Role of sleep for memory consolidation and general cognition in patients with Parkinson's disease

Soraya Lahlou

Integrated Program in Neuroscience

McGill University, Montreal

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Abstract

Parkinson's disease is a neurodegenerative disease that is initially diagnosed on the basis of motor symptoms such as rest tremor and bradykinesia but also involves symptoms in other domains such as cognition, sleep and autonomic function. It is the second most common neurodegenerative disease and it is estimated that over 100,000 Canadians are living with Parkinson's disease according to the Public Health Agency of Canada (*Mapping Connections*, 2014). The disease process of Parkinson's disease is characterized by early loss of dopaminergic neurons in the brainstem and this progresses over time to involve other neurotransmitter systems and other brain regions. Cognitive impairment is frequent and greatly reduces quality of life, however there are currently no known treatments to effectively target cognitive function in patients. This is partly due to a lack of understanding of the mechanisms which underlie cognitive dysfunction in patients. Sleep is significantly impaired in Parkinson's disease and though the importance of sleep in maintaining healthy cognition is well-established, the contribution of sleep disturbances to the cognitive dysfunction of Parkinson's disease is poorly understood. The overall goal of this thesis is to determine whether a better understanding of the period of sleep can provide a window into understanding the cognitive dysfunction of Parkinson's disease.

The first part of this thesis aims to understand how dopamine contributes to specific sleep-dependent cognitive processes. It is well-established that sleep plays a crucial role in memory consolidation – the process by which newly acquired information is integrated into long-term memory (Dudai et al., 2015). Chapter 2 examines if dopamine deficiency in Parkinson's disease interferes with the process of overnight consolidation of motor memories. Though it has been demonstrated that motor memory consolidation is modulated by dopamine, it is unclear if this process is impaired in patients and if dopamine medication may remediate this. Chapter 3 aims to examine the relationship between sleep-dependent memory consolidation and specific features of sleep micro-architecture known to be important for consolidation and known to be altered in PD. Specifically, we were interested in sleep spindles because these are oscillations known to be crucial for the process of consolidation during sleep (Rasch & Born, 2013; Schabus et al., 2004), and because these are among the oscillations that are altered in patients (Christensen et al., 2015; Latreille et al., 2015). Chapter 4 aims to better understand the neural mechanisms underlying the association between sleep oscillations and more general cognitive performance. We were

interested in how functional connectivity in different oscillations contributes to broader cognitive function in patients, as this may be the mechanism underlying the relationship between sleep oscillations and cognition.

Importantly, sleep is a potentially modifiable factor and interventions, such as pharmacological therapies and non-invasive stimulation using sound, that enhance various aspects of sleep already exist. Studies have even shown that is possible to influence specific sleep oscillations, enhancing their spectral power, their density and potentially their connectivity across the scalp. Considering sleep disturbances often appear before the appearance of cognitive deficits, targeting sleep might offer a way to reduce the burden and even delay cognitive deficits in PD. This is particularly important as treatments for cognition in PD are currently lacking.

Résumé

La maladie de Parkinson (MP) est une maladie neurodégénérative initialement diagnostiquée sur la base de symptômes moteurs tels que le tremblement au repos et la bradykinésie, mais qui implique également des symptômes dans d'autres domaines comme la cognition et le sommeil. La MP s'agit de la deuxième maladie neurodégénérative la plus courante, et il est estimé que plus de 100 000 Canadiens vivent avec la maladie de Parkinson, selon l'Agence de la santé publique du Canada (Mapping Connections, 2014). Le processus pathologique de la MP se caractérise par une perte précoce des neurones dopaminergiques dans le tronc cérébral, et progresse pour impliquer d'autres systèmes de neurotransmetteurs et d'autres régions cérébrales. Les troubles cognitifs sont fréquents et réduisent considérablement la qualité de vie, mais il n'existe actuellement aucun traitement connu permettant de cibler la fonction cognitive chez les patients. Cela est en partie dû à un manque de compréhension des mécanismes sous-jacents. Le sommeil est considérablement perturbé dans la MP, et bien qu'il soit bien établi que le sommeil est important pour le maintien d'une cognition saine, la contribution des troubles du sommeil aux dysfonctionnements cognitifs, particulièrement dans la MP, est mal comprise. L'objectif global de cette thèse a pour but de déterminer si une meilleure compréhension du sommeil peut offrir une meilleure compréhension des dysfonctionnements cognitifs dans la MP.

La première partie de cette thèse vise à comprendre comment la dopamine contribue à des processus cognitifs dépendants du sommeil. Il est bien établi que le sommeil joue un rôle important

dans la consolidation de la mémoire – le processus par lequel les informations nouvellement acquises sont intégrées dans la mémoire à long terme (Dudai et al., 2015). Le deuxième chapitre examine si la réduction de dopamine dans la MP interfère avec le processus de consolidation de la mémoire motrice. La dopamine joue un rôle important dans la consolidation de la mémoire motrice, cependant il n'est toujours pas clair si ce processus est altéré chez les patients et si les médicaments dopaminergiques peuvent y remédier. Le troisième chapitre vise à examiner la relation entre la consolidation de la mémoire et certaines caractéristiques de la microarchitecture du sommeil importantes pour le processus de consolidation et altérées chez les patients avec la MP. En particulier, nous nous sommes intéressés aux fuseaux de sommeil, car il s'agit d'oscillations connues pour être cruciales dans le processus de consolidation (Rasch & Born, 2013; Schabus et al., 2004), et font partis des oscillations altérées chez les patients (Christensen et al., 2015; Latreille et al., 2015). Le quatrième chapitre vise à mieux comprendre les mécanismes neuronaux qui pourrait expliquer l'association entre les oscillations du sommeil et la cognition. Nous nous sommes intéressés à la connectivité fonctionnelle, dans différentes oscillations, et comment celle-ci contribue à la fonction cognitive globale chez les patients, car cela pourrait être un des mécanismes expliquant la relation entre les oscillations du sommeil et la fonction cognitive.

Il est important de noter que le sommeil est un facteur potentiellement modifiable. En effets, des interventions, telles que des thérapies pharmacologiques et la stimulation non invasive par le son existent déjà. Des études ont même montré qu'il est possible d'influencer des oscillations spécifiques pendant le sommeil, en augmentant leur puissance spectrale, leur densité et potentiellement leur connectivité. Étant donné que les troubles du sommeil apparaissent souvent avant l'apparition des déficits cognitifs, cibler le sommeil pourrait offrir une manière de réduire les déficits cognitifs dans la MP. Cela est d'autant plus important, vu que les traitements pour les déficits cognitifs chez les patients sont actuellement inexistants.

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Chapter 1. Introduction

Parkinson's disease

The main pathological feature of Parkinson's disease (PD) is the loss of dopaminergic neurons in the midbrain due to the abnormal deposition of phosphorylated alpha-synuclein. These aggregates, known as Lewy bodies, ultimately lead to neuronal death. The substantia nigra and the ventral tegmental area are the two main dopaminergic nuclei of the brain. The downstream projections from neurons in these two areas make up the nigrostriatal system, the mesolimbic system and the mesocortical system. In PD, loss of dopamine neurons primarily occurs in the substantia nigra, part of the nigrostriatal pathway, well before the apparition of motor symptoms and, as motor symptoms appear, degeneration progresses to other regions (Biondetti et al., 2020; Braak et al., 2003; Fearnley & Lees, 1991). By the time motor symptoms are prominent enough for a clinical diagnosis, 40% to 60% of dopaminergic neurons are estimated to have already degenerated. These neurons provide the main dopaminergic input to the striatum, one of the main afferent structures of the basal ganglia (Graybiel & Grafton, 2015). The striatum is an important hub that is functionally connected to the cortex and the thalamus (Alexander et al., 1986; Nakano et al., 2000). As such, dopaminergic dysregulation and the related dysfunction that occurs in basal ganglia circuitry, as well as cortico-striatal and thalamo-cortical circuitry, has potential implications for a wide range of neurologic domains that depend on these networks.

In addition to motor symptoms, non-motor symptoms are also present from the earliest stages of the disease. These include sleep disturbances, neuropsychiatric symptoms (e.g., depression, anxiety) and changes to cognitive function (Barone et al., 2009; Chaudhuri & Naidu, 2008). These symptoms may appear before or around the time of PD diagnosis or may appear later in the disease course. Some of the cognitive changes observed in PD can be understood by considering the anatomical distribution of the neuropathological changes. For one, dopaminergic projections to the cortex are important for different aspects of cognition; in healthy adults, enhancing dopamine availability promotes cognitive control (Westbrook et al., 2020) and working memory (Luciana et al., 1992). In PD, disturbed dopaminergic signalling to the cortex, either through mesocortical or mesolimbic projections, is associated with executive deficits (Monchi et

al., 2006). However, cognitive deficits in patients go beyond executive dysfunction and affect other cognitive domains, including memory, attention and visuospatial deficits, which are not explained by dopaminergic deficits alone. At the later stages of the disease, these deficits can at least partly be explained by the more generalized cortical atrophy that has been observed in PD (Zeighami et al., 2015). However, at the earlier stages of the disease, before degeneration has extended to involve cortical regions, it is possible that other factors, such as impaired sleep and altered sleep architecture, play a role in the cognitive deficits of Parkinson's disease.

Cognitive changes in Parkinson's disease

Cognitive deficits are amongst the most important non-motor manifestations of the disease. Individuals with Parkinson's disease are up to 6 times more likely to develop cognitive impairment compared to healthy adults (Aarsland et al., 2001). An important focus of research studying cognitive dysfunction in Parkinson's disease has been on aspects of cognition thought to be dependent on dopamine, such as the learning of habits and motor sequences. Dopaminergic projections to the striatum carry reward signals that are important for reinforcing actions that lead to successful outcomes, thus allowing for the stamping in of cognitive and motor sequences (Graybiel & Grafton, 2015). Though dopamine deficiency is a central feature of Parkinson's disease and one that is imminently treatable through dopamine replacement therapy, it is not the sole cause of cognitive dysfunction in patients. Emerging evidence suggests that other mechanisms, including cholinergic or noradrenergic dysfunction, and neuroinflammation, may also play a role in contributing to cognitive impairments (Aarsland et al., 2021). Increasingly, disturbances in sleep and sleep oscillations have gained attention (Zahed et al., 2021; Y. Zhang et al., 2020) as they are common in PD and may further worsen cognition in patients (Latreille et al., 2015; Memon et al., 2023; Wood et al., 2021).

Role of dopamine in learning and memory in Parkinson's disease

Dopamine is known to influence multiple cognitive processes (Aarts et al., 2011; Nieoullon, 2002), and learning has received considerable attention in PD due to its clear dependence on dopamine (Foerde & Shohamy, 2011). Dopamine release in the striatum is crucial for modulating cortico-striatal transmission and inducing synaptic plasticity in the striatum, which is necessary for learning (Pisani, Centonze, Bernardi, & Calabresi, 2005; Shen, Flajolet,

Greengard, & Surmeier, 2008). This has evident implications for learning in Parkinson's disease. Indeed, many studies have demonstrated that PD patients show deficits in various forms of learning (Foerde & Shohamy, 2011), with much of the focus being on motor learning—due to the nature of PD. Patients show deficits in the learning of motor sequences (Dan et al., 2015; Ghilardi et al., 2003), even when these sequences are learned unconsciously (Hayes et al., 2015; Siegert et al., 2006). This learning deficit also extends to non-motor sequences, such as the incremental learning of stimulus-response associations (Foerde & Shohamy, 2011). For instance, patients are impaired when learning to select which stimulus best predicts a reward or a desired outcome (Ashby et al., 2003; Knowlton et al., 1996), or when learning a specific sequence of stimulus-response associations leading to a reward (Shohamy et al., 2005).

Learning behavioural sequences, whether habits or motor sequences, requires time – both prolonged training time and time for the processes of consolidation to take effect. However, much of the work studying these processes in humans, including in PD patients, has not been able to capture the time-dependent nature of these forms of learning. Instead, most studies have focused on measuring the effect of dopamine on the initial process of acquisition of new learning, without measuring the effects of dopamine on processes that occur offline, such as consolidation, and which are also essential for learning. A critical time window during which consolidation occurs is during sleep. Dopamine is thought to contribute to time-dependent consolidation through its role in plasticity. During learning, dopamine is believed to 'tag' specific synapses important for a memory (Redondo & Morris, 2011), which facilitates later modification of those synapses. Dopamine may also interact with sleep-dependent aspects of consolidation (Isotalus et al., 2023), by boosting sleep oscillations, though this is much less clear.

There is a wealth of evidence in the animal literature supporting the role of dopamine in memory consolidation (Duszkiewicz et al., 2019; Takeuchi et al., 2016), i.e., the time-dependent process by which experience-dependent internal representations (i.e., memory) are transformed, integrated and further distributed across the brain (Dudai et al., 2015). In the human literature, evidence for dopamine's role in consolidation is mostly constrained to studies using indirect manipulation, via reward or novelty (Abe et al., 2011; Ferreri et al., 2020; Fischer & Born, 2009; Murayama & Kitagami, 2014; Patil et al., 2017; Widmer et al., 2016), with few studies directly controlling dopamine (Asfestani et al., 2020; Feld et al., 2014; Isotalus et al., 2023).

Mechanistically, consolidation has been conceptualized to happen at two broad levels; cellular consolidation, which is thought to stabilize the memory trace, and systems consolidation, which is thought to make the memory more robust and efficient by allowing its re-organization across cortical and subcortical areas (Dudai et al., 2015; Genzel & Wixted, 2017). At the cellular level, dopamine's role seems to be two-fold: first, dopamine has been shown to be necessary for maintaining both the structural and the functional synaptic changes that result from long-term potentiation (Huang & Kandel, 1995; Moncada et al., 2011; Sajikumar, 2004), and second, dopamine also modulates the time window in which long-term potentiation may occur (Duszkiewicz et al., 2019; Takeuchi et al., 2016; Wang et al., 2010).

While both habit and motor learning depend on striatal dopamine for plasticity, evidence from the human neuroimaging literature has shown that recruitment of dopaminergic brain regions is also crucial for the successful consolidation of motor learning (Albouy et al., 2008; Debas et al., 2014; Doyon et al., 2003, 2009; Pinsard et al., 2019). Some evidence also suggests that dopamine may modulate sleep-specific systems consolidation mechanisms (Isotalus et al., 2023) – which may then interact with either motor or declarative memory consolidation. It has indeed already been shown that sleep, and particularly sleep oscillations, influences motor memory consolidation (Fogel et al., 2014; Laventure et al., 2016). Integrating these findings, motor consolidation may be impaired in Parkinson's disease due to its reliance on dopamine and potential sleep-specific consolidation processes.

Non-dopamine dependent cognition

Over the course of the disease, Parkinson's patients manifest with a wide range of cognitive impairments that extend beyond those that can be directly linked to dopaminergic degeneration. Deficits exist across cognitive domains, spanning executive function, attention, memory, visuospatial ability and language (Litvan et al., 2012). Some of these deficits are thought to arise following the spread of neurodegeneration to the cortex. For instance, deficits in visuospatial abilities are thought to reflect a more posterior cortical pattern of neurodegeneration, not associated with dopamine circuits.

Memory in particular is a domain of cognitive dysfunction in Parkinson's disease that may reflect several different underlying causes. Memory can be subdivided into different components, such as habitual and procedural learning mentioned above, as well as declarative memory. Habitual

and procedural learning are dependent on the striatum and have been shown to be impaired in PD: patients show impairments in the learning of implicit motor rules (Siegert et al., 2006) and implicit learning of probabilistic stimulus-response rules, which reflect habitual learning (Witt et al., 2002). However, memory deficits in Parkinson's patients are not constrained to these striatal-dependent forms of learning. There is also evidence of explicit or declarative memory deficits in Parkinson's disease. Declarative memory refers to memory for facts, events and knowledge of the world (Tulving & Markowitsch, 1998). On tests of declarative memory, patients tend to show worse free recall of word-lists but relatively intact recognition (Bezdicek et al., 2019; Breen, 1993; Weintraub et al., 2004), which has been shown to indicate the presence of a specific deficit in memory retrieval in PD. Interestingly, the hippocampus, which is a central structure for declarative memories, is largely spared in the earlier stages of PD (Braak et al., 2003), suggesting that the declarative memory impairments of Parkinson's disease could reflect mechanisms other than neurodegeneration (Litvan et al., 2012).

One possible mechanism linking both procedural and declarative forms of memory that might be susceptible to PD-related effects is consolidation. Though this has been much less studied than other memory processes, a few studies provide preliminary evidence for impaired consolidation in both motor (Terpening et al., 2013) and declarative memory (Hanoğlu et al., 2019).

In addition to the role of dopamine in consolidation, which is discussed above, other aspects of PD degeneration may contribute to consolidation. For instance, the locus coeruleus, which is the source of cortical noradrenergic innervation, is also a region that degenerates early in PD. Loss of integrity of this region, as assessed with neuromelanin-weighted imaging, has been associated with worse cognition across multiple domains in patients (Prasuhn et al., 2021). In addition, the locus coeruleus is thought to play a role in modulating sleep, which may have consequences for consolidation. For instance, noradrenergic firing from the locus coeruleus influences the structure of NREM sleep and the underlying sleep oscillations (Osorio-Forero et al., 2021, 2023), and modulation of this firing in animals is linked to successful consolidation (Osorio-Forero et al., 2021; Swift et al., 2018). Locus coeruleus activity during wakefulness has also recently been associated with sleep quality in older adults (Koshmanova et al., 2023).

Though non-exhaustive, the above review highlights that multiple mechanisms, both direct and indirect, likely contribute to cognitive dysfunction in PD patients. Sleep in particular, because it is known to be significantly affected in PD and because it is also known to be a state that modulates cognition, may contribute to cognitive dysfunction in PD. The following section will review the literature on sleep deficits in PD and their relationship to cognitive dysfunction.

Relationship between sleep disturbances and cognitive deficits in PD

Sleep is a dynamic state in which the brain transitions between patterns of distinct oscillatory activity throughout the night, which are accompanied by changes in respiration, heart rate, temperature, and muscle tone (Carskadon & Dement, 2005). Sleep is classified into alternating stages of non-rapid eye movement (NREM), subdivided into stages 1 to 3, and rapid-eye movement (REM) sleep. The entry to sleep starts with NREM stage 1, the lightest stage of sleep, and continues to stages 2 and 3 of NREM. These last two stages of sleep are characterized by the emergence of sleep spindles and slow-waves, waveforms of 12 – 15 Hz and 0.5 – 4 Hz, respectively. Slow-waves reflect two distinct oscillations, a slow-oscillation of under 1 Hz and a delta oscillation between 1 and 4 Hz (Steriade, 2006; Timofeev & Chauvette, 2013), however, in the context of human sleep, these are often grouped under the term 'slow-waves' and will be referred as such for the rest of the thesis. REM sleep occurs about 80 minutes following initial sleep onset, and is characterized by vivid dreams, rapid eye movements and the loss of muscle tone. A sleep cycle is completed at the end of a REM episode, and a full night of sleep comprises of an average of 5 sleep cycles. Sleep can be studied at multiple levels, looking at the overall architecture (e.g., the amount of time spent in different sleep stages, the total amount of sleep, etc.) as well as the spectral components of sleep. In PD patients, sleep is demonstrably changed at both levels.

In both research and clinical settings, sleep is measured using polysomnography – which includes measuring the electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG), measuring the electrical brain activity, eye movements and muscle tone, respectively. Neuronal activity changes throughout sleep, with large groups of neurons either increasing or decreasing their firing rate or firing in bursts. The resulting electric field can be detected at a distance, using electrodes on the scalp. EEG has high temporal resolution, but low

spatial resolution since the signal measured is far from the neuronal source. Consequently, scalp EEG reflects an attenuated form of the underlying cortical sources, and predominantly reflects activity from neurons organized perpendicular to the scalp (Lopes da Silva, 2013). Sleep oscillatory activity can be grouped into frequency bands of interest, commonly these are grouped as delta (0.5 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz) and sigma (12 – 15 Hz) bands. Sleep spindles and slow waves can also be detected using specific detection algorithms following criteria on frequency, amplitude and duration. The high temporal resolution of EEG makes it a great tool to assess the dynamic changes in neuronal firing during sleep. Additionally, this insight into the underlying electrical brain activity is important for understanding cognitive processes that depend on sleep.

Sleep disturbances in PD

In Parkinson's disease, sleep disturbances come second to cognitive impairments, with multiple large cohort studies assessing their prevalence at ~60% (Barone et al., 2009; Ratti et al., 2015). The spectrum of sleep disturbances in PD is broad and includes excessive daytime sleepiness, obstructive sleep apnea, difficulty maintaining or initiating sleep, as well as parasomnias like restless leg syndrome, periodic limb movements and REM-sleep behaviour disorder (RBD) (Comella, 2007). The latter is an important predictor of developing Parkinson's disease (Postuma & Berg, 2019), with the majority being diagnosed after a mean of 11 to 14 years following RBD onset (Iranzo et al., 2006, 2013; Schenck et al., 2013).

The progression of PD is marked by changes in both the quality and the architecture of sleep, including changes in specific sleep stages and sleep oscillations. With disease progression, there is a decrease in the total amount of sleep, accompanied by increased latency to the first sleep episode (Diederich et al., 2005). Sleep architecture also changes over the course of the disease. These changes are characterized by an increase in NREM stage 1, the lightest stage of sleep, and a decrease in REM and deeper NREM stages 2 and 3 (Diederich et al., 2005; Y. Zhang et al., 2020). There are, in addition, notable changes to the sleep EEG activity (Zahed et al., 2021), with reductions in the amount and the morphology of sleep spindles (Christensen et al., 2015; Latreille et al., 2015) and slow-waves (Latreille et al., 2015). Sleep spindles reflect the burst firing along thalamo-cortical tracts (Steriade, 1999; Steriade et al., 1993) whereas slow-waves reflect the

synchronized firing of thalamo-cortical and cortical neurons, with distinct depolarized and hyperpolarized peaks (Steriade et al., 1993). Aside from changes to discrete oscillation, reduction in the sigma (Latreille et al., 2016) and delta frequency bands (Amato et al., 2018), often a proxy to spindle and slow-wave activity, have been documented in patients.

Sleep disturbances as a mechanism for cognitive deficits in PD

Different sleep and sleep-related symptoms have been associated with worse cognition in PD (Pushpanathan et al., 2016). For instance increased excessive daytime sleepiness (Naismith et al., 2011), presence of RBD (Pagano et al., 2018), sleep efficiency (Stavitsky et al., 2012), obstructive sleep apnea, self-reported sleep disturbances (E. J. Kim et al., 2014), and percentage of NREM-3 (Bugalho et al., 2021; Wood et al., 2021) have all been associated with worse cognitive outcomes, either cross-sectionally or over time. Sleep oscillations, which more closely measure brain activity than other measures of sleep, have also been associated with worse cognition in patients, though there are fewer studies examining the association between specific oscillations and cognition in PD. Two studies investigating this found that lower sleep spindle and slow-wave density were associated with worse cognition (Memon et al., 2023; Wood et al., 2021) and one study found that decreased spindle density predicted future cognitive decline (Latreille et al., 2015), suggesting that measuring sleep oscillations could be useful as a marker of cognitive dysfunction and may even reflect a specific mechanism linking sleep and cognition.

The association between sleep oscillations and cognitive function observed in patients are not exclusive to PD as they have also been observed in normal aging (Guadagni et al., 2021; Lafortune et al., 2014), in mild cognitive impairment and in Alzheimer's (Gorgoni et al., 2016). For instance, one study found that decreased spectral power in delta, sigma and theta frequency, reflecting reduced oscillatory activity at these frequencies, during NREM sleep was associated with increased cognitive impairment after a 1-year follow-up in healthy older adults (Taillard et al., 2019). Another prospective study of older women showed that higher alpha power during NREM sleep at baseline was associated with a higher risk of developing MCI or dementia after a 5-year follow-up (Djonlagic et al., 2019). These findings further support the notion that sleep oscillations can be markers of cognitive dysfunction, although it remains unknown if changes to

these oscillations directly contribute to cognition or are merely a marker of an underlying disease process.

There are a few possible mechanisms by which sleep alterations in PD could directly contribute to impaired cognition. It is already well established that sleep oscillations support memory consolidation and therefore one possibility is that altered oscillations and the associated disruptions to memory consolidation that this likely causes could represent a mechanism for the more general cognitive dysfunction of PD. Another possibility is that sleep oscillations reflect an underlying brain state that directly or indirectly, supports cognitive processing more broadly, i.e. beyond specific sleep-dependent processes such as consolidation.

The following sections review the literature on the role of sleep in cognition in relation to the mechanisms proposed above.

Sleep and memory consolidation

The changes to sleep and sleep oscillations observed in PD have direct implications for sleep-dependent cognitive processes such as memory consolidation. Compared to an equivalent period of wakefulness, sleep accelerates consolidation (Jenkins & Dallenbach, 1924; Korman et al., 2007, 2015; Lahl et al., 2008; Nishida & Walker, 2007). In some cases, sleep is also necessary for consolidation (Debas et al., 2010). Sleep is thought to be an ideal state for consolidation to occur because new learning, which can cause interference, is kept to a minimum (Genzel & Wixted, 2017). In addition, the synchronous neuronal firing which occurs during sleep is optimal to enable the distribution of the memory engram across the brain (Rasch & Born 2013). In the last decades, the sleep processes that subserve memory consolidation have been extensively studied in both rodents and human participants (Brodt et al., 2023; Klinzing et al., 2019). The re-organization of the memory engram, from the hippocampus to the cortex, initially happens through reactivation of the memory trace during sleep (Peyrache et al., 2009; Sutherland, 2000), which allows the cortex to potentiate relevant synaptic connections.

Through its distinct oscillations, NREM sleep is thought to play an important role in enabling both replay and the reorganization of memory during sleep (Boutin & Doyon, 2020; Peyrache & Seibt, 2020). In fact, a large body of evidence points to the role of NREM sleep in memory consolidation (Ackermann & Rasch, 2014; Fernandez & Lüthi, 2020; Klinzing et al.,

2019). More specifically, oscillations of NREM sleep provide an opportune window for consolidation to happen. The rapid burst-firing of sleep spindles is well suited to trigger long-term potentiation in the relevant synapses (Rosanova & Ulrich, 2005), which is necessary in supporting memory. Sleep spindle density, the number of spindles per minute of sleep, is a standard metric used in sleep research and correlates with consolidation of both declarative (Schabus et al., 2004; Tamminen et al., 2010) and procedural memory (Fogel et al., 2017; Laventure et al., 2016). Drugs that incidentally increase spindle activity, such as zolpidem, also enhance memory consolidation beyond control conditions (Carbone et al., 2024; Mednick et al., 2013; J. Zhang et al., 2020), offering causal evidence for the role of spindles in humans.

Further evidence for the importance of spindles to memory consolidation comes from studies on aging. Sleep spindle activity changes considerably in older adults, with studies showing that aging is associated with a decrease in the total number, the density and the amplitude of spindles (Guazzelli et al., 1986; Nicolas et al., 2001; Purcell et al., 2017). Importantly, this global reduction in spindle activity has been shown to mediate age-related decline in both motor and episodic memory consolidation (Fogel et al., 2014; Mander et al., 2014). The relationship between spindles and memory consolidation in older adults is also linked to reduced activation of circuits and brain regions recruited during memory consolidation (Fogel et al., 2014; Mander et al., 2014).

While age-related changes in spindles and consolidation are well-documented, it is unclear how PD might affect these processes. A few studies have suggested that consolidation may be impaired in PD beyond just the effects of aging (Dan et al., 2015; J. P. Grogan et al., 2015, 2017), but whether this is caused by the sleep disturbances of PD is unknown. Given that spindle activity is reduced in PD patients, one possibility is that the reduced spindle activity negatively impacts consolidation.

