings are pooled from three different days, whereas SD recordings were within the same 3-4 h timespan, and therefore also include time-on-task effects (Doran et al., 2001). **E**: Same as B for LAT (N=17). The LAT distinguishes slow trials as 0.5 s < RT < 1 s (yellow) and lapses as trials where no response was given. **F**: Percentage of LAT trials that are lapses, split into 6 quantiles based on the distance from the fixation point, such that 1 is closest and 6 is furthest (N=17). 100% indicates all trials in that quantile were lapses (either EO or EC). Gray indicates BL trials, red SD trials. Darker shades reflect EC, lighter shades EO. Error bars indicate the interquartile range.

4.3.2 At no timepoint were theta bursts more likely to occur during lapse trials

To determine whether there was a temporal relationship between theta bursts and lapses, we looked at the proportion of trials containing a theta burst at every timepoint from 2 seconds before to 4 seconds after stimulus onset, split by trial outcome. We conducted paired t-tests for each timepoint relative to the average amount of theta present in the session block (BL, SD), with false-discovery rate (FDR) correction for multiple comparisons. Therefore, significant positive values indicate that theta was more likely to occur than average at that time point for that trial outcome during that session.

To validate this analysis, we first applied it to the relationship between eye-closures (EC) and trial outcomes during SD (Figure 4.3A). EC occupied on average 17% [14, 21] of SD. Occurrences of EC were significantly higher than average during lapse trials, peaking 0.1 s after stimulus onset (N = 17, t = 5.87, p_{fdr} < .001, g = 1.95), when the stimulus was largest and before participants could respond (Figure 4.2D). Additionally, occurrences of ECs were significantly higher than average in the seconds before (max t: -1.9 s; N = 17, t = 3.12, p_{fdr} = .011, g = 1.04) and after lapse trials (max t: N = 17, t = 3.65, p_{fdr} = .005, g = 1.21). Vice versa, EC were significantly below average for both fast and slow trials before and during stimulus presentation. Notably, the proportion of EC was briefly higher at stimulus onset for slow responses relative to fast ones (slow vs fast 0 s: N = 17, t = 5.74, p < .001, g = 0.85), suggesting this contributed to the delay. After slow and fast trials, there was a brief rebound of EC. When time-locking trials to the response (Figure 4.3D), the rebound onset for both slow and fast responses overlapped, suggesting that this was a response-locked reflex to blink after the trial was over. This analysis illustrates how EC are both a direct cause of lapses (peaking during stimulus window), as well as an indicator of an overall non-responsive state (higher EC in surrounding timepoints likely reflecting microsleeps).

In Figure 4.3B and E, we used the same analysis for theta bursts during SD, locked to the stimulus and the response respectively. Theta bursts occupied 43% [19, 62] of SD recordings. At no point in time were theta bursts more common during lapse trials relative to the recording average, either before (max t: -1.2 s; N = 17, t = 1.53, p_{fdr} = .702, g = 0.51), during (max t: 0.0 s; N = 17, t = 1.67, p_{fdr} = .698, g = 0.55) or after the stimulus (max t: 1.3 s; N = 17, t = 1.83, p_{fdr} = .698, g = 0.61). No timepoint was significant for fast or slow trials either, although there were decreases in theta bursts just after the stimulus window ended (fast max t: 1.4 s, N = 17, t = -4.38, p_{fdr} = .055, g = -1.46; slow max t: 1.0 s, N = 17, t = -2.23, p_{fdr} = .698, g = -0.74), with a few timepoints significant when trials were locked to the response (Figure 4.3E).

The same analyses were done for alpha bursts (Figure 4.3C,F), which occupied 75% [65, 88] of SD. There was still no difference in proportion of alpha bursts either before (max t: -1.2 s, N = 17, t = 1.25, p_{fdr} = .484, g = 0.41) or during the stimulus of lapse trials (max t: 0.2 s, N = 17, t = -1.62, p_{fdr} = .319, g = -0.54), although there was a trending decrease in alpha after the trial (max t: 2.0 s, N = 17, t = -2.59, p_{fdr} = .088, g = -0.86). For fast and slow trials, contrary to previous findings (Huang et al., 2007), we found more alpha just before

fast responses (max t: -1.6 s; N = 17, t = 4.21, p_{fdr} = .013, g = 1.40) and to a lesser extent before slow responses (max t: -1.6 s; N = 17, t = 3.34, p_{fdr} = .033, g = 1.11). The effect was also more sustained for fast compared to slow trials (Figure 4.3C). However, in agreement with previous results (Nir et al., 2017), we also found a decrease in alpha peaking immediately after the stimulus ended for fast trials (max t: 0.6 s, N = 17, t = -4.95, p_{fdr} = .007, g = -1.64), which was more attenuated and delayed during slow trials (max t: 1.1 s, N = 17, t = -3.80, p_{fdr} = .021, g = -1.26). Figure 4.3F reveals this effect to be response-locked rather than stimulus locked. This dip was followed by a rebound increase during fast trials (max t: 2.0 s, N = 17, t = 6.70, p_{fdr} < .001, g = 2.22), delayed during slow trials (max t: 2.9 s, N = 17, t = 4.79, p_{fdr} = .007, g = 1.59).

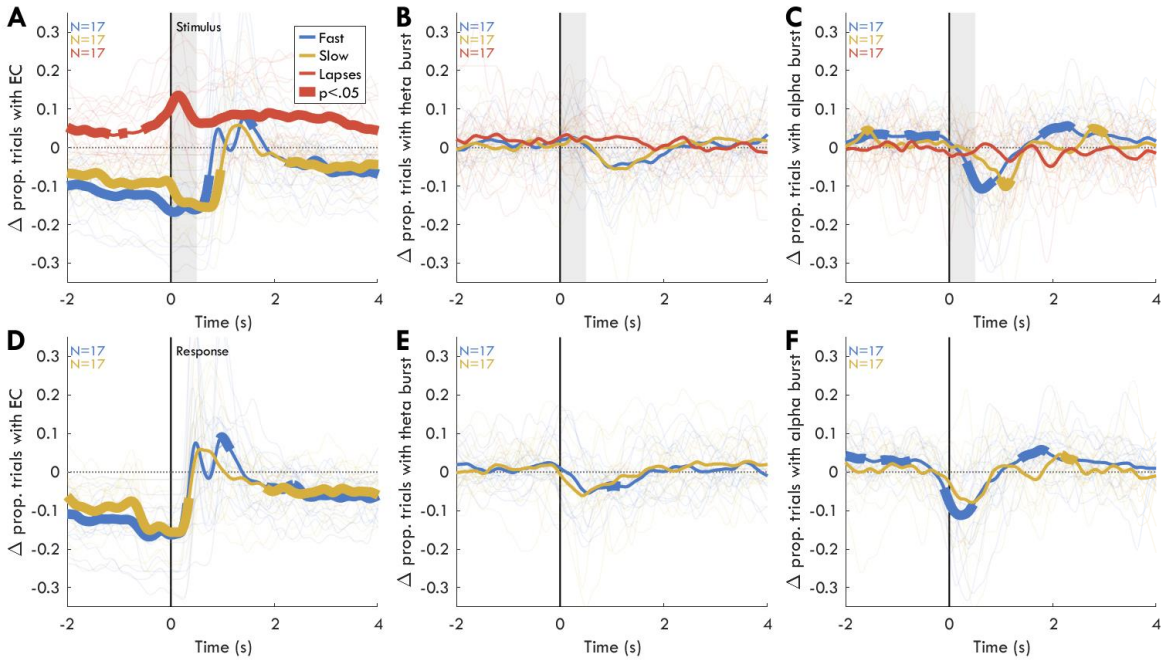

Figure 4.3: Distribution in time of eyes-closed and bursts relative to trial outcomes during sleep deprivation. **A**: Difference in proportion of trials with EC for each outcome type relative to the recording average amount of EC, such that values at 0 (dotted horizontal line) represents no difference from the average. The thick vertical line represents stimulus onset, and the gray patch the time in which the stimulus was visible. Light thin colored lines represent individual averages, medium lines indicate the group average, and thick segments reflect timepoints in which the difference was statistically significant, with p< .05, FDR corrected for multiple comparisons. Sample sizes are indicated in the top left. **B**: Same as A, but for theta bursts. Trials during which eyes were closed during the stimulus window were excluded. **C**: Same as B for alpha bursts. **D-F**: Same as A-C, with trials locked to the response instead of stimulus onset. Acronyms: FDR, false discovery rate. EC, eyes closed.

We conducted the same analyses for the BL session block (Figure 4.4). For EC (Figure 4.4A,D), which occupied 6% [4, 8] of BL, the only major difference from SD was that there was no significant increase in EC during lapses in the seconds before or after the trial (max t: -1.5 s, N = 17, t = -1.59, p_{fdr} = .257, g = -0.53). This reflects the fact that microsleeps were not present at BL.

For theta bursts (Figure 4.4B,E), occupying 29% [12, 37] of BL, again no window showed significant differences for lapses (max t: 0.0 s, N = 11, t = -1.57, p_{fdr} = .398, g = -0.64), although fewer participants had sufficient lapse trials for this analysis. However, fast trials had a higher proportion of theta during the stimulus (max t: 0.1 s, N = 18, t = 5.49, p_{fdr} = .002, g = 1.78), followed by a negative deflection after the response (max t: 1.4 s, N = 18, t = -6.20, p_{fdr} = .001, g = -2.01). This was not present for slow trials (max t: 1.0 s, N = 14, t = -2.66, p_{fdr} = .146, g = -0.96), although there was a significant post-response decrease (max t: 2.0 s, N = 14, t = -3.68, p_{fdr} = .033, g = -1.34).

For alpha, occupying 80% [73, 90] of BL, the effects observed during SD were either the same or more pronounced (Figure 4.4C,F). There was no significant timepoint for lapse trials (max t: 0.5 s, N = 11, t = -2.35, p_{fdr} = .127, g = -0.95), although again the sample size was limited. Instead, alpha was higher than average before fast trials (max t: -1.0 s, N = 18, t = 5.23, p_{fdr} = .001, g = 1.69), but not slow trials (max t: -1.0 s, N = 14, t = 1.01, p_{fdr} = .590, g = 0.37). Then, the negative deflection around the response was even larger than during SD for both slow trials (max t: 0.8 s, N = 14, t = -4.54, p_{fdr} = .005, g = -1.65) and fast trials (max t: 0.4 s, N = 18, t = -6.04, p_{fdr} < .001, g = -1.95), both of which were more time-locked to the response than the stimulus (Figure 4.4F). As with SD, there was a positive rebound in alpha after fast trials (max t: 2.7 s, N = 18, t = 6.05, p_{fdr} < .001, g = 1.96), but not slow trials (max t: 1.5 s, N = 14, t = -2.11, p_{fdr} = .161, g = -0.76).

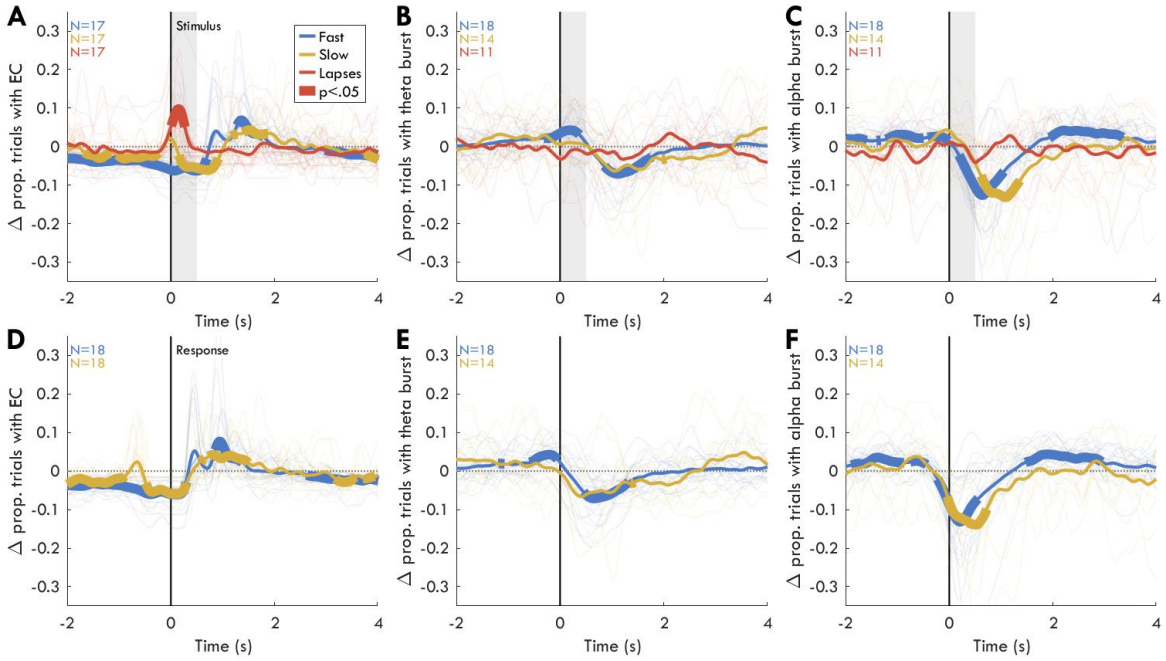

Figure 4.4: Distribution in time of bursts and eyes-closed relative to trial outcomes during baseline recordings. Same as Figure 4.3. **A,D**: eyes closed. **B,E**: theta bursts. **C,F**: alpha bursts. N.B. for lapses and slow trials, the N is lower (indicated in top left) because some participants did not have enough of such trials to be included in this analysis. The N is different between A and B,C because the burst analyses excluded trials with EC.

4.3.3 At no channel were theta bursts more likely to occur for lapses

The previous results were conducted pooling bursts from all channels and may have masked local effects. We therefore conducted the same analysis for bursts detected in each channel, collapsing time into four windows: Pre, -2 to 0 s from stimulus onset; Stimulus, 0 to 0.3 s from onset; Response, 0.3 to 1 s from stimulus onset; and Post, 2 to 4 s from stimulus onset. Figure 4.5 shows the topographies during SD comparing the proportion of theta or alpha bursts relative to the recording averages of each channel, split by trial outcome for the different time windows. FDR correction was applied for each topography to correct for multiple comparisons across channels.

For theta bursts during SD (Figure 4.5A), no channel showed a significant difference from the average during any window for any trial outcome. The largest effect observed for lapse trials was more theta in channel 19 in the Pre stimulus window (N = 17, t = 3.74, p_{fdr} = .112, g = 0.15), although the effect size was so small it would require over 200 participants for sufficient statistical power (see Methods and Figure

4.7). Both fast and slow trials showed a broad decrease in the Response window, which is in agreement with the trends observed in Figure 4.3B, however these were non-significant and the effect sizes small (fast max channel 50; N = 17, t = -2.66, p_{fdr} = .232, g = -0.10; slow max channel 110; N = 17, t = -3.62, p_{fdr} = .148, g = -0.10).

For alpha during SD lapse trials (Figure 4.5B), there were two channels showing a significant decrease during the Post window, although the effect size was small (max channel 92; N = 17, t = -5.56, p < .001, g = -0.27). This matches the trending decrease observed in Figure 4.3C, which may reflect an overall decline in alpha across the recording. The previously reported increase in alpha Pre for fast trials did not survive correction for multiple comparisons across channels, although the effect was trending (max channel 53; N = 17, t = 4.04, p_{fdr} = .059, g = 0.19). There were widespread decreases of alpha in the Response window for fast trials, significant in 63% of channels, peaking in occipital-parietal areas (max channel 59; N = 17, t = -6.46, p_{fdr} < .001, g = -0.90). The positive rebound during the Post window of fast trials was occipital (N = 17, t = 4.66, p_{fdr} = .017, g = 0.32). For slow trials in the Response window, 15% channels in a left occipital-parietal cluster showed significant decreases (max channel 52; N = 17, t = -4.86, p_{fdr} = .008, g = -0.75).

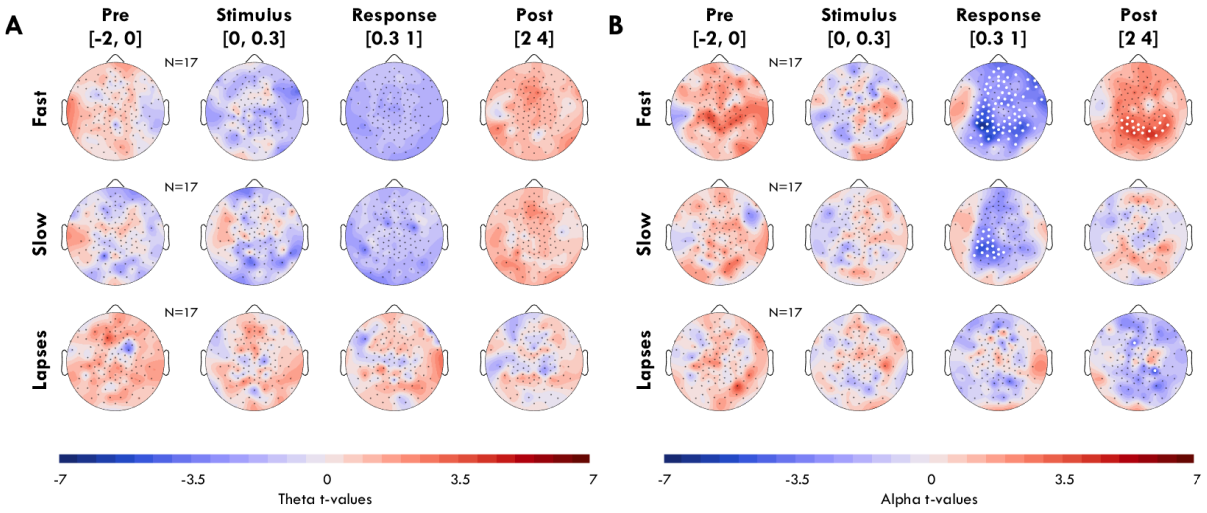

Figure 4.5: Difference in burst proportion by trial window and outcome during sleep deprivation. **A**: Difference in theta burst proportion from session average for different trial outcomes (rows) and time windows (columns), with the seconds ranges indicated in square brackets. Color indicates t-values comparing the proportion of theta for a given outcome in a given time window to the recording average for a given channel, such that red indicates more theta relative to the recording average. White dots indicate statistically significant differences, p < .05. FDR correction was applied for each topography. Sample size is indicated for each trial outcome. **B**: Same for alpha.

During BL, the overall effects for theta bursts were not substantially different from sleep deprivation, with no electrode showing significant effects (Figure 4.6A; p_{fdr} > .184). The "theta boost" observed during the stimulus window of fast trials did not result in any significant changes in any channel.

Instead for alpha, all the effects previously described during SD were stronger and more widespread during BL. Alpha was significantly higher during the Pre window for fast trials in 38% of channels, with a central-occipital focus and separate frontal cluster (max channel 71; N = 18, t = 5.07, p_{fdr} = .003, g = 0.15). While significant, the effect size is much smaller here, indicating that this relationship between alpha and trial outcome is more robust in time than in space. The stimulus window for fast trials also showed significantly less occipital alpha than average in 34% of channels (max channel 96; N = 18, t = -5.74, p_{fdr} = .003, g = -0.31), anticipating the even stronger effect during the response window in 95% of channels

(max channel 67; N = 18, t = -6.90, p_{fdr} < .001, g = -0.61), followed by the positive rebound in 90% of channels in the Post window (max channel 59; N = 18, t = 6.03, p_{fdr} = .001, g = 0.23). Late trials only showed significant decreases in the Response window in 62% of channels (max channel 67; N = 14, t = -8.04, p_{fdr} < .001, g = -0.65).