Sleep and cognitive function

Sleep oscillations have also been shown to be associated with and predictive of broader cognitive status (Guadagni et al., 2021; Lafortune et al., 2014; Latreille et al., 2015; Taillard et al., 2019; Wood et al., 2021), i.e., cognitive function that goes beyond memory consolidation. In the context of consolidation, sleep oscillations reflect periods of enhanced communication between brain regions relevant to the memory being consolidated (Boutin et al., 2018; Cowan et al., 2020).

Though unexplored to date, a similar mechanism might underlie the relationship between sleep oscillations and more general cognitive function.

One potential mechanism explaining the role of sleep for general cognitive health is that the networks that support the oscillatory activity of spindles also overlap with the brain regions involved in cognition – i.e., structures recruited during spindle activity include the hippocampus and parahippocampus areas, and the basal ganglia (Caporro et al., 2012; Fogel et al., 2017; Schabus et al., 2007; Tyvaert et al., 2008). Indeed, it has been shown that functional connectivity between those regions, time-locked to spindle activity, correlates with reasoning abilities and fluid intelligence in younger adults (Fang et al., 2019, 2020). These findings underscore an important property of sleep oscillations: they involve the coordinated activation of distinct brain regions. This coordinated activity is also evident across the scalp, as sleep oscillations often occur simultaneously on EEG (Contreras et al., 1997). Understanding functional connectivity during sleep oscillations can provide valuable insights into the mechanisms by which sleep supports cognitive function. Preliminary evidence supporting this line of thought already exists; Bouchard et al. (2020) have demonstrated that increased functional connectivity in the delta frequency band was correlated with better performance on the Trail-Making Test Part A.

Sleep is a dynamic state, as such the functional connectivity may vary by stages of sleep, with different implications for cognition. Functional connectivity during sleep has been examined using both fMRI and EEG-derived measures of activity. As sleep progresses from light NREM-1 sleep to NREM-2, there is a transient increase in BOLD functional connectivity (Larson-Prior et al., 2009; Spoormaker et al., 2010) which is then followed by a breakdown of cortico-cortical connectivity during NREM-3 (Boly et al., 2012; Horovitz et al., 2009; Spoormaker et al., 2011). Graph theory has further shown that this pattern of reduced connectivity is accompanied by an increase in *small-worldness*—which defines a network with increased connectivity amongst local nodes with sparse long-range connections, supporting both segregated and distributed modes of information processing (Bassett & Bullmore, 2006). A recent study investigating frequency-dependent network-level functional connectivity using high-density EEG has corroborated the reduction in connectivity from NREM-2 to NREM-3, this time across source-localized networks and across frequency bands (Titone et al., 2024). These findings highlight the complexity of sleep and suggest that the effects of sleep oscillations on cognition may differ depending on the specific

sleep stage because of the different connectivity profiles of different sleep stages. Understanding this may provide us with better insight into the relationship between sleep, sleep oscillations and cognition.

Functional connectivity during sleep has been shown to change with aging. Using sleep EEG, one study found that older adults had higher functional connectivity in NREM-3 than in NREM-2 compared to younger adults who showed the expected pattern of lower connectivity in NREM-3 (Bouchard et al., 2019). These differences were most prominent at the slower frequencies, namely delta and theta. This pattern of increased functional connectivity in older adults has also been observed with fMRI, although these were observed when moving from light NREM-1 to NREM-2, where older adults show increased connectivity between frontal clusters of default mode, frontoparietal and limbic networks compared to younger adults, (Daneault et al., 2021). Although delta connectivity in NREM-2—one of the primary frequency bands showing age-related changes in this study—has been shown to correlate with one aspect of cognition in both young and older adults, the implications of these connectivity changes for cognition, particularly in PD, remain unclear.

The current thesis

As reviewed in the previous sections, a vast body of evidence supports both the role of dopamine and of sleep oscillations in the consolidation of memory, as well as the role of sleep for broader cognition. However, the mechanisms by which these contribute to both sleep-dependent and broader cognition in PD remain unknown. This thesis consists of three separate studies that address this gap by focusing on different aspects of the relationship between sleep and cognition that are relevant to PD. The first two studies focus on specific cognitive processes known to be sleep-dependent whereas the third study focuses on more general cognitive performance.

In Chapter 2, we aimed to address whether dopamine deficiency in PD interferes with the overnight consolidation of motor memory. To answer this, we measured overnight motor memory consolidation in two groups of PD patients, one tested On and one tested Off dopaminergic medications, and compared them to healthy older controls. In healthy adults, motor memory consolidation recruits dopaminergic brain regions known to be affected in Parkinson's disease,

e.g., the striatum, hence our focus on motor memory. It is unknown if restoring normal dopamine levels in Parkinson's disease patients would benefit consolidation. We assessed motor memory consolidation in two ways: 1) by measuring the change in performance across a two-day delay, and 2) in separate groups of participants, we also measured how these changes were affected by an additional interference manipulation. This interference manipulation consisted of having participants learn a second, different sequence 2 h after the initial acquisition which allowed us to probe whether susceptibility to interference is influenced by dopamine state. We hypothesized that dopamine state during the acquisition of learning would positively affect consolidation, leading to better motor memory after the two-day delay.

In Chapter 3, we aimed to address the relationship between sleep-dependent memory consolidation and specific features of sleep important for this process, i.e., sleep spindles. In patients, sleep spindle activity is reduced, and this is associated with cognitive decline. However, whether reduced spindle activity plays a role in the cognitive deficits of Parkinson's disease by interfering with sleep-dependent cognitive processes remains unknown. To answer this, we measured declarative memory consolidation in a group of PD patients before and after a night of sleep. Here, we assessed declarative memory consolidation using a verbal paired-associates task administered before and after sleep. In addition, we also measured the temporal dynamics of sleep spindles, specifically their clustering intro trains of spindles, as this has been proposed to be another mechanism underlying sleep-dependent memory consolidation (Boutin & Doyon, 2020). We hypothesized that lower sleep spindle density and reduced clustering of spindles into trains during NREM sleep would be associated with worse overnight memory consolidation in patients.

In Chapter 4, we aimed to understand whether functional connectivity during sleep underlies the relationship between sleep oscillations and cognition. In the previous study, we showed that sleep spindles were associated with sleep-dependent cognition; however, the relationship of sleep spindles and other sleep oscillations to broader cognitive function is still unclear. Sleep oscillations reflect the coordinated activation of distinct brain regions. Coordinated activation during rest, as measured with resting-state fMRI, in the wake state is already well-established to play an important role in cognition (Stevens & Spreng, 2014). Whether coordinated activity during sleep similarly reflects underlying brain processes that support cognition is not known. In Chapter 4, we address this gap by measuring EEG functional connectivity across

canonical sleep oscillations. We were particularly interested in NREM sleep as oscillations during this stage (e.g., spindles and slow waves) are known to relate to cognition. The aims of the study were two-fold; first, we sought to identify whether EEG functional connectivity during NREM sleep was altered in patients compared to healthy older adults, and second, we sought to identify the relationship between functional connectivity across frequency bands and cognitive function. We hypothesized that PD patients compared to controls would show lower EEG functional connectivity during NREM-2 and higher connectivity during NREM-3, reflecting more pronounced age-related differences and that this pattern would be associated with worse cognitive performance. We predicted that differences in connectivity would be most evident in the delta and sigma bands, corresponding to the frequency bands where oscillations are most notably altered in patients.

In the last chapter (Chapter 5), I review the results from each study in the context of current knowledge and discuss how these results advance our understanding of the potential mechanisms underlying cognitive dysfunction in PD.

Chapter 2. Preserved motor memory in Parkinson's disease

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Abstract

Patients with Parkinson's disease, who lose the dopaminergic projections to the striatum, are impaired in certain aspects of motor learning. Recent evidence suggests that, in addition to its role in motor performance, the striatum plays a key role in the memory of motor learning. Whether Parkinson's patients have impaired motor memory and whether motor memory is modulated by dopamine at the time of initial learning is unknown. To address these questions, we measured memory of a learned motor sequence in Parkinson's patients who were either On or Off their dopaminergic medications at the time of initial learning. We compared them to a group of older and younger controls. Contrary to our predictions, motor memory was not impaired in patients compared to older controls and was not influenced by dopamine state at the time of initial learning. To probe post-learning consolidation processes, we also tested whether learning a new sequence shortly after learning the initial sequence would interfere with later memory. We found that, in contrast to younger adults, neither older adults nor patients were susceptible to this interference. These findings suggest that motor memory is preserved in Parkinson's patients and raise the possibility that motor memory in patients is supported by compensatory non-dopamine sensitive mechanisms. Furthermore, given the similar performance characteristics observed in the patients and older adults and the absence of an effect of dopamine, these results raise the possibility that aging and Parkinson's disease affect motor memory in similar ways.

Keywords: Parkinson's disease, memory, consolidation, dopamine, motor sequence learning, cognition, aging

Introduction

It is well established that the striatum and striatal dopamine play a fundamental role in motor learning (Doyon et al., 2009a; Graybiel and Grafton, 2015; Yin and Knowlton, 2006). More recent evidence also suggests that the striatum – a subcortical structure that is richly innervated by dopaminergic neurons – plays a specific role in the memory consolidation phase of human motor learning (Debas et al., 2014; Doyon et al., 2003; Perrin and Venance, 2019; Pisani et al., 2005), but surprisingly little work has been done to establish the exact role that dopamine plays in this process. Parkinson's patients, who lose the dopaminergic projections to the striatum, are impaired at certain aspects of motor learning. Recent evidence hints that they have an additional impairment in motor memory consolidation, but whether this relates directly to their dopaminergic loss is unknown (Dan et al., 2015; Doyon, 2008; Fernandes et al., 2017; Olson et al., 2019; Terpening et al., 2013). Meanwhile, if, and how, dopamine supports motor memory is of considerable clinical interest. Most patients with Parkinson's disease, despite best efforts at pharmacologic dopamine replacement, spend considerable amounts of time in the low ('off') dopamine state. Establishing whether dopamine supports long-term memory for motor skills would determine whether the consequences to a patient of being in a low or high dopamine state actually extend beyond the typically considered short window of medication effect.

Consolidation is generally defined as an active and time-dependent process during which initially labile memories are strengthened and rendered resistant to interference (Dudai et al., 2015; Walker et al., 2003). In the case of motor memory consolidation, a behavioural hallmark of this process is the offline improvement of performance (Fischer et al., 2002; Robertson et al., 2004). Multiple lines of evidence using animal models suggest that dopamine plays a role in memory consolidation. For example, in rodents, pharmacologic studies have shown that, across different forms of memory, manipulating dopamine around the time of the initial learning of a task influences memory consolidation for that task (Bethus et al., 2010; McNamara et al., 2014; Takeuchi et al., 2016; White et al., 1993). In humans, functional neuroimaging studies have provided indirect support for a role of striatal dopamine in motor consolidation by showing that changes in striatal BOLD activity during the initial learning are predictive of the off-line improvement in performance (Albouy et al., 2013a, 2015; Debas et al., 2010; Pinsard et al., 2019). It has also been

shown that humans retain a motor skill better if they are provided with reward at the time of the initial learning of that skill –a behavioural manipulation thought to indirectly engage the dopaminergic system (Abe et al., 2011).

These findings raise the possibility that striatal dopamine loss in Parkinson's patients may lead to impaired motor memory. Aging may also impact memory in Parkinson's patients. Indeed, older adults do not show the offline improvements typically seen in younger adults, though they do maintain their performance across a delay, indicating that some aspects of a motor memory are nonetheless consolidated (Spencer et al., 2007; Wilson et al., 2012). Though most studies on motor learning in Parkinson's patients have focused on the initial acquisition of a motor skill rather than subsequent memory consolidation of that skill (Clark et al., 2014; Hayes et al., 2015; Ruitenberg et al., 2015), two recent studies have shown an absence of offline gains in Parkinson's patients, thereby providing preliminary evidence for the presence of impaired motor memory consolidation (Dan et al., 2015; Terpening et al., 2013). However, neither of these studies manipulated dopamine medications. It therefore remains unknown whether the presence of dopamine at the time of initial acquisition of a motor skill plays a specific role in enhancing the subsequent memory of that skill. This has implications for understanding whether the motor memory deficits of Parkinson's disease are distinct from those related to aging.

To address these questions, we measured motor memory consolidation in two groups of Parkinson's patients, one tested On and one tested Off dopaminergic medications, and compared them to healthy older controls. We also validated our task design in a group of young controls. All participants were initially trained to repeatedly tap a 5-element sequence (Doyon, 2008; Doyon et al., 2003; Korman et al., 2007; Pinsard et al., 2019). Motor memory consolidation was assessed in two ways: 1) we measured the change in performance across a two-day delay, and 2) in separate groups of participants, we also measured how these changes were affected by an interference manipulation. The interference manipulation consisted of having participants learn a second, different sequence two hours after the initial acquisition (Korman et al., 2007). This allowed us to probe whether susceptibility to interference is influenced by dopamine state. We hypothesized that dopamine at the time of initial acquisition would positively affect the consolidation phase of learning and lead to better motor memory at the delayed retest. Specifically, we predicted that

patients On dopaminergic medications would exhibit better maintenance of performance across the delay and reduced susceptibility to interference compared to patients Off medication.

Contrary to our predictions, we found that dopamine state at the time of initial acquisition did not influence motor memory maintenance. Overall, memory maintenance in the patients was similar to that of older adults and neither group showed offline gains. Interestingly, we also found that, unlike the young adults, neither older adults nor patients were susceptible to interference conducted two hours after initial learning. These results raise the possibility that motor memory in Parkinson's patients relies on compensatory extra-striatal and non-dopamine-dependent mechanisms, and that these mechanisms may be similar to those that explain age-related differences in motor memory consolidation.

Methods

Participants

Parkinson's patients and controls were recruited from the Center for Parkinson's Disease and other Movement Disorders at the Columbia University Medical Center or from the Michael J Fox Foundation Trial Finder website. Fifty-two patients were recruited but four were excluded either because of missing data or because of performance inclusion criteria (see section 2.4). The analyses were conducted on 25 patients who were tested OFF their dopaminergic medications (PD-OFF; mean $\pm$ SD age: 62.0 $\pm$ 7.60, disease duration 6.6 $\pm$ 3.9 years), and 23 patients who were tested ON their dopaminergic medications (PD-ON; mean $\pm$ SD age: 63.2 $\pm$ 7.0, disease duration: 6.8 $\pm$ 3.24 years). All patients were receiving levodopa and endorsed levodopa responsiveness. In addition, 9/25 PD-OFF and 10/23 PD-ON were also being treated with a dopamine agonist. Participants had to use their non-dominant hand for the motor task. In the case of the PD-OFF, the non-dominant hand was also the less affected hand in 11/25. In the PD-ON it was the less affected in 11/23. Twenty-three healthy older controls were also tested (HC; Male 10, mean age 62.2 (SD = 7.52)). Sample size was determined based on recent studies of motor learning in Parkinson's patients and based on feasibility of recruitment. Demographic and clinical details are provided in **Table 1**.

To establish the validity of the task, thirty-four young controls were also recruited through local advertisements (19 males, mean age 21.3 (SD = 4.37), 28 right-handed). None had active neurologic or psychiatric disease.

Medication manipulation

Parkinson's disease patients were in the same drug state for both the acquisition phase of the task and the delayed memory test (i.e. ON dopaminergic medications for Day 1 and Day 3 or OFF for both; **Figure 1**). Details of the study design are provided below. Patients tested ON took their usual dose of medications 1 hour before the start of testing. Patients tested OFF dopaminergic medication were instructed to take their last dose the evening before the experiment (average time since last dose = 17 hours). This represents at least 10 half-lives for the carbidopa-levodopa, which all participants were taking, and approximately two half-lives for the dopamine agonists. We did not manipulate dopaminergic medications during the period between the two testing days, patients were told to take their medications as they usually do. In particular, we did not manipulate overnight dopaminergic intake (this applies only to Night 1; during Night 2, which preceded Day 3, patients were either ON or OFF according to their group assignment). As a result, some patients were receiving dopamine replacement during the period of sleep of Night 1, either from short-acting medications taken just before bed, or from longer-acting dopamine agonists taken in the afternoon or evening. This was the case for a similar proportion of patients in each group (11/25 PD-OFF and 12/23 PD-ON; p = 0.8). Exploratory analyses were conducted examining these subgroups.

	Healthy controls (n=23)	Parkinson's OFF (n=25)	Parkinson's ON (n=23)
Age	62.2 (7.52)	62.0 (7.60)	63.2 (7.02)
Sex (male)	10/23	13/25	15/23
Education (years)	17.6 (2.40)	18.9 (2.24)	18.7 (2.76)
MoCA [a]	28.2 (1.51)	28.4 (1.59)	28.3 (1.73)
Digit Span total [b]	13.0 (2.07)	12.3 (1.86)	13.2 (1.91)
UPDRS-III [c]	n/a	25.7 (8.76)	23.2 (7.96)
Hoehn & Yahr stage	n/a	2.13 (0.34)	2.09 (0.29)
LEED (mg) [d]	n/a	630 (232)	668 (318)
Disease duration	n/a	6.60 (3.93)	6.83 (3.24)
Right-handed	19/23	18/25	20/23
Used less affected hand	n/a	10/25	11/23

Table 1. Demographic and clinical characteristics of participants retained for analyses.

Table shows mean (SD). [a] MoCA = Montreal Cognitive Assessment; [b] Digit Span total = sum of forward and backward span;

[c] UPDRS = Unified Parkinson's Disease Rating Scale-Part III, tested ON in ON group, and OFF in OFF group; [d] LEED = Levodopa equivalent dosing, includes levodopa, dopamine agonists, amantadine, monoamine oxidase inhibitors and catechol-O-methyl transferase inhibitors

Motor sequence learning task and Interference manipulation

Participants performed a computerized version of the motor sequence learning task adapted from Karni et al. (Karni et al., 1995, 1998). This task has been extensively used to study motor learning consolidation and its underlying processes in humans. Participants were trained to tap a 5-element sequence on a keyboard, as fast and accurately as possible, using 4 keys (F, G, H, J) which were labelled 1, 2, 3, 4 respectively. The sequence to learn was 4-1-3-2-4. All participants used their non-dominant hand and were instructed to use only 4-fingers, excluding the thumb, such that the pinky pressed the 1, the ring finger the 2, the middle finger the 3 and the index the 4 (in the case of left-hand use). The task consisted of a training phase and of three tests (baseline, post-training

and post-delay; **Figure 1**). First, participants completed a baseline test of performance where they were given four 30-second trials during which they were required to repeatedly generate the entire sequence as many times as possible. Speed and accuracy were both emphasized. The numbers representing the sequence (i.e., "4-1-3-2-4") remained on the screen at all times. Participants had a 30-second break between trials to rest their hand. Then, during the training phase, participants were given eight blocks of training during which they were required to perform the sequence 20 times. Participants received feedback for correct or incorrect performance after each series of 5 keys pressed in the form of a green or red fixation cross. A post-training test of performance, identical to the baseline test, immediately followed the training.

Participants were randomly assigned to one of two conditions: the Interference condition (10 PD-ON, 12 PD-OFF and 10 healthy controls) or the No Interference condition (13 PD-ON, 13 PD-OFF and 13 healthy controls). In the case of the Interference condition, two hours after the end of training, participants were trained to perform a new 5-element sequence composed of the same elements but in the reverse order (4-2-3-1-4), following the same procedure as the initial training. The two-hour delay was chosen because it has been shown that this interval is within a time-window during which the newly acquired motor skill is susceptible to interference (Korman et al., 2007). In the No Interference condition, participants stayed in the lab for the same amount of time but did not perform any particular task. During the 2-hour delay, both groups completed another task which has been reported separately (Sharp et al., 2020). All participants returned two days later for a post-delay test following the same procedure as the baseline test. The task was implemented using the PsychoPy2 Experiment Builder (v1.82.00) (Peirce, 2007, 2008).

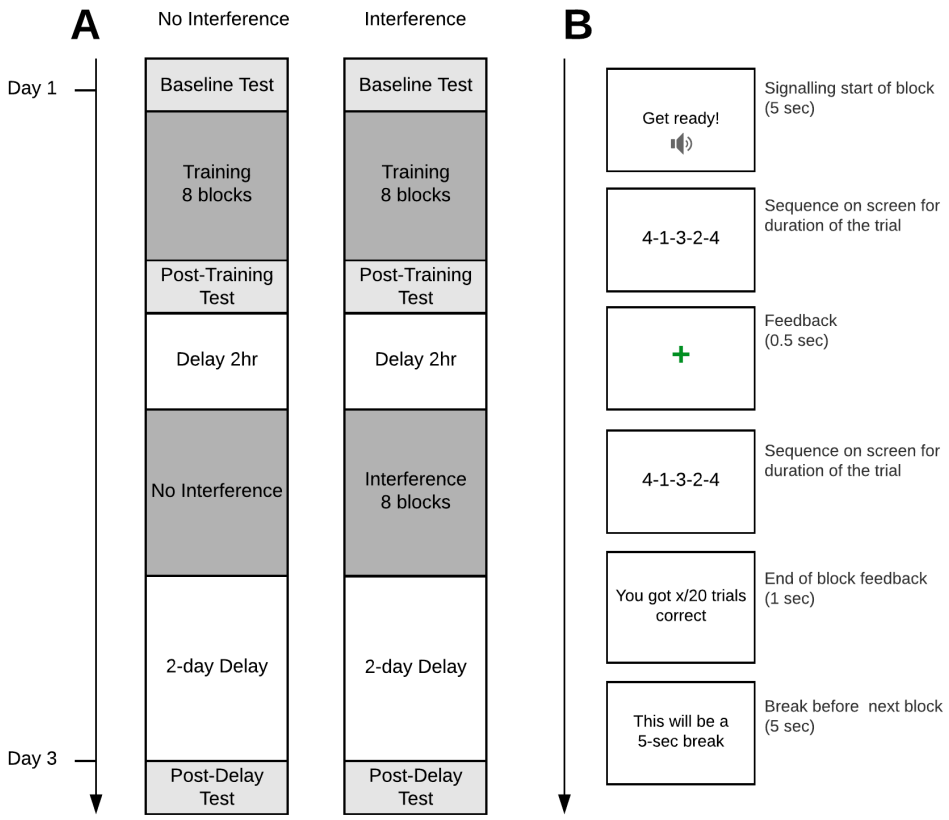

Figure 1. Schematic of the experimental design and trial sequence. (**A**) Participants were assigned to either the Interference or No interference condition. All groups were first assessed on their baseline performance (Baseline test). The test consisted of repeatedly tapping the target sequence '4-1-3-2-4' as fast and accurately as possible for 4 trials of 30 seconds. Participants were then trained on the motor sequence over 8 blocks of 20 trials and received feedback on their performance. A Post-training test immediately followed. Two hours later, the Interference group was trained on a new sequence composed of the same elements but in reverse order ('4-2-3-1-4') for 8 blocks of 20 trials, whereas participants in the No Interference group did not undergo this procedure but remained in the lab for the same amount of time. All participants returned to the laboratory two days later and were tested on the original sequence (Post-delay test). Each of the three tests followed the same procedure. (**B**) Trial sequence during the training phase: a "Get ready!" screen accompanied by a sound signaled the beginning of a block, participants then performed the target sequence, which remained visible on the screen until 5 keys had been pressed. Feedback was given in the form of a green fixation cross for correct trials or a red fixation cross for incorrect trials. At the end of each block, the screen displayed how many sequences out of 20 were correctly performed, followed by a 5-second break prior to the next training block.

Analysis

The following post-hoc exclusion criteria were applied to the data: First, we excluded from the analysis participants whose average number of correct sequences at post-training was outside of 2 SD of their group mean. This criterion was applied only to post-training performance because it was used as a baseline to measure memory across the delay. As a result, one PD-ON and one PD-OFF patient were excluded completely. Second, we excluded 1 HC who scored zero on three out of the four trials at both the baseline and post-delay tests indicating poor task engagement. Finally, single trials from any of the test sessions with zero correct sequences were substituted with the average of the trial before and after, because it was assumed that these isolated instances reflected misuse of the keys rather than true poor performance. The removal of single trials occurred in 7 participants (2 HC, 3 PD-OFF and 2 PD-ON). If this occurred on more than one trial of the test session but affected only a single test, the whole test session was removed from the analysis; this occurred in 2 participants: 1 PD-OFF and 1 HC had a single test session removed. The other single instance when a test session was removed was when a participant significantly underused the allotted test time (one HC used only 2 of the 30 seconds allotted for a test trial on a baseline test). The final samples were as follows: 23 HC, 25 PD-OFF, 23 PD-ON and 34 Young controls.

In keeping with previous approaches to analyzing performance on this task, we computed a performance index (PI = number of correct sequences / duration * 10), which integrates both accuracy and duration, as our main measure of performance (Dan et al., 2015). The duration of a trial is calculated as the time from the first key press to the last key press, which allowed us to account for the fact that participants occasionally exhibited a slight delay after the onset of the trial before they made their first key press. The performance index also accounts for errors since keys pressed in error necessarily reduce the time available to produce a correct key press. We performed additional exploratory analyses using number of correct sequences and mean duration of correct sequences as outcome measures. These analyses are presented in the Supplementary materials.

Our main analyses focused on examining the differences between groups in the maintenance of performance across the delay and in the susceptibility to interference. We ran a three-way mixed ANOVA on the performance index derived from the post-training test and the post-delay test, with test as a within-subject factor and group and interference condition as between-subject factors (Test

[Post-Training, Post-Delay] x Group [HC, ON, OFF] x Interference [Int, NoInt]). We examined within group differences using two-sample t-tests. All tests are reported with uncorrected degrees of freedom, except for the test comparing performance change across conditions in young adults, which yielded a significant Levene's test. To examine the evidence for the null, we computed Bayes Factors for within-group differences using the 'BayesFactor' package in R version 4.0.5 (Lawrence, 2016; Morey & Rouder, 2018). We also report the results of equivalence tests and provide power curves for a range of effect sizes in the Supplementary Material (Supplementary Figure 7 and 8).

To determine if there were significant differences in baseline performance between groups and between condition assignment we ran a two-way ANOVA on the performance index, with group and interference condition as between-subject factors (Group [HC, ON, OFF] x Condition [Int, NoInt]). To determine if there were significant group differences in the change of performance from baseline to post-training (i.e., the degree of benefit derived from training), we ran a two-way mixed ANOVAs on the performance index, with group as a between-subject factor and test as a within-subject factor (Group [HC, ON, OFF] x Test [Baseline, Post-Training]).

We conducted exploratory analyses to control for the possible effect of overnight dopamine replacement on performance change across the delay. First, we ran a two-way mixed ANOVA (Group [ON, OFF] x Test [Post-Training, Post-Delay]) in the subset of participants who were not receiving dopamine overnight. Then, to directly compare performance change in patients receiving overnight dopamine replacement to those who were not, we ran a second two-way mixed ANOVA (Overnight dopamine [On, Off] x Test [Post-Training, Post-Delay]).

Results

Replication of previous findings in young adults

First, we validated we were able to replicate the findings typically observed in young adults. Specifically, it has been repeatedly shown in healthy young adults that 1) offline gains in performance occur over an overnight delay, and 2) that interference administered two hours after the initial learning leads to a reduction of offline gains (Doyon, Korman, et al., 2009; Korman et

al., 2003; Robertson et al., 2004; Walker et al., 2002). As expected, the young healthy controls showed an offline improvement in performance after the two-day delay (mean of change in performance index: 0.83 units, 95% CI [0.61, 1.05], t= 8.05, df = 17, $p < 0.005$). Furthermore, we found a trend suggesting that participants who underwent interference after learning showed less offline-gains than those who did not (between-condition difference in offline-gains = -0.533, 95% CI [-0.02, 1.08], t= 2.00, df=20.24, p = 0.059) (**Supplemental Figure 1**).

	YC		**HC**		**PD-OFF**		**PD-ON**	
	No Int (n=18)	**Int** (n=16)	**No Int** (n=13)	**Int** (n=10)	**No Int** (n=13)	**Int** (n=12)	**No Int** (n=13)	**Int** (n=10)
Baseline	6.12 (2.34)	5.33 (1.75)	4.22 (2.23)	4.66 (2.50)	3.88 (3.28)	3.99 (1.80)	3.92 (1.74)	3.44 (2.20)
Post-training	7.95 (2.16)	7.37 (1.70)	5.56 (1.97)	5.81 (1.97)	4.90 (2.07)	4.69 (2.26)	5.43 (1.43)	5.08 (2.23)
Post-delay	8.78 (2.36)	7.68 (1.91)	5.23 (2.31)	5.78 (2.21)	4.60 (2.28)	4.41 (2.02)	5.24 (1.89)	4.54 (2.45)

Table 2. Mean performance indices

Table 2 shows mean (SD) Performance index for each session.

Baseline performance and training gains in older adults and patients

Table 2 presents performance indices for all groups and for each condition. We found no evidence to suggest group differences (Group [HC, OFF, ON]: F(2, 62)=0.87, p=0.42, η^2_P = 0.027), or condition differences in baseline performance (Condition [Int, NoInt]:F(2, 62)=0.002, p=0.95, η^2_P = 0.001). To examine group differences in post-training improvement, we collapsed across Interference conditions because the training occurred before the interference. We found no evidence to suggest group differences in training-derived performance improvement (Group [HC, OFF, ON] x Test [Baseline, Post-Training]: F(2, 62)= 2.01, p=0.14, η^2_P =0.061; **Figure 2**). Using number of correct sequences or sequence duration as outcome measures instead of the performance index yielded a similar pattern of results (Supplementary Figures 2 and 4).

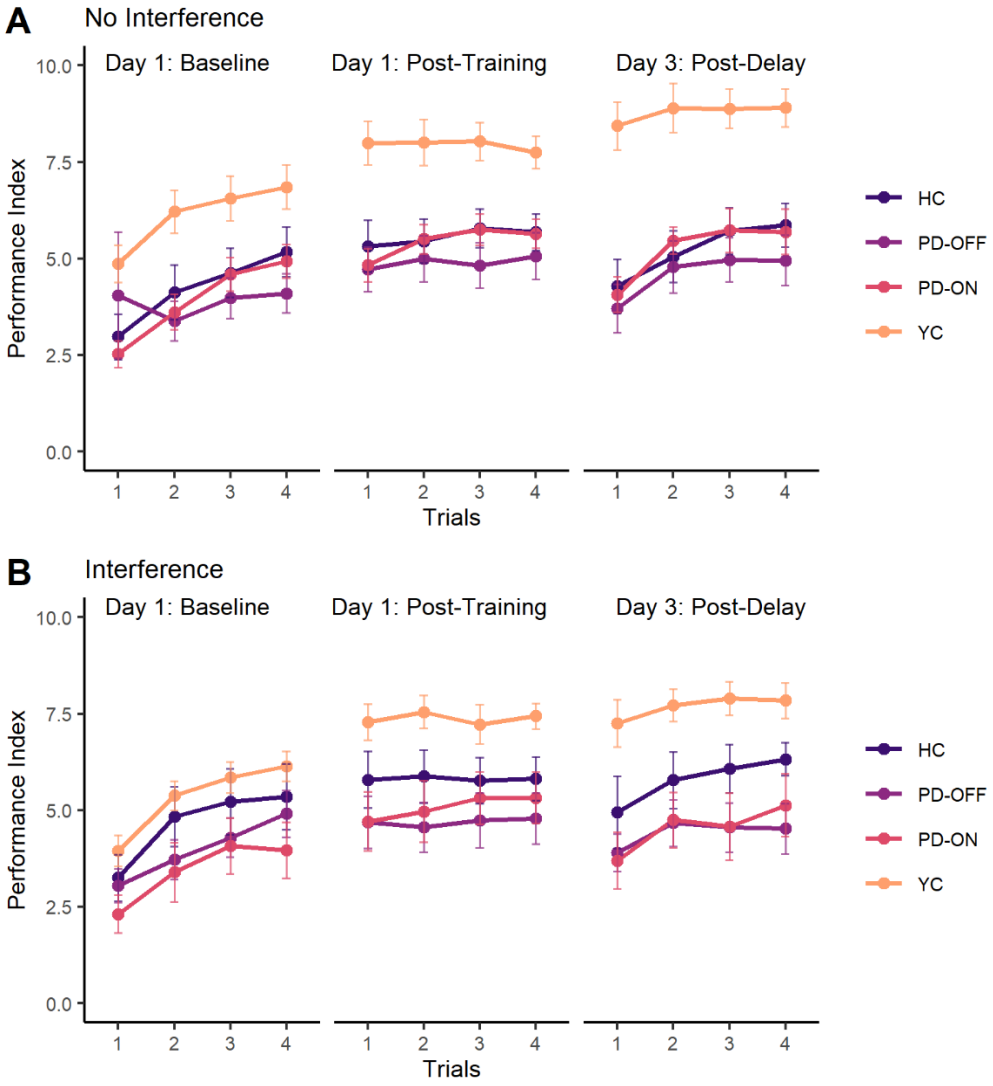

Figure 2. Test performance. Performance measured with the Performance index (i.e., number of correct sequences/duration * 10) is shown across trials (1-4) for each of the three test sessions (baseline, post-training and post-delay) for all four groups (YC, HC, PD-OFF and PD-ON). Conditions are presented separately: participants that did not undergo the interference (A) and those that did (B). Participants across groups and conditions show similar baseline performance, similar improvements from training and similar maintenance of performance across the two-day delay. Error bars represent s.e.m. within group and trial.

Motor memory maintenance and susceptibility to interference in older adults and patients

We first hypothesized that the low dopamine state of Parkinson's patients would affect motor memory, and that patients OFF at the time of initial learning would show worse maintenance of

motor memory across the two-day delay than patients ON and healthy controls. However, using a repeated-measures ANOVA to compare the change in performance, we found no evidence to suggest group differences in the degree of maintenance of memory across the delay (Group [HC, OFF, ON] x Test [Post-Training, Post-Delay]: $F(2, 65)= 0.32$, $p=0.72$, $\eta^2_P = 0.01$). In fact, unlike the young adults, none of the groups showed offline gains. Instead, there was a trend toward a slight decay in memory in the controls and patients OFF (mean change in performance index: HC -0.33 units, p=0.06; OFF -0.29 units, p=0.03; ON -0.19 units, p=0.32). We also examined whether motor symptom severity was associated with memory but found no correlation between the UPDRS-III scores and performance change across the delay (Supplementary Figure. 6).

We also hypothesized that patients OFF medication would show more susceptibility to interference than patients ON and healthy controls. However, we found no evidence to support a difference between groups in the maintenance of performance when comparing participants who had undergone the interference to participants who hadn't (Group [HC, OFF, ON] x Interference [NoInt, Int] x Test [Post-Training, Post-Delay]: $F(2, 65)=1.00$, $p=0.37$, $\eta^2_P=0.03$).

To further examine the effects of interference, we measured, within each group, the difference in memory maintenance across the delay between the participants who underwent the interference manipulation and those who did not. There was no effect of interference in any of the three groups. Specifically, memory maintenance was not worse in participants who had undergone interference than in participants who had not (HC: t= -1.07, p=0.29; PD-OFF: t= -0.05, p=0.95; PD-ON: t=0.95, p=0.35) (**Figure 3**). Because the absence of an effect of interference on memory maintenance in all groups was unexpected, and because these within group comparisons were conducted by comparing the smaller sub-groups assigned to each condition, we additionally computed Bayes factors for each t-test to attempt to quantify the evidence in support of the null hypothesis. In all three groups, the Bayes factor for the t-test examining the effect of interference on memory maintenance suggested weak support for the null hypothesis over the alternative ($BF_{HC}=1.70$, $BF_{OFF}=2.71$, $BF_{ON}=1.82$).

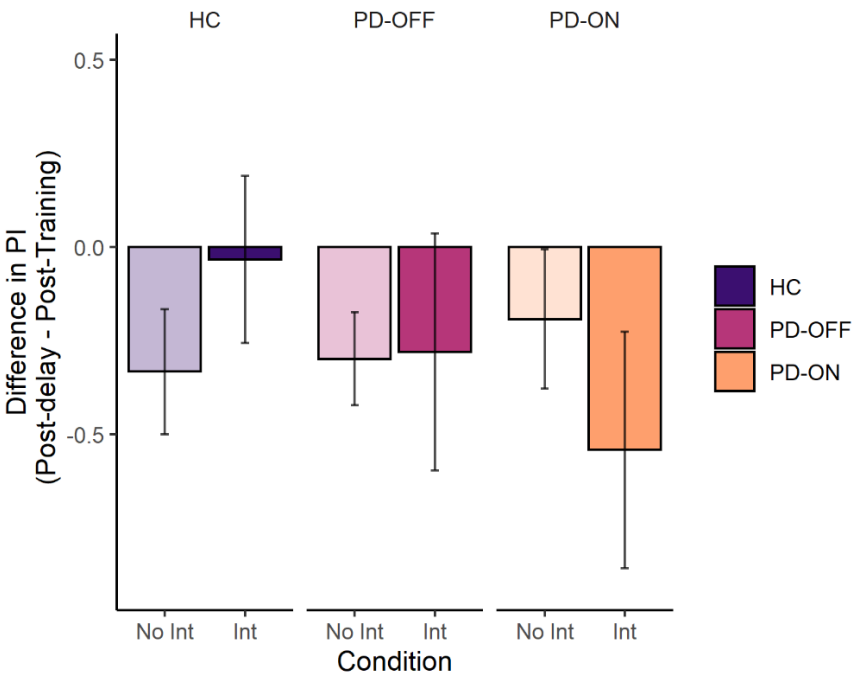

Figure 3. Change in performance across the two-day delay and effect of interference. Change in performance was calculated as the difference between the mean performance at the Post-Delay test and at the Post-Training test. Negative values represent a decay in performance across the delay. There were no differences in the degree of maintenance of performance between groups nor was there an effect of interference on the maintenance of performance. Error bars represent s.e.m. within group and condition. No Int=No interference condition; Int=Interference condition.

We also conducted exploratory analyses to control for a possible effect of overnight dopamine replacement on memory. Though we did not experimentally manipulate overnight dopamine, a subset of participants was receiving dopamine replacement overnight as part of their regular treatment regimen, and this could also influence memory. We therefore conducted a set of analyses to isolate the effect on memory of dopamine during acquisition from the effect of dopamine overnight. We focused on the subset of participants from each group who were not receiving any dopaminergic medications overnight. This allowed us to isolate the effect of dopaminergic replacement at the time of acquisition on consolidation. Though this is a smaller sample (14/25 PD-OFF and 11/23 PD-ON), the pattern of results is similar to those obtained in the full sample with no evidence to suggest a difference in performance maintenance between the groups (Group [OFF, ON] x Test [Post-Training, Post-Delay]: $F(1, 21)=2.72$, $p=0.11$, $\eta^2_P=0.115$). Second, to

examine the effect of overnight dopamine within each group, we compared patients who were receiving overnight dopamine replacement to patients who were not. In patients ON at the time of initial acquisition, there was a trend to suggest that overnight dopamine replacement was associated with better memory maintenance (difference = 0.66 PI units; Overnight dopamine [On, Off] x Test [Post-Training, Post-Delay]: $F(1, 21)=4.19$, $p=0.053$, $\eta^2_P = 0.166$), but this was not the case in patients OFF (difference = 0.23 PI units; Overnight dopamine [On, Off] x Test [Post-Training, Post-Delay]: $F(1,23)=0.50$, $p=0.48$, $\eta^2_P =0.022$).

Effects of aging on motor memory consolidation

Though the absence of off-line gains in older adults has previously been shown in the literature, the effects of interference on motor memory in older adults have been largely under-explored. We therefore compared memory maintenance and susceptibility to interference between younger and older adults. First, as expected, in a three-way mixed ANOVA (Group [YC, HC] x Test [Post-Training, Post-Delay] x Interference [Int, NoInt]), there was a small but significant Group*Test interaction ($F(1, 53)=15.20$, $p=0.0002$, $\eta^2_P = 0.223$) indicating that, across interference condition, older adults differed from young adults in the change in performance that occurred across the two-day delay. We then specifically examined the change in performance across the delay in sub-groups who did not undergo interference. In a two-way mixed ANOVA (Group [YC, HC] x Test [Post-Training, Post-Delay]) in this subset of participants we found that younger adults showed a greater improvement in performance across the delay than older adults (Group [YC, HC] x Test [Post-Training, Post-Delay]: $F(1, 29)=38.98$, $p < 0.000001$, $\eta^2_P = 0.573$). Further post-hoc analyses confirmed that, as reported above, younger adults showed a significant improvement in performance across the delay (PI difference = 0.83; $t(27)=8.05$, $p < 0.00001$) whereas older adults merely maintained a similar level of performance (PI difference = -0.33; $t(12)= -1.99$, $p=0.069$).

We also compared the susceptibility to interference between groups. We found a significant three-way interaction (Group [YC, HC] x Test [Post-Training, Post-Delay] x Interference [Int, NoInt]: $F(1, 53)=4.68$, $p=0.03$, $\eta^2_P = 0.081$) indicating that the younger and older adults were differentially susceptible to the interference manipulation. As reported above, and as previously shown using this task, the younger adults showed a statistical trend suggesting that interference caused a reduction in offline gains (change in performance index: NoInt = 0.83, Int = 0.30; $t = 2.00$, df =

20.24, p = 0.059). In contrast, in older adults, the change in performance across the delay was very similar in both the interference and no interference conditions (change in performance index: NoInt = -0.33, Int = -0.03; t= -1.07, df=17.75, p = 0.29).

Discussion

Motor learning consolidation is known to depend on the striatum and, in keeping with dopamine's role in supporting corticostriatal plasticity, has generally been thought to depend on dopaminergic inputs to the striatum (for a recent review see Doyon et al., 2018). There is also accumulating evidence from the field of declarative memory or hippocampal-dependent learning, that dopamine state around the time of initial learning plays a role in the later memory for what was learned (Bethus et al., 2010; Chowdhury et al., 2012; Sharp et al., 2020). However, whether dopamine at the time of initial learning of a motor skill similarly modulates the later memory for that skill, and whether this process is altered in Parkinson's patients remains unknown. Here, we investigated whether Parkinson's patients have impaired memory of motor learning, and whether memory can be facilitated by dopamine replacement at the time of learning. Contrary to our predictions, we found that the degree of motor memory impairment was not greater in patients than in older controls, and was not influenced by dopamine state at the time of initial learning. Specifically, performance was maintained across a two-day delay in patients to the same extent as it was in older controls, yet, in contrast to younger controls, neither the patients nor the older controls showed offline gains in performance. To examine the effects of dopamine and disease on post-learning consolidation processes that are thought to be occurring in the early hours after initial learning, we also used an interference manipulation that has been previously used to probe consolidation processes (Korman et al., 2007). Interestingly, though young controls showed the expected susceptibility to interference delivered two hours after learning, patients On or Off dopaminergic medications and older adults did not show a reduction of their memory following interference. These findings suggest that motor memory in Parkinson's disease, which was preserved in patients to the same degree as in older adults, is supported by non-dopamine sensitive and possibly extra-striatal mechanisms. Furthermore, given the absence of susceptibility to interference in both patients and older adults, these findings raise the possibility of a shared, age-related mechanism underlying the inability to improve offline.

Consistent with previous work we found that though Parkinson's patients did not exhibit offline gains, they did maintain their motor memory to the same extent as older adults. Our findings extend this previous work by additionally showing that dopamine state at the time of initial acquisition of the motor skill did not influence memory maintenance, nor the susceptibility to interference. These results are surprising considering the well-established link between motor memory and striatal activity (Albouy et al., 2013b, 2008; Debas et al., 2014, 2010; King et al., 2017), and suggest that Parkinson's patients are, at least to some extent, relying on non-striatal and non-dopamine-sensitive compensatory mechanisms for the maintenance of motor memories. Recruitment of compensatory processes in Parkinson's patients has been well described (Appel-Cresswell et al., 2010; Palmer et al., 2010; Yu et al., 2007). One possible compensatory substrate is the cerebellum, which has been proposed as a region that plays a compensatory role for both motor and non-motor processes in Parkinson's disease (Wu & Hallett, 2013). Several functional neuroimaging studies in Parkinson's patients using a variety of motor tasks have demonstrated increased task-related activity in the cerebellum (Palmer et al., 2009; Wu and Hallett, 2005; Yu et al., 2007) as well as increased functional connectivity of the cerebellum in the setting of relatively normal motor performance (Festini et al., 2015; Mentis et al., 2003; Palmer et al., 2009; Simioni et al., 2016; Wu et al., 2009). For instance, in Parkinson's patients OFF medication, better motor performance was associated with increased motor-task-related BOLD activity in the cerebellum (Palmer et al., 2009) and increased cerebellar-putamen functional connectivity (Simioni et al., 2016). No study has specifically investigated the role of the cerebellum in the process of motor memory in Parkinson's patients. However, given evidence of increased activity in the cerebellum of Parkinson's patients during execution of simple motor tasks, it is plausible that the cerebellum may also be involved during the acquisition of a motor skill, which may render the subsequent process of memory independent of the striatum and, in the case of Parkinson's disease patients, independent of their dopamine state. Another possible substrate for compensatory motor memory is the hippocampus. The hippocampus, like the cerebellum, remains relatively spared in the earlier stages of Parkinson's disease and in patients who are free of dementia, as was the case for the patients included in our sample (Hawkes et al., 2010) and could therefore potentially be recruited to support motor memory. Indeed, several studies have shown that the striatum and the hippocampus both support the consolidation of motor sequence memories (Albouy et al., 2013b, 2008), though it has been proposed that they support distinct aspects of consolidation on this task (Albouy et al., 2015).

An important open question is whether compensatory mechanisms remain effective beyond the first years of the disease. The average disease duration in our PD sample was seven years (range of 2 to 20 years) so it is possible that compensatory mechanisms were active to a different extent according to the stage of the disease.

We did not find evidence that dopamine at the time of the initial acquisition of motor learning influences the subsequent memory of that learning. Our motivation for choosing to focus on dopamine at the time of acquisition was informed by evidence that the degree of involvement of the striatum at the time of initial learning predicts offline consolidation and later memory (Albouy et al., 2013b, 2008; King et al., 2017). This is also consistent with models of corticostriatal plasticity, which propose that dopamine release in the period surrounding activation of a synapse influences plasticity (Calabresi et al., 2007; Wickens, 2009). However, evidence from the study of episodic, or hippocampal-dependent memory, which also shows a clear beneficial effect of dopamine at the time of initial encoding on later memory, specifically shows that this effect is tied to the interaction between dopamine and an environmental signal such as reward (McNamara et al., 2014; Redondo and Morris, 2011; Sharp et al., 2020; Shohamy and Adcock, 2010; Wang et al., 2010). We did not manipulate reward during learning. Thus, it is possible that simply restoring dopamine is not sufficient, and that an environmental trigger for dopamine release is also necessary for a beneficial effect on memory to occur. Indeed, several recent studies of motor learning, including one that relied on a sequence learning task similar to ours (Wächter et al., 2009), have shown that reward can enhance the retention of motor memories in healthy controls (Abe et al., 2011; Galea et al., 2015). Future work will be necessary to determine whether the combination of reward and dopamine replacement could enhance motor memory in Parkinson's patients, or whether reliance on extra-striatal compensatory mechanisms eliminates these potential beneficial effects.

Dopamine state during the early post-encoding period and during overnight sleep may also be important but little research exists to guide hypotheses. Two recent studies in healthy young adults where participants received either a dopamine agonist or antagonist overnight showed no effect of treatment condition on maintenance of motor memory (Asfestani et al., 2020; Feld et al., 2014). However, given that these were young adults who were presumably already dopamine 'replete', it

is unclear how to extend these findings to Parkinson's patients. In the current study, we used levodopa to induce the ON state during the initial learning. However, given the 1.5-2-hour half-life of levodopa, it is reasonable to assume that patients ON were still ON in the early post-encoding period, whereas the patients OFF remained OFF. Our finding that patients ON and OFF did not differ in their memory maintenance suggests that dopamine state during the early post-encoding period is not a key modulator of subsequent consolidation. Exploratory analyses examining the effect of overnight dopamine within each group, comparing patients who were receiving dopaminergic medications overnight to those who were not, revealed a possible benefit of overnight dopamine state on consolidation but only in patients who were also ON at the time of initial acquisition. This raises the possibility of an interaction between the neural processes underlying the initial learning and those underlying the later consolidation process. Future studies specifically manipulating dopamine at the different critical periods of the consolidation process are required.

An unexpected finding in our study is the fact that memory maintenance in older adults was not susceptible to interference. The older adults therefore differed from the younger adults in two key ways: they did not show offline gains, and did not show susceptibility to interference. Previous work has similarly demonstrated the absence of offline gains in older adults (Fogel et al., 2014; Spencer et al., 2007; Wilson et al., 2012). This suggests that age-related impairments in consolidation could be due to age-related changes in sleep, such as reduced spindles (Fogel et al., 2014; Harand et al., 2012; King et al., 2013; Wilson et al., 2012). However, the absence of a susceptibility to interference in older adults points to an additional mechanism. Specifically, our results suggest that the early consolidation processes that take place in the first few hours following learning – a phase when the memory is still labile and susceptible to interference – are either compromised in older adults and patients, or are occurring at a different, possibly later, timepoint (Korman et al., 2015, 2007; Nettersheim et al., 2015; Walker et al., 2003). Whether the mechanism underlying this change is similar in the patients and the older adults remains to be determined, but recent evidence showing that corticostriatal networks are indeed important even at this early post-learning stage (Censor et al., 2014), and are altered in older adults across the consolidation period (Fogel et al., 2014), suggests that the cause of disrupted consolidation may be shared.

The main limitation of our study is the relatively small sample size, which limited the effect sizes we were powered to detect. For instance, when comparing baseline performance or performance maintenance between groups, we were powered to detect a small-to-medium effect of at least $\eta 2 = 0.38$ whereas for the within-group investigation of the effect of interference on performance maintenance, we were only powered to detect large effects ranging from $d = 1.31$ to $d = 1.19$. Another limitation is the between-subject design that was used to test the effect of medication manipulation on motor memory consolidation in Parkinson's disease. Though patients were randomized to the medication groups, there are certain aspects of Parkinson's disease that we did not control for but that could influence motor memory. For instance, REM-sleep behaviour disorder, which is prevalent in Parkinson's disease, is associated with EEG changes during REM sleep and could therefore influence sleep-dependent cognitive processes like memory (Fantini et al., 2003). Similarly, the similar UPDRS III scores in the ON and OFF patients indicates similar motor disability despite being tested under different medication conditions. This suggests that the patients ON might have had more advanced disease (i.e. if tested OFF, they presumably would have had worse disability), and raises the possibility that the absence of a difference in motor memory between the patients ON and OFF could be explained by more advanced disease in the patients ON. We think this is unlikely because other proxy measures of disease progression that are not sensitive to medication state (disease duration, total levodopa equivalent dose and MoCA scores) were similar between groups, and we found no association between UPDRS III score and memory within each group.

In conclusion, our findings demonstrate that motor memory in Parkinson's patients is similar to that of older adults: both patients and older adults were able to maintain their performance but neither group showed offline gains. Furthermore, we showed that neither patients nor older adults were susceptible to an interference manipulation. These similarities suggest that changes in motor memory seen in Parkinson's disease might be explained by age-related mechanisms (King et al., 2013; Korman et al., 2015), and further suggest a shared neural substrate for motor memory across groups. We also found that dopamine at the time of initial learning did not influence later memory for that learning. This suggests a reliance on extra-striatal and non-dopamine-sensitive networks for motor memory in Parkinson's patients and, given the similar pattern of performance observed in the patients and older adults, could provide clues for identifying the mechanisms that underlie

age-related changes to motor memory. An important future step will be to leverage neuroimaging to identify key compensatory mechanisms and begin to understand the evolution of compensation over the course of aging and disease, as well as factors that influence the success of such compensation. Future work will also be required to establish, in both healthy aging and Parkinson's disease, the mechanisms that affect memory consolidation across the full timeline of this process, from the point of initial learning to delayed retrieval. We found an absence of susceptibility to early interference in both the older adults and the patients, suggesting that the process of memory transformation is already altered in the first few hours following learning. Sleep alterations, believed to contribute to motor consolidation deficits in aging, may represent an even more important mechanism in patients (Latreille et al., 2016, 2015). Identifying such factors will be important as there is evidence for effective sleep therapies in Parkinson's patients (Gros et al., 2016; Kaminska et al., 2018; McCarter et al., 2013) and even recent evidence that dopamine state may impact the relationship between sleep and memory (Isotalus et al., 2020).

Declarations of interest:

None

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Chapter 3. Sleep spindle density and temporal clustering are associated with sleep-dependent memory consolidation in Parkinson's disease

Preface

In the previous chapter, I demonstrated that dopamine state during motor learning did not affect overnight motor memory consolidation. Given that memory consolidation depends on sleep, it is important to consider the role of sleep itself. Sleep spindles are oscillations characteristic of NREM sleep and have been shown to be crucial in supporting consolidation. Importantly, sleep spindle activity is reduced in Parkinson's disease, and this change has been linked with cognitive impairment. However, no study has examined if the alteration to sleep spindles that occurs in PD specifically impacts sleep-dependent cognitive processes. To address this gap, Chapter 2 investigated whether sleep spindle density is associated with overnight memory consolidation in PD. Additionally, we considered how sleep spindles are clustered into 'trains', as it has recently been suggested that this organization of spindle activity may be important for efficient memory consolidation. We demonstrated that a higher density of sleep spindles at frontal leads during NREM-3 was associated with better overnight declarative memory consolidation. We further demonstrated that the clustering of sleep spindles into trains was associated with consolidation. Our findings suggest that changes in sleep spindle activity, commonly observed in PD, may represent one mechanism by which poor sleep contributes to worse cognition in patients.

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Abstract

Study Objectives: Sleep is required for successful memory consolidation. Sleep spindles, bursts of oscillatory activity occurring during non-REM sleep, are known to be crucial for this process and, recently, it has been proposed that the temporal organization of spindles into clusters might additionally play a role in memory consolidation. In Parkinson's disease, spindle activity is reduced, and this reduction has been found to be predictive of cognitive decline. However, it remains unknown whether alterations in sleep spindles in Parkinson's disease are predictive of sleep-dependent cognitive processes like memory consolidation, leaving open questions about the possible mechanisms linking sleep and more general cognitive state in Parkinson's patients.

Methods: The current study sought to fill this gap by recording overnight polysomnography and measuring overnight declarative memory consolidation in a sample of thirty-five Parkinson's patients. Memory consolidation was measured using a verbal paired-associates task administered before and after the night of recorded sleep.

Results: We found that lower sleep spindle density at frontal leads during non-REM stage 3 was associated with worse overnight declarative memory consolidation. We also found that patients who showed less temporal clustering of spindles exhibited worse declarative memory consolidation.

Conclusions: These results suggest alterations to sleep spindles, which are known to be a consequence of Parkinson's disease, might represent a mechanism by which poor sleep leads to worse cognitive function in Parkinson's patients.