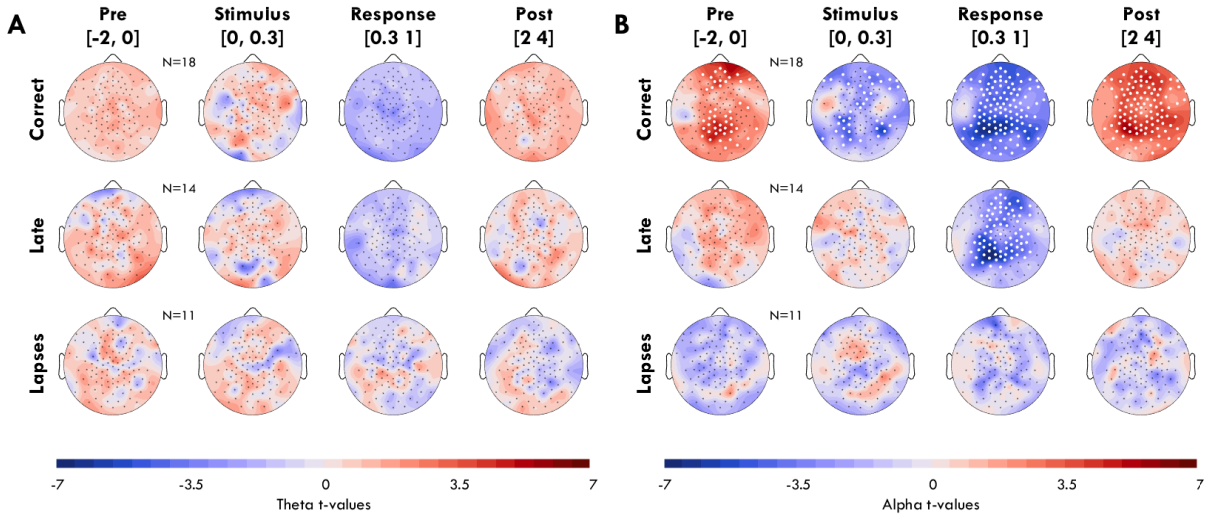

Figure 4.6: Topography of burst proportions per trial type during baseline. Same as Figure 4.5. **A**: Theta bursts. **B**: Alpha bursts.

4.4 Discussion

With this study, we wished to determine whether theta bursts contribute to eyes-open behavioral lapses during sleep deprivation, given that both bursts and lapses increase with time awake (C. Anderson et al., 2010; Basner & Dinges, 2011; Snipes et al., 2023). Our results showed if anything the opposite of what we expected. We did not find any significant relationship between lapses and theta bursts at any point in time (Figure 4.3B) nor at any channel (Figure 4.5A) either at baseline or during sleep deprivation. Instead, at baseline theta bursts were significantly more likely to occur during the stimulus window of fast trials (Figure 4.4B). The timing of this effect, peaking 0.1 s after and significant already before stimulus onset, indicates that the presence of a theta burst when a target stimulus appears actually boosts performance.

How could theta bursts characterize sleep deprivation, a time when behavioral performance is impaired, if theta is instead predictive of better performance at baseline? A possible explanation is that theta is a marker of cortical inactivity in task-*irrelevant* areas. The fact that the BL theta boost is visible in time (Figure 4.4B) but not any specific channel (Figure 4.6A) could be because it's not the presence of theta in specific task areas that helps, but rather the presence of theta in non-specific task-irrelevant areas that incidentally suppresses (or marks the absence of) conflicting neuronal activity. Supporting this association between theta and local deactivation, functional magnetic resonance imaging (fMRI) studies have found frontal-midline theta during rest and task recordings to be anticorrelated to brain oxygen metabolism from its source, the anterior cingulate cortex of the default mode network (Scheeringa et al., 2008, 2009).

In our previous paper, we also found that sleep deprivation theta originates primarily from cortical areas *not* required for the ongoing task (Snipes et al., 2022). However, sleep deprivation theta especially in the LAT was quite widespread. It's possible that the theta boost can only happen with more limited distributions of theta, and the theta during SD may not be "precise" enough to confer a behavioral benefit.

Therefore, small doses of theta at BL may be beneficial, but there's too much theta during SD for the same effect. Alternatively, the general impairment of the brain during sleep deprivation may be so severe that the little boost that theta from task-irrelevant areas provides doesn't make a difference. It's still possible that theta occurs in task-relevant areas during SD, but this might be rare enough not to be visible in our analyses.

This interpretation is highly speculative. A more traditional hypothesis would be that the presence of BL theta could reflect a moment of higher synchrony across task areas, thus facilitating transmission when the stimulus appears, producing faster reaction times (Polanía et al., 2012). Instead the theta bursts during sleep deprivation may reflect a different "type" of theta, masking the presence of cognition-theta that created the BL theta boost. To determine whether the BL theta boost is related to theta in task-relevant or task-irrelevant areas would require higher spatial resolution of the bursts, either through source localization or better yet, intracortical recordings. All the same, the fact that sleep deprivation theta does not have a link to performance outcome supports our previous finding that it primarily originates from task-irrelevant areas.

4.4.1 Alpha as a non-monotonic marker of vigilance

While the relationship between theta and vigilance in the literature was ambiguous, alpha activity has been traditionally associated with *inattention,* reflecting within-session fluctuations in vigilance (Hanslmayr et al., 2011; Makeig & Jung, 1996; Sauseng et al., 2005). For example, in a study by Huang et al. (2007), well-rested participants performed a sustained attention driving task with similar "game mechanics" to the PVT and LAT (occasional driving adjustment required every 3 to 7 s). When sorting trials into low and high performance, the authors found that low performance "drowsy" trials were anticipated by higher alpha power, followed by a negative and then positive deflection, neither of which was present for alert trials. Instead, we found the opposite: prior alpha is higher for fast trials rather than slow or lapse trials, and the post-response deflections are more pronounced. The effect is present during SD (Figure 4.3C) but is even stronger during BL sessions (Figure 4.4C, Figure 4.6B).

A possible explanation for these opposing results is that alpha and vigilance follow a non-linear relationship. Recent work by Pfeffer et al. (2022) found that alpha activity and pupil diameter follow an inverted U pattern, such that both small pupils (indicating low vigilance) and large pupils (indicating high vigilance) are associated with lower alpha compared to intermediate values. Given the generally slow reaction times of the LAT (Figure 4.2B), the higher subjective sleepiness ratings during this task even when performed under normal baseline conditions (Figure 2.3A, page 41 of Snipes et al. [2022]), and the deliberately soporific conditions during these recordings (dark room, armchair), it's likely that already our baseline task was more comparable to Huang's "drowsy" state. Therefore, well-rested and extremely alert conditions as seen in Huang's study will result in low alpha, from which drops in alertness (and performance) will result in increased alpha. Instead in our study, participants were already quite drowsy at baseline such that further drops in alertness resulted in *decreased* alpha. Therefore, the pre-stimulus alpha across these two studies follows the same inverted U relationship described in Pfeffer et al. and can explain our seemingly contradictory results. The fact that alpha has a non-linear relationship with vigilance also makes sense given that alpha actually decreases with sleep deprivation (Cajochen et al., 2002; Snipes et al., 2023), so it cannot be a monotonic marker of alertness.

4.4.2 Limitations

The biggest limitation of this study is the small sample size. While we had more than enough power to detect both the increase in theta bursts as well as the increase in lapses with sleep deprivation, it is still possible that there is an effect of theta bursts on lapses, but it is relatively small and would require more participants to detect. Therefore, we cannot definitively conclude that theta bursts do not predict lapses at all, just that if the effect is there, it is not particularly strong.

It is also important to note that the method we used for burst detection differs from prior studies that relied on spectral power; it discounts differences in amplitude, and gives the same weight to small and large oscillations. Therefore, differences from previous results are to be expected and require careful interpretation. The alpha dynamics we observe are remarkably similar to those reported from power analyses (Huang et al., 2007; Nir et al., 2017), however the increase in theta during fast trials at BL has not previously been reported to our knowledge, and was not visible in the topography (Figure 4.6A). Therefore, this effect may not emerge when measuring spectral power with lower spatial resolution, or it may even be spurious; either way, it will be important to replicate this finding with a similar analysis on an independent dataset before drawing too many conclusions on the "theta boost." Additionally, there is room for improvement in the burst detection, and it may eventually be possible to sort between "sleepiness bursts" and baseline "cognition bursts," if they are ever proven to be qualitatively distinct.

4.4.3 Conclusion

In conclusion, while theta bursts robustly characterize the EEG during sleep deprivation, and behavioral lapses are substantially higher, there is no temporal link between the two that would suggest any causal relationship. We did find that alpha bursts during both sleep deprivation and baseline reflected variations in vigilance, however unlike in previous studies, alpha predicted better performance, likely because participants were at higher levels of sleepiness already at baseline. Therefore, neither oscillation directly causes lapses, nor reflects reduced vigilant states during sleep deprivation. It remains an open question what theta bursts during sleep deprivation are, but they may be primarily generated from unused cortical areas, and therefore have no behavioral correlates.

4.5 Methods

Different data from this experiment has previously been reported in Snipes et al. (2022) where the overall study design, participant selection, and EEG preprocessing was established, and in Snipes et al. (2023) where the burst detection method was developed and reported. These previous publications were exploratory analyses conducted in order to refine the analysis pipeline and better understand the increase in theta power observed during sleep deprivation. The data analyzed in this paper was deliberately set aside for this manuscript to test the hypothesis of whether a given EEG signal could explain behavioral lapses.

4.5.1 Participants

18 participants completed the experiment. University student applicants were screened for good health, good sleep quality, and at least some sleep deprivation vulnerability. 19 participants were recruited, and one participant dropped out midway. Mean age was 23 ± 1 years old, 3 were left-handed, all had normal or corrected-to-normal vision, and self-reported no hearing impairments. Data collection and interaction

with participants was conducted according to Swiss law (Ordinance on Human Research with the Exception of Clinical Trials) and the principles of the Declaration of Helsinki, with Zurich cantonal ethics approval BASEC-Nr. 2019-01193.

4.5.2 Experiment design

The full experimental schedule is depicted in Figure 4.1A. Participants came to the laboratory for two experimental bouts: baseline, and extended wake. During the baseline, participants went to bed at their habitual bedtime, and were free to wake up whenever they chose. On average they slept 8.0 ± 0.5 h. In the morning, they were provided breakfast and had at least 40 minutes from when they woke up to when they began task recordings. During the extended wake bout, participants slept only 4 hours, were kept awake 24 h, alternating between watching TV, rest recordings (Snipes et al., 2023), and breaks. We refer to this as a *4/24 extended wake* paradigm.

The main experiment task block consisted of 6 counterbalanced tasks performed at a computer desk at three timepoints (tallest blocks in Figure 4.1A): the morning after the baseline night, the same time during extended wake, and after 20 h of extended wake (Snipes et al., 2022). These task blocks included the LAT and PVT. However, these two tasks were also performed under soporific conditions: seated in an armchair with footrest and headrest, lights turned off, with the task projected onto a wall. These soporific recordings are the ones analyzed in this manuscript. The soporific LAT and PVT were performed in counterbalanced order with the desk task blocks, and then additionally the evening before and the morning after the extended wake bout. The soporific LAT was then performed two more times after the last task recording of SD. PVT data reported in Figure 4.2 comes from the one baseline and one sleep deprivation soporific recordings. The LAT BL session block was composed of the recordings from baseline, evening before, and morning after the extended wake bout, marked in peach in Figure 4.1A. N.B. these were at three different circadian times: mid morning, evening, and midday. The LAT SD session block was composed of the first counterbalanced recording after 20 h of wake, and the final two repetitions, marked in red in Figure 4.1A. Therefore, for half the participants, the three SD LAT tasks were performed after more than 22 h awake, back to back, whereas for the other half, the first SD LAT (and SD PVT) was performed around 20 h awake, before the 2 h computer task block.

The Lateralized Attention Task: The LAT is a 12 min visual-spatial reaction time task, modelled after the PVT (Basner & Dinges, 2011). 6 blocks (2 min each) alternated between having the left or right visual hemifield in white, and the other in black (Figure 4.1B). Participants had to maintain fixation on a red rectangle in the center of the screen, and covertly attend to the white half of the screen. Every 2-10 s a feint grey circle (1 cm radius, #F7F7F7) would appear randomly in any location of the illuminated hemifield and shrink away completely within 0.5 s. While faint, the stimuli were still above detection threshold levels for all participants when presented near the fixation point. Participants were instructed to press a button (on a MilliKey button box) before the circle disappeared, in which case the circle would freeze and flash green. Responses earlier than 0.1 s were considered false alarms. Responses from 0.5 to 1 s after the circle completely disappeared were considered late. If 5 stimuli were missed consecutively, an alarm would sound to wake up the participant (this occurred at least once for almost every participant during SD, but not BL). During the delay periods, 50 ms pink noise tones were presented every 1.5-5 s at ~50dB. Participants were instructed to ignore these tones. Overall, participants had between 100-130 trials per recording. One participant completed only 1 SD LAT, another participant completed only 2 SD LAT. All others had 3 BL and 3 SD EEG recordings.

The 0.1 s and 1 s cutoffs for considering trial responses was decided a-priori, based on typical adult reaction times in the PVT, in order to exclude false-alarms. While there may have been a few RTs slower than 1 s, during sleep deprivation 99% of RTs were within 830 ms. Compared with the ~33% of trials resulting in a lapse, this clearly indicates that the vast majority of lapses would have happened regardless of the 1 s cutoff.

4.5.3 EEG analysis

EEG data was recorded at 1000 Hz with Cz reference. Preprocessing and data analysis were done using EEGLAB (Delorme & Makeig, 2004) and custom MATLAB scripts (R2019b, R2022b, R2023a). Data was downsampled to 250 Hz and filtered between 0.5-40 Hz. Major artifacts were identified visually, and physiological artifacts (eye movements, heartbeat, muscle activity) were removed with independent component analysis (ICA). Further details are provided in Snipes et al. (2022).

Bursts were detected using cycle-by-cycle analysis (Cole & Voytek, 2019), with adaptations previously published (Snipes et al., 2023). The reason for using cycle-by-cycle analysis over other methods was to dissociate changes in the amplitude of oscillations from their actual occurrence, both of which increase for theta bursts with time awake, and increase and decrease for alpha bursts, respectively.

To identify bursts, first clean EEG data was filtered in narrow overlapping bands 4 Hz wide, from 2 to 14 Hz, and for each band, zero-crossings were identified. Then, negative oscillation peaks were detected in the unfiltered data as minimum values between each downward and upward zero-crossing timepoints. If a sufficient number of consecutive peaks met the criteria for an oscillation cycle, these were classified as a burst. This procedure was run both on the signal and its inverse. Overlapping bursts were removed, keeping only the longest burst. Bursts were then sorted as theta and alpha based on the mean peak-to-peak period. In our previous publication, cycles had to meet a single set of criteria to be considered a burst. Here, we chose three sets of criteria which together captured a larger fraction of oscillatory activity. These were identified through trial-and-error on the PVT soporific data, with the goal of capturing as much of the oscillatory signal that could be visually identified.

First, we used the same criteria as the previous publication. 4 consecutive cycles had to have similar consecutive periods (minimum ratio of .6), similar consecutive amplitudes (.6), similar rising and descending amplitudes (flank consistency; .5), a minimum proportion of *timepoints* that changed amplitude in the correct direction of the cycle (monotonicity in time; .6), and a minimum proportion of the *amplitude* that changed in the correct direction of the cycle (monotonicity in amplitude; .6). These criteria identified fairly regular oscillations.

Then, we identified short bursts that relaxed the above criteria but introduced an additional minimum amplitude threshold. Only 3 consecutive cycles needed to have: consecutive period ratios of .3, the peaks had to be prominent relative to the surrounding signal (there couldn't be any values between the previous peak's ascending midpoint and the current peak's descending midpoint, or the current peak's ascending midpoint and the next peak's descending midpoint), and the positive to negative peak amplitude had to be above 25 μV. This identified both short and longer bursts that had an irregular form but were undeniably oscillations emerging from the background signal.

Lastly, we identified long bursts that had at least 6 peaks with slightly more relaxed criteria from the clean set. Consecutive periods had to have a minimum ratio of .5, amplitude consistency of .5, flank consistency of .5, time monotonicity of .5, and amplitude monotonicity of .6. These criteria were selected to

capture bursts that were just below the thresholds previously set but were readily distinguishable from noise by their length. As with overlapping frequencies, when there were overlapping bursts detected with these three different sets of criteria, only the longest was kept. For this reason, no further distinction was made between bursts captured with the different criteria.

To quantify whether a burst was more likely to occur at a given timepoint for a given trial outcome (Figure 4.3, Figure 4.4), we calculated the proportion of trials which contained a burst, for each trial type at every timepoint. First, a vector of ones and zeros is created for every sample of the recording, indicating whether a burst was present or not in any channel. This vector was then epoched for every trial, centered on either the stimulus or response triggers recorded in the EEG, as is typically done for event related potentials (ERPs). Timepoints containing noise were not considered, nor were timepoints with eyes-closed. Trials were excluded if more than 50% of the data was missing, for either reason. Furthermore, trials during which eyes were closed at least 50% of the time during the stimulus window were also excluded (because the lapse would have been due to the eye-closure). Separately for every trial type at every timepoint, the number of trials containing a burst was divided by the total number of trials for that type, thus obtaining the proportion of bursts as a value between 0 and 1 across time. Participants were excluded if any trial type had fewer than 15 trials in total; for this reason, the sample size is always provided in the figure. The values for each participant were additionally smoothed over 0.3 s using a lowess filter for visualization purposes, and did not affect the results; the significantly higher theta at t = 0 s for BL fast trials remained significant without the filter. These proportions split by trial type were then compared statistically to the overall proportion of timepoints containing a burst during that session block, FDR corrected for multiple comparisons within each figure.

To determine the proportion of bursts across channels (Figure 4.5, Figure 4.6), the same procedure was done, except separately for each channel. The burst proportions were then averaged within the four windows (Pre: −2-0 s; Stimulus: 0-0.3 s; Response .3-1 s; Post: 2-4 s). The Pre window was chosen a-priori. The stimulus/response windows were split based on reaction times, such that only 1% of RTs were < 0.3 s and thus in the stimulus window. The Post window was chosen a-posteriori to explore further the rebound observed in Figure 4.3C.

4.5.4 Eye tracking

Eye tracking was done with Pupil Core “glasses” from Pupil Labs. These were eyeglass frames with two rear-facing infra-red cameras. Pupil Player software estimates pupil diameter from the video and provides a confidence value for that estimate; these confidence values were used to determine when participants had their eyes open or closed, with values <.5 considered eyes closed. Consecutive timepoints with confidence values over 0.5 that lasted less than 50 ms were still considered eyes-closed, and consecutive timepoints under 0.5 and less than 50 ms long were considered eyes open. Multiple technical failures resulted in data loss such that 6 participants had only 2 BL eye-tracking recordings, one participant had only 1 SD eye tracking, and one participant had no SD eye-tracking.

4.5.5 Statistics

For the data in Figure 4.3 to Figure 4.6, paired t-tests were performed comparing the proportion of trials with bursts (or eye-closure) to the general recording’s proportion of timepoints with bursts. All p-values within each plot (all timepoints for each trial type or all channels) were adjusted for false-discovery rate

(FDR) using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995). The largest t-values are reported in the text.

Hedge's g effect sizes were calculated to quantify the "meaningfulness" of the t-test results. Using Cohen's rule of thumb, Hedge's g around 0.2 is considered small, 0.5 considered medium, and 0.8 large (Becker, 2000; J. Cohen, 1988). However, given our small sample size it is important to consider what effect sizes we actually had power for. We therefore conducted post-hoc statistical power analysis (MATLAB function *sampsizepwr*) to identify the sample size required for a given effect size, with $\alpha = .05$ and $1-\beta=.8$, plotted in Figure 4.7. For the full 18 participants, we had statistical power for effect sizes over 0.68, and with 10 participants we had power for effect sizes over 0.94.

When reporting mean values in the text, instead of also providing standard deviations, we indicate the interquartile range (25% and 75% of participants' values). This can be more informative when results are close to floor or ceiling (e.g. Figure 4.2B).

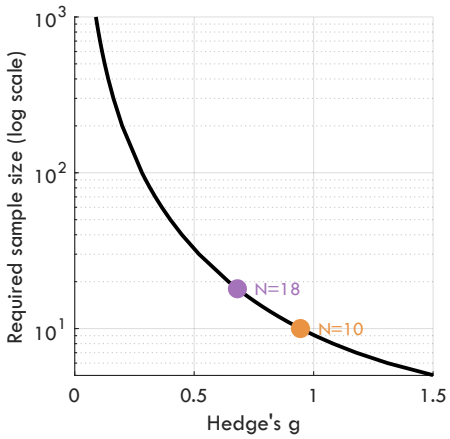

Figure 4.7: Required sample size for a given effect size, based on statistical power analysis, with $\alpha = .05$ and $1-\beta=.8$. Y axis is on a logarithmic scale. Colored dots indicate the lowest and highest sample sizes included in this paper. N.B. small effects of 0.2 would require around 200 participants to detect.

4.6 Supplementary material

4.6.1 Theta bursts contribute to at least half of the increase in theta power

Cycle-by-cycle analysis was used to identify theta (4-8 Hz) and alpha bursts (8-12 Hz). To evaluate the success of the algorithm in capturing these bursts, we visually inspected the power spectra of regions of interest (ROI) known to contain substantial oscillatory activity: the Front ROI during sleep deprivation for theta, and the Back ROI at baseline for alpha. The EEG power spectrum consists of the combination of a *periodic* component caused by oscillatory activity, and an *aperiodic* component reflecting the "background noise" of the EEG. When represented on a log-log scale, the 1/f aperiodic component appears as a downward-sloping straight line, from which periodic quasi-gaussian bumps emerge. The more this bump is reduced after removing timepoints containing bursts, the more successful the burst detection.

Figure 4.8A illustrates the degree of theta burst removal, and Figure 4.8B illustrates the same for alpha, in the EEG spectrum with eyes-open. For alpha, almost the entire periodic component is removed. For theta, a good portion of the periodic component is removed, although the remaining spectrum is still elevated compared to the aperiodic trend. This suggests that some frontal theta activity may not be as

regular as occipital alpha, and therefore not captured by the burst detection. When calculating the burst-related increase in theta power during sleep deprivation, we estimate that 53% [18, 82] of sleep-deprivation theta was captured. Visual inspection revealed that there were still bursts with more irregular waveforms that were not captured with cycle-by-cycle analysis; therefore this is an underestimate of the contribution of theta bursts to sdTheta.

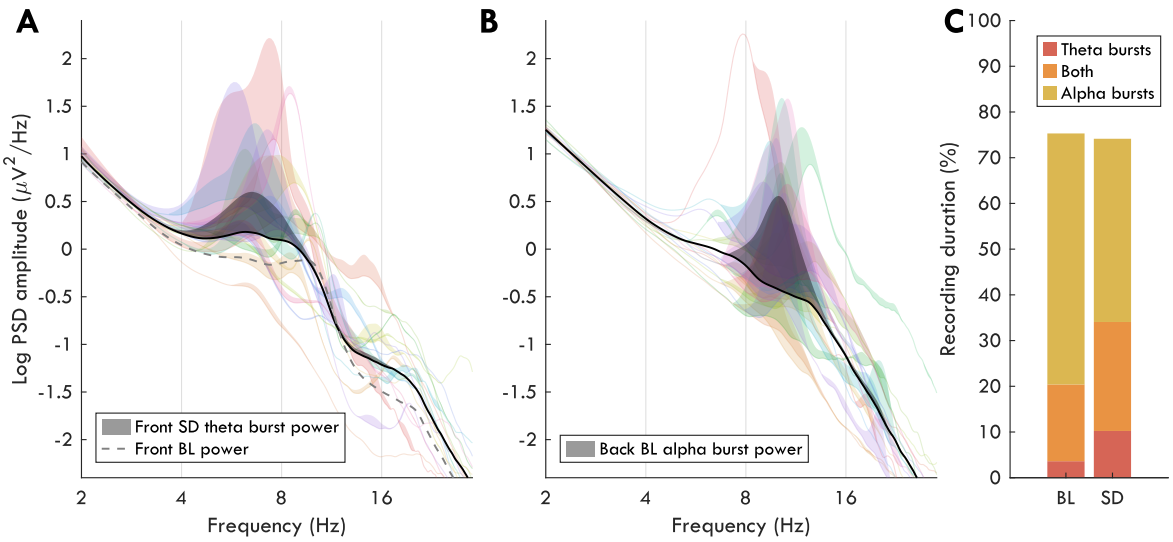

Figure 4.8: Oscillation burst detection. From the LAT burst detection. **A**: Power spectrums during SD with and without theta bursts for the Front ROI for eyes-open data. Each colored patch reflects a participant (N=17), such that the thin bottom line is the spectrum without bursts, and the filled in area reflects the spectrum with bursts. The black line and patch reflect the group average. The gray dotted line is the average Front ROI power spectrum during BL recordings, without theta bursts. The data was log-transformed, and the x axis is on a log scale. To improve visual comparison by increasing the overlap of individual participants, each spectrum was centered using mean delta power. This did not affect the group averages. **B**: Same as A, but comparing EEG power with and without alpha bursts in the back ROI during BL recordings (N=18). N.B. the right-most green participant for which not much alpha was removed was because the spectrum peak was ~14 Hz, outside the pre-selected range for alpha. **C**: Proportion of recordings during which a theta (red) or alpha burst (yellow) occurs (N=17). Orange represents time in which theta and alpha co-occurred. Whitespace reflects time in which neither burst was detected.

tldr; a little more than half of sdTheta is captured as bursts.

5 DISCUSSION

In the introduction, I covered what the literature had to say about theta and provided a list of possible explanations for the increase in theta power with sleep deprivation (section 1.7, page 30). Then throughout the three publications I tried to narrow down the correct answer. The easiest option to test was fmTheta: I conducted a short-term memory task to determine whether sdTheta also originated from the same medial prefrontal areas (section 2.4.2, page 42). I found that in fact sdTheta originated both within and well-outside the ACC (Figure 2.4, page 42), and so was not a strict subset of fmTheta. Interestingly, the sources of sdTheta were rather task-unrelated areas (Figure 2.9, page 49), which is still something in common with fmTheta. Furthermore, fmTheta bursts seemed to get larger with time awake (Figure 2.11, page 51). Therefore, the distinction between sdTheta and fmTheta was muddled.

To resolve the contradictory evidence, I switched from power analyses to cycle-by-cycle analysis (section 3). Like this, I could separately determine whether the increase in theta power was driven by changes in the quantities of oscillations or increases in their amplitude. I found in fact that both were true: pre-existing oscillations like fmTheta would increase in amplitude, and new oscillations became more common across the scalp with time awake (Figure 3.5, page 78). This increase in amplitudes supports the synaptic homeostasis hypothesis; increasing wake means increased neuronal connectivity. The increase in theta bursts was independent of this effect. Therefore, fmTheta was still found during sleep deprivation, with larger waves than ever, but additional theta bursts were popping up all over the place. But what were these sdTheta bursts, and what did they do? The results from the final paper seems to suggest that these bursts don't do anything at all.

5.1 Theta bursts during sleep deprivation as local rest

A key finding used to demonstrate that theta activity was local sleep in wake was its association with behavioral lapses in rats (Vyazovskiy et al., 2011). Because off-periods anticipated lapses and off-periods created theta events, and higher theta power characterized sleep deprivation in both rats and humans, the assumption was that sdTheta reflected local sleep. However, this assumption no longer holds given that sdTheta in humans is substantially more affected by bursts of theta rather than single theta events. Since these theta bursts had not previously been studied, it was an open question what they were; they could have been a compensation mechanism to maintain wake and stable performance, or some other manifestation of local sleep. In either case, there should have been a temporal relationship between theta bursts and behavioral outcomes. The LAT was the most likely task to see an effect, given it had both substantial increases in theta and behavioral lapses with time awake. However, I found no relationship between lapses and bursts, nor fast trials and bursts during sleep deprivation. So, neither local sleep nor compensation.

A possible explanation for why sdTheta does not affect behavior is because it could primarily originate from task-unrelated cortical areas. In general, the more engaging a task, the less widespread sdTheta; the most active task, the speech fluency task, produced the least sdTheta. Furthermore, speaking produced even less theta than silent practicing (section 2.6.3, page 67). More specifically, during a *spatial* game the areas responsible for object *recognition* were generating large amounts of theta, and during passive music listening the areas involved in high-order motor control generated the most theta (section 2.4.4, page 44). Instead, sdTheta was low in motor areas for the game, and low in object recognition areas for music. This could have meant that there was something wrong with the source localization, or that there wasn't sufficient spatial resolution, or maybe I hadn't read enough literature to grasp the importance of those

areas. But the fact that fmTheta has *also* been associated with task-unrelated areas, supported by a larger pool of evidence (section 1.5.1, page 24), makes for a compelling case that sdTheta could also come from unused cortical areas.

In the LAT, there was a relationship between *fast* trials and theta bursts at baseline, but it was unusual. Theta bursts were more likely to occur exactly when the stimulus was present and leading to a fast response, with peak timing just after the stimulus appeared and already significant just before stimulus onset. Therefore, given that the stimuli occurred at random, this means there was a causal relationship between spontaneous theta bursts and faster responses. Even more unusual was that this effect did not originate from any specific topographical source, as one would expect for an oscillation boosting performance (Figure 4.6, page 105). Again, under normal circumstances I would dismiss the timecourse result as spurious, but theta from unused cortical areas offers a possible explanation. Theta in task-unrelated areas (of which fmTheta is just one prominent example) could indicate inactivity of these areas, which means less competition with task-areas. Since task-unrelated areas will outnumber task-related ones, this didn't appear as coming from a specific collection of sources. Therefore, the effect was significant in time but not in space. The fact that sdTheta becomes increasingly widespread with time awake could then mean that theta overwhelms the brain and no longer offers a benefit because theta starts to be as likely in task-unrelated as task-related networks, or the brain is just too tired to derive a benefit from a reduction of competing networks.

As it happens, this relationship with unused areas may not even be specific to theta. The association with fMRI inactivity also exists for alpha oscillations (Goldman et al., 2002; Scheeringa et al., 2012), although it is already intuitive by the fact that alpha from visual areas increases in amplitude whenever eyes are closed (Kirschfeld, 2005). Likewise, alpha acts as an inverted attention spotlight: it is higher in cortical areas responsible for the visual region that is *not* being attended (Rihs et al., 2007; Sauseng, Klimesch, Stadler, et al., 2005).[1] This has led to the interpretation of alpha as a default resting state for primary sensory areas (Schomer & Silva, 2011). A slightly fancier interpretation is that alpha reflects a reduced "refresh rate" with which these areas receive and process sensory inputs (Mathewson et al., 2009; VanRullen, 2016).

Given that theta activity likewise originates from unused areas, maybe it's the same phenomenon as alpha activity. Zhang et al. (2018) find that theta and alpha form a gradient across the brain, with faster frequencies originate from the back, and slower frequencies from the front. Therefore, different frequencies would reflect location-specific preferences, not different neural processes. I find this gradient a noteworthy observation, however I don't think that theta and alpha are strictly the same oscillation. They show opposite changes across time, with theta increasing and alpha decreasing with sleep deprivation (Figure 3.5, page 78), and they have different circadian phases, with alpha lowest at night, and theta lowest in the WMZ (Cajochen et al., 2002). All the same, they may similarly reflect inactivity.

For both theta and alpha, the question then becomes whether this inactivity is just a passive form of neuronal idling, or whether these oscillations reflect an active component in focusing attentional resources. For alpha, the debate has been going on a lot longer, and the answer that emerged seems to be that it's a bit of both. Depending on the task, alpha power will decrease in attended visual areas in

[1] The primary visual cortex is a large occipital area that fairly neatly maps the visual field (Sereno et al., 1995), with the left hemisphere responsible for the right visual hemifield, and vice versa. Rihs therefore found that alpha is higher in left visual areas when attending the left visual field, and vice versa.

anticipation of incoming stimuli, and it will increase in contralateral visual areas, suggesting inhibition (Rihs et al., 2009). Likewise, rhythmic TMS at 10 Hz worsened visual detection when visual inputs were supposed to arrive at the stimulated visual cortex, and improved detection when inputs were in the contralateral hemifield (Romei et al., 2010).[1] Such experiments don't exist yet for sdTheta, but they may provide similar answers.

As mentioned, theta at baseline could conceivably reflect functional inhibition, explaining the theta boost in the LAT. There's even more evidence of this for fmTheta; as discussed in the introduction, fmTheta has been systematically associated with externally focused attention, resisting distractions, and reduced mind wandering. Likewise, I found the highest fmTheta to occur during the tablet game. Gaming in general is characterized by strong focused attention and imperviousness to distractions, which is something in common with (successful) meditation; the difference between the two is an external vs internal locus of control. fmTheta might reflect the inhibition of the DMN, resulting in more focused attention, and the theta boost observed in the baseline LAT may be a similar manifestation for other brain areas. Functional inhibition could be behind sdTheta as well, but the evidence is more thin.

Supporting the idea of inhibition, sdTheta did not come from just anywhere during the different tasks; it seemed to originate primarily from frontal and higher-order association areas. Given that the source localization was done with theta power, this could just reflect higher homeostatic sleep pressure in these regions and not an increase in the amount of bursts. However, it could also reflect the increased need to inhibit unspecific but highly interconnected areas to maintain performance during sleep deprivation, like fmTheta inhibiting the ACC during focused attention. Further supporting inhibition, the areas showing the most sdTheta originated rather from competitive instead of completely unrelated cortical areas. The game's largest sdTheta source was the object recognition pathway, areas not functionally relevant to the task but conceivably in direct competition with spatial cognition (the actual requirement of the game).

Supporting more the idea of sdTheta as a passive marker of disengagement was that the theta boost at baseline was no longer present during sleep deprivation. If sdTheta inhibiting task-unrelated areas was a form of compensation against sleep deprivation, it should have resulted in an even stronger association with fast trials, and if it was inhibition unintentionally entering task-networks it would have been associated with lapses or slow trials. The fact that the baseline effect disappears instead suggests that the increase in theta with sleep deprivation is not functional, and masks whatever beneficial theta effect might have already been present. However, again, this is one type of analysis in one task, a task specifically designed to not allow for compensation mechanisms. Future evidence could tip the scales.

If sdTheta bursts are not a form of inhibition but rather a reflection of disengagement, the question then becomes: does this correspond to a passive lack of activity, or could they be genuinely restorative? A distinction is usually made between *rest* which counteracts fatigue, and *sleep* which counteracts everything else. Both are restorative, but the understanding is that sleep involves sacrificing responsiveness for restorative processes that can't otherwise happen while the brain is awake. If task-unrelated areas are disengaged, this would already be sufficient for some degree of restoration. Theta as a form of local rest could explain also why theta power characterizes the EEG with increasing time on task and mental fatigue, assuming this form of theta exists independently from sdTheta with time awake (section 1.2.2,

[1] *TMS is transcranial magnetic stimulation, and unlike tACS, it is usually applied in very short pulses, perceived as auditory clicks. The sham condition in this case were rhythmic pulses at 5 Hz and 20 Hz, indicating that the effect wasn't just because participants were getting their brains zapped.*

page 13). The original hypothesis of theta reflecting local sleep however would take this one step further and assume a short-term loss in responsiveness for the sake of recovery.

Therefore, there are actually three possibilities for what happens in task-unrelated areas. Theta could reflect inhibition for the sake of reducing distractors and improving performance. Theta could reflect disengagement and therefore rest. Or theta could reflect genuine sleep. From my data, I lean more towards the second option, that theta reflects rest; theta as inhibition should have been behaviorally relevant, and theta as sleep is unlike any form of sleep currently observed. However, many more experiments during sleep deprivation are needed to find the answer.

tldr; sdTheta may not have any behavioral correlates because it originates from unused cortical areas; either because it is inhibiting conflicting networks, or just reflects rest.

Box 5.1: Redundancy and compensatory recruitment hypotheses

The biggest difference from Vyazovskiy's 2011 study in rats was that in humans, theta during sleep deprivation was driven largely by bursts and not little slow waves. However, the fact that these bursts don't affect behavior is an equally noteworthy difference. It is still possible that theta events in rats are the same as theta bursts in humans, but the reason sdTheta bursts do not cause any behavioral outcomes may be because we have substantially larger brains (Herculano-Houzel, 2009).

The "redundancy hypothesis" posits that humans have larger brains than is strictly necessary for short-term survival, and such large brains are instead meant to compensate for accumulating brain trauma with age, allowing for longer lifespans (Glassman, 1987; Humphrey, 1999). During acute sleep deprivation, such neural redundancies would also allow greater resistance to local sleep events, maintaining behavior at nominal levels for longer. Vyazovskiy observed behavioral lapses in rats during a sugar pellet reaching task with only 6 hours of sleep deprivation; we can only reliably see behavioral impairments after over 16 h of extended wake. Therefore, the sdTheta bursts in humans may have substantially less behavioral relevance than the theta events in rats, maybe only slightly delaying reaction times in humans (Hudson et al., 2020), imperceptible with how I analyzed the data.

This brain redundancy may occur in two ways: more neurons can be dedicated to the same function (e.g. left and right hemisphere redundancies), or additional unspecialized areas can be recruited under higher task demands. The latter is known as the "compensatory recruitment hypothesis" (Drummond & Brown, 2001) based on the fMRI finding that additional brain areas show increased activity during sleep deprivation compared to baseline when performing the same task, and this increase is positively correlated with improved performance (Chee & Choo, 2004; Drummond et al., 2005). In both cases, reserve areas help maintain task performance, differing only in how specialized the reserves are. This argument applies to any form of local detriment; the more redundant networks a species has, the longer it can remain unaffected by an adverse event or cortical impairment.

tldr; sleep deprivation may not have an impact on humans as it has in rats, because we have larger brains that can compensate for local sleep better.

5.2 How to reconcile sdTheta, fmTheta, and cogTheta

Given that both fmTheta and sdTheta seem to originate from unused cortical areas, this would resolve the theta paradox for two major manifestations of theta in humans. However, this does not explain the discrepancy with the ample literature linking theta to actual cognitive functions like memory encoding and long distance coherence which *does* occur in task areas. The initial reconciliatory hypothesis I had was that sdTheta might reflect some form of executive control compensation mechanism, although as described in the previous section, the evidence I've collected doesn't really seem to support this.