Keywords: Parkinson's disease; memory consolidation; sleep, spindles; cognition

Brief summary

Sleep — particularly spindle activity — is critical for memory consolidation, a core cognitive process. Changes to the architecture and oscillations of sleep are well documented in Parkinson's disease (PD) and have been associated with worse overall cognition. However, whether altered sleep plays a causal role in this relationship, by directly interfering with sleep-dependent cognitive processes, or whether it represents a mere epiphenomenon of advancing disease, remains

unknown. Our study is the first to investigate a possible direct relationship between sleep and cognition in PD. We show that sleep spindles and their temporal clustering into 'trains' relate to impairments in overnight declarative memory consolidation in patients. These findings are an important first step towards identifying modifiable sources of cognitive impairment in PD.

Introduction

Disturbed sleep is common in Parkinson's disease [1,2] and has been linked to cognitive dysfunction [3,4]. Recently, there has been growing interest in examining alterations in sleep microarchitecture because specific neural oscillations of sleep have been proposed as potential biomarkers of cognitive state in Parkinson's disease [5–7]. However, the mechanisms linking sleep microarchitecture to cognition in Parkinson's patients remain unclear. In particular, whether altered sleep plays a direct causal role in the cognitive deficits of Parkinson's disease by interfering with sleep-dependent cognitive processes remains unknown.

It has repeatedly been shown that Parkinson's patients have fewer sleep spindles, a type of fast oscillation with a frequency in the range of 11 to 16 Hz that occurs in non-rapid eye movement (NREM) stage 2 and stage 3 sleep [8,9]. This observation stands out because sleep spindles are well-established to play a role in memory consolidation [10]. Research in healthy adults has shown that greater spindle density (the number of spindles per minute of sleep) is associated with better sleep-dependent memory consolidation of both procedural [11,12] and declarative memories [13–15]. Sleep spindles are thought to reflect bursts of thalamo-cortical neuronal activity, which in turn are thought to promote the neuronal plasticity necessary for memory consolidation [16,17]. Additional evidence in support of the role of spindles in memory comes from studies in which sleep was pharmacologically manipulated with zolpidem. The increase in spindle count caused by zolpidem was associated with enhanced next-day memory performance in both healthy adults and individuals with schizophrenia [18,19]. To date, no study has investigated the relationship between sleep microarchitecture changes that occur in Parkinson's disease and specific sleep-dependent cognitive processes. Meanwhile, identifying such a link could provide a potential mechanism to explain the association observed in Parkinson's disease between sleep microarchitecture and overall cognitive function.

The temporal dynamics and clustering of sleep spindles may also be important for memory consolidation. It has recently been shown that some spindles occur in quick succession, a

phenomenon referred to as 'spindle trains' [20]. This temporal clustering has been proposed as another mechanism of sleep-dependent memory consolidation because the repeated occurrence of spindles is believed to reflect repetitive reactivation of the memory engram, hence allowing for re-processing and further consolidation of memories [20]. In young adults, the occurrence of spindles in trains has been associated with better overnight motor memory consolidation [21,22]. In older adults, a similar relationship has been observed for declarative memory consolidation [23].

In the present study we aimed to determine if sleep spindles and their temporal dynamics are associated with overnight declarative memory consolidation in patients with Parkinson's disease. Sleep, and in particular sleep architecture and sleep oscillations, are of interest because they are potentially modifiable and therefore present potential treatment targets [24,25]. Though the relationship between sleep spindles and memory consolidation is well established in healthy and older populations [26,27], there are many changes that occur in PD, such as the early loss of dopaminergic and noradrenergic neurons [28], that could also affect memory consolidation [29–32] and could therefore interfere with the relationship between sleep spindles and memory consolidation. Furthermore, given that alterations to sleep spindle have been shown to predict future cognitive decline [33], identifying a relationship between spindles and a specific sleep-dependent cognitive process such as memory consolidation could provide some preliminary insights as to whether altered sleep contributes to the development of cognitive dysfunction in Parkinson's disease as opposed to being a mere marker of disease progression and severity. We measured overnight sleep microarchitecture and overnight declarative memory consolidation using a standard verbal paired-associates memory task in a group of patients with Parkinson's disease. We hypothesized that lower sleep spindle density and lesser clustering of spindles into trains during NREM sleep would be associated with worse overnight memory consolidation in Parkinson's patients. Our results were broadly consistent with these hypotheses but the relationships we observed between sleep spindles and declarative memory consolidation were specific to NREM-3. By demonstrating a relationship between sleep microarchitecture and performance on a sleep-dependent cognitive process in Parkinson's disease, our results raise the possibility that impaired sleep could play a role in cognitive function more broadly in Parkinson's patients by interfering with specific sleep-dependent cognitive processes, though prospective studies will be required to examine this.

Materials and methods

Participants

Forty-five patients with Parkinson's disease were recruited from the McGill University Hospital Centre and from the Quebec Parkinson Network, a registry of patients interested in research. All participants had a diagnosis of Parkinson's disease confirmed by a neurologist and were taking dopaminergic medications for their PD symptoms. Importantly, none were taking overnight dopaminergic medications. Participants were recruited as part of a larger multi-night interventional study on the effects of overnight levodopa on obstructive sleep apnea, the results of which will be published separately. Participants in the present study were tested only on the initial overnight screening visit of that study (i.e., before the initiation of the intervention), which served the purpose of identifying patients with obstructive sleep apnea for enrolment in the interventional study. Because our study took place on the screening visit, our sample included patients with and without obstructive sleep apnea (65% with moderate or severe OSA), which is consistent with previously reported estimates of OSA in Parkinson's disease [34]. None had major health issues, neurological disorders other than Parkinson's disease or active psychiatric disorders. Six participants had missing memory recall data and two had an EEG recording of bad quality based on visual inspection. Thirty-seven participants were thus retained for the analyses. Two participants were excluded because they were identified as outliers based on their memory performance before sleep (recalled 0 and 3 out of 25 words). The final sample consisted of thirty-five participants. Demographic and clinical characteristics of the final sample are presented in Table 1. All participants provided written consent and were compensated for their participation. The study was approved by the McGill University Health Centre Research Ethics Board and all procedures were performed in accordance with the appropriate institutional guidelines.

Overall procedure

All participants completed questionnaires about their clinical history and underwent a Unified Parkinson Disease Rating Scale – Part III motor assessment [35] and a Montreal Cognitive Assessment (MoCA) during the evening portion of their overnight visit. As detailed below, memory testing took place in the evening and the following morning. Patients were instructed to take their usual dopaminergic medications 45-60 minutes prior to both sessions in order to control for the effects of dopamine medication state on recall. The evening session was scheduled between

5 and 6 PM to ensure that the dopaminergic medications were taken no later than 5 PM so that they could reasonably be considered in the off medication state once the overnight recording started around 10 PM.

Table 1 Demographic and clinical characteristics

N=35	Mean (range)
Age	65.5 (47 - 81)
Sex, % men	65.7%
Education (years)	15.8 (9 - 22)
MoCA[a]	26 (18 - 30)
Digit span (total) [b]	11.5 (8 - 16)
UPDRS-III[c]	23.3 (7 – 51)
Disease duration	3.4 (0 – 26)
LEED[d], mg	492.7 (200 – 11,641)
Apnea-Hypopnea index	23.6 (2.3 – 70.5)

Table shows mean with the range in parantheses.
[a] MoCA = Montreal Cognitive Assessment
[b] Digit span total represents the sum of forward and backward digit span
[c] UPDRS-III = Unified Parkinson's Disease Rating Scale Part III, tested ON dopamine medication
[d] Levodopa equivalent dosing; includes levodopa, dopamine agonists, amantadine, monoamine oxidase inhibitors and catechol-O-methyl transferase inhibitors

Memory consolidation task

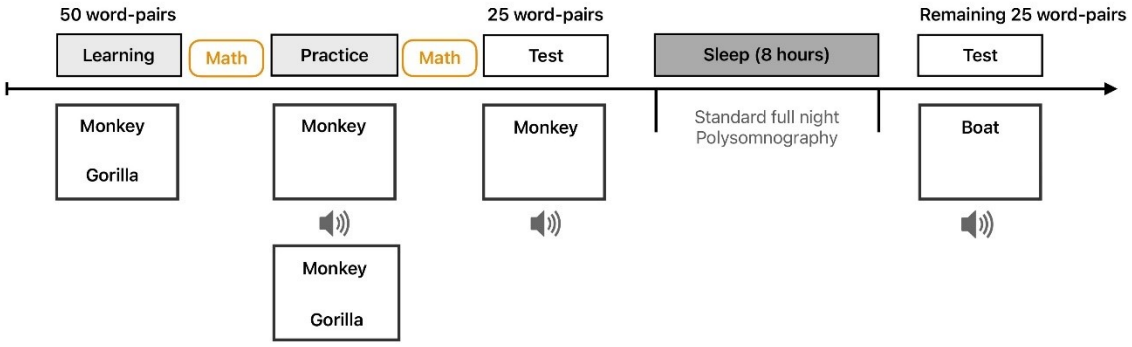

Figure 1. Schematic of experimental design. (**A**) Participants learned 50 semantically related word-pairs in the evening. During the initial learning block, all 50 word-pairs were presented one at a time and participants were instructed to remember them. This was followed by a practice block where one word was presented and participants had to verbally recall its associate. After a tone indicated the end of the recall period, the correct word was presented on screen. The practice block was immediately followed by the pre-

sleep recall test where memory for one half of the pairs (randomly selected) was tested. Participants completed simple arithmetic problems for 1 minute between each block. The post-sleep recall test took place the following morning and memory for the remaining 25 pairs was tested. Overnight polysomnography included 6 EEG leads (F3, F4, C3, C4, O1, O2) referenced to the contralateral mastoid, bilateral electrooculogram, submental electromyography.

We used a computerized verbal paired-associates learning task adapted from previous studies investigating sleep-dependent memory consolidation [13,36,37]. The task consisted of a learning and a practice block, followed by a pre-sleep and a post-sleep memory recall test (**Figure 1**). Stimuli consisted of 50 pairs of semantically related words (e.g. friend-loyalty; painting-gallery). A French word list was created by translating the English list and was reviewed by a bilingual (native French and English) speaker to qualitatively ensure that no major differences existed in the perceived frequency and difficulty of the words. In the learning block, each word pair was presented on screen for 4 seconds in a random order. In the practice block, the first word of each pair was presented on screen and participants had 3.5 seconds to verbally recall its associate. Following a tone that announced the end of the recall period the correct answer was presented on the screen for 4 seconds. The practice block was immediately followed by a pre-sleep memory recall test where memory for only one half of the word pairs (25 randomly selected pairs) was tested in the same manner, except that the correct answer was not displayed. To prevent active rehearsing, participants were given simple arithmetic problems to solve for 1 minute between blocks. All testing in the evening occurred on average 3:59 hours (SD=37.8 minutes) before sleep. Memory for the remaining half of the word pairs was tested the following morning around 7am. Participants were tested in their first language, either French (n=22) or English (n=13). As age, disease duration, MoCA and memory recall performance did not differ between the two language groups, we conducted all analyses on the full sample. We measured memory consolidation by calculating the overnight relative change in memory performance (i.e., (morning performance – night performance)/night performance).

Overnight polysomnography

The polysomnography montage consisted of 6 EEG leads (F3, F4, C3, C4, O1, O2), following the 10-20 system and referenced to the contralateral mastoid, a bilateral electrooculogram (EOG), and submental electromyography (EMG). Respiratory inductance plethysmography was used to

determine thoracoabdominal motion, and a nasal pressure and oronasal thermistor were used to determine airflow. Signals were recorded using the Polysmith software (Nihon Kohden, Irvin, USA), with a sampling frequency of 200Hz. Sleep stages were visually scored on 30-second epochs following the American Academy of Sleep Medicine (AASM) criteria [38]. The recording night (i.e., lights were turned off and patients were ready to sleep) started on average at 10:23 PM (SD = ±34 minutes) and finished at 6:00 AM (SD= ±25 minutes). PSG outcomes of interest included total sleep time, sleep efficiency, wake-after sleep onset (WASO) and percentage of time spent in each sleep stage. The scoring of sleep apneas and hypopneas was done according to standard AASM criteria [38]. The apnea-hypopnea index was measured as the average number of apneas or hypopneas within an hour of sleep.

Detection of sleep spindles and trains of spindles

The detection of sleep spindles was performed on all EEG leads (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1) during NREM epochs free of artefacts. Artefacts were first detected using an automatic algorithm and, following visual inspection, were rejected from analyses. A band pass filter of 11.1 Hz to 14.9 Hz was applied using a linear phase finite impulse response (FIR) filter (3dB at 11.1 and 14.9 Hz) and the signal was forward and reverse filtered to ensure zero phase distortion and to double the filter order. The root mean square (RMS) of the resulting filtered signal was calculated using a 0.25 second time window and thresholded at the 95th percentile. If at least two consecutive RMS points surpassed the duration threshold of 0.5 seconds, a spindle was detected. Our main variables of interest were sleep spindle density (count per minute), amplitude (μV) and frequency (Hz), as these measures have previously been associated with cognition in patients with Parkinson's disease [5,6].

Spindle trains were counted at each lead on artefact-free periods of sleep and consisted of a minimum of two sleep spindles occurring within 6 seconds [20]. As we found no significant differences between spindle density or spindle trains between the hemispheres, we averaged the results of the left and right leads together. For spindle trains, we computed three measures: i) proportion of spindles occurring as part of a train, ii) density of spindles occurring as part of a train (i.e., number of spindles part of a train/minutes in sleep stage of interest), and iii) density of spindles occurring outside a train.

Statistical analyses

To measure the relationship between spindle characteristics and memory consolidation, we computed Pearson's correlations between each spindle characteristic and overnight change in memory and did this separately for frontal and central leads and for NREM-2 and NREM-3. We present the p-values for the significant associations between spindles and memory consolidation, adjusted for four comparisons (i.e., Leads [Frontal, Central] x Sleep stage [NREM-2, NREM-3]) using the Holm-Bonferroni method. Analyses stratified on allegiance to a train (e.g., density of spindles inside trains vs. density of spindles outside trains) were conducted only for frontal leads during NREM-3 based on the findings in the first set of analyses, and thus were adjusted for two comparisons (see Table S1). We additionally calculated bayes factors to provide an estimate of the evidence in favor of the alternative hypothesis over the null hypothesis for our main results using the BayesFactor package in R [39]. A Bayes factor (BF) between 1 and 3 suggests anecdotal evidence for the alternative hypothesis H_1, factors between 3 and 10 suggest substantial evidence for H_1 and factors between 10 and 30 suggest strong evidence for H_1. All analyses were conducted in R version 4.0.5 and RStudio version 1.4.1106.

Results

Table 1I Memory performance and polysomnography

N=35	Mean (range)
Memory performance	
Words recalled at night, %	57.3 (24 – 88)
Words recalled in the morning, %	35.5 (0 – 72)
Overnight change in memory (absolute)	-5.4 (-12 - -1)
General sleep measures	
Total sleep time, min	300.5 (118.5 – 423.5)
Sleep efficiency, %	75.7 (43.3 – 95.7)
NREM 1, %	17.4 (2.4 – 43.1)
NREM 2, %	60.8 (34.8 – 86.4)
NREM 3, %	8.4 (0 – 26.6)
REM, %	13.3 (0.1 – 31.8)
Apnea-Hypopnea index	23.6 (2.3 – 70.5)
Spindle characteristics	
Density (NREM 2)	2.96 (1.42 – 3.85)
Density (NREM 3)	2.35 (0.26 – 6.69)
Amplitude (NREM 2)	23.9 uV (12.9 – 37.1)
Amplitude (NREM 3)	22.1 uV (12.7 – 34.0)
Frequency (NREM 2)	12.5 Hz (12.0 – 13.1)
Frequency (NREM 3)	12.3 Hz (11.8 – 13.0)

Proportion of spindles in train (NREM 2)	0.51 (0.35 – 0.73)
Proportion of spindles in train (NREM 3)	0.39 (0 – 0.72)

Table shows mean with the range in parentheses.
NREM = Non-rapid eye movement
REM = Rapid eye movement
Words recalled at night and in the morning denote the number of words recalled out of 25, in percentage. Overnight change in memory denotes the difference between the number of words recalled in the morning compared to the night.

Relationship between spindle density and memory consolidation

The average overnight relative change in memory was -0.41 (SD=0.0023, range -0.0007 to 1) indicating that, as expected, participants correctly recalled fewer words in the morning (mean=8.8 words, SD=4.7) than at night (mean=14.3 words, SD=4.1). We found a significant relationship between spindle density measured in frontal leads during NREM-3 and the overnight relative change in memory such that a higher spindle density was associated with less reduction in memory overnight (R=0.46, p=0.006, p_{adj}=0.024, Bayes $Factor_{10}$=9.8), but not for spindles measured at central leads, nor for spindles measured during NREM-2 (Central NREM2: R=-0.04, p=0.82, BF_{10}=0.81; Central NREM-3; R=0.2, p=0.27, BF_{10}= 0.64; **Figure 2** and **Supplementary Table 1**). Because the specificity of the effect to NREM-3 sleep and to the frontal leads was somewhat unexpected we ran additional analyses to examine whether significant differences between frontal and central leads in NREM-2 and NREM-3 existed (such as total spindle count, spindle density, artefact-free periods) that could potentially explain this specificity. Overall, no significant differences were found. These analyses are presented in the Supplement and in **Supplementary Figure S1**.

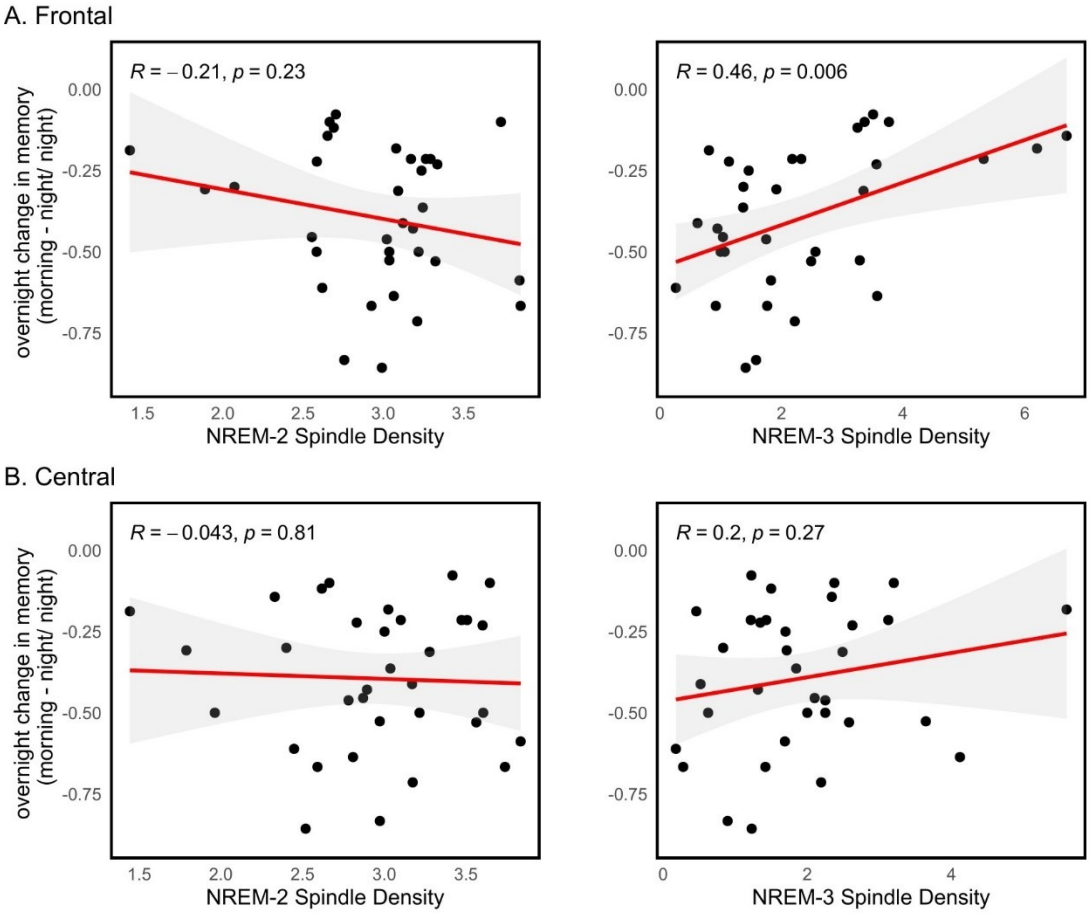

Figure 2. Relationship between sleep spindle density and memory consolidation. Spindle density is shown for A) frontal and B) central leads during both NREM-2 and NREM-3 sleep in association with the overnight relative change in memory, where negative values represent worse memory performance in the morning than at night. Higher density (# spindles/min of sleep) of frontal sleep spindles in NREM-3 was associated with less overnight forgetting (R=0.46, p=0.006). Red line denotes the regression line, and shaded areas represent the 95% confidence interval.

Relationship between spindle trains and memory consolidation

Because of prior evidence suggesting a role for the temporal clustering of spindles in memory consolidation [20,22,23], we examined the relationship between spindle trains and overnight memory change. We found that a higher proportion of spindles occurring in trains (as opposed to outside of trains) in NREM-3 at frontal leads was associated with less overnight reduction in memory performance (R=0.46, p=0.0057, p_{adj}=0.02, BF_{10}=10.13; Figure 3C). This effect was again specific to frontal spindles occurring in NREM-3 sleep. There were no statistically significant associations between spindle trains (neither number of trains nor proportion of spindles in trains) during

NREM-2 and the overnight change in memory (Number of trains: R=-0.19, p=0.26; Proportion of spindles in trains: R=-0.23, p=0.17; BF ranging from 0.47 to 0.65; see Table S1). In addition, we separately computed spindle density for spindles occurring as part of a spindle train and for spindles occurring independent of a train. We found that higher density of spindles occurring *inside* a train was associated with less overnight reduction in memory performance (R=0.52, p=0.002, p_{adj}=0.004, BF_{10}=27.9; Figure 3A), whereas there was no statistically significant relationship between density of spindles occurring *outside* of trains and overnight memory (R=0.2, p=0.2, BF_{10}=0.7; Figure 3B).

We also measured the absolute number of trains that occurred in NREM-2 and NREM-3, but the results did not show any significant association with overnight memory change (Frontal leads in NREM-3: R=-0.05, p=0.8, BF_{10}=0.4; Figure 3D. Frontal leads in NREM-2: R=-0.16, p=0.39, BF10=0.5; see Table S1). Finally, we compared the characteristics of spindles occurring inside trains versus those occurring outside trains and found no difference with regards to the amplitude and frequency of the spindles (amplitude: t=-0.09, p=0.92; frequency: t=-0.76, p=0.44). However, we found a trend for the duration of the spindles, such that spindles inside trains were longer than spindles outside trains (duration: t=-1.85, p=0.07). Overall, these results suggest that the clustering of spindles into trains is important for the overnight consolidation of declarative memory and this effect does not seem to depend on differences in the characteristics of the spindles.

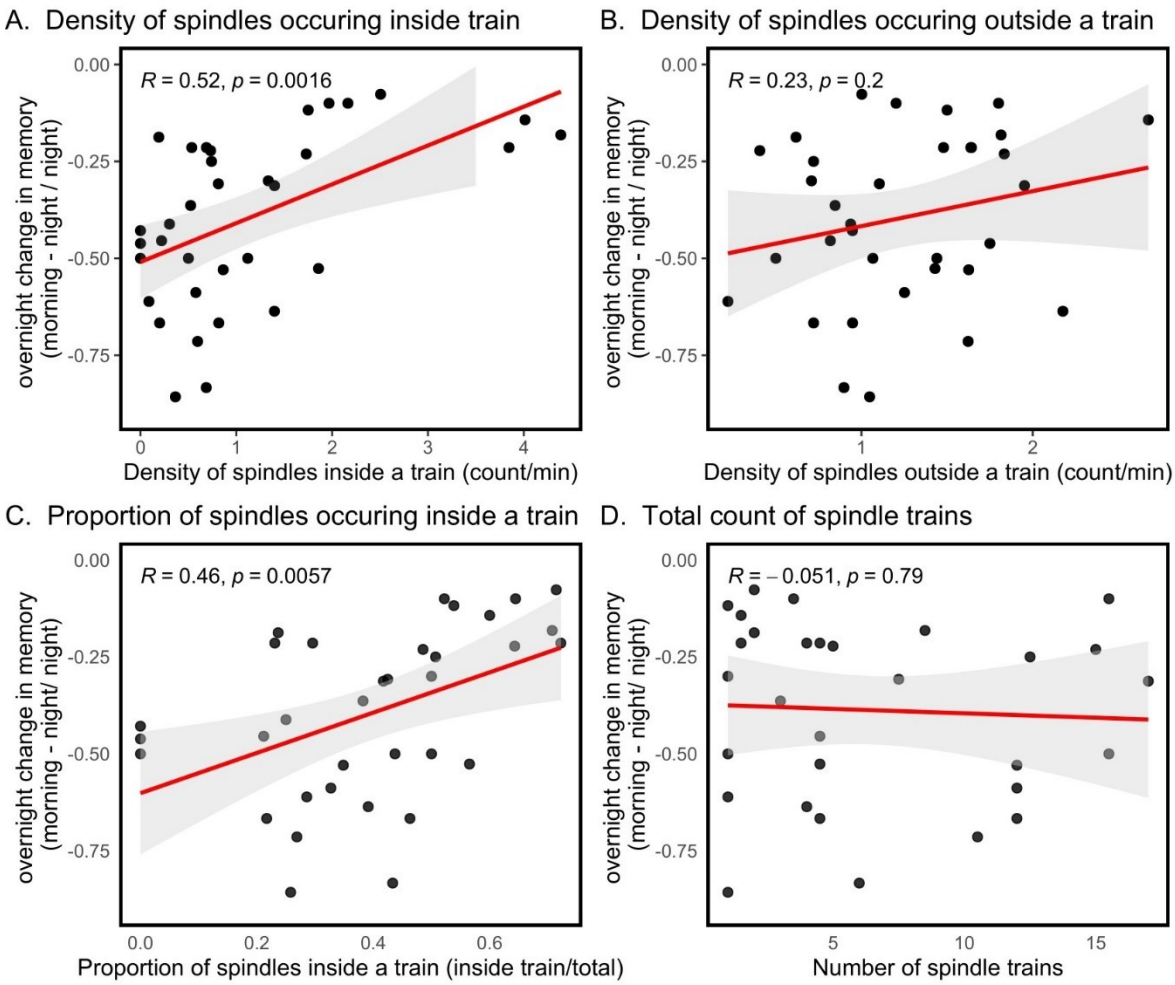

Figure 3. Relationship between memory consolidation and clustering of spindles in NREM-3 at frontal leads (A) Relationship between density of spindles occurring inside trains (count/min) and change in memory overnight, where negative values indicate worse performance in the morning than at night. Increased density of spindles occurring inside trains was associated with less reduction in memory overnight (R=0.52, p = 0.001) **(B)** Density of spindles occurring outside of trains was not associated with the overnight change in memory. **(C)** Relationship between proportion of spindles occurring inside trains (relative to the total number of spindles) and change in memory overnight. A higher proportion of spindles occurring inside trains was associated with less reduction in memory overnight (R=0.46, p=0.005). **(D)** Total train count was not associated with change in memory overnight. Red lines denote regression lines and shaded areas denote the 95% confidence intervals.

Relationship between general measures of healthy sleep and memory consolidation

To determine if the relationships we found between spindle density and spindle trains and memory consolidation were specific to spindles or merely a reflection of overall quality of sleep, we also computed standard measures of sleep architecture and related them to memory consolidation. As expected, we did not find statistically significant associations between memory consolidation and percentage of time spent in each sleep stage (N1%: R=0.17, p=0.33; N2%: R=-0.04, p=0.79 ; N3%: R=-0.16, p=0.36 ; REM%: R=0.04, p=0.81), number of minutes spent in each sleep stage (N1: R=0.02, p=0.87, N2: R=-0.05, p=0.74, N3: R=-0.18, p=0.29, REM: R=0.008, p=0.96), total sleep time (R=-0.06, p=0.74), and sleep efficiency (R=0.03, p=0.86). Because obstructive sleep apnea is common in Parkinson's disease and is associated with cognitive performance [4], we also computed two standard metrics of obstructive sleep apnea. Neither the apnea-hypopnea index (R=-0.097, p=0.59), which reflects the average number of apneas and hypopneas per hour of sleep, nor the time spent under 90% oxygen saturation (R=-0.27, p=0.18) were associated with overnight memory change.

Relationship between spindle measures and overall cognitive performance

We also wanted to determine if the relationships we found between spindle density and spindle trains and overnight change in memory were specific to memory consolidation (a sleep-dependent cognitive process) or whether these same measures of spindles were also correlated with overall level of cognitive function, as measured by the MoCA. We found that higher frontal spindle density during NREM-3 was associated with higher MoCA scores (R=0.44, p=0.01, BF_{10}=6.5). However, there was not a statistically significant association between the proportion of spindles occurring inside trains and MoCA score (R=0.23, p=0.17, BF_{10}=0.8). Unsurprisingly, higher MoCA scores were associated with less overnight reduction in memory performance (R=0.46, p=0.005, BF_{10}=10.12).

Discussion

Changes in sleep micro-architecture are commonly reported in patients with Parkinson's disease and have been found to be predictive of cognitive decline [5,6,8]. However, whether changes in sleep micro-architecture could contribute to cognitive dysfunction by interfering with sleep-dependent cognitive processes or whether they are merely a marker of more severe disease is unclear. In a group of patients with Parkinson's disease with average disease duration of 3.5 years we measured

overnight declarative memory consolidation, a cognitive process known to depend on sleep [40]. We recorded overnight sleep EEG with a focus on sleep spindles because these are sleep oscillations known to play a role in memory consolidation [14]. We found that lower spindle density during NREM-3 and lower density and proportion of spindles occurring inside trains of temporally clustered spindles were associated with worse overnight declarative memory consolidation. In contrast, standard measures of sleep macro-architecture (i.e., general measures of sleep health) were not associated with memory consolidation. These findings suggest that reduced spindles, known to be a feature of sleep in Parkinson's patients, and in particular, reduced clustering of spindles into trains, may play a role in the cognitive deficits observed in Parkinson's patients, and thus advance our understanding of the importance of preserved sleep architecture for cognition in Parkinson's disease.

Our results are broadly consistent with findings in healthy younger and older adults showing that higher spindle density is associated with better overnight preservation of memory [11–13,15,41]. We additionally found that greater clustering of spindles into trains was associated with better consolidation in Parkinson's patients, which is also consistent with recent work in young and older adults [20–23]. One proposed mechanism for the relationship between spindles and memory consolidation is that spindles could facilitate the reactivation of a memory engram and the integration of a memory trace into relevant brain networks during sleep [10,16,42–44]. In addition to the potential importance of the temporal organization of spindles for information processing, some evidence suggests that spindles occurring inside trains could have certain characteristics, such as higher amplitude and longer duration, that reflect a process beneficial for memory consolidation[21,23]. In our sample, however, the amplitude and duration of spindles occurring inside trains did not differ significantly from those of spindles occurring outside trains. This suggests that, even in the absence of higher amplitudes and longer duration, the temporal organization of spindles may play a role in the consolidation of a memory trace. Overall, by showing that not only a higher density of spindles, but more specifically, a higher density of temporally clustered spindles, are associated with better overnight memory consolidation, our results provide the first evidence of a possible mechanism directly linking sleep alterations to mnemonic cognitive function in Parkinson's patients.

Our study did not include a sample of healthy older adults for comparison, and therefore our results cannot speak to the specificity of these effects in Parkinson's patients. Indeed, aging has also been associated with a reduction in spindle density and this reduction has been associated with impaired memory consolidation [45–47]. However, in Parkinson's disease, the reduction in sleep spindle density is more pronounced than in healthy older adults, hence suggesting that our findings are particularly relevant to Parkinson's patients [6,8,9,48]. Reduced spindle density in Parkinson's patients has also been shown to be predictive of future cognitive decline, further highlighting the possible importance of considering the role of altered sleep spindles in the development of cognitive dysfunction in PD. Much less is known about aging effects on the temporal clustering of spindles. One study found that the proportion of clustered spindles and the length of train of clustered spindles decreased with age, and that shorter trains were associated with worse declarative memory consolidation [23]. Our study is the first to report on sleep spindle trains in Parkinson's disease, therefore it remains unknown if the effect of Parkinson's disease on spindle trains is similar to that of the disease on spindle density, i.e. an enhancement of age-related effects. Interestingly, animal studies have shown that noradrenergic activity from the locus coeruleus, a structure known to be affected by neurodegeneration early in Parkinson's disease [49], modulates the clustering of spindles into trains [50,51], suggesting that this clustering might be disproportionately affected by Parkinson's disease. Though future work comparing Parkinson's patients to older adults is necessary, taken together, our results raise the possibility that the relationship between spindle trains and memory consolidation might be especially relevant to consider in Parkinson's disease.

We found that higher spindle density was associated with better consolidation during NREM-3 but not NREM-2. Previous findings examining the relationship between spindles and memory consolidation have been inconsistent on this point: a relationship has been found for spindles in NREM-2 [15] as well as NREM-3 [52], but most studies seem to collapse across NREM-2 and NREM-3 [12,17,37,46,53], hence leaving it unclear whether the associations between spindle density and memory are specific to a particular stage of sleep. It is also unknown whether the functional role of spindles differs in NREM-2 and NREM-3, and whether this has implications for memory consolidation. One possibility is that different types of memory are preferentially consolidated during different stages of sleep. In keeping with our findings, declarative memory consolidation, as measured using tasks similar to ours, has primarily been reported in association with NREM-3 oscillations, and in particular, in association with the coupling that occurs between spindles and

slow waves [19,54]. In Parkinson's disease, most research has focused on deficits in procedural memory consolidation, but even these deficits have not been measured in association with alterations in sleep micro-architecture [55,56]. Whether our findings linking sleep alterations to declarative memory consolidation would translate to the domain of procedural memory consolidation is an important open question given the relevance of motor learning to the disease and given the potentially modifiable nature of these sleep alterations.

We also found that the relationship of spindle density and spindle trains to overnight declarative memory consolidation was specific to spindles measured at the frontal leads, which is consistent with previous studies in younger adults [37,53]. Two studies that measured both fast (13 – 15 Hz) and slow (11-13Hz) spindles found that the relationship to memory consolidation was specific to slow spindles [37,53]. In our sample, the majority of spindles detected (at both central and frontal leads) would be classified as slow spindles (68%, refer to **Table S2**). Although evidence for distinct functional roles for fast and slow spindles is mixed [23,57], the fact that the majority of spindles in our sample were slow spindles could explain why the association we observed with declarative memory consolidation was specific to spindles measures at frontal leads, because spindles measured at this location are predominantly slow spindles [58].

We also found that better overall cognitive function, as measured with the MoCA, was associated with increased frontal sleep spindle density during NREM-3, and that higher MoCA scores were associated with better overnight memory consolidation. Because no previous research has examined the relationship between overnight memory consolidation and more general cognitive function (neither in younger nor in older adults) it is unknown how memory consolidation contributes to more general cognitive function, and whether sleep supports both separately or whether sleep's beneficial effect on consolidation supports more general cognitive function by, for instance, reducing the cognitive resources required to re-learn information. Our study was not designed to address this because our only measure of general cognitive function was the MoCA, which is designed to be a screening tool for cognitive impairment and is not designed to provide a continuous linear measure of cognitive function[59]. Nonetheless, the fact that performance on the MoCA, which combines multiple domains of cognitive function and includes only a test of short-

term memory, was associated with the overnight *change* in memory normalized to baseline (short-term) memory performance is interesting and will require further study.

Though our current study focused specifically on sleep spindles during NREM sleep, other aspects of sleep have been shown to relate to memory consolidation. More time spent in slow-wave sleep[60], as well as increased spectral power in the slow-wave band has been associated with better consolidation[61]. In addition to this, the relationship between slow waves and memory consolidation also seems to depend on their coupling with sleep spindles and other rhythms such as hippocampal sharp-wave ripples[62,63]. In our study, we did not find an association between time spent in slow-wave sleep (i.e., NREM-3) and overnight memory consolidation.

There were several limitations to our study that are important to note. First, our sample of Parkinson's patients included patients with and without obstructive sleep apnea, a sleep disorder that is very common in Parkinson's disease, occurring in up to 60% of patients. In our sample, 65% of participants were considered to have moderate to severe obstructive sleep apnea. Obstructive sleep apnea has been associated with poor cognitive function[4] and it is possible that it could also affect sleep oscillations[34], since obstructive sleep apnea reduces uninterrupted sleep time which could in turn affect spindles and other oscillations. Second, our relatively small sample size prevented us from having the statistical power to address the clinical heterogeneity in Parkinson's disease, and to conduct stratified analyses to examine the contributions of different clinical characteristics such as obstructive sleep apnea and baseline cognitive function, all factors that might be expected to influence the relationship between sleep micro-architecture and memory consolidation. Mood symptoms of Parkinson's disease, such as depression, anxiety and apathy, were not measured in this study but might also affect task performance and sleep. Third, the single-night polysomnography may not provide a reliable assessment of sleep structure. Finally, the cross-sectional study design and the absence of a control group prevent any conclusions about the causal role of sleep in cognition.

In summary, we found that lower sleep spindle density, already known to be reduced in Parkinson's disease to a greater extent than in healthy older adults, and lesser spindle clustering were associated with worse overnight declarative memory consolidation, a specific sleep-dependent cognitive process. This represents an important first step towards delineating the effects of Parkinson's disease-related sleep impairments on cognition in Parkinson's patients. Our results lend support to

the recently observed relationship between abnormal sleep spindles and the risk of developing cognitive impairment, but several questions remain unanswered. First, future work will be required to determine if impaired memory consolidation in itself could represent a mechanism underlying cognitive impairment, by resulting, for instance, in the diversion of cognitive resources towards the repeated encoding of information that would otherwise already be consolidated and remembered. Alternatively, memory consolidation may be but one of many cognitive processes directly affected by reduced spindle density and clustering, all of which could contribute to more global cognitive impairment. These questions are all the more important considering that impaired sleep micro-architecture is highly prevalent in Parkinson's disease and potentially modifiable through both existing pharmacological interventions, and through more recently described non-pharmacological interventions such as closed-loop auditory stimulation during sleep [64].

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Competing interests

The authors declare no competing interests.

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Chapter 4. EEG functional connectivity during NREM sleep is associated with cognitive function in patients with Parkinson's disease and healthy older adults

Preface

In the previous chapter, I demonstrated that sleep spindle density and the temporal clustering of spindles into 'trains' were associated with overnight memory consolidation in PD. These findings are important as they enhance our understanding of the ways by which impaired sleep, specifically altered spindles, may contribute to worse cognition. However, overnight memory consolidation reflects a specific cognitive function that is thought to be directly dependent on sleep. Meanwhile, sleep spindles, as well as other sleep oscillations, have also been shown to correlate with cognitive function more broadly but the mechanisms underlying this association are unclear. Recent evidence suggests that fMRI functional connectivity during discrete oscillations correlates with certain aspects of cognitive function, and preliminary findings suggest a similar relationship between frequency bands on scalp EEG. In this chapter, we aim to investigate if EEG functional connectivity in canonical frequency bands is associated with cognitive function in PD. We focus on NREM-2 and 3 sleep stages given that oscillations during these stages of sleep have been associated with cognitive performance. We also aim to determine whether NREM sleep connectivity is altered in PD compared to older adults. Our findings offer new perspectives on how altered sleep, particularly functional connectivity, may contribute to worse cognition in patients.

Abstract

Changes to sleep are common in Parkinson's disease (PD) and have been associated with worse cognitive performance. Much of this work has focused on either global measures of sleep architecture or on specific oscillations (e.g., sleep spindles). More recently, EEG-derived functional connectivity has also emerged as a possible predictor of cognitive function, but little is known about the degree to which patterns of EEG connectivity during sleep can explain cognitive function in PD. The current study sought to investigate if functional connectivity in canonical frequency bands (i.e., delta, theta, alpha, low sigma, high sigma) was associated with cognitive function in PD. We focused on NREM-2 and 3 stages given that oscillations during these stages of sleep have been associated with cognitive performance.

In NREM-2, we found that PD patients had higher connectivity in delta and theta frequency bands and lower connectivity in low and high sigma bands compared to older adults. A similar pattern was observed in NREM-3, where PD patients had higher connectivity in the delta frequency band and lower connectivity in low and high sigma frequency bands. Multivariate analyses revealed distinct patterns of connectivity in NREM-2 and in NREM-3 that significantly explained cognitive performance across PD patients and older adults. In NREM-2, we identified a pattern of functional connectivity reflecting higher connectivity in delta, theta and alpha and lower connectivity in low and high sigma, and this was associated with worse cognitive performance across domains. Post-hoc analyses revealed that this pattern of connectivity was predominantly expressed in PD patients. In NREM-3, we identified a pattern of functional connectivity reflecting higher connectivity across all frequency bands associated with both better and worse performance on different cognitive tests. This pattern was similarly expressed across both patients and older adults. These findings suggest that NREM sleep functional connectivity differentially explains cognition in PD and older adults, reflecting both PD-specific associations with worse cognition and age-related changes in connectivity. These results offer new perspectives on how altered sleep, particularly functional connectivity, may contribute to worse cognition in patients.

Introduction

Sleep is a dynamic state during which the brain transitions between patterns of distinct oscillatory activity throughout the night (Carskadon & Dement, 2005). In patients with Parkinson's disease, sleep is disturbed (Zhang et al., 2020) and changes to the oscillatory activity that occurs during non-REM sleep have been shown to be associated with cognition (Memon et al., 2023; Wood et al., 2021). However, the mechanisms underlying the association between non-REM oscillatory activity and cognitive function are unknown (Latreille et al., 2015). Sleep oscillations are known to directly support specific aspects of sleep-dependent cognitive processing, most notably, memory consolidation, i.e. the strengthening of memory that occurs overnight (Diekelmann & Born, 2010; Rasch & Born, 2013), and this may provide some clues. The relationship between sleep oscillations and memory consolidation is thought to be supported by the coordinated recruitment of subcortical and cortical brain regions during these oscillations—enabling the inter-regional dialogue necessary for consolidation to occur (Gais & Born, 2004). Whether the increase in coordinated brain activity during non-REM sleep oscillations similarly contributes to broader cognitive function in Parkinson's disease is not known.

In the descent to sleep, it has been shown that there is a transient increase in BOLD connectivity during NREM-2 (Larson-Prior et al., 2009; Spoormaker et al., 2010) followed by a breakdown of cortico-cortical connectivity in NREM- 3 (Boly et al., 2012; Horovitz et al., 2009; Spoormaker et al., 2011). Whether these dynamic changes in connectivity during NREM sleep stages have implications for cognitive function is not known. However, these findings highlight the need to study the stages of NREM sleep separately, because their distinct patterns of connectivity may differentially influence cognition.

Connectivity during NREM sleep also appears to change with aging. Recent studies have shown that older adults have a reduced capacity to effectively 'dis-connect' during NREM sleep compared to young healthy adults (Bouchard et al., 2019; Daneault et al., 2021). Using sleep functional MRI, which because of its high spatial resolution can provide a measure of connectivity within specific networks, age-related differences in connectivity were demonstrated in sensorimotor, attentional, limbic, frontoparietal, and default-mode networks (Daneault et al., 2021). Using sleep EEG, which because of its high temporal resolution can measure connectivity at multiple frequency bands, age-related differences in connectivity were found to be most

significant at slower frequencies (i.e., delta and theta frequency bands) (Bouchard et al., 2019). Furthermore, in contrast to the progressive reduction in connectivity observed in younger adults as sleep deepens from NREM-2 to NREM-3, older adults showed the opposite pattern with higher connectivity during NREM-3. Interestingly, this study also showed that the altered connectivity observed in older adults was associated with cognitive performance. Whether Parkinson's disease causes further changes to connectivity during NREM sleep and whether connectivity is associated with cognitive performance in Parkinson's patients is unknown. Meanwhile, because oscillatory activity during sleep is potentially modifiable (Marshall et al., 2006; Ngo et al., 2013), determining whether it relates to cognitive performance in Parkinson's patients could provide a novel therapeutic target for enhancing cognition.

The goals of the current study were (i) to identify whether EEG functional connectivity during NREM sleep is altered in Parkinson's disease compared to controls, and (ii) to determine if NREM sleep connectivity measured at different frequency bands is associated with cognitive performance across different domains of cognition. We hypothesized that patients would show lower connectivity during NREM-2 but higher connectivity during NREM-3 compared to healthy older adults, effectively showing an exaggeration of the effects of age on connectivity (Bouchard et al., 2019). We further hypothesized that these differences would be most marked in the delta and the sigma bands, considering that the oscillations occurring in these frequency bands (i.e., slow waves and spindles, respectively) are known to be affected by Parkinson's disease. As for the relationship between connectivity and cognition, we hypothesized that both the reduced connectivity during NREM-2 and the increased connectivity during NREM-3 (i.e., an inability to 'dis-connect') would be associated with worse cognition.

Method

Participants

Patients with Parkinson's disease (N=61) were recruited from the Hôpital du Sacré-Coeur de Montréal as part of a longitudinal study on sleep and cognitive function in Parkinson's disease (Anang et al., 2014). Healthy older adults (N=35), recruited by word-of-mouth and through newspaper advertisements, were included for baseline comparisons. All participants underwent

one night overnight polysomnography, a complete neuropsychological assessment, and a clinical and neurological exam. Diagnosis of Parkinson's disease was confirmed by a neurologist. Participants were excluded if they had dementia. The study was approved by the ethics committee from the Hôpital du Sacré-Coeur and all participants gave written informed consent prior to participation.

Participants were excluded from further analyses if there was complete absence of REM sleep on their recording (N=1) and if there were significant artefacts for most of the overnight recording on one electrode or more (N=8). The final sample consisted of 52 PD patients and 34 older adults. Demographic, clinical and sleep characteristics of the final sample are presented in

Table 1.

	PD patients (N=52)	**Older adults (N=34)**	**p-value**
Sex (male)	29/52 (56%)	19/34 (56%)	1
Age	65.5	66.1	0.7
MMSE	28.8	29.3	0.02
Disease duration (yrs)	4.1	-	-
UPDRS-III	21.9	-	-
LEED	486.9	-	-
Cognition [a]			
Executive function	-1.22	-0.19	< 0.0001
Memory	0.04	0.6	0.004
Attention	-0.59	0.17	< 0.0001
Language	2.72	4.64	< 0.0001
Visuospatial ability	0.32	0.84	< 0.0001
Sleep Characteristics			
Wake (mins)	114.8	86.5	0.03
Total Sleep (mins)	350.3	380.1	0.07
NREM-1 (mins)	66.9	62.4	0.5
NREM-2 (mins)	202.6	229.2	0.03
NREM-3 (mins)	21.2	25.1	0.5
REM, mins	59.4	63.5	0.45
Apnea-Hypopnea Index	3.58	5.66	0.08
RBD	24/52 (46%)	-	-

Table 1. Demographic, sleep and clinical characteristics. Table shows means. [a]Composite scores for each cognitive domain were calculated as the average of the performance for the following tests: Trail Making Test Part B (time), semantic verbal fluency, Stroop Colour Word Test Part 4-3 (time and error) for executive function; Rey Auditory Verbal Learning Test (sum of trials 1 to 5, list B, immediate and delayed

recalls, and recognition) for memory; Digit Span from the Wechsler Adult Intelligence Scale Version III (WAIS-III), Trail Making Test Part A (time), Stroop Colour Word Test Part 3-2 (time and error) for Attention; Phonemic fluency for Language; and Rey Complex Figure Test, and the Block Design from the WAIS-III for Visuospatial ability. MMSE = Mini Mental State Examination, UPDRS-III = Unified Parkinson's Disease Rating Scale PART III (tested on dopamine medication), LEED = levodopa equivalent dosing (includes levodopa, dopamine agonists, amantadine, monoamine oxidase inhibitors, and catechol-*O*-methyl transferase inhibitors), NREM = non-rapid-eye-movement sleep, RBD = REM-sleep behaviour disorder.

Cognitive testing

All participants underwent a comprehensive neuropsychological examination of five cognitive domains. Executive function was assessed with the Trail Making Test Part B (time), semantic verbal fluency, and Stroop Colour Word Test Part 4-3 (time and error). Attention was assessed with the Digit Span from the Wechsler Adult Intelligence Scale (WAIS), Trail Making Test Part A (time), and Stroop Colour Word Test Part 3-2 (time and error). Language was assessed with phonemic verbal fluency. Memory was assessed with the Rey Auditory Verbal Learning Test (sum of trials 1 to 5, list B, immediate and delayed recalls, and recognition). Visuospatial function was assessed with the copy of the Rey Complex Figure Test, and the Block Design from the WAIS. All neuropsychological tests were z-scored to published local norms in healthy adults, previously published (Gagnon et al., 2009).

Overnight Polysomnography

The polysomnography montage consisted of 10 EEG leads (F3, F4, C3, C4, P3, P4, T3, T4, O1, O2) referenced to the contralateral mastoid, a bilateral electrooculogram, and submental electromyography. A nasal canula or an oronasal thermistor were used to monitor airflow. Electrodes on the left and right anterior tibialis muscles recorded leg movements. Signals were recorded using a Grass polygraph (amplifier gain 10 000; bandpass 0.3-100Hz) and were then digitized at a sampling rate of 256 Hz using Harmonie software (Stellate Systems). Sleep stages were visually scored on 30-s epochs according to the American Academy of Sleep Medicine criteria (Berry et al., 2015). In Parkinson's disease patients, REM sleep was scored according to the Lapierre and Montplaisir method (Lapierre and Montplaisir, 1992; Montplaisir et al., 2010).

Polysomnographic outcomes of interest included total sleep time, sleep efficiency, wake after sleep-onset (WASO), percentage and time spent in each sleep stage. The scoring of sleep apneas and hypopneas was done according to standard AASM criteria, and the apnea-hypopnea index (AHI) was measured as the average number of apneas or hypopneas within an hour of sleep.

Coherence Analysis

We used coherence to measure the functional connectivity between electrodes across the scalp. Coherence is a measure of the linear relationship between the spectral modes of two signals in the frequency domain, reflecting the degree to which the signal between two electrodes is coupled at a given frequency (Nolte et al., 2004; Nunez et al., 1997). It is a value between 0 and 1 because it is normalized to the spectral power of each electrode and reflects the coupling between the phases of both electrodes. On scalp EEG, brain activity is recorded far from the underlying neuronal generator, as such the scalp acts as a conducting medium. This is referred to as volume conduction and may blur the signal by reflecting a composite of multiple neuronal sources. Coherence is a complex number composed of a real and imaginary part, with the real part representing connectivity at a zero-phase lag. Volume conduction happens instantaneously so we can mitigate its effect by only using the imaginary part of coherence. Imaginary coherence was averaged for each frequency band of interest: delta (0.5 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), low sigma (12 – 14 Hz) and high sigma (14 – 16 Hz). For a given subject and a given pair of electrodes, imaginary coherence was averaged across all epochs for each frequency band, resulting in one value per electrode pair for a given frequency band per subject which was Z-transformed. This was done for NREM-2 and NREM-3.

Group differences in connectivity

To assess differences in functional connectivity between patients with Parkinson's disease and healthy controls, we compared the Z-transformed mean for a given pair of electrodes between groups and computed a Welch t-statistic. This was done for each frequency band and for NREM 2 and 3 separately. Due to the high number of statistical tests undertaken, we further corrected for the Family-wise Error Rate by setting a False Detection Rate threshold (FDR) for each frequency band, resulting in a total of five thresholds. To select our FDR thresholds, we created a null hypothesis from our data using permutations (5000 iterations). To create this null hypothesis, we randomly re-assigned group membership to each participant, either PD or controls, and computed

a Welch T-statistic between groups for each electrode pair. The maximum t-statistic across all pairs was retained. This was done 1000 times, allowing us to build a distribution of t-statistic under the null hypothesis. Values which corresponded to an alpha level of 0.05 were retained as the FDR threshold. This was done for each frequency band and the threshold was used to select the electrode pairs with an imaginary coherence value considered to be significantly different between groups.

Partial Least Squares

Due to the high dimensionality of functional connectivity data, we opted to used Partial Least Squares (PLS), a multivariate approach which allows us to identify the patterns of functional connectivity best associated with cognition (McIntosh & Lobaugh, 2004; McIntosh & Mišić, 2013). PLS achieves this by identifying sets of mutually orthogonal latent variables that maximize the covariance between two datasets and reflect weighted linear combinations of the original variables. To perform this, we construct a **Y** matrix, where each columns represent a cognitive test, and an **X** matrix, where each columns represent an electrode pair for a given frequency band. The rows of both matrices represent each subject. A singular value decomposition (SVD) was applied to the cross-correlation of the **X** and **Y** matrix, as follows:

$$\mathbf{R} = \mathbf{X}'\mathbf{Y} = \mathbf{USV}'$$

This results in a left singular vector (**U**) which contains the weights for each electrode pair, a right singular vector (**V**) containing the weights for each cognitive test, and a diagonal matrix of singular values (**S**). Each singular value is proportional to the covariance explained by a latent variable, where the $\mathbf{S}_i$ singular value represents the covariance between the $\mathbf{U}_i$ and $\mathbf{V}_i$ pair of vectors (i.e., $\mathbf{LV}_i$). Subject-level 'brain scores' were computed by projecting the original connectivity data (**X**) unto the PLS-derived weights stored in the left singular vector (**U**). The same can be done to compute a subject-level 'cognition score', by projecting the original cognition data (**Y**) unto the weights stored in the right singular vector (**V**). We conducted separate PLS models for NREM-2 and another for NREM-3.

Permutations and bootstrapping

Permutations were used to assess the statistical significance of latent variables (5000 permutations), where the original datasets were randomized to create a null hypothesis. PLS is then repeated for each iteration, to create a distribution of singular values under the null hypothesis.

Statistical significance for the singular values of our original PLS are tested against the permuted distribution of singular values under the null hypothesis. We used bootstrap resampling (5000 bootstrap samples) to assess the reliability of the weights for each electrode-pair by frequency band and for each cognitive test (McIntosh & Lobaugh, 2004). The data is resampled with replacement (i.e., observations may be repeated), and a distribution for the weights of each electrode-pair per frequency band and each cognitive test is generated. These distributions are used to estimate the 95% confidence intervals for our weights from the original PLS model. Using the bootstrapped distribution for each weight, we calculated the ratio between each weight and its bootstrap-estimated standard error. This bootstrap ratio (BSR) is equivalent to a z-score, assuming the distribution is normal. BSR were thresholded at 95% confidence interval to identify connections that significantly contributed to the overall EEG connectivity pattern.

Post-hoc and sensitivity analyses

To assess group differences in the expression of the connectivity patterns for each LV and in the correlation strength between connectivity and cognition, we performed independent samples t-tests on subject-level brain scores between groups and correlated them with subject-level cognition scores by groups. Given that results from the PLS analyses reveal patterns, we also sought to map these associations more directly to our original data with the aim of isolating specific links between connectivity for a given frequency and individual cognitive tests. To do so, we extracted the coherence value for the edge with the highest bootstrap ratio in each frequency band and correlated it with all the cognitive tests significantly contributing to the cognitive pattern. This was performed for each significant latent variable, and we corrected for multiple comparisons, across five frequency bands, using Bonferroni correction.