A different solution could instead be that there are at least two types of theta oscillations happening in different places: one reflecting cortical inactivity in task-unrelated areas; and the other, less prominent, reflecting cortical computation in task-related areas. Supporting this, I found that not only did theta have different sources, but also extremely heterogeneous waveforms, suggesting different oscillators (Figure 5.1). These differences were most noticeable across individuals, but even within the same participant, theta oscillations could look quite different. It may eventually be possible to categorize theta oscillations not just by source or frequency, but also by morphology; in which case there may be a more systematic dissociation between cogTheta and fmTheta / sdTheta. More advanced analyses are likely necessary, since it seems that rest-related theta like fmTheta and sdTheta are more prominent on the surface EEG, and cogTheta only really emerges with intracortical data or careful trial averaging.[1]

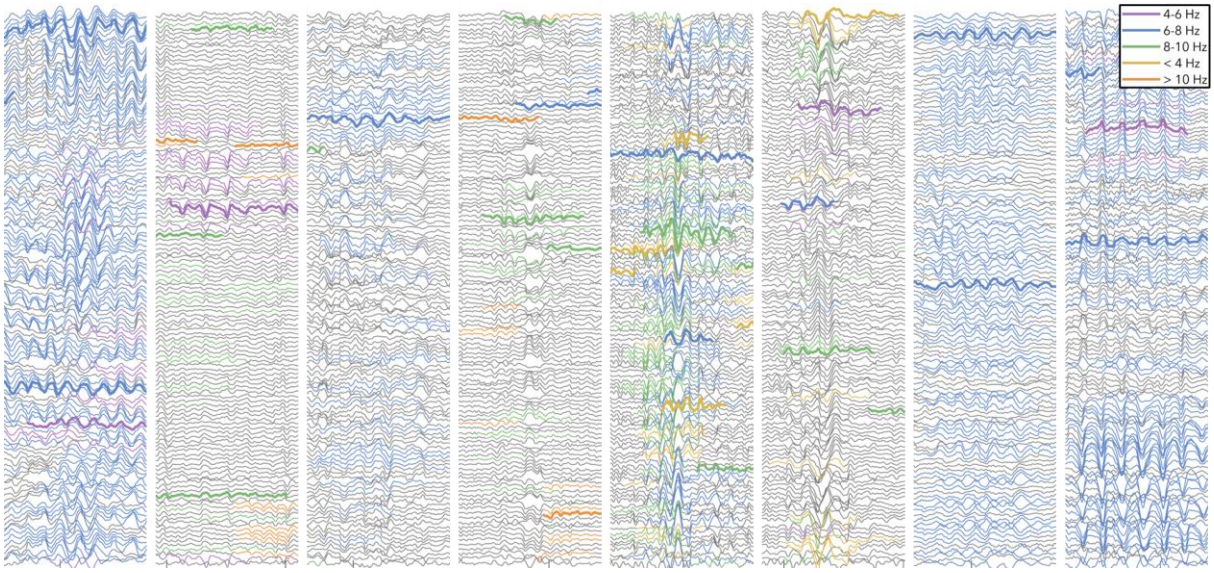

Figure 5.1: Examples of sdTheta. Taken from the last measured LAT from 8 different participants. 123 channels, each segment is about 1.25 s.

Alternatively, it may be possible to create a "general theory of theta." Buzsáki in 1996 suggested that maybe oscillations act as a low-energy inhibitory mechanism: only neuronal spikes at the correct phase will successfully transmit to downstream neurons. Therefore, an oscillation is as much about facilitating neuronal communication of the relevant network, as suppressing that of an interfering network. When

[1] *This dissociation between intracortical and surface results is a similar story to that of gamma. Both intracortical recordings and surface EEG showed increased gamma power related to visual perceptual binding (Tallon-Baudry & Bertrand, 1999), but it was later revealed that the effects on the surface were due to ocular microsaccades (Yuval-Greenberg et al., 2008), and the surface EEG gamma was not present when muscles were paralyzed (Whitham et al., 2007). Moral of the story: just because you see the same thing both intracortically and on the scalp, doesn't mean that it is the same.*

theta oscillations occur in hub areas such as the ACC, it could therefore reflect not overall disengagement as much as an increase in specificity of what information get transmitted from one brain area to the next. Essentially, theta oscillations filter messages from areas outside of the specifically engaged task network, and this corresponds to the cognitive phenomenon of focused attention. Therefore, it's not necessarily that theta reflects a blanket inhibition, but rather a more selective inhibition allowing for more streamlined communication between task-relevant networks. The fact that theta from (mostly) task-irrelevant areas is of higher amplitude than cogTheta might not be a coincidence. If a given area has more task-unrelated rather than task-related networks, then theta across these areas might be of comparable phase and therefore appear larger on the cortex.

This explanation would have been easier to accept if the results from section 4.3.2 had been inverted, and theta was more related to fast responses during sleep deprivation; if theta was higher for fast trials during SD, more so than BL, then the greater amount of sdTheta during the LAT was acting as compensation to maintain the same level of performance. Still, I would argue that this one result is not enough to dismiss this interpretation of a unified theory of theta altogether. More evidence is needed, either way. Until then, I think a lot of fruitful research can move forward relying on theta oscillations as biomarkers, without being overly concerned about what they are actually doing.[1]

tldr; theta oscillations could filter information by inhibiting task-irrelevant areas.

Box 5.2: Frontal midline theta reflects an optional compensation mechanism

Frontal-midline theta is not measured in all individuals (Mitchell et al., 2008), which begs the question: why not? Sometimes, oscillations aren't visible on the surface EEG just because of structural brain differences, however the proportion of participants with fmTheta depends a lot on the task, so individuals differ on which conditions they produce it. A possible explanation is that fmTheta reflects a special compensation mechanism that some individuals employ to maintain performance on a task they would otherwise struggle with. It may even be the case that it's a mechanism some individuals have, and others simply have not.

Ferreira et al. (2019) found that in a task requiring suppressing distractor information, frontal-midline theta was high at the beginning of the task, and decreased with practice in young adults, but not older adults. This may suggest that as the task becomes more familiar, the extra boost provided by fmTheta is no longer needed. Likewise, fmTheta may be a mechanism more often relied on in younger individuals, whereas older individuals are sufficiently experienced not to need it (or unfortunate to have lost it).

A similar interpretation is that fmTheta reflects *cognitive control*, i.e. a goal-directed bias over habitual responses (Cavanagh & Frank, 2014). While this could also explain the sporadic nature of fmTheta, it does not explain why a pleasant game would have higher theta than a traditional cognitive task (Figure 2.6, page 45); after all, it requires more conscious control to stay on a boring task than an enjoyable one. For this reason, I lean towards fmTheta reflecting the consequence of a special brand of focused attention, above and beyond what would be strictly needed to perform the task.

tldr; since fmTheta doesn't exist in all participants, it is likely optional.

[1] *For more on what it means for an oscillation to be "doing" something, see Box 7.1 in section 7.2.2, page 136.*

5.3 Amplitudes as markers of sleep and synaptic homeostasis

While theta bursts remain a mystery for now, an important step forward with this thesis was clarifying the association between oscillation amplitudes and sleep homeostasis (section 3, page 70). This involved a bit of a paradigm shift in how the relationship between oscillations and homeostasis is conceived. By moving beyond specific oscillations (theta in wake and delta in sleep), I instead focus more generally on the effect that the microscopic synaptic changes will have on the macroscopic EEG.

The synaptic homeostasis hypothesis (SHY) is still under debate regarding what synaptic plasticity really is, what physical/chemical changes it corresponds to, and to what extent upscaling and downscaling of synapses is specific to wake and sleep (personal communication with detractors). Non-invasive research in healthy humans is usually ill-suited to resolving these questions, but SHY provided testable predictions on what we should observe in the EEG: increased oscillations with time awake (Figure 5.2). The idea is that we accumulate memories throughout the day by progressively strengthening synaptic connections, but this can't go on forever. Therefore, sleep is needed to selectively "downscale" synapses that are not important and consolidate the ones that are. The fact that slow wave activity decreases across sleep and increases according to prior wake was considered a consequence of this process: the stronger the connections between neurons, the larger the oscillations (Tononi & Cirelli, 2003).

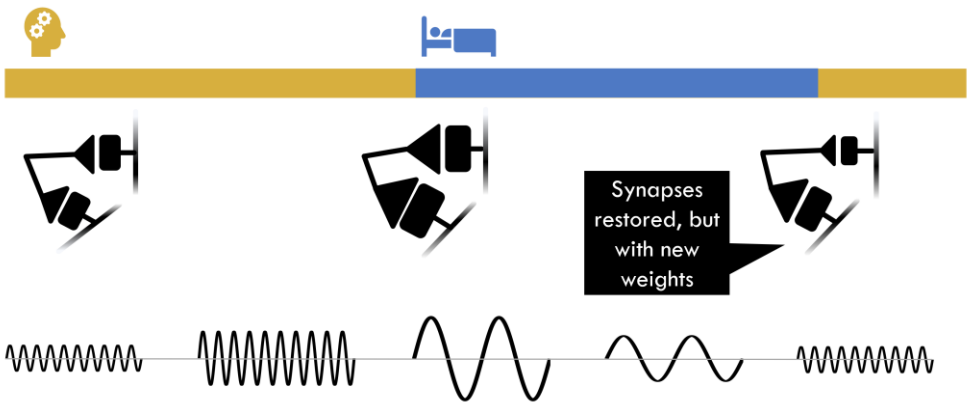

Figure 5.2: The synaptic homeostasis hypothesis (Tononi & Cirelli, 2014). During wake, synapses increase in strength, resulting in higher amplitude oscillations. During sleep, synapses are "downscaled" so the overall synaptic balance is restored, but with new weights reflecting new memories (and forgotten old memories). This process is reflected in decreases in slow wave amplitudes during sleep, and increasing theta amplitudes during wake.

The relationship between SWA and homeostasis is evident already as just changes in delta power. As it happens, periods in which slow waves are present are pre-selected, in essence controlling for "quantities" of slow waves, but wake oscillations do not similarly get staged. Periods with oscillations are pooled with periods without, so quantity is no longer controlled for. To find the same effect in wake as in sleep, analytical measures like cycle-by-cycle analysis were needed, that did not rely on amplitudes to define the existence of the oscillation.

The fact that oscillation amplitudes increase with time awake is likely driven by an increase in the strength of connectivity between neurons. Of course, many other factors will also affect oscillation amplitudes, as I saw with the wake maintenance zone and different tasks, but SHY does provide a very good explanation for why amplitudes increase across wake and decrease after sleep. I find that it makes much more sense that synaptic homeostasis would affect all oscillations in the same way, rather than it being

a property specific to just theta and delta.[1] I only quantified theta and alpha, but I strongly suspect it holds for beta oscillations, since beta power also increases with time awake (Figure 2.10, page 50). Furthermore, even sleep spindle amplitudes increase following sleep deprivation, despite overall quantities decreasing (Knoblauch et al., 2003). To reiterate then, theta is not a marker of homeostasis; amplitudes are.

However, a lot more replication work needs to be done before shouting this fact from the rooftops. It needs to be seen whether these changes in amplitude follow all the same effects as SWA, across age, naps, longer bouts of sleep deprivation, local effects, species differences, etc. No matter what, oscillation amplitudes are unlikely to ever be as robust a marker of sleep homeostasis as SWA itself, but it has the advantage of being an independent marker, as well as substantially easier to record than sleep. Once such work is done, I think there are a lot of applications for using amplitudes to quantify sleep and synaptic homeostasis.

An underappreciated aspect of the two-process model that I think these results highlight really well, is the profile of accumulating sleep pressure during the first hours of wake. Subjectively, we only start to notice the lack of sleep once we stay awake into our habitual sleep window, but what the two-process model predicts, and oscillation amplitudes show, is that the fastest accumulation of sleep need happens from the very beginning. This means that our brains will be differently receptive to new material in the morning compared to afternoon and evening. Obviously, night classes would not exist if it weren't still possible to learn in the second half of the day, but there's at least in theory an inherent advantage to classes in the morning. Most research regarding learning and sleep and time of day focuses on memory consolidation, but it would be especially interesting to test other aspects like fatigability, cognitive flexibility, etc., ideally while keeping constant circadian effects. Along the same lines, people with a morning chronotype are generally considered advantaged because their preferred window coincides with the societally chosen window for school and work, but it may also be that they are lucky to have their circadian peak overlapping with their homeostatic peak (of performance).

The fact that the brain changes so dramatically also means that neuroscience and psychology experiments should take special care in choosing the timing of their recordings. It's not that morning or afternoon measurements are intrinsically better or worse, but one or the other may be more beneficial for a given experiment. For example, TMS produces stronger motor evoked potentials (MEPs) with higher sleep pressure (Huber et al., 2013; Ly et al., 2016) so would be more visible in the late afternoon, but if the desired effect is to produce plastic changes, maybe early morning stimulation will have more of a lasting impact. Certainly, it would be inadvisable to collect recordings too spread out across the day, as this introduces unnecessary variability in the data.

All of this is to say, wake research should start paying more attention to sleep homeostasis. The fact that oscillation amplitudes are so affected by time awake is a good reminder of this. Furthermore, they provide an accessible objective marker that could be used to keep track of such changes.

tldr; oscillation amplitudes could be an easy measure of homeostatic sleep pressure independent from slow wave activity in sleep. It's also a reminder of how quickly the brain changes throughout the day.

[1] *Occam's razor.*

5.3.1 Magnifying oscillations with sleep deprivation

For most experiments, being sleep deprived falls under the category of "extremely bad confound." However, the fact that time awake amplifies oscillations could make sleep deprivation a unique opportunity to investigate more subtle waves. In some respects, this is what is already done for patients with epilepsy; they get sleep deprived so their seizures get worse which improves source localization. The results of fading short-term memory fmTheta during sleep deprivation (section 2.4.3) and reduced pre-trial alpha during sleep deprivation (section 4) might advise against using sleep deprivation to study oscillations. However, investigations more interested in the electrophysiological system itself, for example source localization or travelling wave analyses, might benefit from the clearer signal.

Gamma activity is notoriously difficult to measure on the surface EEG (Whitham et al., 2007), and most reliable research on this oscillation comes from intracortical data (Yuval-Greenberg et al., 2008). However, when visually inspecting the sleep deprived EEG, in one participant, I noticed these high-frequency gamma spindles (Figure 5.3). At first, I thought this might be a muscle artefact, but their peak comes from the channels furthest from any muscles. The fact that they were exactly at 30 Hz also made me think they might be an electrical artefact, but no other participant had them, they came in bursts like spindles, and again, the topography was very physiological. These were barely visible during baseline recordings; they didn't stand out from the 1/f background activity and they were even more indistinguishable from muscle artefacts. In general, the sleep deprived EEG appeared substantially more heterogeneous across individuals, but upon closer inspection, many of these differences could already be spotted at baseline, once you knew what to look for. Therefore, sleep deprivation acts as a magnifying glass for oscillations.

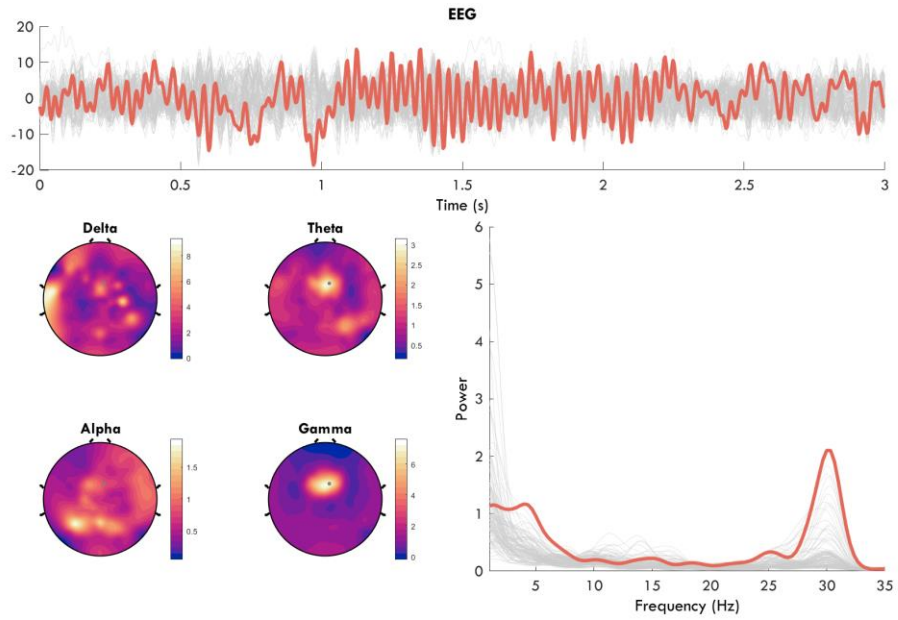

Figure 5.3: Gamma burst visible during sleep deprivation. Top: 3 second section of EEG with a prominent gamma burst during the LAT task in P07. Bottom left: topographies of delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and gamma (25-35 Hz) power during the above burst. Color scale is spectral power in $\mu V^2/Hz$. Bottom right: power spectrum, untransformed, of the burst. The gray dot in the topographies indicates the channel highlighted in red in the other plots. The gray lines of those plots indicate the other channels.

tldr; sleep deprivation makes oscillations bigger, so if you have trouble seeing them, sleep-deprive your participants first.

Box 5.3: Diagnosing and treating rumination in depression with fmTheta

One of the most pernicious symptoms of depression is rumination, a vicious cycle of negative thoughts. Rumination has been linked to fMRI activity and structural abnormalities in the ACC and the DMN (Burkhouse et al., 2017; Drevets et al., 2008; Kaiser et al., 2019; Kühn et al., 2012). During resting-state EEG, rumination should be visible as a reduced occurrence of fmTheta in patients compared to healthy controls, with more time spent ruminating being anti-correlated with the *duration* of fmTheta.[1] However, on the flip side more time spent ruminating across a day should result in a larger increase in the *amplitudes* of fmTheta. This effect may disappear the longer the individual experiences rumination and depression, as there could be fewer plastic changes, and negative thought patterns consolidate with time. Pizzagalli et al. (2002) found that fmTheta power was predictive of depression treatment success, which may reflect either a still-plastic ACC, or less severe rumination (Korb et al., 2009).

A better understanding of the link between rumination, plasticity, and fmTheta may help with diagnosis, monitoring, and even treatment of depression. When at rest, the overall quantity of fmTheta bursts may reflect (the lack of) rumination, which could be a useful diagnostic indicator of depression for children and adolescents, who have different depressive symptoms from adults and are therefore more difficult to diagnose (Battle, 2013). Supporting this, Murphey et al. found lower fmTheta during a short term memory task in patients with depression (O. W. Murphy et al., 2019). From there, fmTheta can be used to monitor the degree of rumination, and the extent to which plastic changes are still possible for this area.

From my data, the most reliable way to elicit fmTheta was when playing the tablet game; this would make playing games a well-controlled condition, suitable for children, which suppresses the ACC and therefore rumination. This may even explain why gaming, depression, and rumination often go hand-in-hand (Kökönyei et al., 2019): playing videogames may be a way for children and adolescents to self-medicate rumination, which they subjectively experience as "escapism." If gaming manages to control rumination and induce fmTheta, and fmTheta amplitudes reflect plastic changes in this area, then repeated frontal EEG recordings in children and adolescents with depression playing games may help monitor the progression of the disorder and the extent to which plastic changes can still occur. Specifically, fmTheta amplitudes increasing substantially across a day would indicate a still-plastic but overworked ACC. Instead, if fmTheta amplitudes don't change as much, this may indicate a loss of plasticity due to entrenched rumination.