As additional sensitivity analyses, we also correlated the brain scores from each significant latent variable with general sleep characteristics and apnea severity, to understand if the patterns of functional EEG connectivity covarying with cognition were driven by other aspects of sleep. In addition to this, considering the low amount of NREM-3 in our sample, we ran a third PLS model only including participants who had spent at least 5 minutes in NREM-3, to ensure results were not confounded.

Results

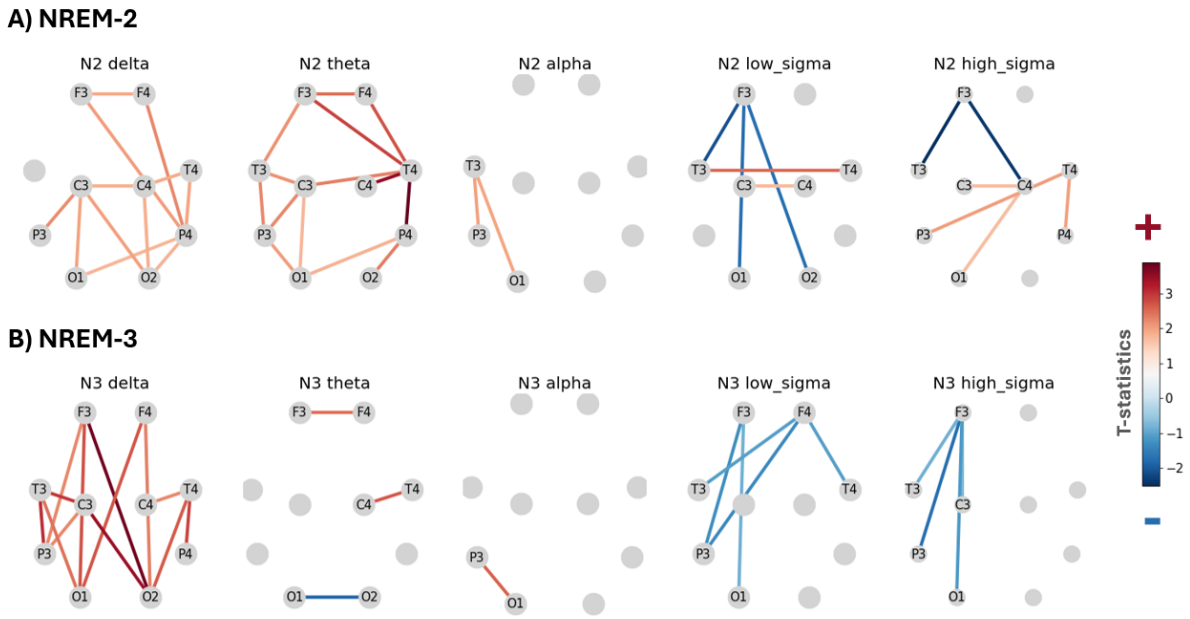

Figure 1. Group differences in functional connectivity between PD patients and controls. The colors of the edges reflect the T-statistic (PD > Controls). The edges shown above are the ones which the t-statistic surpassed the False Detection Threshold obtained through permutations (one threshold per frequency band and per NREM stage).

Group differences in functional connectivity between patients and controls

In NREM-2, compared to older adults, PD patients had higher connectivity in delta and theta frequency bands and lower connectivity in the sigma band (Figure 1). For the delta and theta bands, these differences were observed across the scalp, while for the low and high sigma bands, these differences were observed in the left fronto-temporal leads. Patients also showed higher connectivity between centro-temporal leads in sigma frequencies, and higher connectivity in left temporo-parietal and temporo-occipital leads in the alpha frequency. In NREM-3, a similar pattern of group differences was observed: patients showed higher connectivity in the delta band across the scalp, and lower connectivity in the sigma band at the left frontal, temporal, parietal and occipital leads. Higher connectivity in PD patients was also noted between frontal and right centro-temporal leads in theta, and left parieto-occipital in alpha. We also observed lower connectivity

between occipital leads in theta. Overall these results show a pattern of generally higher connectivity in PD patients at slower frequencies (i.e., delta, theta) and lower connectivity at faster frequencies (i.e., sigma), which is more pronounced on the left.

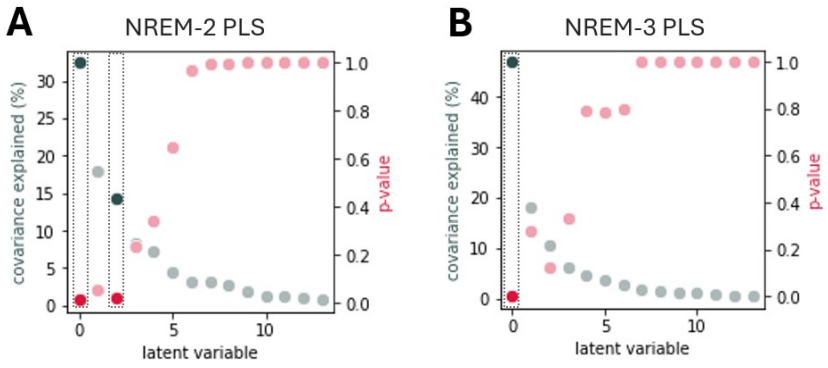

Figure 2. Percentage of covariance explained, and significance of each latent variables identified through PLS. A) In NREM-2, two latent variables reached significance, indicated by dotted rectangles. These correspond to LV1 and LV3. B) In NREM-3, only one latent variable reached significance.

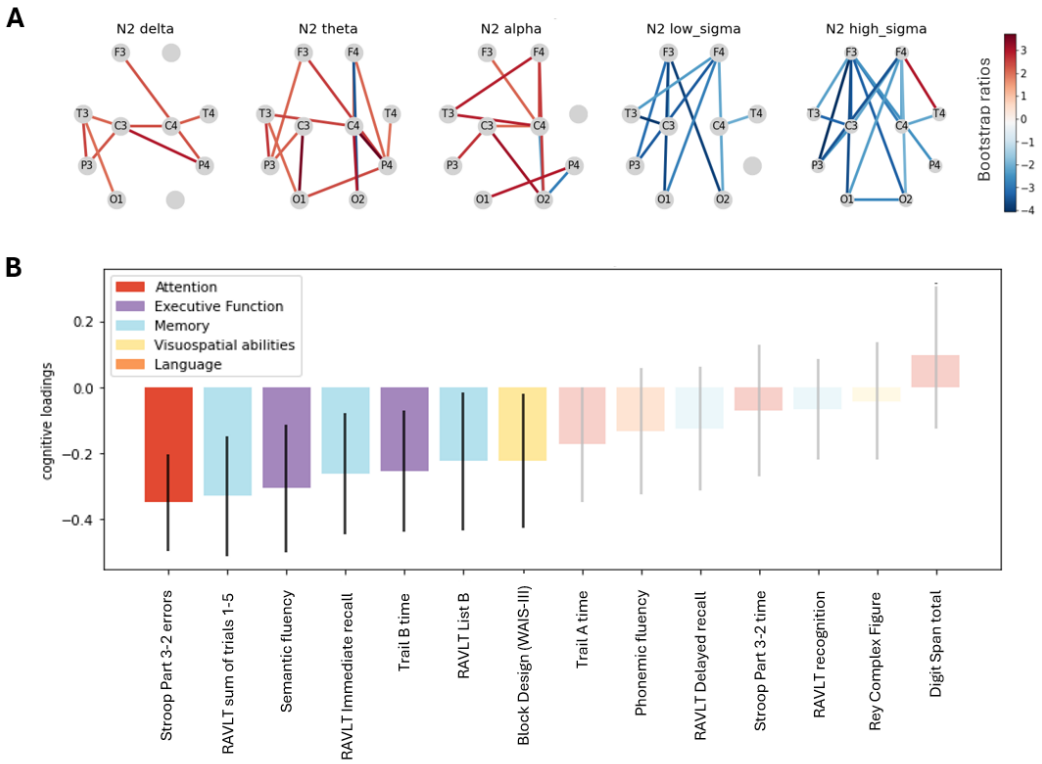

Figure 3. Latent Variable 1 of the NREM-2 PLS (LV1_nrem2). A) Connectivity pattern associated with cognition. Visible edges represent edges with bootstrap ratios thresholded at 2.58 ($p < 0.1$), colors indicate

the values of the edge's bootstrap ratio. B) Cognitive variables and their correlation coefficient with the connectivity pattern. Variables that are not greyed out have a 95% confidence interval that does not cross zero. As such, these significantly contribute to the connectivity pattern.

Connectivity in NREM-2 shows a pattern associated with worse cognition across domains that is predominantly expressed in PD patients

The first latent variable (LV1_nrem2) of the PLS analysis relating connectivity during NREM-2 to cognitive performance explained 32% of the covariance between connectivity and cognition (p=0.07; Figure 2). LV1_nrem2 revealed a pattern of higher connectivity in delta, theta and alpha frequencies, and lower connectivity in low and high sigma bands that was associated with worse performance on measures of attention (Stroop errors), memory (RAVLT total score, immediate recall, and interference list), executive function (semantic fluency and Trails B) and visuospatial ability (WAIS III block design) (Figure 3). Post-hoc analysis comparing the expression of this brain score across groups showed that this pattern of connectivity was predominantly expressed by the PD patients (t=-2.38, p=0.01). LV1_nrem2 highlights a pattern of connectivity associated with worse cognition which may reflect PD-specific components of the relationship between sleep and cognition.

Additional pattern of connectivity identified in NREM-2 shows mixed associations with cognition

The third latent variable (LV3_nrem2) explained 14% of the covariance between connectivity during NREM-2 and cognition (p=0.02; Supplementary Material Figure S1). It revealed a pattern of higher connectivity at theta, alpha, low and high sigma frequency bands and lower connectivity in the delta frequency band that was associated with worse memory performance (RAVLT recognition), better attention (Stroop Errors) and better language ability (phonemic fluency). The expression of the connectivity pattern (i.e., brain score) was not significantly different between PD patients and older adults (t=1.13, p=0.26). In contrast to the LV1_nrem2, LV3_nrem2 might reflect a pattern of connectivity, associated with mixed cognition, that may reflect age-related changes common to both patients and controls.

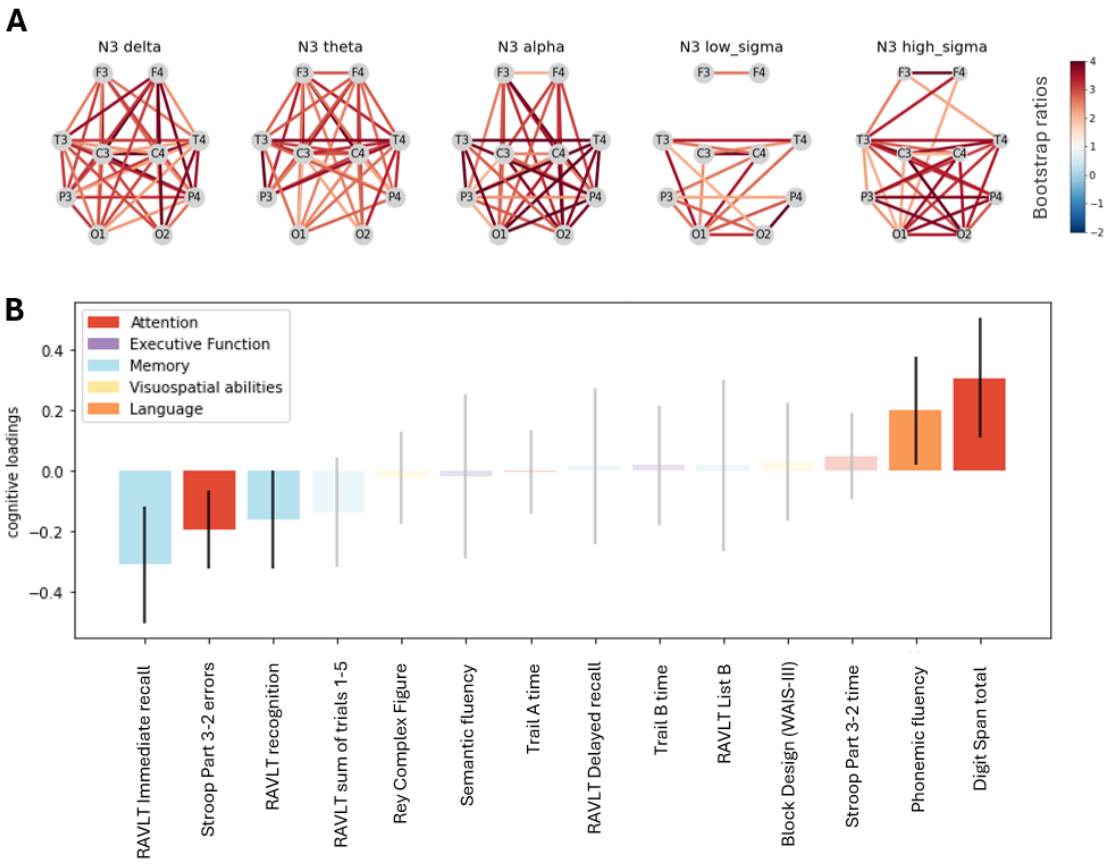

Figure 4. Latent Variable 1 of the NREM-3 PLS (LV1_nrem3). A) Connectivity pattern associated with cognition. Visible edges represent edges with bootstrap ratios thresholded at 2.58 ($p < 0.1$), colors indicate the values of the edge's bootstrap ratio. B) Cognitive variables and their correlation coefficient with the connectivity pattern. Variables that are not greyed out have a 95% confidence interval that does not cross zero. As such, these significantly contribute to the connectivity pattern.

Connectivity in NREM-3 similarly shows mixed associations with cognition and does not differ across patients and controls

We conducted a separate PLS analysis to examine the relationship between connectivity during NREM-3 and cognitive performance. Only the first latent variable (LV1_nrem3), which explained 47% of the covariance, reached statistical significance ($p<0.01$; Figure 2). The identified connectivity pattern showed that higher connectivity across all leads and across all frequencies was associated with worse performance on some tests of attention (Stroop Errors) but better

performance in others (Digit Span), as well as worse memory (RAVLT immediate recall) and better language ability (phonemic fluency) (Figure 4). The pattern of widespread high connectivity was similarly observed in both patients and controls (t=-0.19, p=0.84). We conducted an additional PLS model to consider possible confounding effects of low NREM-3 duration by including only the participants who had at least 5 minutes of NREM-3 (HC= 24, PD = 29; Supplementary Material Figure S2). This model identified only one significant LV that explained 20% of the covariance (p=0.01). This LV reflected an association between higher functional connectivity predominantly in the alpha band, and higher connectivity in the theta and sigma bands, which was associated with worse memory (RAVLT list B) but better attention (Digit Span) and visuospatial abilities (Rey Complex Figure Copy, WAISS-III Block Design). Overall, the pattern of connectivity identified in relation to cognition was similar in this subset of participants with longer NREM-3 sleep time suggesting that the individuals with short durations of NREM-3 were not driving the associations we found above.

To better understand the specific contribution of each frequency band to specific cognitive tests, we extracted coherence from edges with the highest bootstrap ratio for each frequency. The divergent associations with cognition were observed for all the edges selected, across all bands (Supplementary Figure S3). In other words, connectivity in the same edge was both positively associated with memory while simultaneously negatively associated with language, and exhibiting a similar divergent relationship with both measures of attention.

Correlation between brain scores and measures of sleep macro- and micro-architecture

We conducted additional exploratory analyses to assess if the connectivity profiles linked to cognition were associated with other aspects of sleep micro-architecture (Figure 5). We were particularly interested in the relationship between sleep oscillations (spindles and slow waves) and connectivity patterns (i.e., brain scores) during NREM-2 and NREM-3. In the case of NREM-2, we found that higher expression of the LV1-derived brain score (which reflected a pattern of lower connectivity in the sigma bands and was associated with worse cognition across all domains) was significantly correlated with lower sleep spindle density, but only in patients (R=-0.35, p=0.01). In the case of NREM-3, higher expression of the brain score (which reflected a pattern of increased connectivity across all frequency bands associated with mixed cognition) was associated with

lower slow-wave density, and again, this was only in patients (R=-0.29, p=0.04). These results suggest that there is a relationship between the expression of oscillations and the expression of the connectivity profile associated with cognition. This is especially noteworthy in the case of NREM-2 where the connectivity profile reflected lower connectivity in the frequency band of spindles.

Given the variability in sleep macro-architecture across individuals, we also examined the correlations between time spent in each sleep stage and the expression of the connectivity brain score. For the NREM-2 brain score, we found that fewer minutes spent in NREM-2 was associated with higher expression of the brain score in the healthy older adults (R=-0.35, p=0.04) but not in the PD patients (R=0.03, p=0.8), in whom the brain score was more strongly expressed. Similarly, for the NREM-3 brain scores, we found that, in both patients and healthy older adults, fewer minutes spent in NREM-3 was associated with higher expression of the brain score (PD: R=-0.45, p=0.001; Controls: R=-0.44, p=0.01). Considering the higher prevalence of sleep apnea in both older adults and PD patients, we also correlated the brain scores with the apnea-hypopnea index, however we found no associations (NREM-2: Controls, R=-0.06, p=0.74; PD, R=0.09, p=0.34; NREM-3: Controls, R=0.11, p=0.54; PD, R=0.18, p=0.08).

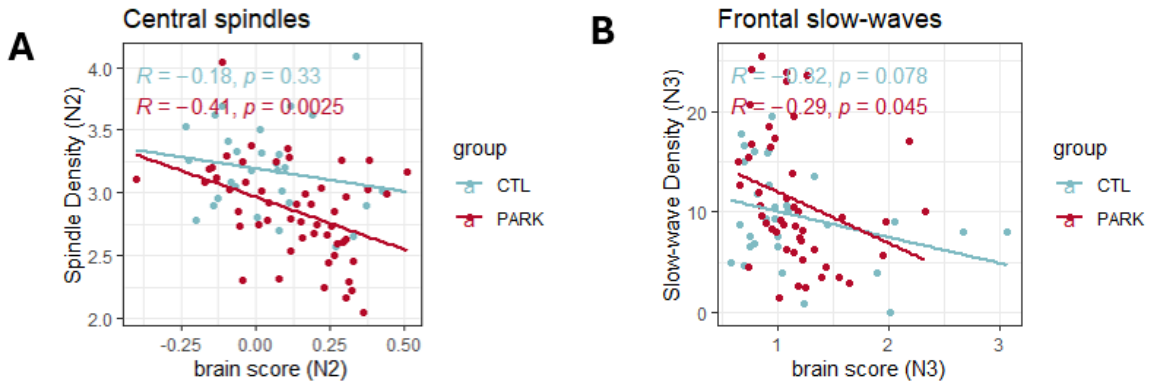

Figure 5. Correlation between sleep oscillations and expression of brain scores from LV1_nrem2 and LV1_nrem3. A) Correlation between sleep spindle density detected on central leads (where spindle activity is at its highest during N2) and LV1_nrem2 brain scores, between control and patients. B) Correlation between slow wave density detected on frontal leads (where slow wave activity is at its highest during N3) and LV1_nrem3 brain scores, between control and patients.

Discussion

In the current study, we investigated the relationship between connectivity across stages of NREM sleep and cognitive function in patients with Parkinson's disease and healthy older adults. First, we found that functional connectivity in both NREM-2 and 3 was considerably altered in PD patients compared to healthy controls with a pattern of higher connectivity in delta and theta bands and lower connectivity in the low and high sigma bands. Second, we found that functional connectivity during NREM-2 and NREM-3 stages was associated with cognitive performance, with stage-specific patterns of connectivity differentially explaining cognitive performance.

Lower connectivity at low and fast sigma frequencies in NREM-2 and 3 in PD patients compared to older adults

As predicted, we found lower connectivity in low and high sigma bands in patients compared to controls across both stages of NREM. The low and high sigma bands correspond to the frequency of spindles, which are oscillations that have consistently been shown to be altered in PD, particularly in characteristics like amplitude and density (Christensen et al., 2014, 2015; Latreille et al., 2015; Papp et al., 2022). Sleep spindles reflect highly synchronized brain activity. In younger adults, peaks in coherence (one measure of connectivity) are observed in the sigma band (Achermann & Borbély, 1998). Lower connectivity at this frequency band is therefore consistent with the notion that spindles are reduced in PD patients. Our results also suggest a left laterality to the reduced connectivity at the spindle frequency band. A few studies have demonstrated a similar pattern, although in the alpha band and during wakefulness. These studies do not measure sigma activity, as this is not typically studied in the context of wake. One study has suggested that lower left fronto-parietal coherence in the alpha band, during wake, is associated with executive dysfunction (Teramoto et al., 2016), another showed that left fronto-temporal phase-lag index was associated with higher apathy in patients (Hatz et al., 2017). Another group has shown that synchronization likelihood, a metric measuring the synchronization between two time-series, was lower in left parieto-occipital leads in the alpha band in PD patients with dementia compared to patients without dementia (Bosboom et al., 2009). Whether the laterality of our findings reflects the generally more verbally-dependent cognitive assessments used or whether it reflects the particular anatomical distribution of degeneration in this sample of PD patients is beyond the scope of this study but will be an interesting question for future research. Overall, these

results raise the possibility that functional connectivity during sleep could be used as a marker of disease, but more work will be required to establish the effects of PD on connectivity patterns and how this changes as the disease progresses.

Higher delta connectivity in both NREM-2 and 3 in patients compared to older adults

Contrary to predictions, we found higher connectivity at delta and theta frequency bands in patients compared to older adults. In general, the literature seems to point to sleep changes in PD being of similar quality but greater magnitude than those caused by aging (Carrier et al., 2001; Christensen et al., 2015; Latreille et al., 2015; Memon et al., 2023; Nicolas et al., 2001). In the case of the slower frequencies (i.e., delta and theta), it has been shown that older adults show overall lower functional connectivity than younger adults (Bouchard et al., 2019). The paradoxically higher connectivity we found in the PD patients therefore goes in the opposite direction, and yet, does not appear to be protective since, especially in the case of NREM-2, higher connectivity in these bands is associated with worse cognition. More research is required to better understand the relationship between oscillatory activity at the different frequency bands and functional connectivity.

A few studies have attempted to examine this relationship during wakefulness using different neuroimaging techniques to assess frequency-based connectivity in PD patients and may provide some insights about brain functional connectivity measured at different oscillatory frequencies (Bertrand et al., 2016; Wiesman et al., 2023). One study found that awake PD patients had lower connectivity – assessed by EEG phase synchrony – at slower frequencies, and also found that the reduced connectivity was more pronounced in patients who went on to develop dementia at follow-up (Bertrand et al., 2016). Lower frequencies were also found to have higher complexity, as measured with multi-scale entropy, which reflects higher variability in the signal (Bertrand et al., 2016). The authors proposed that this could reflect disrupted information integration, where networks become more randomly organized (Bertrand et al., 2016). More recently, a study measuring wake connectivity using MEG showed that, in PD patients, neurophysiological slowing (which is measured as an increase in the spectral power of slower relative to faster frequencies, and has often been observed in PD (Morita et al., 2011; Soikkeli et al., 1991)) — was also observed at the level of connectivity. The authors found that there was a shift to higher connectivity at slower

frequencies in PD and that the higher connectivity at slower frequencies was associated with worse memory (Wiesman et al., 2023). One interesting takeaway from these studies is that during wake, connectivity at the slower frequencies is a predictor of cognitive function in PD. While the results of our PLS analysis suggest that during sleep, connectivity at both slower and faster frequencies is associated with cognition, the relationship between higher connectivity at the slower frequencies and worse cognition is observed in both sleep and wake. The relationship between functional connectivity during wake and sleep remains an understudied area, but one possibility for how the two states relate to each other is that the pattern of connectivity that appears during wake is conserved into the descent to sleep and preserves its relationship to cognition. Indeed, in the case of PD patients, the aberrant high connectivity at lower frequencies observed in wake also appears to be maintained into sleep. A recent study showed that functional connectivity at slower frequencies could discriminate between NREM stages 2 and 3 and wake; in particular, delta connectivity seemed to flexibly change between wake, NREM-2 and NREM-3 (Imperatori et al., 2021). It is therefore possible that this flexible adaption of delta connectivity is changed or lost with PD, which may further explain our findings.

NREM-2 connectivity pattern associated with worse cognition is unique to PD

We identified a pattern during NREM-2 where higher connectivity in delta, theta and alpha frequency bands, and lower connectivity in low and high sigma bands were associated with worse cognition across all domains. Only one other study has examined the relationship between EEG-derived functional connectivity during sleep and cognition in adults and in general found very little relationship between connectivity during NREM sleep and cognition (Bouchard et al., 2019). This contrasts with our results where, in both NREM 2 and NREM3 we found patterns of connectivity associated with cognitive performance. The inconsistencies between these results can likely be explained by differences in methodology: instead of using regression models to examine the relationship of connectivity at individual pairs of leads with cognition, we used PLS to identify a pattern of connectivity across the brain that was associated with cognition. A notable element of the connectivity pattern we identified in NREM-2 is that lower connectivity in sigma was associated with worse cognition, and this pattern was significantly more expressed in PD patients than older adults. Given that, as discussed above, spindle oscillations correspond to the sigma frequency band, this is largely consistent with evidence that altered spindles in PD are associated

with impaired cognitive performance (Christensen et al., 2015; Lafortune et al., 2014). Furthermore, we found that lower spindle density in PD patients was associated with greater expression of this connectivity pattern. These findings therefore provide greater, albeit indirect, support for the proposal that altered spindles in PD patients contribute to impaired cognition and suggest that altered brain connectivity is a potential mechanism underlying this association.

In addition to finding higher connectivity at the slower frequencies in PD patients compared to controls, we found that the higher connectivity at slower frequencies was associated with worse cognition. This is interesting because, in keeping with the wake literature discussed above, it suggests that the oscillations of different frequency bands make different contributions to cognitive performance and that these are differentially sensitive to disease. Future work will be required to better understand the role of connectivity in carrying out the processing and restorative functions of sleep in the service of cognition.

It is important to note that the second significant latent variable identified by the PLS in NREM2 differed from LV1 in two key ways: it was similarly expressed in patients and older adults and it identified a pattern of lower (rather than higher) connectivity at the slower frequency band of delta that was associated with worse cognition, in particular, memory. Perhaps not surprisingly, given its expression in both PD patients and older adults, this pattern of connectivity bore greater similarity to those previously described in the literature (Bouchard et al., 2019).

NREM-3 connectivity pattern suggests shared aspects between patients and older adults that may reflect age-related changes to sleep and cognition

A consistent finding in the literature on sleep connectivity is that a breakdown in functional connectivity, as measured by both sleep EEG and sleep fMRI, occurs across the descent from wake into NREM-3, with connectivity during NREM-3 – the deepest stage of NREM sleep – being at its lowest, and that this pattern is lost with aging, suggesting an inability to disconnect that is problematic (Bouchard et al., 2019). In keeping with this, the PLS analysis identified a pattern of increased connectivity across all frequency bands though the relationship to cognition was mixed. Post-hoc tests revealed that there were no differences between patients and older adults in the degree of expression of the connectivity pattern, suggesting this might not be a PD-specific finding but rather might reflect age-related changes common to both groups. Interestingly, this

connectivity pattern was associated with better performance on some tasks (semantic fluency and digit span), worse performance on others (immediate declarative memory and Stroop performance) and, in the case of most tasks, close to absent associations. The one other study that has examined the relationship between cognition and connectivity did not find an association in NREM-3, suggesting that though this is a pattern of connectivity that emerges with aging, its contribution to cognition in older adults and patients is questionable.