Even better, fmTheta can be used to *train* young individuals to better control rumination, using neurofeedback. Neurofeedback works by providing a real-time visual or auditory stimulus indicating the presence of a desirable or undesirable brain signal. Individuals first practice regulating this brain signal using an overt stimulus, preferably learning to both increase and decrease its occurrence, and then they learn to do so without the cue. Given that fmTheta can easily be recorded with a single electrode on the forehead, this may be one of the most accessible and easy to implement forms of neurofeedback. Furthermore, by conducting feedback training in the late afternoon, fmTheta may be particularly visible and improve signal quality. Then, feedbackless practice in the morning may help actually consolidate learning.

tldr; fmTheta reflects an area that is compromised in depression, so it could be used as a diagnostic and treatment tool.

[1] *Andersen et al. (2009) contradicts this prediction in healthy participants; they found that theta power was higher during rumination than a neutral counting control. However, this effect was driven by lateral occipital theta instead of fmTheta. Generally, all the conditions they investigate would have low fmTheta, and the fact that occipital areas showed more theta than frontal areas is a good indication of that. Furthermore, counting is often used as a control for arithmetic fmTheta experiments, which show that more intense math results in more theta. Therefore, I do not find these results discouraging.*

5.4 The wake maintenance zone

An unanticipated perk of the 4/24 extended wake paradigm is that it highlights the WMZ, something that usually requires as much as 40 h of sleep deprivation to observe (McMahon et al., 2018; Shekleton et al., 2013; Zeeuw et al., 2018). By shortening sleep to only four hours, sleep pressure from the previous day hasn't fully dissipated. More importantly, this also adds an extra four hours of wakefulness, resulting in higher sleep pressure around the WMZ (Figure 5.4). Even this relatively minor difference in experiment design was sufficient to clearly observe effects of the WMZ on subjective sleepiness, pupillometry, microsleeps, and both theta and alpha oscillation amplitudes (section 3). Needless to say, a 4/24 paradigm is substantially easier to conduct than an 8/40 paradigm (section 2.6.4.2, page 69). The only real limitation is not being able to observe more than a single 24 h period.

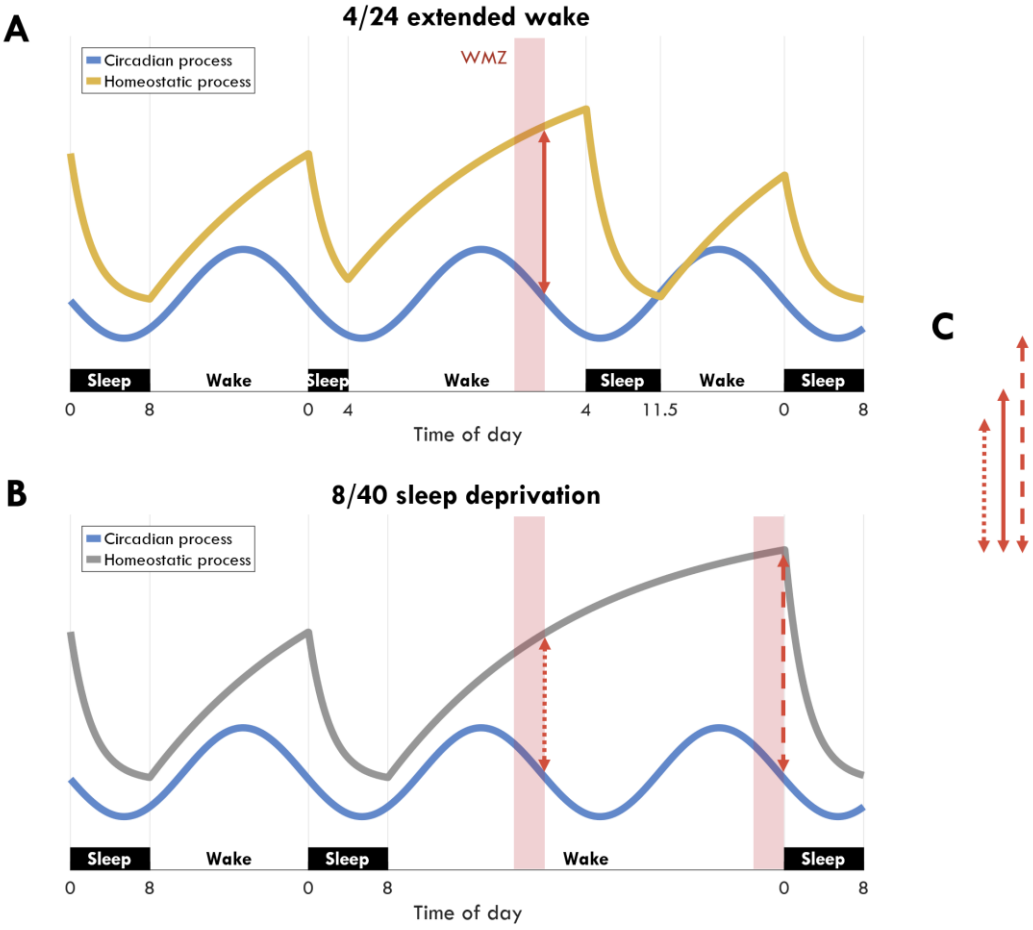

Figure 5.4: Difference in sleep pressure between a 4/24 and a classic 8/40 sleep deprivation paradigm. These curves were created based on the equations in Achermann & Borbély (2003). **A**: 4/24 extended wake paradigm in which the second half of the sleep window is eliminated, and the lucky individual has to stay awake for 24 h. **B**: A classic 8/40 sleep deprivation paradigm, in which an extremely unfortunate participant skips an entire night of sleep, and only gets to sleep in the sleep window of the next night. Sleep pressure is much higher, but this design "wastes" the first WMZ, and also doesn't measure effects after the second one to determine the underlying sleep pressure trajectory. **C**: Comparison of sleep pressure amplitudes of the three WMZ from the two paradigms (8/16, 4/24, 8/40).

I suspect that the WMZ may be a human-specific circadian mechanism to maintain synchrony between the 24 h light/dark cycle and the "homeostatic cycle" of alternating wake and sleep. Essentially, because we have uniquely long continuous periods of both sleep and wake, it's easier for the sleep/wake pattern to become desynchronized from circadian rhythms than it would be if we spontaneously took naps all the time. More than at any other time of the day, the hours just before habitual sleep are the ones in which

it is worst to go to sleep, as anyone who has tried to recover from jetlag will know. If you go to sleep too early, inevitably, you will wake up in the middle of the night and the misery never ends. Therefore, the WMZ (when correctly synchronized to your time zone) will give that little push needed to reach the proper sleep window, if for whatever reason sleep pressure is unusually high that evening.

While the WMZ bears a close resemblance to crepuscular rhythms in some species (Ackermann et al., 2020; García-Allegue et al., 1999; Refinetti, 2020), it differs in that it doesn't affect overt behavior (Lieberman et al., 1989; Samson et al., 2017), and instead mostly influences ability to go to sleep (Dijk & Czeisler, 1995). This may seem like an inconsequential distinction, but if the WMZ has a different function from activity-promoting circadian rhythms, this would suggest different evolutionary pressures and therefore potentially different mechanisms driving the effect. As suggested by Strogatz (1987), an overactive WMZ could be behind sleep-onset insomnia, although sometimes what people identify as insomnia is just attempting to fall asleep within this window, expecting it to be as easy as delaying sleep (Macedo, 2021). Solutions to disorders of the WMZ may not necessarily overlap with those that would be identified for classic circadian rhythms. For this reason, more research is needed into the WMZ, and if it doesn't exist in other animals, more work will be needed in humans. The 4/24 extended wake paradigm can help.

tldr; the WMZ makes sure that you don't go to sleep too early and mess up your circadian clock, but since this may be human specific, we need to figure out creative ways to study it.

5.4.1 The neural pathways behind the WMZ

If the WMZ is human specific, this makes it substantially more difficult to investigate the underlying mechanisms. As it is, there are very few publications about the WMZ, which is why hopefully the 4/24 paradigm can speed up discovery. In the meantime, I have pieced together some hypotheses on the pathways involved.

In our data, we show effects of the WMZ on pupillometry; this means that somehow, the circadian signal of the suprachiasmatic nucleus (SCN) must make it to the pupil, as well as the rest of the cortex which desynchronizes during the WMZ. The SCN generally displays 24 h periodic rhythms, firing either during the day or at night, depending on the species (Aston-Jones et al., 2001; Hastings et al., 2007), although exceptions have been found. In mice, despite SCN neurons mostly firing during the day when the animal sleeps, a subset of "siesta neurons" fire during the night, and optogenetic stimulation of these neurons induces nighttime but not normal daytime sleep (Collins et al., 2020). Of course, this pattern reflects the inverse of the WMZ, however a similar mechanism could be responsible.

After the SCN, another likely critical structure linked to the WMZ is the lateral hypothalamus (LH), containing wake-promoting orexin neurons (Sakurai, 2007).[1] Studies in mice show that stimulation of orexin neurons results in pupil dilations (Grujic et al., 2022). Patients with narcolepsy, who are orexin-deficient, don't show any change in sleep onset latency during the WMZ (Dantz et al., 1994),[2] indicating that the

[1] *Orexin neurons, also called hypocretin neurons, are localized almost exclusively in the lateral hypothalamus, and they are involved in other important things like feeding behavior. They in turn activate other wake-promoting cholinergic, dopaminergic, and noradrenergic neurons.*

[2] *Results by the Esther Werth group replicate this finding but haven't been published yet.*

WMZ alerting signal has to pass through the LH. Since narcoleptic patients have a mostly intact melatonin production (Blazejova et al., 2008) the circadian system just before the LH must otherwise be intact. Curiously, Blazejova et al. report that a subset of patients have a slightly altered melatonin profile, peaking just before habitual sleep onset then decreasing across the night. This may mean that the WMZ normally suppresses melatonin release, acting as a sleep gate as suggested by Lavie (1986), but maybe more of a "flood gate," holding off the sleep-promoting effects of melatonin until exactly sleep onset.

After the LH, it is more difficult to pin down where the WMZ signal continues, because the LH projects to basically all the wake-promoting nuclei (Sakurai, 2007; Saper et al., 2010), which all affect pupil diameters (Lloyd et al., 2022; Reimer et al., 2016). Originally, I focused on the LC, a nucleus involved in gating sleep stage transitions (Osorio-Forero et al., 2022), whose activity is linked to alertness and responsiveness to novel stimuli (P. R. Murphy et al., 2014). Instead, since we did not see any changes in pupillary responses to oddball tones (Figure 3.7C, page 80), this may not be the primary pathway of the WMZ. Another projection of the LH is to dopaminergic areas of the ventral tegmental areas (VTA), but maybe this can be ruled out as well. Spontaneous blink rates have previously been found to be an indirect measure of dopamine activity (Jongkees & Colzato, 2016), and was hypothesized to reflect a compensation mechanism to counteract sleep deprivation (Barbato et al., 2007). As it happens, we did not see any change to blink rates during the WMZ (Figure 3.8A, page 81).

Another option could be the cholinergic neurons of the basal forebrain (BF), also linked to pupil diameters (Reimer et al., 2016). Cholinergic wake-promoting neurons in the BF are progressively inhibited by adenosine (Rainnie et al., 1994), which builds up in the BF following an increasing saturating exponential function (Porkka-Heiskanen et al., 2000). Adenosine inhibits cholinergic activity in the BF, which therefore decreases the wake drive. Caffeine is an adenosine antagonist, and therefore counteracts this effect, which is how coffee keeps us alert (Boonstra et al., 2007). The hypothalamus activity during the WMZ may therefore be an endogenous "caffeine boost," inhibiting the inhibition of the accumulated adenosine, and allowing the BF to exert a wake-promoting signal to the rest of the cortex. This could explain the decrease in theta during sleep deprivation following caffeine consumption (Landolt et al., 2004). Interestingly, in pupil diameter standard deviations, rather than means, we see both this saturating curve as well as a dip in the WMZ (Figure 3.7). Therefore, part of the alerting mechanism of the WMZ may be via the BF, but not exclusively. Finally, it's also possible there may be a more direct connection between the LH and pupil diameters.

All of this is speculation, of course. It may be possible to obtain proof by using simultaneous pupillometry and fMRI as was done in Lloyd et al. (2022). The 4/24 paradigm can be repeated, although with the fixation recordings conducted in the scanner. Then, the exact timing of individuals' WMZ can be correlated to increases in activity in the various nuclei of the AAS, thus identifying the networks involved. In a second step, pharmacological studies may be able to selectively inhibit activity in these nuclei and could theoretically stop the WMZ, again detected with a 4/24 paradigm. Changes to the WMZ can be observed both in EEG theta power and ocular microsleeps, the two most sensitive outcome measures to the WMZ (Table 3.1, page 75), as well as subjective sleepiness. Quantifying all three independent effects is ideal, as it could always be that pharmacological interventions affect the outcome measure but not the actual WMZ effector.

Once the mechanisms behind the WMZ are identified in healthy individuals, the next step would be to diagnose patients who have a compromised WMZ. A simple adaptation of the 4/24 paradigm would make for a very feasible diagnostic test: have participants restrict their sleep at home, then begin in the mid-

afternoon, maybe with a 5 minute auditory oddball EEG recording every 30 minutes, until well past their habitual sleep onset. This could also be done by adapting the multiple sleep latency test (MSLT) or the maintenance of wakefulness test (MWT) already used in the clinic (Doghramji et al., 1997); instead of starting in the morning as is usually done, the recordings could start in the afternoon. If there are pharmacological agents that can suppress or enhance the WMZ, and the WMZ is deemed compromised for that patient, then they can also be appropriately treated.

tldr; the WMZ alerting signal is likely relayed though the same area that is compromised during narcolepsy, the lateral hypothalamus. The 4/24 paradigm and theta can be used to better study this window.

5.4.2 Avoiding the WMZ in sleep studies

Many sleep studies either aim to improve sleep or evaluate how sleep improves performance. More often than not, this means recording subjective and objective measures before and after sleep. For the morning recordings, the current practice is to wait at least half an hour, although ideally more than an hour, after wake onset before conducting any tests to avoid the sleep inertia window (Trotti, 2017). I would suggest that the same should be done for the WMZ (Figure 5.5).

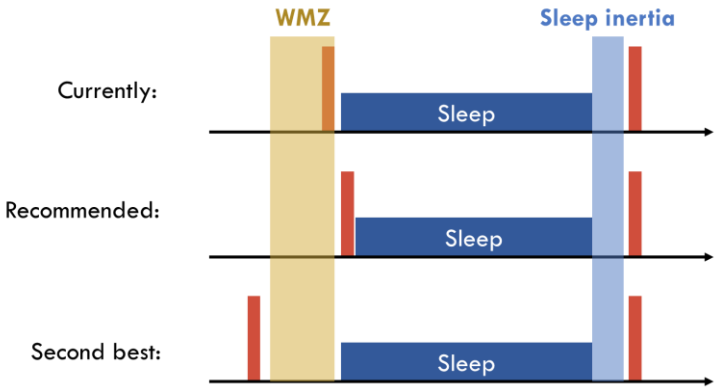

Figure 5.5: Possible wake recordings for sleep studies. Typically, evening wake recordings are conducted in the middle of the WMZ and may therefore not accurately reflect the build-up in sleep pressure that occurred during the day. Likewise, sleep inertia will reduce performance and alter the EEG immediately following wake onset. For this reason, wake recordings should avoid both the WMZ and the sleep inertia window.

Sleep inertia is quite evident every morning for almost everyone, therefore it is arguably the more important aspect to control for. The WMZ instead seems to only appear under elevated levels of sleep pressure, and in some outcome measures more than others. However, there's no reason to believe it isn't present every evening. Theta power for example seems to already be affected by the WMZ under normal evening conditions (Finelli et al., 2000; Zeeuw et al., 2018). It is also likely that the WMZ will affect some systems more than others, and until we've identified which ones, the best experiment designs should aim to avoid the WMZ entirely.

An option could be to briefly delay sleep onset and conduct the tests/measurements instead, then allow participants to start sleep maybe up to an hour after their habitual bedtime. This would mean of course slightly elevated sleep pressure, but not outside the norm of night to night variability. It may even help participants fall asleep more easily, as is done for fMRI sleep studies. The second best approach may be to conduct the tests before the WMZ. This can be a bit tricky, as the WMZ onset may be more variable,

and it would then mean waiting for several hours before actual sleep onset. However, if the test block is quite long, then this would be preferable.

tldr; don't perform pre-sleep tasks in the WMZ.

5.5 Local seep in wake

My original hypothesis was that sdTheta would correspond to local sleep events, like in rats. It turned out however that the bulk of sdTheta power in humans seems to come from bursts of oscillations rather than single isolated events. In the Vyazovskiy 2011 paper, they do not explicitly specify whether the EEG theta occurred primarily in isolation or in bursts, but the "representative example" they provide is of an isolated wave. Therefore, it appears that the increase in sdTheta bursts in humans is different from these local sleep events. When visually inspecting the EEG, there were occasionally single theta waves that stood out from the background signal (Figure 5.1), but these were infrequent and therefore did not affect the overall recording power, and likewise couldn't have contributed to the bulk of behavioral lapses. However, it may still be possible for local sleep to be behind such lapses, just not visible as high-amplitude theta waves.

5.5.1 A better marker

Slow waves make for the most obvious marker of sleep, but they are not the only change in the EEG, and certainly not the first. In humans especially, the transition from wake to sleep is extremely slow, going through several minutes of NREM 1. In my own experiment, even after 24 h of sleep deprivation, participants still took on average 5 minutes to reach NREM 2 (Table 2.1, page 41). This transition stage is defined mostly by the lack of anything notable (alpha, spindles, etc.), and sometimes the only reliable marker for scoring is slow rolling eye movements (Berry et al., 2012; Santamaria & Chiappa, 1987). Furthermore, the onset of sleep is gradual in space, progressing from front to back (Ferrara & De Gennaro, 2011; Marzano et al., 2013). Altogether, this would suggest that if there is local sleep during sleep deprivation, it should take the form of NREM 1.

But how to quantify local NREM 1? As mentioned, sleep is systematically characterized by steeper slopes in the background EEG, already beginning with NREM 1 (Figure 7.7, page 141). Therefore, it may be possible to identify brief periods of sleep in individual EEG channels based on changes in the 1/f aperiodic spectrum. With the current tools, this would mean using a shifting window around 1 s, and perhaps focusing on the slope of the higher frequencies (>15 Hz) as these are better resolved in short windows. A local sleep event could therefore take the form of a briefly steeper slope in the aperiodic signal. This would not necessarily be visible as a change in power, which is why its relationship to lapses may have gone unnoticed up to this point. This may even explain why previous studies (Andrillon et al., 2021; Bernardi et al., 2015; Fattinger et al., 2017) were able to find associations between behavioral deficits and theta events, by specifically *not* discriminating periodic from aperiodic activity (section 3.6.3, page 96); an increased spectral tilt would result in more "theta waves," so they indirectly mark periods of local NREM 1. Generally, their effect sizes are small, which may be due to the fact that theta would be an imperfect proxy for the change in slope.

It is generally understood that even if sleep stages are scored using specific markers such as spindles, k-complexes, etc., there is some fundamental state that persists between these events, such that a plain segment of NREM 2 is different from a plain segment of wake, even if there are no spindles or alpha waves. Unlike these sporadic events, the aperiodic activity should persist in these plain periods, making it a much more fundamental marker of underlying stage. For this reason, I think local sleep might be better defined by changes in aperiodic activity than by more obvious microarchitecture events. Explicitly quantifying the local changes in aperiodic activity may be the key to explaining behavioral lapses observed during sleep deprivation.

tldr; the change in background EEG activity might be a better marker for local sleep in wake than theta oscillations.

5.5.2 A slower marker

I mentioned how occasionally during sleep deprivation there were isolated theta waves that might resemble the one in Vyazovskiy et al., but it's also possible that a true equivalent with rats is also present in humans, but at a slower frequency. Slow waves tend to be slower in humans than in rodents (Achermann & Borbély, 1997; Hubbard et al., 2020), hippocampal theta in rodents might correspond instead to ~3 Hz activity in humans (section 1.4, page 19). Therefore, we may have been looking at the wrong band.

Some studies have found links between delta waves in wake with fatigue and task lapses (Quercia et al., 2018). Other experiments found links between delta waves, mind blanking and mind wandering (Andrillon et al., 2021). More recently, a study in patients with epilepsy found a direct link between off-periods in spike rates and wake cortical slow waves (Walker et al., 2023), present to a lesser extent also in Parkinson's patients.

Altogether, these results would point to slow waves appearing in wake in humans, but individually there's reason for reservation. Most analysis methods used to identify single waves suffer from the limitations described in section 3.6.3, and patients with epilepsy have disease-linked "off-periods" which may not truly translate to the general population. Furthermore, these studies rarely use data during sleep deprivation, despite this being the time most likely to show intrusions of sleep. It's not impossible that slow waves occur already a couple hours after waking up, and maybe more so in a boring task or after a long task. But I would first expect such sleep events to be present during sleep deprivation, and to a greater extent, before presuming that a signal during low sleep pressure is actually a form of sleep. After all, it's possible that delta waves are a legitimate part of the wake EEG, and they are disruptive to behavior, without being homologous to slow waves.

However, in my data I did see real slow waves during sleep deprived wake, such as the one in Figure 5.6, which were not present (or not obvious) when participants were well rested. Unfortunately, like the single theta events (Figure 5.1), these were quite rare, present in only a couple individuals. Most often, they were simultaneous with eye-closure, indicating whole-brain sleep. However, a few of these were unambiguously slow waves during eyes-open wake, with amplitudes that are never seen in healthy well-rested adults, and with negative deflections that could be explained by off-periods (Nir et al., 2011). They closely resembled the initial slow waves observed at sleep onset. There might have also been smaller sleep slow waves, but whether these were the same as in sleep is harder to prove. The fact that the background

activity of the EEG is not white noise, but rather colored noise, makes it very easy to identify patterns when there are none.

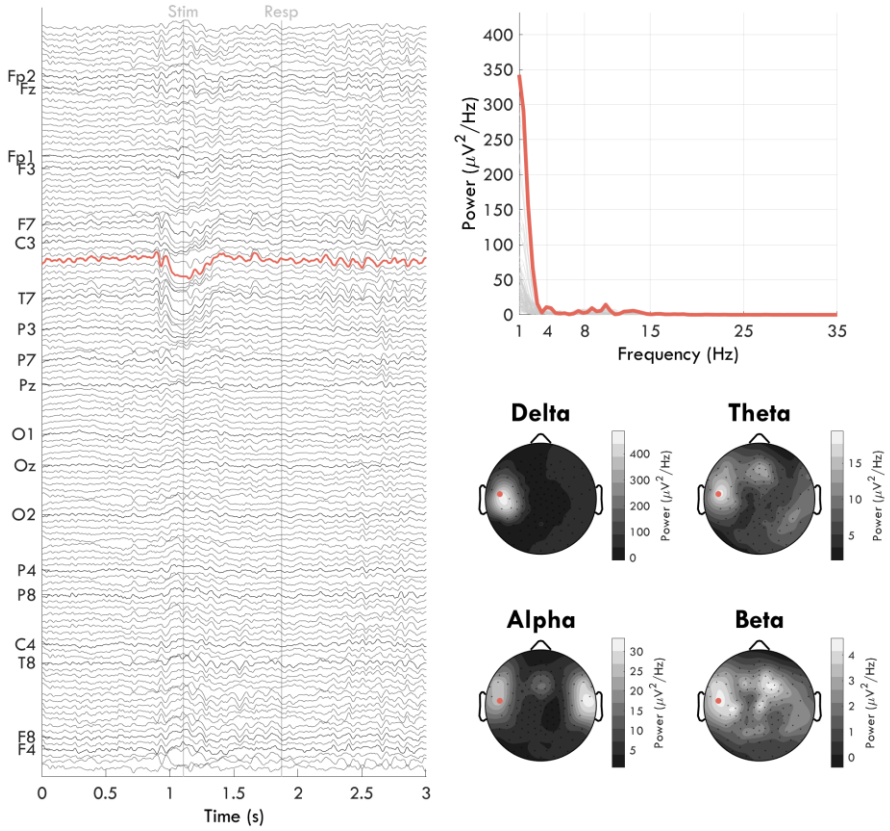

Figure 5.6: slow oscillation during eyes-open sleep deprivation. Observed during the LAT. This was a clear example of an oscillation that resembles a slow wave, with a large amplitude and primarily a negative deflection, peaking over the left ear while a stimulus was shown. The participant was still able to respond, although quite delayed. These events were rare, and generally the EEG from these channels during sleep deprivation was quite peculiar for this participant.

So, from my anecdotal evidence, I would say there *are* intrusions of slow waves in wake during sleep deprivation, but at least with a 4/24 paradigm there were not enough of them to reliably study. To further investigate these slow waves in wake, I would recommend even longer sleep deprivation, more participants, and either multiple sessions of the LAT with more frequent stimuli, or a task involving continuous inputs. I would also recommend more conservative wave-detection methods, eliminating spurious events from the 1/f aperiodic activity. One day, it may even be possible to confirm whether these are driven by neuronal spiking off-periods.

tldr; slow waves actually happen during sleep deprivation, but they are rare.

Box 5.4: Are delta waves in sleep actually oscillations?

The existence of slow oscillations in sleep is undeniable. Look, it's like a massive spindle:

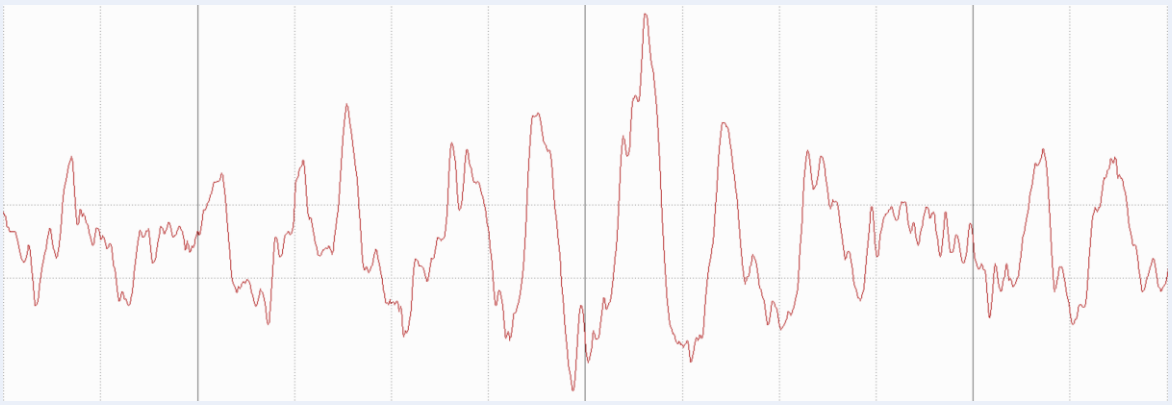

Figure 5.7: Periodic slow waves in NREM 3. Screenshot from sleep scoring program. Space between vertical dotted lines is 1 s. Horizontal dotted lines indicate ±37 µV. Data is filtered between 0.5 and 40 Hz, downsampled to 128 Hz.

However, as discussed in section 7.2 (page 135) not all EEG signals that go up and down can be considered strictly oscillations. As anyone who has ever scored EEG knows, most of NREM sleep is not characterized by beautiful massive sinusoids, but rather something like this:

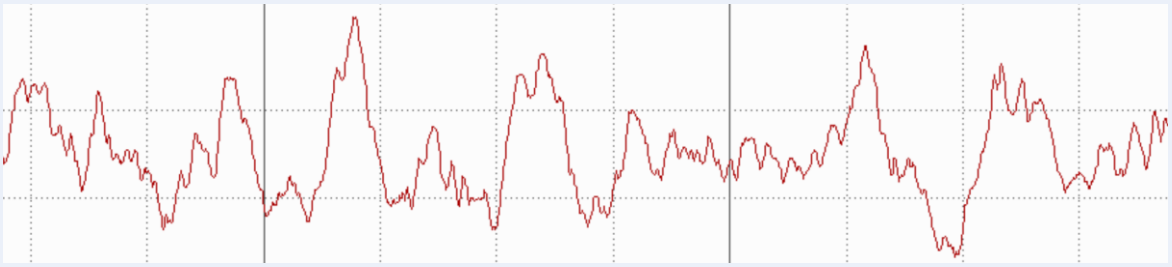

Figure 5.8: Aperiodic slow waves in NREM 3.

The problem is that this last signal is not made of oscillations *per se*. In fact, when simulating just the 1/f aperiodic EEG activity, by sufficiently increasing the steepness of the slope, you get an extremely similar signal:

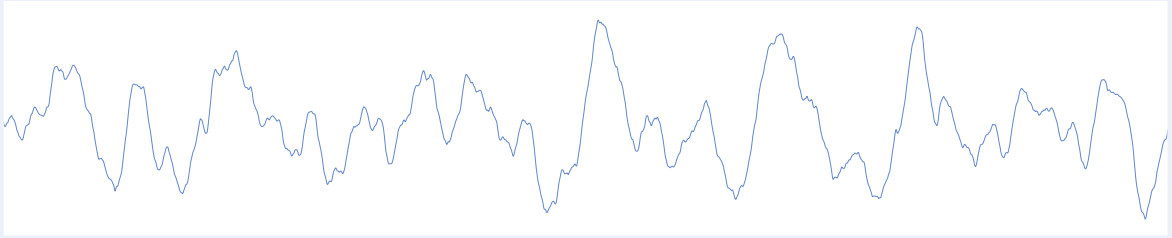

Figure 5.9: Simulated colored noise resembling NREM 3. Same as in Figure 1.2, page 15.

Therefore, at least some if not most of NREM slow waves are actually just how the tilt in the spectrum of the aperiodic EEG manifests itself. The fractal nature of the 1/f means that the increase in slower frequencies is strictly related to the decrease in high frequencies, and no specific "band" is more important. However, because the pivot point of the changing slope is somewhere in the spindle range (Bódizs et al., 2021), the effect appears largest in the delta range (Figure 5.10). Additionally, because sleep scoring is done visually by identifying slow waves using a minimum amplitude threshold, the slower (<4 Hz) waves are the only ones that go over the threshold, even if technically the changes in the theta range across the night are almost as pronounced and equally related to dissipating sleep pressure.

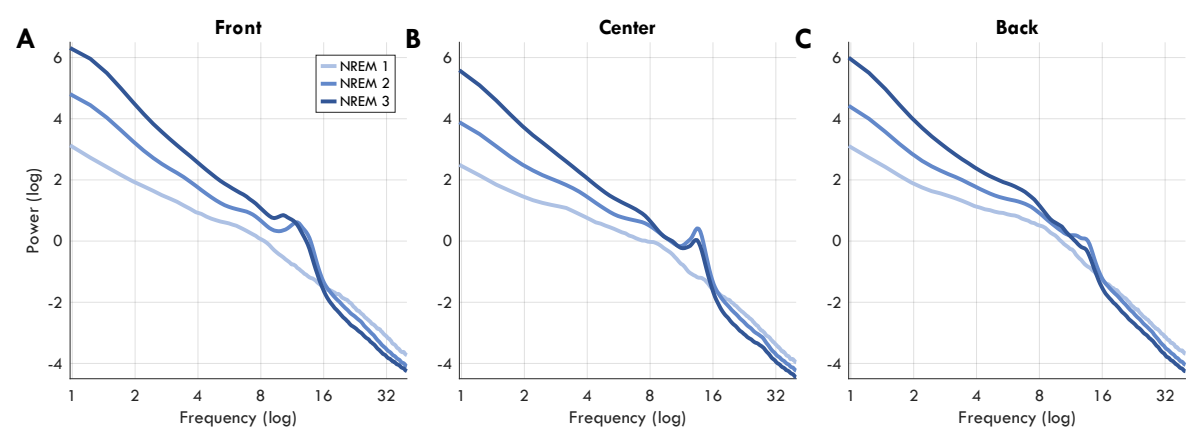

Figure 5.10: NREM sleep stages spectra, log-log scale. From 18 participants, baseline night. This finding was first published in a larger dataset in Schneider et al. (2022).

However, slow oscillations independent of the aperiodic background really do happen, both as bursts and isolated events. K-complexes are large negative deflections that characterize NREM 2 (Figure 7.2, page 137), and it's also possible to identify smaller, more local single-slow-wave negative deflections, like in Figure 5.6. An FFT around such events clearly create "bumps" that emerge from the 1/f even though there is only one wave (Perrenoud & Cardin, 2023), however across long time windows, if there aren't many and they are extremely variable, they get lost in the spectrum average.[1] Additionally, there are genuine periodic bursts like in Figure 5.7 during NREM 3. However, the 1/f background activity during NREM 3 has the same amplitude as K-complexes and single slow waves, so they are no longer distinguishable from each other. All this to say, NREM has both single isolated slow waves and slow oscillation bursts, distinct from the background activity, but specifically during NREM 3 you cannot easily tell them apart because of how steep the 1/f slope is, especially when not occurring in bursts like in Figure 5.7.

Achermann & Borbély (1997) actually find a periodic spectral bump emerging from the 1/f between 0.75 and 1.5 Hz, specific to the first two NREM cycles and specific to NREM 3 and not NREM 2, which they call slow oscillations. Most current analyses of aperiodic spectrums stop at 1 Hz (like mine), because they're based on data that is high-pass filtered at 0.5 Hz, and power is calculated over 4 s windows, tapered, so not suited for oscillations < 1 Hz. Instead, Achermann & Borbély used very clean data and 20 s epochs. They showed that these slow oscillations were not strictly homeostatic because they did not decrease from the first to the second cycle. But if slow oscillations show a different timecourse across sleep, and they end at around 1.5 Hz, then what is the 1-4 Hz "slow wave activity" (SWA) with which we quantify sleep homeostasis across NREM sleep?

If spectra are a reliable indicator of whether a signal in time is periodic or aperiodic, then the evidence indicates that almost everything between 1.5-4 Hz is actually aperiodic: there is no bump in the spectrum in this range for any NREM stage (Figure 5.10). In fact, when looking at the change in spectra across the night on a log-log scale, it's obvious that the main change is the tilt in the aperiodic slope, rather than a change in periodic amplitude (Figure 5.11), which I had instead observed in wake for theta power during sleep deprivation (Figure 2.22, page 65). This can be masked when looking at the full spectrum from 0 Hz with only the y axis log-transformed, because sleep data is filtered under 0.5 Hz, giving the illusion of a bump.

[1] *The periodic bump in the spectrum becomes narrower the more similar cycles are present in the signal.*

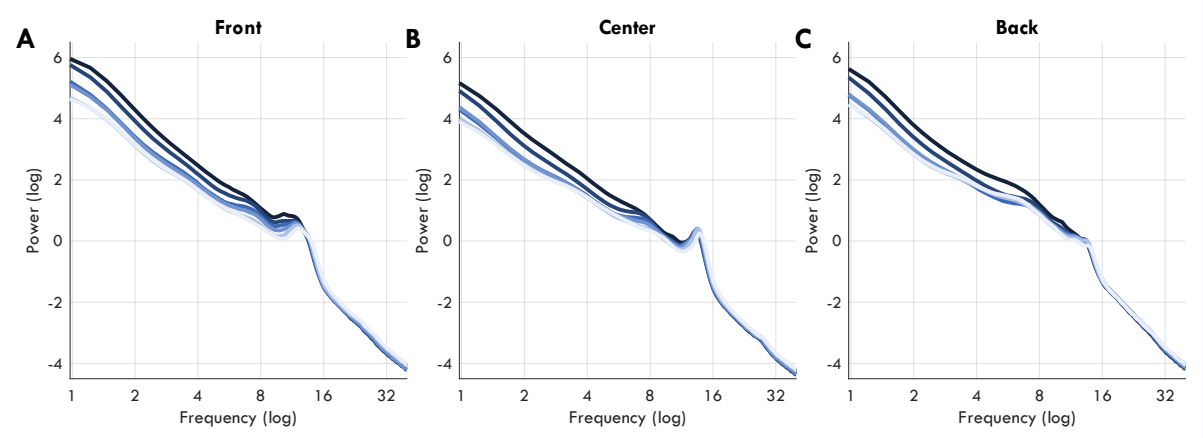

Figure 5.11: Overnight changes in NREM sleep, log-log scale. 18 participants. Each participant's baseline night was divided into 6 parts, and NREM 2 and NREM 3 were averaged. The lighter the spectrum, the later the sleep cycle. This finding has been published with a larger dataset in G. Horváth et al. (2022).

What this means is that homeostatic findings regarding 1-4 Hz delta power are not about oscillations at all, but rather the slope of the background EEG activity. For example, the change in SWA following sleep deprivation is also just a tilt in the spectrum (Figure 5.12). Instead, results that specifically focused on single waves around 1 Hz are likely to have captured more of the periodic slow oscillations and single slow wave events (Jaramillo et al., 2020; Krugliakova et al., 2022; Ngo et al., 2013; Sousouri et al., 2022), although not exclusively.

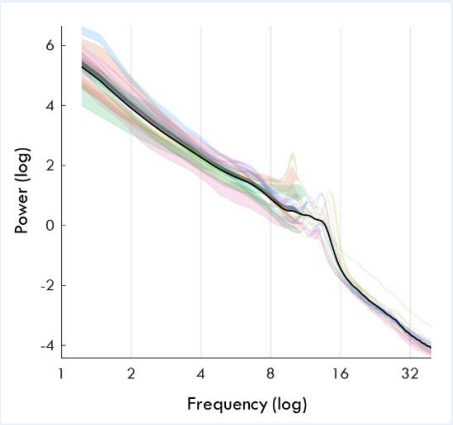

Figure 5.12: Change in slope following sleep deprivation. This is comparing the first hour of NREM during the Pre night of the extended wake period, to the first hour of the Post night after 24 h of wake. Each colored patch represents the increase in power for each participant.

What about all the animal literature linking slow waves to off-periods? There are two possible explanations. First, as mentioned already for theta (section 1.4, page 19), oscillations in rodents tend to be faster than in humans, and therefore "slow oscillations" that are around 1 Hz in humans could easily be around 2-3 Hz in rodents (Hubbard et al., 2020). Therefore, findings related to off-periods and 1-4 Hz waves in rodents could correspond to off-periods and 0.75-1.5 Hz waves in humans. Second, it may well be that "background activity" is also composed of on- and off-periods of spike rates; the main difference from "real" slow waves would be in the synchronization of these off-periods, and how predictable their durations are. For oscillations, the end of the off-period would be predictable with the first quarter of the LFP oscillation (i.e., 4x later), whereas for aperiodic waves it would be indeterminable. Events like K-complexes may be somewhere in-between. Moving forward, I would recommend separating analyses on slow oscillations, and the aperiodic background activity.

tldr; slow wave activity is often just aperiodic background activity, not oscillations.