Conclusion

In the current study, we demonstrate that EEG functional connectivity during NREM sleep is altered in PD patients compared to older adults. We also provide evidence that connectivity during NREM sleep stages 2 and 3 is associated with cognition, where connectivity in NREM-2 was associated with worse cognition across domains, while connectivity in NREM-3 showed a mixed association with cognition. While the NREM-2 connectivity pattern was significantly more expressed in PD patients than older adults, the NREM-3 pattern did not differ between groups and seems to recapitulate previous findings on age-related changes in connectivity profiles. Overall, these results suggest that changes in connectivity in NREM-2 may uniquely contribute to cognitive performance in PD and that this association might be revealing of the mechanism underlying the association between altered spindles and cognition in PD patients.

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Chapter 5. General Discussion

The first two studies presented in this thesis investigated sleep-dependent cognition, initially focusing on dopamine and sleep spindles, as both are known to modulate cognition and both are altered in Parkinson's disease (PD). Our results show that reduced sleep oscillations, specifically reduced sleep spindles, but not dopamine state, are associated with overnight memory consolidation in PD. These results raise the possibility that the reduction in sleep spindles caused by PD, and the associated impairment in consolidation, might represent a neural mechanism underlying impaired cognition in patients. However, sleep oscillations, including, but not limited to, sleep spindles, are also known to be associated with broader cognitive function – not just sleep-dependent processes like memory consolidation. The third study presented in this thesis investigated functional connectivity as a possible neural mechanism underlying the association between sleep oscillations and general cognition. We found that functional connectivity during NREM-2 and 3 was changed in patients compared to older adults. We also identified patterns of connectivity reflecting both PD-specific associations with worse cognition and age-related changes in connectivity. These findings provide a new perspective on the possible mechanisms through which sleep is associated with cognition.

In this general discussion, I will relate my thesis findings to the broader literature and will focus on the role of dopamine in consolidation, the interactions between dopamine and sleep, the significance of sleep oscillations for cognition, and the potential identification of a PD-specific profile of sleep and cognition.

Dopamine may not be necessary for motor consolidation but might still have a positive effect

The results from our first study suggest that dopamine state, at the time of initial acquisition, is not necessary for the later consolidation of motor memory. This raises questions about the mechanisms underlying motor memory consolidation in both patients and older adults. In Chapter 2, we discussed potential explanations such as the presence of compensatory extra-striatal mechanisms involving the cerebellum. Another important finding was that the performance of patients, regardless of dopamine state, mirrored that of older adults: neither group showed the

performance gains typically observed following motor memory consolidation, nor were they susceptible to interference from another motor sequence. In older adults, the absence of gains following motor memory consolidation has previously been observed and has been attributed to age-related changes in sleep (Fogel et al., 2014, 2017). Specifically, older adults show a reduction in sleep spindles and this reduction has been associated with reduced activation in the cortico-striatal network (Fogel et al., 2014). Therefore, the absence of performance gains observed in both our patient groups and older adults may reflect reduced recruitment of cortico-striatal networks. In PD patients, this may be further compounded by compensatory extra-striatal mechanisms. Together, these two mechanisms could explain the similar maintenance of memory observed in older adults and in patients, especially those Off dopamine therapy.

The relationship between dopamine and memory is complex, and there is evidence that the dopamine precursor levodopa delivered overnight may enhance some aspects of sleep spindles, which may modulate memory (Isotalus et al., 2023). How dopamine could interact with sleep oscillations remains unclear, but these findings are interesting considering we show a trend for a beneficial effect of overnight dopamine on motor consolidation in our exploratory analyses (Chapter 2). Though we do not directly measure sleep, this beneficial effect could be due to an interaction with sleep, possibly by modulation of spindle activity and increased recruitment of cortico-striatal structures. However, in our analyses, this trend was only observed for PD patients who were also On dopamine during learning—suggesting an interaction between dopamine state during learning and over consolidation (J. P. Grogan et al., 2017). While these results are interesting, they should be interpreted with caution due to the small sample size. Future work, with bigger cohorts, on the interaction of dopamine administration and sleep oscillations in PD and older adults is needed.

Findings from recent studies on the role of dopamine for consolidation increasingly suggest that, though dopamine-related processes can enhance consolidation (e.g., through signaling of reward and novelty (Cowan et al., 2021; Duszkiewicz et al., 2019), dopamine administration or dopamine blockade during the consolidation window does not have the expected effects. In Asfestani et al. (2020), overnight administration of Sulpiride, a dopamine D2-like receptor blocker, did not hinder preferential consolidation of reward-associated memory. These findings are surprising considering that, if dopamine is needed during the consolidation window, then one

would expect to block preferential consolidation associated with rewarded stimuli. This might seem at odds with previous findings from the same group (Feld et al., 2014), where activation of dopamine D2-like receptors, with Pramipexole, enhanced consolidation of low reward items to the same level as that for high reward items—effectively wiping out effects of preferential consolidation, as everything was consolidated. Together these results seem to suggest that dopamine's role, at least when it comes to the consolidation of reward-associated memories, might not be necessary but can have a positive effect.

In another study, overnight administration of levodopa in older adults was shown to increase slow-wave sleep duration and sleep spindle amplitude (Isotalus et al., 2023). However, participants on levodopa overnight had worse memory for words which were presented once during learning compared to those presented twice. However, this was also observed in the control group only after re-testing on the third day, suggesting that while forgetting was inevitable, it may be accelerated by dopamine. Isotalus et al. (2023) also demonstrated that administration of levodopa right before encoding or retrieval had no effects on memory, suggesting that the observed effects are due to dopamine during the consolidation window. The authors conclude that dopamine's effect on declarative memory consolidation might be through accelerated forgetting, by forgetting weak but not strong memory engrams, and these effects were not due to dopamine either at encoding or retrieval.

The findings from this last study seem hard to reconcile with that of Asfestani et al. (2020) and Feld et al., (2014). However, an important distinction is that these two studies deal with reward-associated memory. Having a reward signal may be an important tag that further triggers consolidation, even in the case of a low reward. Another key difference lies in the dopaminergic agents used: while Sulpiride and Pramipexole act on dopamine D2-like receptors, levodopa, once converted to dopamine, can act on both D1 and D2 receptors. It's not clear how activation of different dopaminergic receptors and different pathways might subserve consolidation. While these studies provide insightful information into the potential role of dopamine in consolidation, they focus on declarative memory consolidation—which has slightly different neural correlates than motor memory consolidation. Dopamine might be particularly relevant in motor consolidation, considering the recruitment of the cortico-striatal network.

To summarize, our findings demonstrate that motor memory consolidation is similar across patients and older adults, irrespective of dopamine state during learning, and may instead reflect age-related mechanisms. However, it is plausible that dopamine, or dopamine precursors, and sleep mechanisms interact overnight and subsequently affect consolidation. In this thesis, we did not have a study addressing the interaction between dopamine and sleep, but we did address the relationship between sleep and memory consolidation in patients, which will be the focus of the next section.

Multiple aspects of sleep spindles correlate with cognition in Parkinson's disease

In the second study, we demonstrate that both sleep spindle density and their temporal clustering into trains are associated with overnight memory consolidation in patients. It is well-established that sleep spindles are crucial for effective sleep-dependent consolidation, however, this relationship had not been investigated in PD before our study. It has also been recently proposed that the repeated expression of spindles, in close temporal proximity (i.e., 'trains'), might be a critical mechanism for effective consolidation—through repeated reactivation of the memory engram. Though we are unable to directly address this mechanism, we demonstrate that both these aspects of spindles correlate with declarative memory consolidation in Parkinson's disease. In the third study, we show that functional connectivity in the low and high sigma frequency is significantly lower in patients compared to healthy controls, and this is observed in both NREM2 and NREM3. Though we could not correlate this with sleep-dependent memory consolidation, we show, through our multivariate analyses, that lower connectivity across a connectivity pattern that includes low and high sigma is associated with worse performance across cognitive domains—primarily attention, memory and executive function.

This gives three possible ways by which spindles may contribute to worse cognition in PD: i) through a decrease in density, ii) 'weak' temporal clustering of spindles in trains, or iii) through lower functional connectivity across the scalp. These could also all be happening at the same time. In our exploratory analyses in Chapter 4, we show that the expression of the functional EEG pattern which captures lower connectivity in sigma (as well as higher connectivity in delta, theta and alpha) negatively correlates with sleep spindle density. However, it is not clear how specific this

correlation is to just functional connectivity in the sigma band, considering this PLS-identified pattern reflects changes in other frequency bands as well.

Though conceptually related, it is also unclear how the ability to consolidate (Chapter 3) specifically relates to broader cognitive function (Chapter 4). Though sleep spindles are necessary for sleep-dependent consolidation, their exact contribution to broader cognition remains unclear. This could be explained in two ways: either consolidation impacts not only memory but other cognitive domains as well (i.e., sleep spindles would support cognition through consolidation), or sleep spindles may influence cognition directly, independent of their role in memory consolidation.

Possible mechanisms underlying the association between sleep spindles and cognition

There are a few plausible mechanisms that might explain the relationship between sleep spindles and cognitive function. First, spindle activity may reflect the integrity of the underlying thalamo-cortical network. The thalamus is an important hub which interlinks multiple cortical systems and its projections to the cortex subserve a wide array of cognitive processes (Hwang et al., 2017).

A few studies have already shown an association between characteristics of sleep spindles and various metrics of white matter integrity in this network. Individual differences in white matter diffusivity, including in the thalamo-cortical projections, have been associated with characteristics of sleep spindles (Gaudreault et al., 2018; Mander et al., 2017; Piantoni et al., 2013). Individuals with higher axial diffusivity (reflective of better integrity) in white matter tracts including tracts within and surrounding the thalamus, the internal and external capsule, had higher spindle power (Piantoni et al., 2013). Mean diffusivity along tracts including the thalamic radiations and the corona radiata predict fast spindle density, over central leads, in older and younger adults (Mander et al., 2017). Sleep spindle amplitude and sigma power have also been shown to positively correlate with white matter integrity along several tracts, including the left anterior thalamic radiation, though this was only observed in younger adults and not older (Gaudreault et al., 2018).

One reason that may explain the discrepancy in the findings between young and older adults is the higher variability in white matter integrity with aging, due to possible metabolic, physiological and environmental factors (Gaudreault et al., 2018). It is also possible that, as a result

of aging-associated neurodegeneration, adaptive mechanisms may be activated to regulate the network and adjust connectivity, to compensate for structural changes. This interpretation was proposed by Sanchez et al. (2020) after observing an absence of correlation between spindle characteristics and white matter integrity in patients with chronic, moderate to severe, traumatic brain injury. Their findings also suggest that sleep spindles are very resilient to extensive white matter damage. The changes to spindle activity observed in Parkinson's disease may be a result of either very severe neurodegeneration (this is perhaps less likely considering changes to spindles are observed before overt cognitive decline), or an inability to effectively regulate thalamo-cortical network connectivity—or an interaction between both mechanisms.

The preserved integrity of thalamo-cortical white matter tracts is thought to be important because it likely supports functional connectivity. However, as the findings above suggest, this may be just one of several key characteristics. Ultimately, it is the communication along these projections which is thought to support cognitive function. Sleep spindles may not only reflect the structural health of these pathways but also reflect their capacity to maintain efficient connectivity. Evidence from schizophrenia shows that abnormal functional connectivity in thalamo-cortical tracts during wakefulness is associated with a deficit in sleep spindle density (Baran et al., 2019).

To date, only one study has provided evidence for the relationship between sleep spindle-associated functional connectivity and cognitive function— excluding studies on sleep-dependent memory consolidation. Using combined EEG-fMRI, Fang et al. (2019) demonstrate that in young adults, functional connectivity time-locked to sleep spindles between regions in the thalamo-cortical network correlated with reasoning abilities. More specifically, higher sleep spindle-specific functional connectivity between the anterior cingulate cortex and the left putamen, and between the thalamus and the middle cingulate cortex was associated with better reasoning abilities. Cognitive abilities were assessed using the Cambridge Brain Sciences test, which consists of three domains: Reasoning (spatial rotation, feature match, spatial planning, interlocking polygons), STM (visuospatial working memory, spatial span, paired-associates, self-ordered search), and Verbal (verbal reasoning, color-word remapping, digit span). No correlations were found between functional connectivity during spindles and neither scores on the STM nor Verbal sub-scales. As highlighted by the authors in their discussion, the 'reasoning' factor encompasses abilities belonging to fluid intelligence, whereas both the STM and the Verbal factors relate to

crystallized intelligence. As such, their results demonstrate that spindle-dependent functional connectivity correlates with aspects of fluid intelligence but not crystallized intelligence.

This dichotomy is particularly interesting when considering current knowledge in the aging literature. Though fluid and crystallized abilities are correlated (Tucker-Drob et al., 2022), fluid abilities have been shown to progressively decline with increasing age, much more than crystallized abilities. Sleep spindles have been shown to mainly correlate with cognitive abilities belonging to fluid intelligence (Bódizs et al., 2014; Reynolds et al., 2018). As such, spindles may serve as a more sensitive indicator of age-related changes in cognition.

The above-mentioned studies are all correlational, so it's not possible to ascertain a direction. Although these interpretations imply that thalamo-cortical networks shape spindle activity—and thus their association with cognition— the opposite is also possible. Specifically, spindle activity may be important to maintain the efficiency of the thalamo-cortical network, and, in this way, may directly contribute to good cognitive function. It is plausible that the burst firing of sleep spindles is necessary for inducing plastic changes within the network, which, as a response to neurodegeneration, may be a compensatory mechanism to counteract cognitive decline. There is much less evidence for this, and this is highly speculative. The relationship may be bi-directional as well, and both thalamo-cortical networks and spindle activity may influence each other.

Clustering of sleep spindles may be associated with a broader phenotype of sleep disturbances in PD

The relationship between sleep and cognition is not specific to Parkinson's disease. Indeed, most of the evidence guiding our research questions comes from studies in healthy older adults. Nonetheless, some of the mechanisms we highlight may be particularly relevant to PD. In Chapter 3, the cited rodent literature highlights the role of the locus coeruleus as an important modulator of sleep spindle activity. Although we did not measure degeneration of the locus coeruleus in our study, this is a structure that is known to be affected early in patients (Braak et al., 2003; Del Tredici et al., 2002). The following section will briefly review recent findings highlighting the role of the locus coeruleus in modulating sleep and explore its significance for PD.

As discussed in Chapter 3, increasing evidence identifies the locus coeruleus (LC) as a key structure modulating the clustering of sleep spindles. During NREM sleep, LC firing fluctuates,

oscillating between high and low activity at an infraslow rhythm of approximately 0.02 Hz (Lecci et al., 2017; Osorio-Forero et al., 2021). This fluctuation in firing corresponds to varying concentrations of noradrenaline in the brain. The LC projects widely and innervates both the thalamus and the cortex. In rodents, the effect of LC-noradrenergic firing on spindles is specifically to its projections to the thalamus, and not to the cortex (Osorio-Forero et al., 2021). Osorio-Forero et al. (2021) demonstrated that, in the thalamus, noradrenaline increases the depolarization of thalamo-cortical projections and thalamic reticular neurons, effectively moving them away from the membrane potential required for burst firing (necessary for the spindle rhythm) (Osorio-Forero et al., 2021). Consequently, high activity levels of the LC are associated with a reduction in sleep spindles, whereas low activity levels correspond to an increase in spindles.

In rodent studies, optogenetic stimulation or inhibition of the LC has established a causal relationship between LC firing and spindle activity (Osorio-Forero et al., 2021). Recent work reveals that fluctuations in LC activity are also critical for the normal NREM-REM sleep cycle, with low LC activity facilitating entries into REM sleep and high activity suppressing it (Osorio-Forero et al., 2023). This aligns with findings from other studies demonstrating an increase in spindle activity right before REM onset (Bandarabadi et al., 2020; A. Kim et al., 2012). Other groups have also linked the LC with arousal, demonstrating that stimulating the LC increases micro-arousals and sensory-evoked awakenings from sleep (Hayat et al., 2020). In mice, stress produces an effect similar to LC stimulation, and inactivation of the LC reduced micro-arousals while increasing sleep spindles (Antila et al., 2022). Together, these findings demonstrate the LC's role in modulating the NREM-REM cycle, influencing both sleep spindle activity and their clustering, REM onset, and sleep stability.

These recent observations regarding the LC's role in sleep mirror some of the sleep abnormalities found in patients with PD, such as decreased spindles (Latreille et al., 2015) and fragmented sleep (Diederich et al., 2005). While increased fragmentation is sometimes attributed to the presence of other comorbidities such as periodic leg movements and obstructive sleep apnea (Comella, 2007), heightened sleep fragility due to LC dysfunction could worsen these disturbances. Degeneration of the LC is thought to be reflected by persistent high tonic firing (Janitzky, 2020). Although empirical data supporting this is sparse due to the challenges of

recording LC activity in humans, findings in healthy older adults demonstrate that higher LC activation during wakefulness is associated with worse subjective sleep (Koshmanova et al., 2023).

Understanding the role of the LC in sleep may provide insight into a broader phenotype of sleep impairments in PD and could allow us to target multiple aspects of disturbed sleep by focusing on a single mechanism. Persistent high firing of the LC may lead to a reduction in sleep spindles due to its noradrenergic effect on the thalamus. This persistent activity may also render individuals more susceptible to awakenings, resulting in more sleep fragmentation. One study has shown that PD patients have less stable sleep, as evidenced by lower REM stability (more transitions out and to REM) and lower NREM stability (more transitions out and to NREM) (Christensen et al., 2016). It remains unclear whether these disruptions are solely attributable to LC dysfunction or may involve other aspects of PD-related neurodegeneration, which affects other brainstem nuclei important in regulating sleep (Del Tredici et al., 2002; Sulaman et al., 2023). Identifying a link between the LC and sleep structure—specifically, the overall temporal architecture of spindle activity and transitions between NREM and REM—may offer a promising mechanism for addressing sleep disturbances in PD. Further research investigating this relationship may reveal novel therapeutic avenues for improving sleep in patients.

Understanding PD-specific patterns of sleep connectivity

In our third study, we examined how EEG functional connectivity during NREM sleep changes in PD and explored its relationship to broader cognitive function. Our findings revealed both PD-specific links between connectivity and cognition, as well as broader age-related associations, observed in both patients and older adults. Compared to older adults, patients showed higher delta and theta connectivity during NREM-2 and higher delta connectivity during NREM-3. In contrast, sigma band connectivity, both high and low, was lower in patients across both NREM-2 and NREM-3.

Interestingly, this pattern of altered connectivity in PD also closely mirrors the connectivity profile associated with worse cognition which we identified through PLS analysis. This is further supported by the significantly higher expression of this brain score in PD patients compared to older adults.

Although we are the first to investigate functional connectivity during sleep in PD, some bridges can be made between these findings and previous observations in the literature on wake EEG in patients. A few studies show changes in delta connectivity in PD, though the direction of these effects seems mixed. One group identified that phase synchrony in the delta band was lower for PD patients who further developed dementia (Bertrand et al., 2016), whilst another showed that connectivity, measured by amplitude envelope correlation, was increased in slower bands (delta and theta) compared to faster (alpha and beta). These findings may seem contradictory, but they measure different aspects of the signal (i.e., phase and amplitude, respectively) and are not directly comparable. Similarly, our results may seem to contradict those of Bertrand et al. (2016) as we show different changes in delta connectivity, but we are ultimately comparing two different states of consciousness: wake and sleep.

Though our findings show higher delta connectivity during NREM sleep in PD patients compared to older adults, delta connectivity during wakefulness might appear lower if older adults also exhibit significantly higher delta connectivity. Despite these complexities, delta connectivity seems to be altered in PD, though the nature and direction of these changes remain unclear.

Age-related pattern of connectivity in NREM-3

The literature on functional connectivity during sleep has demonstrated, both with EEG and fMRI, the presence of a breakdown in connectivity in NREM-3. This decrease in connectivity with the descent to NREM-3 also seems to be changed with aging, with older adults showing higher connectivity compared to younger adults (Bouchard et al., 2019). Our findings identified a similar pattern of higher connectivity across all frequency bands associated with a mixed pattern of cognition, with better performance on some tasks (semantic fluency and digit span) and worse on others (immediate declarative memory and Stroop performance). This pattern of higher EEG connectivity was similarly expressed in both patients and older adults, suggesting this is not specific to PD. This may suggest that, while NREM-3 connectivity changes with aging, these changes are not necessarily associated with worse cognition. This is also consistent with findings from Bouchard et al. (2019), who found no significant associations between connectivity in NREM-3 and cognition. These findings are particularly compelling considering our cognitive measures are controlled for age, as we use normalized scores from published norms that account for age, sex, and years of education.

Overall, our findings suggest that higher NREM-3 connectivity may reflect a broader, age-related phenomenon that does not inherently predict worse cognition.

Limitation

Several limitations should be acknowledged. First, the sample sizes were relatively small, which limits our capacity to conduct post-hoc analyses that might account for some of the heterogeneity within PD. In addition, the absence of a control group in the second study restricts our ability to conclude whether there are PD-specific deficits in memory consolidation.

In the third study, the approach we chose is well-suited to handle multivariate data and complex relationships. However, the drawback to this is the inability to isolate specific one-to-one relationships amongst the variables, as PLS identifies an X pattern associated with a Y pattern.

Another general limitation is that we did not examine REM sleep, as the focus of the thesis was on oscillations of NREM sleep, particularly sleep spindles. This focus was both a theoretical and practical choice. The sleep-dependent memory consolidation mechanisms we sought to investigate in our first and second studies focused on sleep spindle activity, and this further informed our third study where we looked at connectivity in NREM-2 and 3. Studying REM sleep involves many challenges, such as the removal of rapid-eye movement artefacts, which were out of the scope of the thesis due to time constraints.

Original contributions to knowledge

The findings in this thesis present evidence for plausible mechanisms that might affect sleep-dependent and broader cognition in PD. First, we provide new results as to the role of dopamine in sleep-dependent memory consolidation in PD, and these results suggest boundaries to dopamine's role in consolidation. Second, we present evidence on characteristics of sleep oscillations that have not been studied in the context of memory consolidation or cognitive function, let alone in PD. We demonstrate that the clustering of sleep spindles might be an aspect of spindle activity that is particularly important for consolidation. These results may influence future research aimed at stimulating sleep spindles, as it may be important to consider the temporal expression of this oscillation when designing effective stimulation protocols. We also demonstrate that the connectivity of sleep oscillations, not constrained to the frequency of sleep spindles, is altered in PD and that these changes are associated with worse cognition. These results expand our

understanding of sleep and sleep oscillations and their role in cognitive function, by considering their connectivity in NREM-2 and NREM-3.

Future directions

The findings from this thesis raise multiple questions. First, it will be important to study sleep as it interacts with dopaminergic medication in PD patients, and whether this improves sleep-dependent consolidation. This would provide valuable insight and may provide easily applicable means to enhance consolidation in patients, by simply adjusting the timing of medication.

Another interesting direction would be to leverage current methods to non-invasively target sleep spindles, such as closed-loop auditory stimulation (Besedovsky et al., 2017; Valenchon et al., 2022). This approach could answer important questions about the role of spindles not only in consolidation but in broader cognitive function, and potentially provide insight into the networks that subserve spindle activity. This question is not specific to PD as such a therapy would be greatly beneficial for the aging population more generally, considering that there is a lack of treatments for cognitive symptoms. It is plausible that enhancing spindle activity may also affect the thalamo-cortical network which supports this activity, and consequently may enhance cognitive function. If spindles are targeted according to the infraslow rhythm reported by Osorio-Forero et al. (2021), this may also affect the broader architecture of sleep and may entrain periods of NREM stability. This might be particularly important for PD patients and other populations who have disturbed and fragmented sleep. Future research will be necessary to further explore these possibilities.

While the work in this thesis has primarily focused on sleep EEG, future studies should also investigate how structural changes, and pathological markers may also contribute to altered sleep oscillations in patients. Integrating both would provide a comprehensive understanding of the ways by which neurodegeneration contributes to poor sleep, potentially interacting with sleep oscillations, and therefore contribute to poor cognition.

Conclusion

In summary, the findings in this thesis provide novel insight into the relationship between sleep and cognition in Parkinson's disease. Though important questions remain, we demonstrate that sleep spindles and sleep oscillations are associated with both memory consolidation and general cognitive function, highlighting their potential as future targets for therapies aimed at

improving cognition through sleep. Future work will be needed to carefully characterize the mechanisms subserving this relationship. Our findings suggest this could be through both the temporal clustering of spindles in consolidation and functional connectivity in cognition. These findings provide a new perspective on how altered sleep may contribute to worse cognition in PD.