6 CONCLUSION

With this thesis I set out to understand the increase in theta power observed during sleep deprivation. Some answers emerged, but "conclusions" may be premature. So instead, I leave you with the following list of the most important takeaways from this work:

1) Theta activity is extremely heterogeneous; within an individual, across individuals, and across species. Careful consideration is needed to disentangle these differences, because it is highly unlikely that all manifestations of theta are the same.
2) The more time spent awake, the more theta bursts occupy the EEG.
    a. These bursts do not affect behavior during sleep deprivation, leaving an open question as to what does.
    b. Instead, they often occupy brain regions that aren't in use.
3) The more time spent awake, the larger all EEG oscillations get, likely reflecting strengthening synapses when forming new memories.
    a. While amplitudes increase, quantities of bursts can decrease, which is why traditional analyses like spectral power are insufficient to detect this effect.
4) If there are intrusions of sleep slow waves during wake, these are not a substantial contributor to the overall increase in theta power with time awake, which is instead mostly driven by bursts.
5) The wake maintenance zone is driven by a circadian signal so powerful that it desynchronizes the cortex, and may be behind some forms of insomnia.
6) The next steps forward should involve better understanding the extreme differences in theta oscillations, and taking more advantage of the spectral slope of the background EEG when defining sleep and wake.

The "theta paradox" remains alive and well. I don't have sufficient information to explain why theta could characterize both sleep deprivation and cognition, but the hypotheses that best explain the data are:

1) There exist at least two different manifestations of theta, one involved in synchronizing neuronal activity to facilitate cognition; and the other, stronger theta, appearing in unused or inhibited cortical areas.
2) Theta oscillations during sleep deprivation and cognition are one and the same, and reflect two sides of the same coin; inhibition of task-irrelevant networks, and synchronization of task-relevant ones.

At the moment, I feel the scales tip more towards the first option. If theta had a functional role, I would have expected it to manifest itself in the LAT, especially given how much theta is present during this task. However, this is just one analysis, in one task, and absence of evidence isn't evidence of absence. More experiments and more analyses are needed to find the right answer. For now, it is enough to have raised awareness about this very paradoxical EEG oscillation.

7 GLOSSARY

7.1 Acronyms

AAL: automated anatomical labeling (atlas)
AAS: ascending arousal system
AASM: American association of sleep medicine (scoring manual)
ACC: anterior cingulate cortex
ADHD: attention deficit hyperactivity disorder
ANOVA: analysis of variance
BF: basal forebrain
BL: baseline; task block condition after 1 h awake after a baseline night of sleep.
BOLD: blood oxygen level dependent (activity)
ch: channel
cps: cycles per second
DICS: dynamic imaging of coherent sources
DMN: default mode network
DOI: digital object identifier
EBRS: European biological rhythms society
EC: eyes closed / eye closures
EEG: electroencephalography / electroencephalogram; see Figure 7.1
EGI: Electrical Geodesics, Inc.
EMG: electromyography / electromyogram
EO: eyes open
EOG: electrooculography / electrooculogram
ERPs: Event-related potentials
EWOQ: experiment web organizer for questionnaires
FDR: false discovery rate (correction)
FFT: fast Fourier Transform
FIR: finite impulse response (filter)
fMRI: functional magnetic resonance imaging
FOOOF: fitting oscillations, one over f.
ICA: independent component analysis
KSS: Karolinska Sleepiness Scale
PSD: power spectral density
PVT: psychomotor vigilance task
LAT: lateralized attention task
LC: locus coeruleus
LFP: local field potential
LH: lateral hypothalamus
MEP: motor evoked potential
MNI: Montreal National Institute
MRI: magnetic resonance imaging
MSLT: multiple sleep latency test
MTL: medial temporal lobe
MWT: maintenance of wakefulness test
N: number (of participants)
N.B.: nota bene (“take note”)
NREM: non-rapid eye movement (sleep)
REM: rapid eye movement (sleep)
ROI: region of interest
RT: reaction times
SCN: suprachiasmatic nucleus

Figure 7.1: High-density EGI EEG net used for this study.

SD: sleep deprivation; task block condition after 22 h awake
SHY: synaptic homeostasis hypothesis
STD: standard deviation
STM: short term memory (task)
SWA: slow wave activity (0.5-4 Hz)
tACS: transcranial alternating current stimulation
tldr: too long, didn't read
TMS: transcranial magnetic stimulation
TV: television :P
WMZ: wake maintenance zone
VAS: visual analogue scale
VTA: ventral tegmental area

7.2 Key EEG concepts

I'm going to assume that the reader has a fairly solid understanding of what EEG is, mostly because this thesis is not of interest otherwise. For the basics of human EEG, see Luck (2014). For slightly more advanced EEG analyses, see Cohen (2014). Instead, the following sections are meant to provide clear definitions to concepts that are not completely agreed upon in the literature, as well as some lesser-known aspects of EEG signals.

7.2.1 Frequency bands

The EEG signal is characterized by oscillations, which makes power spectral analysis an ideal tool to quantify these effects. This is done with an FFT, which converts a signal in time into the frequency domain, basically fitting all the possible sine waves needed to recreate the signal, and identifying the amplitude of each sine wave to determine power at that frequency. Since any signal, even without oscillations, can be represented in this way, not all changes in power for a given frequency means that there is actually an oscillation at that frequency, but it is a simple and often reliable proxy.

EEG oscillations, while quite variable across individuals, are still more likely to occur in the same frequency ranges under the same conditions. Therefore, for convenience, a lot of analyses refer to a fairly standard set of spectral bands, although with some variability in how the exact edges are defined. The following is how this thesis divides the spectrum, from slowest to fastest.

Slow oscillations: the slowest slow waves, between 0.75 and 1.5 Hz, from Achermann & Borbély (1997). These are notable in that they are not strictly homeostatic, remaining constant for the first two NREM 3 cycles, then disappearing. Unlike the higher frequencies of the delta band, these are evidently periodic.

Delta: 0.5-4 Hz spectral power band.

Slow wave activity: technically delta, but here refers specifically to delta activity during sleep. During wake, delta activity is much less prominent.

Theta: 4-8 Hz spectral power band.

Alpha: 8-12 Hz spectral power band, during wake. Highest in occipital regions, with eyes closed.

Sigma: 12-16 Hz spectral power band, during NREM sleep. It is a proxy for spindle activity.

Beta: 15-25 Hz spectral power band.

Gamma: 15-35 Hz spectral power band. Often ranges higher, but in keeping with sleep research, I filter my data at 40 Hz, just under the 50 Hz line noise.

7.2.2 Oscillations vs events

"Oscillation is the repetitive or periodic variation, typically in time, of some measure about a central value (often a point of equilibrium)." – Wikipedia

A curious and defining feature of the mammalian EEG is the presence of **oscillations**. In humans, the clearest most uncontroversial oscillations are alpha bursts in wake originating in occipital areas and thalamocortical spindles in NREM sleep, both of which are nearly perfect sinusoids (Figure 7.2). These are clearly periodic repeating signals, regularly "oscillating" around 0, with waxing and waning amplitudes. There are also non-sinusoidal but clearly periodic rhythms like mu-rhythms in which consecutive "m"s repeat (Figure 7.2),[1] or sawtooth waves which are more triangular.[2] While sometimes oscillations come in continuous trains like hippocampal theta in rodents or eyes-closed alpha in humans, more often than not they appear in bursts, anywhere from a couple of cycles to several seconds long.

The brain also produces **events**. The classic example is a K-complex during NREM 2 sleep, a massive negative deflection in voltage followed by a brief rebound (Figure 7.2). They are called such because a K-complex can be produced by *k*nocking on a hard surface near the sleeping individual. It is in many respects a single-trial event related potential (ERP), orders of magnitude larger than typically observed during wake. ERPs are a stereotyped pattern of positive and negative deflections, locked to an event like a stimulus or a behavioral response, which only really emerge from the noise when averaging the EEG of many trials evoking the same pattern. K-complexes most often occur spontaneously, they are asymmetric, can be phase-coupled to spindles, and only appear one at a time. Both K-complexes and ERPs therefore differ from oscillations in that they are neither repetitive nor fluctuate around a central value.

Other terms used to describe specific features of the EEG throughout this thesis include:

Activity: an umbrella term for any EEG signal of note, without specifying what form it takes.

Background activity: the 1/f aperiodic EEG signal (see next section).

Microarchitecture: also an umbrella term for both oscillations and events; anything clearly emerging from the background EEG.

Waves: a prominent positive or negative deflection in the EEG signal. Like "activity," this does not specify whether it's a single event, a periodic oscillation, or even just a notable part of the 1/f background activity. "Waves" is used instead of "activity" when they have been identified visually.

[1] *Although apparently, its "m" for motor, because it appears over motor areas.*

[2] *See Ebersole & Pedley (2003) or Schomer & Silva (2011) for a complete compendium.*

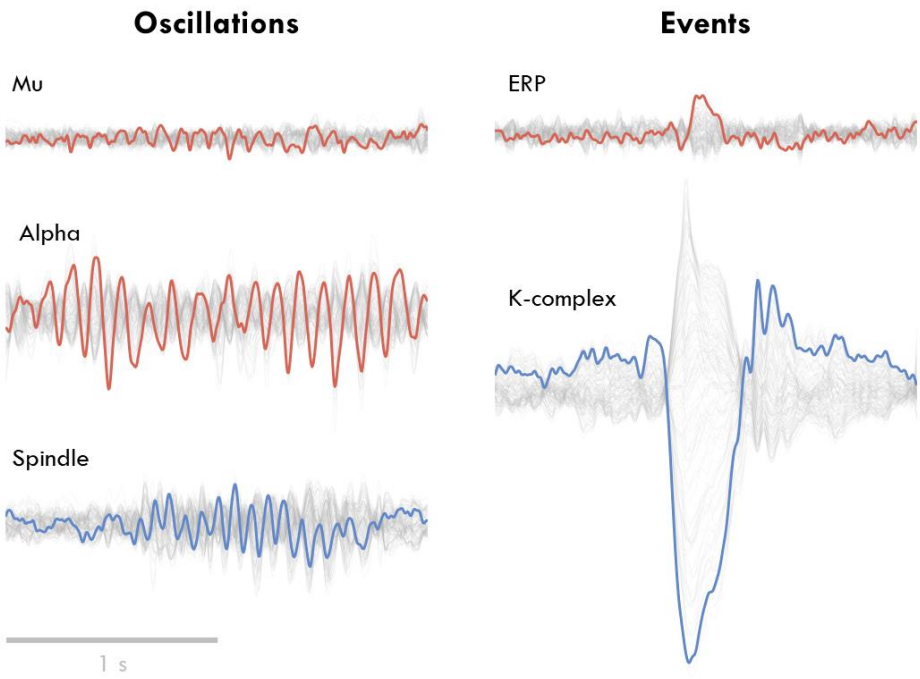

Figure 7.2: Examples of oscillations and events. This is not a comprehensive list. Mu and alpha were taken from wake EEG. The spindle and K-complex were from NREM 2. The ERP was from the LAT, following the appearance of a stimulus. The deflection is likely a P300 wave. Earlier components of an ERP require averaging many trials to sift away the noise.

Box 7.1: Are oscillations epiphenomena or crucial elements of neuronal computation?

It is important to mention that there's the possibility that oscillations don't actually "do" anything, and are just an emergent property of how a collection of neurons' electrical signals accumulate, like the hum of a computer fan. This argument goes that neurons would continue to exchange information regardless of whether there is an oscillation, and the local field potential changes we observe are just the consequence of rhythmic firing patterns across otherwise synchronized neurons.

The opposite view is that oscillations are a necessary form of entrainment; the local field potential creates windows in which a neuronal spike is more or less likely to be transmitted downstream, and this then facilitates synchronized information and inhibits everything else. The most extreme interpretation is that without oscillations, there would be no coherent neuronal activity holding thoughts together. A similar view is that different phases reflect windows of greater or lesser plasticity for memory encoding. Other views are somewhere in the middle.

I am at the moment agnostic as to whether the oscillation itself "does" something, because regardless of the answer,[1] it clearly *reflects* that something different is happening in the brain in that moment. There are precious few neural signals we can capture non-invasively, and we need to milk them for all their worth if we have any hope of learning how the brain works. Throughout this thesis, when I mention theta "doing" anything, I am rather referring generally to the underlying state it reflects, rather than the oscillation itself.

[1] *The non-invasive-stimulation-savvy readers might heartily disagree on the unimportance of this question.*

7.2.3 Aperiodic vs periodic activity

When there are no notable microarchitecture features, the EEG is characterized by approximately 1/f "noise" (Figure 7.3A). This means that, like noise, the changes in voltage are largely unpredictable from the preceding signal, but unlike noise, the spectral profile has a peculiar 1/f relationship, such that lower frequencies have exponentially more power than higher frequencies. In signal analysis, this distinction is often referred to as "white noise" if the power spectrum is flat, and "colored noise" if it is tilted. This property of the EEG has been known for a while (Buzsáki, 2006; Shen et al., 2003), but has recently gained center-stage with the work by Donoghue et al. (2020) and the open-access *fitting oscillations and one-over f* (FOOOF) Python toolbox.

When plotting power on a log-log scale, this exponential relationship becomes linear, and therefore fitting a line (Figure 7.3B) allows for a simple quantification of the overall amplitude of the signal (the intercept, Figure 7.3C), and how much it tilts (the slope, Figure 7.3D). This is referred to as the **aperiodic** component of the EEG. In practice, EEG is not a perfectly "aperiodic" signal, with "knees" bending the spectrum at different points, and various other imperfections. Nonetheless, a linear fit on a log-log scale is a useful approximation.

Instead, any **periodic** signal from oscillations will emerge from this 1/f as a positive bump in the spectrum, from which the relative amplitude can be calculated (Figure 7.3E), as well as the peak frequency (Figure 7.3F). Mounting evidence shows that many changes in EEG power aren't related to oscillations at all, but rather changes in the slope of this background activity, which is why there's a need to reanalyze classic results to determine whether changes in power were driven by periodic or aperiodic changes. It's important to specify that sufficiently regular and frequent events will also create a "periodic" signal in the EEG, although with a wider bell-curve.

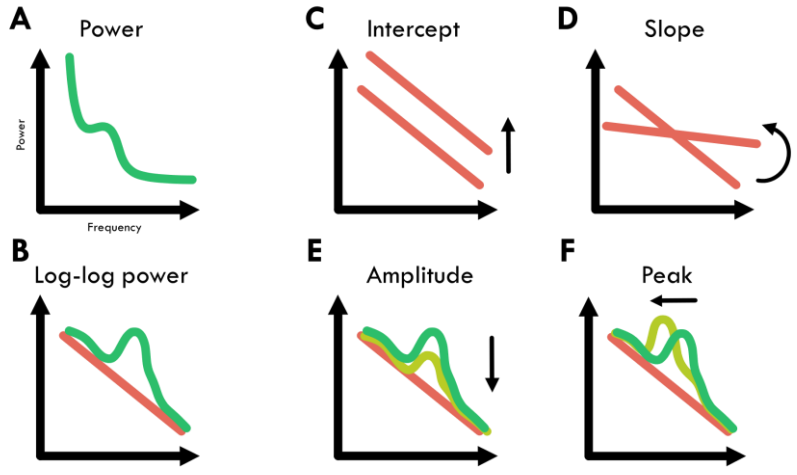

Figure 7.3: Schematic of fitting one-over-f. **A**: Typical untransformed EEG power spectrum; x axis represents frequency, y axis is power. The spectrum follows a 1/f distribution, with slower frequencies having exponentially more power than faster frequencies. On top of this aperiodic curve, "bumps" emerge reflecting periodic activity at that frequency. **B**: The spectrum can be plotted on a log-log scale (apply logarithm to both power values and frequencies), and the aperiodic signal can be fitted with a line. This line can be quantified with an intercept (**C**), and a slope (**D**), respectively how much the whole spectrum shifts in power amplitude, and the degree of difference between lower and higher frequencies. The periodic component can then be characterized by its amplitude (**E**) correcting for the amplitude of the intercept, and the peak frequency (**F**).

The creators of FOOOF argue against referring to the aperiodic signal as "background activity" because there's no reason yet to believe that it is secondary to actual periodic activity. While I agree from an

ontological standpoint, I think it still is appropriate to call it “background” because the aperiodic component is fairly consistent in time, like a background, changing substantially only with changes in vigilant state. Also, in the context of this thesis, it makes sense to refer to the aperiodic signal as “background” because the focus is precisely on the oscillatory activity, regardless of which is more important for the brain. “Noise” is considered even less appropriate, because it implies that it is not reflecting neuronal computation, which is very likely not the case; it’s just that when measured macroscopically on the surface, the specific local signals generating the EEG become indistinguishable.

In practice, just because there’s no obvious periodic signal in the average spectrum, doesn’t mean oscillations don’t occur, just that they are either too irregular and/or too infrequent to emerge from the average. Therefore, methods that look at EEG in time are more reliable at measuring events and oscillations than FOOOF. However, when analyses only involve average power, if there is no obvious bump in the spectrum, then inevitably this quantifies the aperiodic component and not a periodic component.

Box 7.2: Increasing slopes can appear as increased theta power

Attention deficit hyperactivity disorder (ADHD) is probably the most well-studied clinical condition associated with theta activity. Many studies find an increase in theta power in children and adults with ADHD compared to neurotypical controls (Markovska-Simoska & Pop-Jordanova, 2017). More specifically, this difference was best quantified with the theta-beta ratio (Arns et al., 2013). The FDA even approved using it as a diagnostic aid. Recent analysis of ADHD data found instead that the effect was driven by steeper aperiodic slopes in ADHD (Robertson et al., 2019). I was able to replicate this in our own data from the Children’s Hospital of Zurich (Figure 7.4). The fact that it is the aperiodic component that changes, rather than theta oscillations, makes a substantial difference when trying to understand what neural mechanisms drive ADHD. For exactly this reason, aperiodic and periodic signals should be quantified independently as much as possible.

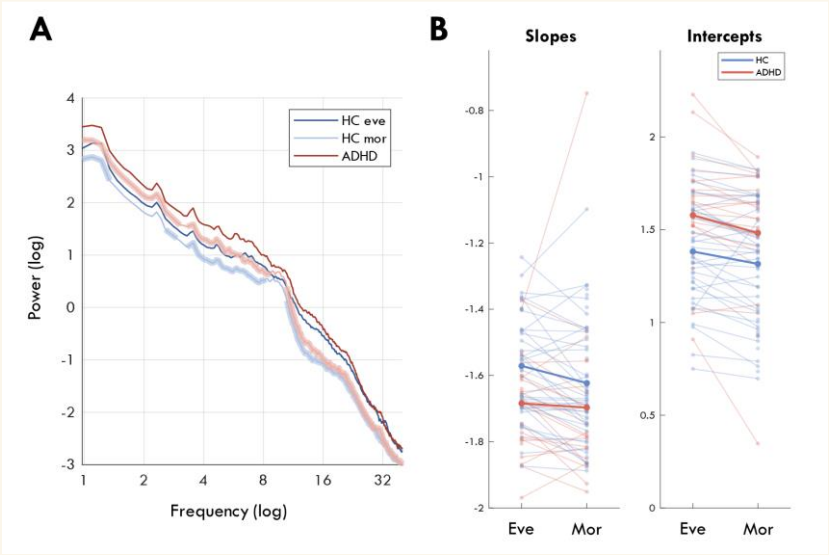

Figure 7.4: Increasing slopes can explain the theta-beta ratio in ADHD. A: Log-log power spectrum of wake EEG data from children with ADHD and sex and age matched controls (HC), the evening (dark) and morning (light) after a night of sleep. At both timepoints, the spectra of ADHD children are steeper than for controls. **B**: The change in slopes and intercepts across sleep. Thin lines represent individual participants, thick lines group average. N.B. “intercept” is literally where the spectrum crosses 1 Hz, so in this case it reflects the same information as the slope. The little recurring bumps are an artefact I haven’t yet been able to track down.

Another case in which differences in power are driven independently by aperiodic and periodic signals is age. Tröndle et al. (2022) found that the decrease in alpha power with age was actually driven by just a decrease in the intercept of the aperiodic activity, while the periodic alpha component actually increased in amplitude. Therefore also for theta, decreases with age (Cummins & Finnigan, 2007) may actually reflect this change in aperiodic slope and intercept. In fact, given that frontal-midline theta is not always present in all individuals and usually has lower amplitudes than alpha, this effect will be even more pronounced for theta power than alpha power. Efforts are currently underway to re-evaluate previous findings and determine when they are driven by periodic or aperiodic changes (Herweg et al., 2020), but it will take some time. Until then, my rule of thumb has been to evaluate the likelihood that an effect could be due to spectral tilt based on whether the changes were shown to be narrow-band or not.

7.2.4 Saddle theta

One highly cited paper on theta activity that I have largely ignored is the Klimesch (1999) review. This is one of the main papers arguing for theta reflecting cognition, while surprisingly also citing literature of theta reflecting sleep deprivation (Cajochen et al., 1995). The theta related to cognition that Klimesch refers to comes from spectrograms like in Figure 7.5, where there is not a bump in the theta range, but rather a slight increase in the "saddle" between delta and alpha. Likewise, the Cajochen paper does not show an increase in a theta peak, but rather a slow alpha peak. Therefore, by assuming that sdTheta is actually alpha, Klimesch maintains that the increase of theta and decrease of alpha reflects cognition. I don't think Klimesch had all the facts when creating his hypotheses, so I have only lightly cited his work.

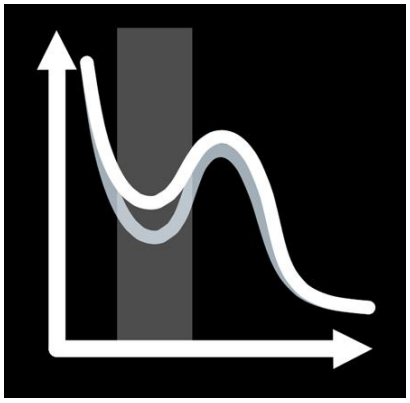

Figure 7.5: theta power saddle. This diagram spectrogram shows an increase in theta power (shaded area) which is not an oscillatory peak, nor a tilt in slope.

7.3 Key sleep concepts

The following sections define the key concepts related to sleep in this thesis.

7.3.1 Sleep stages

Since the early days of EEG, sleep has been divided into discrete stages. While there's always debate about the validity of such an approach, it is invariably useful, and reflects some of the most dramatic changes in the EEG that we know of, short of epilepsy and traumatic brain injury. The stages are manually scored based on the specific microarchitecture of the EEG and EOG, assigning a score to every 20 or 30 s of data. Here are the main sleep stages, as defined by the AASM guidelines (Berry et al., 2012):

Wake

- Alpha rhythms
- Eye blinks, rapid eye movements

NREM 1

- Mostly found at the transition from wake to sleep
- Slow rolling eye movements
- Low-amplitude, mixed-frequency EEG activity, predominantly 4-7 Hz
- Vertex sharp waves (sharp single waves seen in Cz)

NREM 2

- Spindles
- K-complexes

NREM 3

- Slow wave activity, waves from -0.5 to 2 Hz, with peak-to-peak amplitude > 75 µV in more than 20% of the epoch

REM

- Rapid eye movements
- Low chin EMG (muscle tension)
- Sawtooth waves, triangular waves between 2 and 6 Hz

Figure 7.6 is an example of a typical hypnogram, the graph showing the switch in sleep stages across the night. Sleep is made of consecutive cycles passing through each stage, with REM sleep appearing last in the cycle. NREM 3 dominates the first cycle, and progressively decreases with each cycle, and vice-versa REM sleep gets progressively longer.

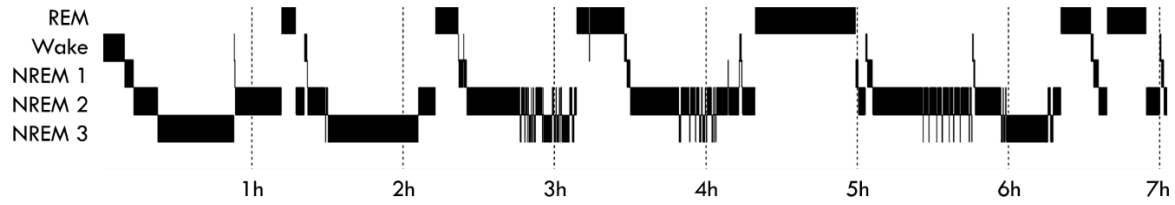

Figure 7.6: Sleep hypnogram for a night. Each black vertical line marks a 20 s epoch to which a sleep stage is assigned.

As can be seen in the power spectra of Figure 7.7, each sleep stage is defined by progressively steeper aperiodic slopes, and occasionally characteristic periodic activity in the theta, alpha, and sigma ranges. However, theta is only periodic in the Front ROI during the Game (fmTheta), despite REM and NREM 1 supposedly being characterized by theta activity.

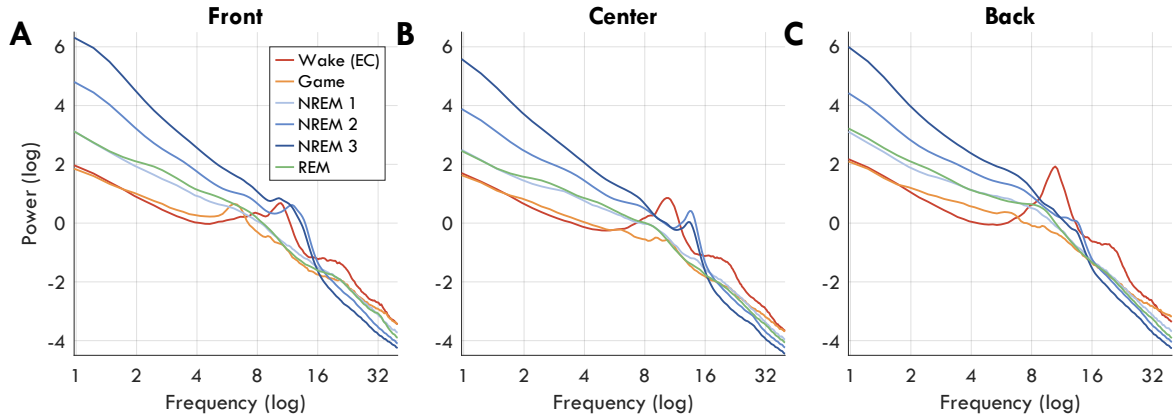

Figure 7.7: power spectrums by sleep stage, log-log scale. From 18 participants. Wake EC was from Fixation Baseline Post. Game was from the Baseline task block. Sleep from baseline night. ROIs are defined as in Figure 2.18.

7.3.2 The two-process model of sleep

The two process model of sleep (Figure 7.8), established by Alexander Borbély (1982) and mathematically developed with Peter Achermann (2003), is a model meant to predict when and for how long an individual will sleep. The **homeostatic process** describes the monotonic increase in sleep need with time awake, which dissipates during sleep as reflected in the exponential decrease in slow wave activity. The **circadian process** describes the 24 h rhythm of the body and brain, which fluctuates independently of whether sleep occurs or not. It is meant to group metabolic and behavioral activity according to when sleep is most or least likely. It can be measured as changes in core body temperature, melatonin concentration, and even subjective sleepiness, when adjusting for time-awake effects (Åkerstedt et al., 1979).

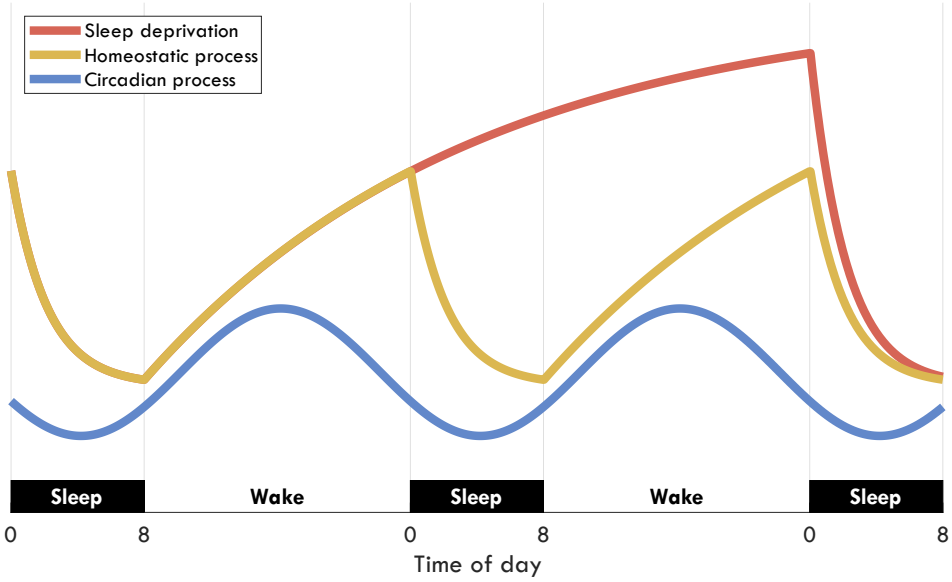

Figure 7.8: two-process model of sleep. The red and yellow lines indicate the homeostatic process, which increases along a saturating exponential during wake, and decreases exponentially during sleep. This red line indicates what happens when sleep does not occur. The blue line indicates the circadian process, which is lowest in the midpoint of sleep and highest during the middle of the day, but does not change depending on when sleep actually occurs.

7.3.3 Sleep deprivation vs extended wake

We have decided to make the distinction between "sleep deprivation" and "extended wake" experiment paradigms. A **sleep deprivation** paradigm is one in which the recordings of interest occur beyond the time window in which an individual should have slept, so from 24 h onwards. An **extended wake** paradigm is one in which the recordings of interest happen between 16 h and 24 h of wake, as in our case. Hans-Peter Landolt helped us arrive to this distinction when working on the second paper, which is why the term does not appear in the first paper, and for consistency we refer to the night-time task block of the extended wake still as sleep deprivation.

7.3.4 Local sleep vs microsleeps

Microsleeps are sleep episodes from 1-15 s long, defined by the traditional markers of sleep onset: loss of alpha, low-amplitude high-frequency activity, eye-closures and rolling eye movements (Hertig-Godeschalk et al., 2020). Instead, **local sleep** often refers to the local presence of a sleep microarchitecture event during wake, mostly slow waves, or theta waves thought to be slow waves (Bernardi & Siclari,

2019). Sometimes, local sleep refers to local differences in slow wave activity but still within NREM sleep (Huber et al., 2004); this is essentially short-hand for "local differences in sleep" but not co-existing sleep stages. However, I only use the term "local sleep" to mean sleep in less than half of the brain.

Effectively, the line is a bit blurry between local sleep and microsleeps. If local sleep can occur as suggested in section 5.5.1, this would make it indistinguishable from microsleeps except for the lack of concurrent changes in ocular behavior, which microsleep researchers don't think is necessary to define a microsleep (private communications with David Schreier). Instead, it may be possible to make a distinction between "whole brain" sleep, in which the brainstem nuclei are consistently suppressing wake and promoting sleep (Saper et al., 2010), and "cortical sleep" which can happen locally, and would give rise to local slow waves and possibly local NREM 1 (Krone et al., 2021). In practice, I would distinguish the two based on whether the individual had their eyes closed or not during the presence of EEG sleep features.

7.3.5 Sleepiness

There are a lot of words in English to describe "sleepiness," and I assign precise meaning to each. Many of these distinctions were inspired by David Schreier.

Sleepiness: the propensity and desire to go to sleep. Objectively quantifiable with sleep onset latencies.

Drowsiness: a low vigilance state, defined by reduced responsiveness to the environment and unfocused thoughts. Often used as a synonym to sleepiness, although I make the distinction that drowsiness can be independent of actual sleep propensity or sleep need. So "soporific conditions" induce drowsiness, but not necessarily sleepiness.

Fatigue: mental fatigue is analogous to muscle fatigue, it is a form of tiredness following intense mental activity but can be mostly reversed with just rest from that activity.

Tiredness: an umbrella term for sleepiness, drowsiness, and fatigue. When people say they are tired, it doesn't matter why, just that they don't want to continue doing what they are doing.

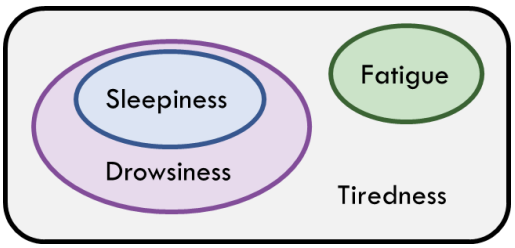

Figure 7.9: Venn diagram of synonyms of tiredness.

Alertness: a state of attentiveness maintained over minutes in which sensitivity to external stimuli is high. Part of the scale of vigilance.

Vigilance: a scale ranging from alert to asleep, describing how attentive the individual is to the environment.

8 ACKNOWLEDGEMENTS

When you've been sitting in a closed room for weeks trying to write a thesis, your day becomes substantially better when you stop to think of all the people that helped along the way. This section ended up stretching out to a comical length, but I found it a fulfilling exercise to trace back all the forces that interacted to make my doctoral degree not only possible, but also an incredibly enjoyable experience.

First and foremost, none of this would have been possible without my supervisor, Reto Huber, who gave me this amazing opportunity of the past four years, with nearly carte-blanche to figure out what these funny little theta waves were. I will always treasure the sequence of "aha!" moments across the years that we shared whenever building off each other's ideas. Then I must thank Nici Wenderoth for all the guidance and advice, keeping me grounded on realistic goals and timelines, as well as providing an external perspective from our insular sleep bubble. Also crucial was the collaboration with Hans-Peter Landolt, who provided his excellent sleep lab, which became like a second home. Thank you also Lars Michels for joining my doctorate committee, I look forward to actually meeting you at my defense!

I could not have completed this study without the whole-hearted dedication that Elias Meier brought to the project. He was with me every step of the way, from data collection to paper writing. With just the two of us, we managed to collect a full sleep deprivation dataset in the middle of the COVID pandemic. Not only was he great company, but he could not have done the job better. His Master's thesis on pupillometry was critical for our second paper. Likewise, Elena Krugliakova was invaluable, both in teaching me the ropes of sleep research, and then collaborating with me on the first paper, conducting source localization that revealed more than I would have imagined and fundamentally shaping the main conclusions of this work. Sarah Meissner and Marc Bächinger created a wonderful collaboration that allowed the project to expand towards pupillometry; a field I had barely heard of. And of course, thanks to Selina for spending hours scoring my sleep data, doing a better job than I could ever hope to do.

All these people made the project and output possible, but what made my work truly excellent was my partner, Simone Accascina. He has been my sounding-board from the first research project I ever worked on, during my Bachelor's in Trento. He has been my safety net from the first time I had to stare down the abyss of a programming editor. Every project I set out to do, I dared do more than I was prepared for, because I always knew he would help me out when I got stuck. Together we wrote an entire online platform for screening participants and gathering questionnaires which was used for at least three different experiments; he debugged a gnarly problem of corrupted data by basically reading bytes in the terminal; he helped connect the entire experimental setup of pupillometry, EEG recording, and behavioral tasks. He taught me the fundamentals of writing good code, without which I could not have done so much of what I did. He has listened to every presentation before I gave it in public, and read all my papers, providing key insights into how to make my work understandable to the rest of the world.

Then I can't forget the help and support I got from my friends and colleagues, Sven Leach, Georgia Sousouri, Melanie Furrer, Joelle Albrecht, Jelena Skorucak, and Maria Dimitriades. Outside our lab, the many nerdy discussions I had with Alejandro Osorio-Forero, Manuel Carro Dominguez, Aurelie Stephan, David Schreier, Lukas Krone; they all gave me so much intellectual inspiration, as well as the motivation to keep investing more in the fascinating world of sleep research.

A doctorate does not exist in a vacuum; I arrived in Zurich with solid foundations that let me hit the ground running. In Maastricht, excellent professors like Peter de Weerd, Elias Formisano, Fren Smulders, and Giancarlo Valente filled my brain which knowledge of how the brain works. Lars Riecke and Lars

Hausfeld got me started on the path of data analysis, but it was Bettina Sorger who showed me how to do actual research. She taught me the attention to detail that can make or break an experiment, how to cajole a participant into trying their best, and most importantly, the hard work that goes into turning an idea into an actual experimental result. Before that, while I was studying psychology in Trento, I got re-directed towards neuroscience by Manuela Piazza and the amazing work she had done on numerosity, then Massimo Poesio trusted me with my first ever EEG experiment at the tender age of 21.

Of course, someone had to pay for all of this. I must thank the Children's Hospital of Zurich for not only giving me a place to work (pre-pandemic), but also paying part of my salary during this PhD. Various funding agencies pitched in, such as the Swiss National Science Foundation, the SleepLoop Flagship project of Hochschulmedizin Zürich, and Hirnstiftung. Of course, ETH not only is giving me this doctorate, but also provided excellent courses, research and educational infrastructure, nearly for free. I don't know how enrollment costs are so low, but it isn't by them acting cheap. Before that, my higher education was covered by generous scholarships for the children of ITER employees, which got me through five years of Bachelors and Masters. Therefore, Swiss, European, American, and many other countries' tax dollars made all this possible. I feel the need to point this out, because I was incredibly lucky to work all this time on basic research, the kind that never sets off to cure cancer or fly to Mars, but exists just to enrich our understanding of the world. This could not have happened if it weren't for generous government contributions to science.

Lastly, I must of course acknowledge how so much of where I am today comes from my parents, Joe Snipes and Francesca Bombarda (Figure 8.1). In many respects I'm a *figlia d'arte*, following in their footsteps to become a research scientist. Not from any interest in their field of physics (heavens no!), but because of all the cool places we got to visit during their conferences. Some of my earliest memories are of hotel halls filled with posters, laser pointers and PowerPoint presentations. At the time, I might have attributed it to the fun of travelling, but now I recognize that what inspired me the most was the freedom it signified. It's a rare thing to think of international borders as little more than extra paperwork. As soon as I was old enough, there were science fairs and crystal-growing experiments. Gauss and Fermi were household names. With what I'm sure were the best of intentions, my dad did not fail to inform me that at my age (9), Gauss had already figured out how to sum up all the numbers from 1 to 100 with a simple equation just to spite his schoolteacher. To say they "paved the way" for my becoming a scientist is an understatement. The role models did not end there. Later in life Giovanna Butticé, my stepmother, joined the scene, making it known that there really were other careers outside of physics: like biology! Through all of them I saw the best of what science could be; the freedom to question everything, the confidence that comes with hard-earned knowledge while also always heading towards the unknown, solving problems no one has solved before, and every year wondering in which awesome place I get to have my next ~~paid vacation~~ conference!

Figure 8.1: Photograph of my mother, by Sam Ogden. She is 8 months pregnant with me. Published in Science (Flam, 1994), in an article about Mediterranean women in STEM.

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