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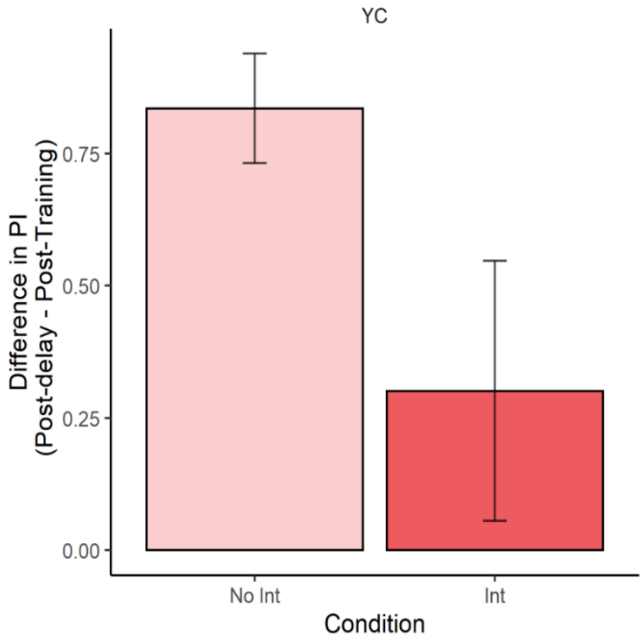
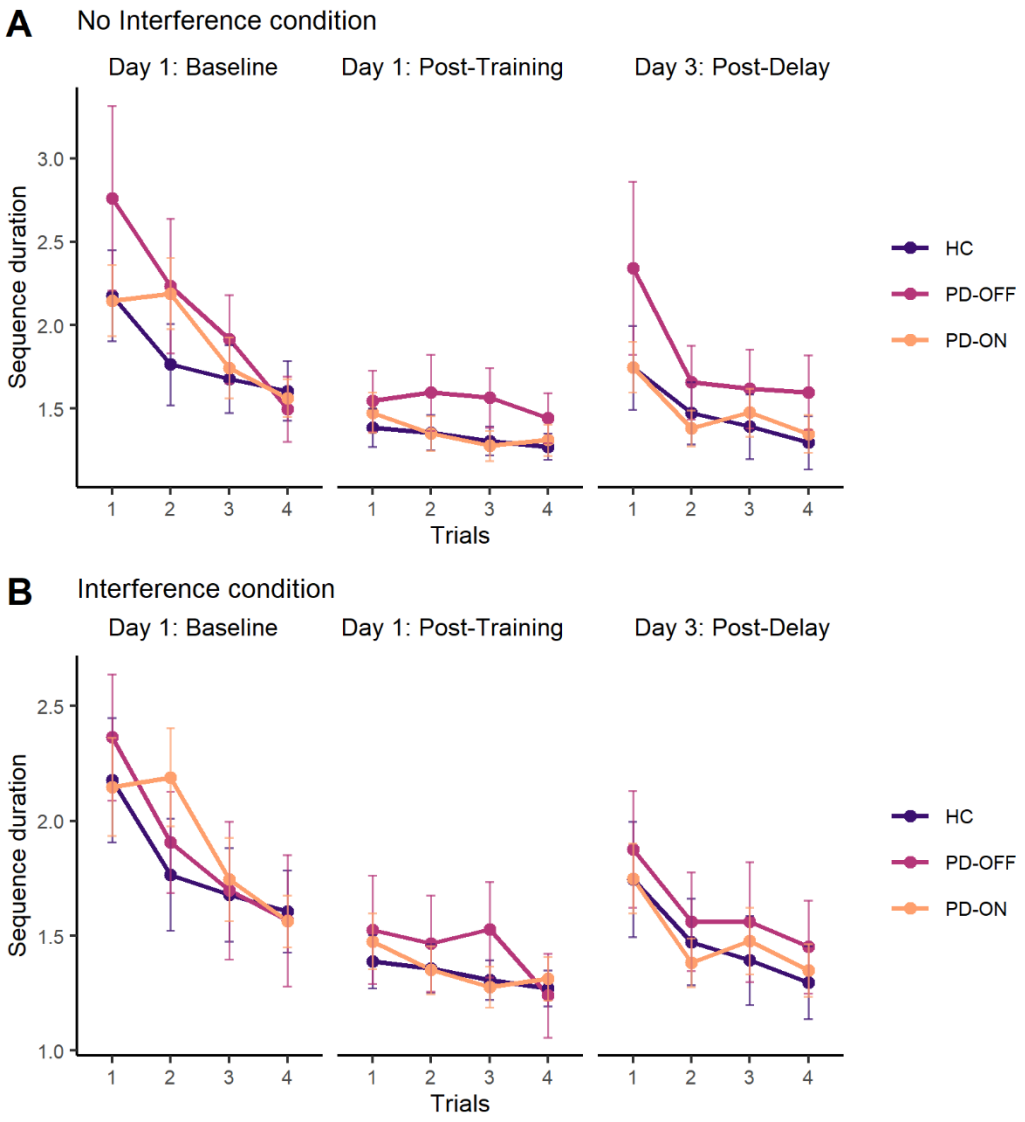
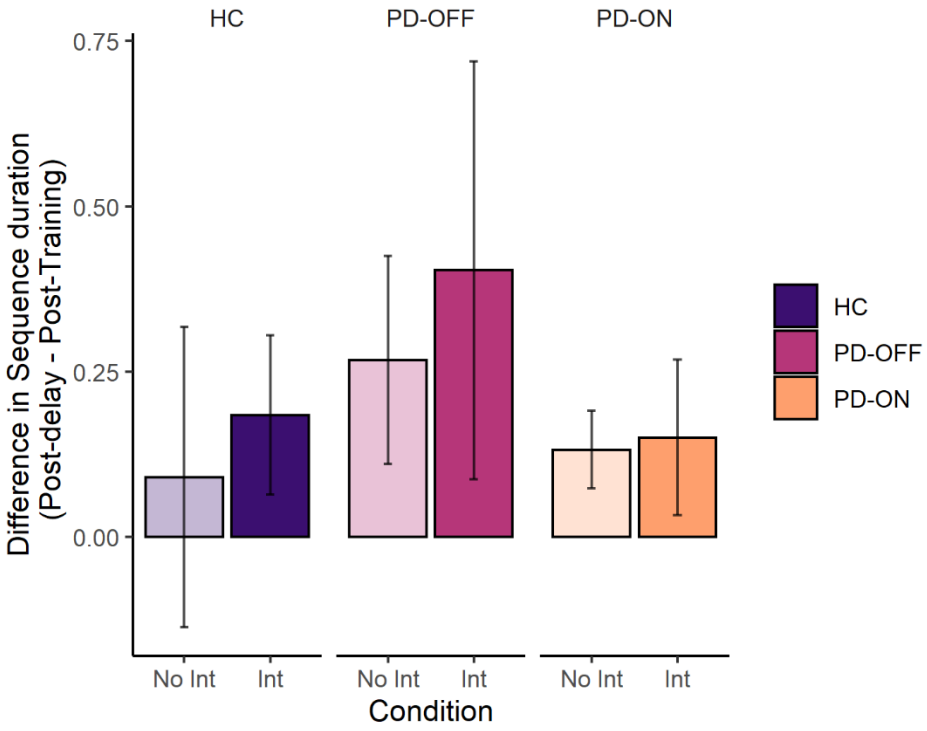
Appendix A: Supplementary Material for Chapter 2



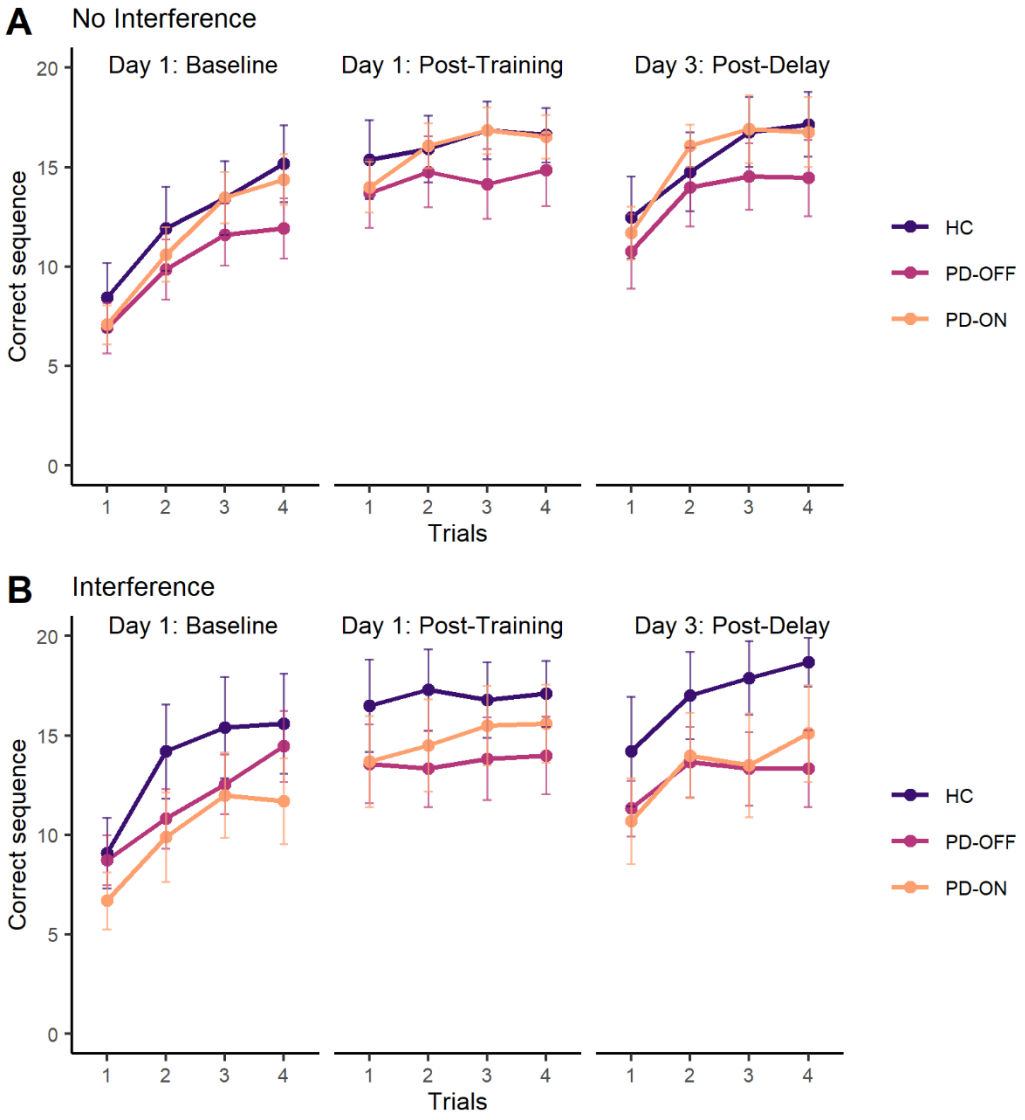
Supplemental figure 1. Change in performance across the two-day delay and effect of interference among the young controls. Change in performance was calculated as the difference between the mean performance index at the Post-Delay test and at the Post-Training test. Negative values represent a decay in performance across the delay and positive values represent gains in performance. Young controls showed an off-line improvement in performance across the delay, and this improvement was significantly reduced in the group that underwent interference (*: $t = 2.00$, $p = 0.05$). Bars represent s.e.m. within group and condition. No Int=No interference condition; Int=Interference condition.



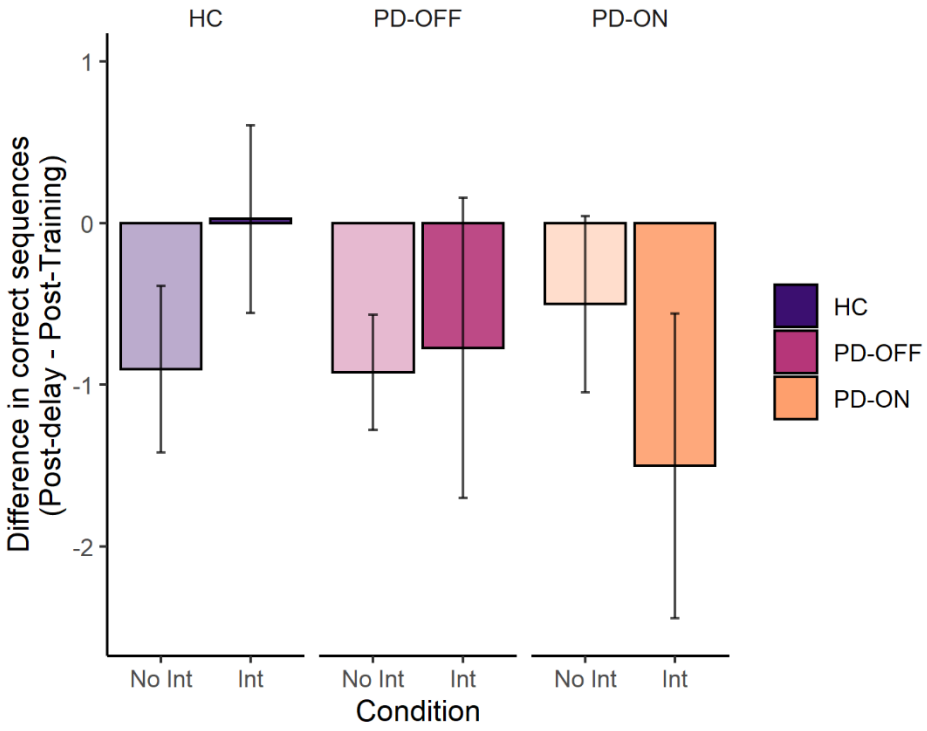
Supplemental figure 2. Test performance (Sequence duration). Performance measured as the average sequence duration is shown across trials (1-4) for each of the three test sessions for all three groups. Conditions are presented separately: participants that did not undergo the interference (A) and those that did (B). Participants across groups and conditions show similar baseline performance, similar improvements from training and similar decay in performance across the two-day delay. Error bars represent s.e.m. within group and trial.



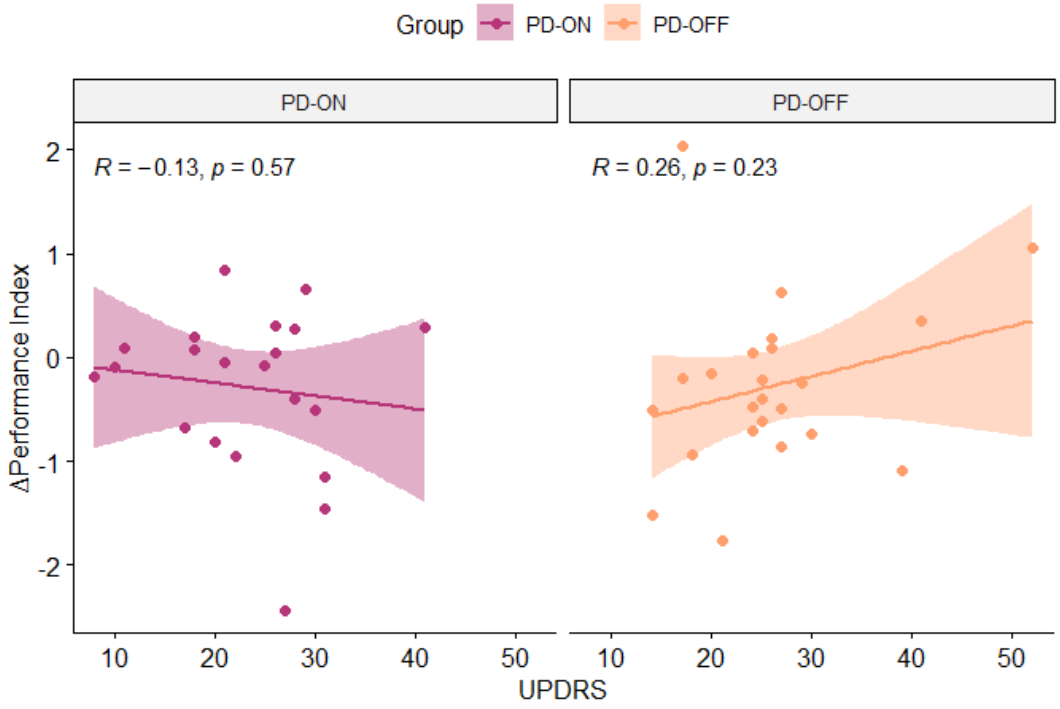
Supplemental figure 3. Change in performance across the two-day delay and effect of Interference on mean sequence duration. Change in performance was calculated as the difference between mean sequence duration at the Post-Delay test and at the Post-Training test. Error bars represent s.e.m. within group and condition Negative values represent a decay in performance across the delay. There were no differences in the degree of maintenance of performance between groups nor was there an effect of interference on the maintenance of performance. No Int=No interference condition; Int=Interference condition.



Supplemental figure 4. Test performance (Correct sequences). Performance measured as the average number of correct sequences is shown across trials (1-4) for each of the three test sessions for all three groups. Conditions are presented separately: participants that did not undergo the interference (A) and those that did (B). Error bars represent s.e.m. within group and trial.



Supplemental figure 5. Change in number of correct sequences across the two-day delay and effect of Interference. Change in performance was calculated as the difference between average number of correct sequences at the Post-Delay test and at the Post-Training test. Error bars represent s.e.m. within group and condition. No Int=No interference condition; Int=Interference condition.



Supplemental figure 6. Correlation between UPDRS-III and performance change across the delay. Change in performance was calculated as the difference between performance index at post-training and at post-delay.

Supplementary Results

In addition to Bayes Factor analysis, we also examined the null effects using equivalence tests. Equivalence tests allow us to assess whether the presence of an effect –as determined by our bounds—can be rejected. Because no previous evidence exists using similar conditions in this population to help guide the choice of effect size, the equivalence bounds were determined based on the smallest effect size we were powered to detect (power = 0.80, alpha = 0.05), which were moderate to large (Lakens, 2018). All analyses were conducted in R version 4.05 using the 'TOSTER' package (Lakens, 2017). To show the range of effect sizes for different power levels in our sample, we also generated power curves using the 'pwr' package in R (Champely, 2020).

Comparison of baseline performance between groups

To compare baseline performance between groups, we performed a one-way equivalence test on Performance Index at baseline across the group (Campbell & Lakens, 2021). Results suggest no difference between the groups (Group [HC, PD-ON, PD-OFF]: $F(2, 65) = 0.819$, $p_{equivalence} < 0.001$, $p_{null} = 0.45$) based on equivalence bounds set using $\eta^2 = \pm 0.38$.

Comparison of maintenance of performance across the delay between groups

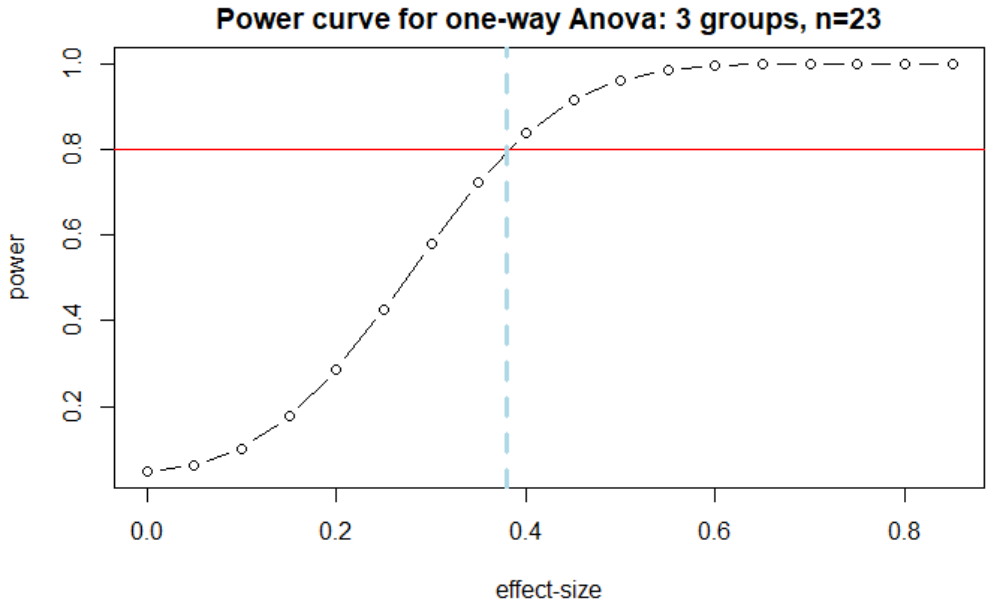
To examine the maintenance of performance across the delay between groups, we performed a one-way equivalence test on the difference in performance across the delay (Δ Performance Index) between the groups. Results suggest no difference between the groups (Group [HC, PD-ON, PD-OFF]: $F(2, 68)=1.288$, $p_{equivalence}< 0.000$, $p_{null} = 0.28$) based on equivalence bounds set using $\eta^2 = \pm 0.38$).

Effect of interference within groups

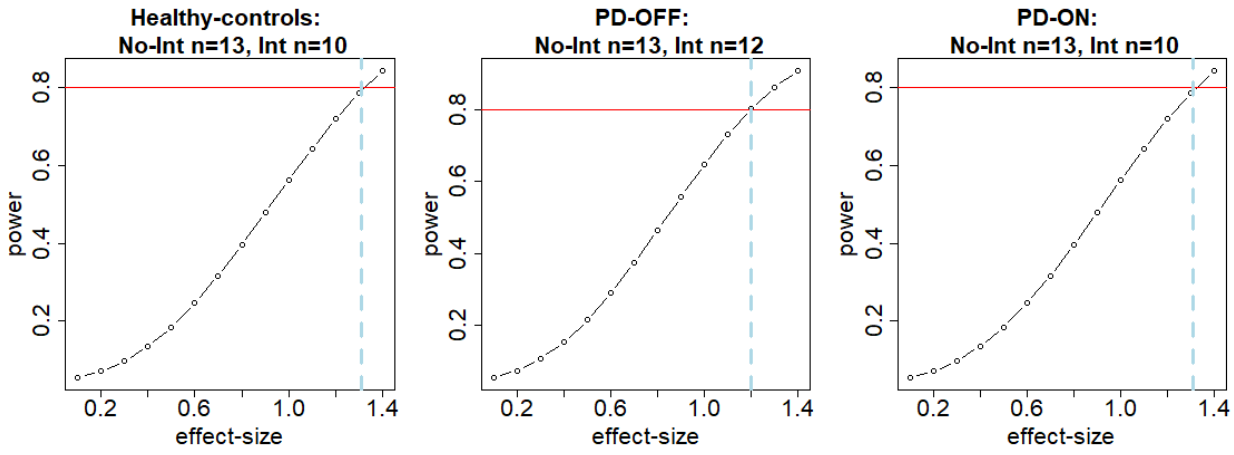
We also performed equivalence tests for the within-group effects of Interference on the difference of performance across the delay. The results of these analyses suggest that group differences are within the equivalence bounds (Healthy controls: $d=1.31$ ($t_{17.74} = 2.01$, $p = 0.03$), $d= -1.31$ ($t_{17.74} = -4.16$, $p = 0.0003$); PD-ON: $d=1.31$ ($t_{14.99}=3.99$, $p =0.0006$), $d = -1.31$ ($t_{14.99}=-3.09$, $p = 0.027$); PD-OFF: $d=1.19$ ($t_{14.32}=2.88$, $p =0.006$), $d= -1.19$ ($t_{14.32}=-2.99$, $p = 0.005$), however in all cases, we were only powered to detect large effects.

Power curves

We plotted power curves for all the equivalence tests previously reported. Power analyses were made using the 'pwr" package in R (Champely, 2020). Due to our small sample size, we were only powered to detect large effects.



Supplemental Figure 7. Power curve for One-Way ANOVA. The sample size was selected according to the smallest group (n=23). Red line corresponds to power of 80%, dashed blue line indicates the smallest detectable effect size.



Supplementary Figure 8. Power against a range of effect size in all three groups. Power is shown for the condition with the smallest sample, i.e., n=10, n=12 and n=10 for HC, PD-OFF and PD-ON respectively. Red lines correspond to power of 80%, dashed blue lines indicate the smallest detectable effect size.

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Appendix B: Supplementary Material for Chapter 3

	NREM-2	NREM-3
Spindle density (Frontal)	R= -0.22, p=0.20, BF_{10}=0.76	**R=0.46, p=0.006, p_{adj}=0.02, BF_{10}=9.78**
Spindle density (Central)	R= -0.04, p=0.82, BF_{10}=0.81	R=0.2, p=0.27, BF_{10}=0.64
# Spindle train (Frontal)	R=-0.19, p=0.26, BF_{10}=0.65	R= -0.05, p=0.79, BF_{10}=0.41
# Spindle train (Central)	R=-0.12, p=0.46, BF_{10}= 0.47	R=-0.16, p=0.39, BF_{10}=0.55
Proportion of spindles in trains (Frontal)	R=-0.23, p=0.17, BF_{10}=0.84	**R=0.46, p=0.0057, p_{adj}= 0.02, BF_{10}=10.13**
Proportion of spindles in trains (Central)	R=-0.13, p=0.42, BF_{10}=0.49	R=0.17, p=0.31, BF_{10}=0.58
Spindle density (# spindles in trains/min)	Not measured	**R=0.52, p=0.002, p_{adj}=0.004, BF_{10}=27.9**
Spindle density (# spindles outside trains/min)	Not measured	R=0.23, p=0.2, BF_{10}=0.77

Table S1. Correlations between sleep spindles and memory consolidation. P_{adj} denotes p-values adjusted for 4 comparisons (except for spindle density inside and outside trains) using the Holm-Bonferroni method.

	NREM-2		NREM-3	
	Slow	**Fast**	**Slow**	**Fast**
Frontal spindles (n ±SD)	196 ±21.2	47 ±36.4	21.2 ±19.9	3.67 ±2.84
Central spindles (n ±SD)	138 ±71.3	107 ±80.9)	13.7 ±15.5	9.04 ±8.62
Frontal spindles (% ±SD)	79.8% ±13.1	20.2% ±13.1	82.0% ±11.9	18.0% ±11.9
Central spindles (% ±SD)	57.4% ±19.2	42.6% ±19.2	55.1% ±20.9	44.9% ±20.9

Table S2. Number and percentage of slow and fast sleep spindles across frontal and central leads for NREM sleep. Sleep spindles were detected in the range of 11.1 and 14.9 Hz. Then, spindles with a frequency of ≤12.99 Hz were categorized as slow sleep spindles, and spindles with a frequency of ≥13.00 Hz were categorized as fast sleep spindles

	Pearson's R	P-value
Total sleep time	-0.08	0.65
Sleep efficiency	-0.01	0.95
Sleep-Onset latency	0.18	0.30
Wake %	-0.07	0.69
N1 %	0.08	0.64
N2 %	0.18	0.30
N3 %	**-0.42**	**0.01 ***
REM %	0.06	0.72
NREM % (N2 + N3)	-0.06	0.71
Apnea-Hypopnea Index	-0.14	0.43

Table S3. Association between metrics of sleep macro-architecture and performance on the MoCA. Pearson's correlation between general sleep macro-architecture and MoCA scores. There is significant negative correlation between percent of time spent in stage N3 and MoCA score (R=-0.42, p=0.01).

Exploratory analyses on central and frontal leads during NREM-2 and NREM-3

We compared spindle density and total count of spindles in both frontal and central leads and during both NREM-2 and NREM-3 (Figure 3), and compared the minutes of artefact-free periods, which is the amount of time devoid of EEG artefact on which the spindle detection was performed. These analyses were conducted to rule out the possibility that the specificity of the results to frontal leads is not due to relatively lower noise at these leads. Interestingly, we found that, although there are no significant differences in total spindle count between frontal and central leads in NREM-3 (paired t-test: t=-1.55, p=0.13), we found that there is a significantly higher spindle density at frontal leads compared to central leads in NREM-3 (paired t-test: t=-2.53, p=0.01), though this does not survive correcting for multiple comparisons.

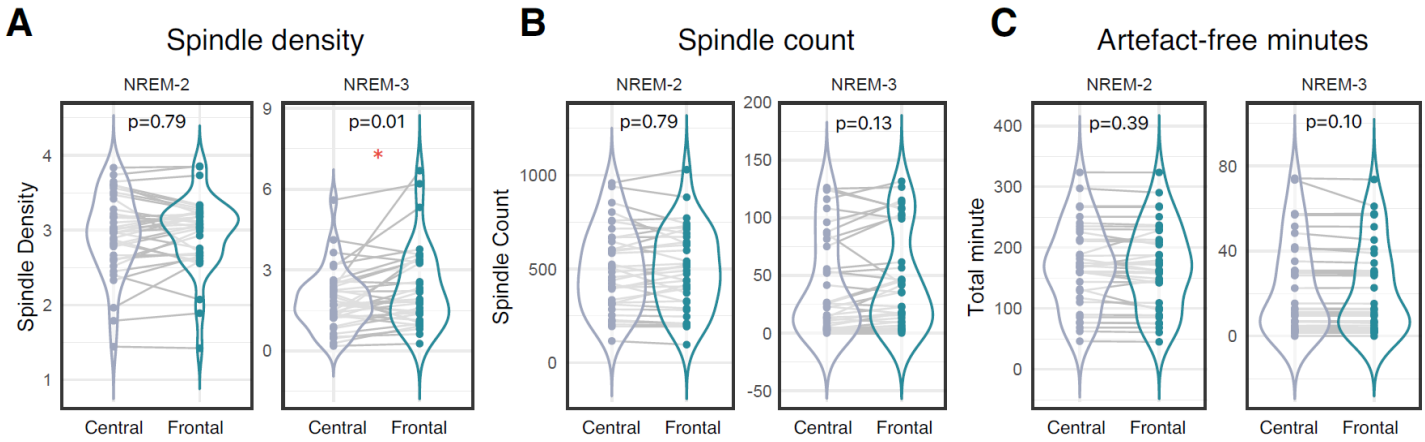

Figure S1. Comparing sleep characteristic between central and frontal leads during NREM-2 and NREM-3. (A) Spindle density, **(B)** count, and **(C)** total artefact-free minutes measured at central and frontal leads during NREM-2 and NREM-3 stages. Artefact-free minutes reflect the minutes free of EEG artefacts where the spindle detection was conducted. **(A)** Spindle density during NREM-3 was higher at frontal leads than at central leads (paired t=-2.61, p=0.01). There was no difference in spindle density between central and frontal leads during NREM-2 (paired t=-0.26, p=0.79). **(B)** No differences in total spindle count between central and frontal leads during NREM-2 (paired t=0.26, p=0.79) and NREM-3 (paired t=-1.57, p=0.13). **(C)** No differences in artefact-free minutes of sleep between central and frontal leads during NREM-2 (paired t=0.86, p=0.40) and NREM-3 (paired t=1.66, p=0.10). Grey lines represent a single participant.

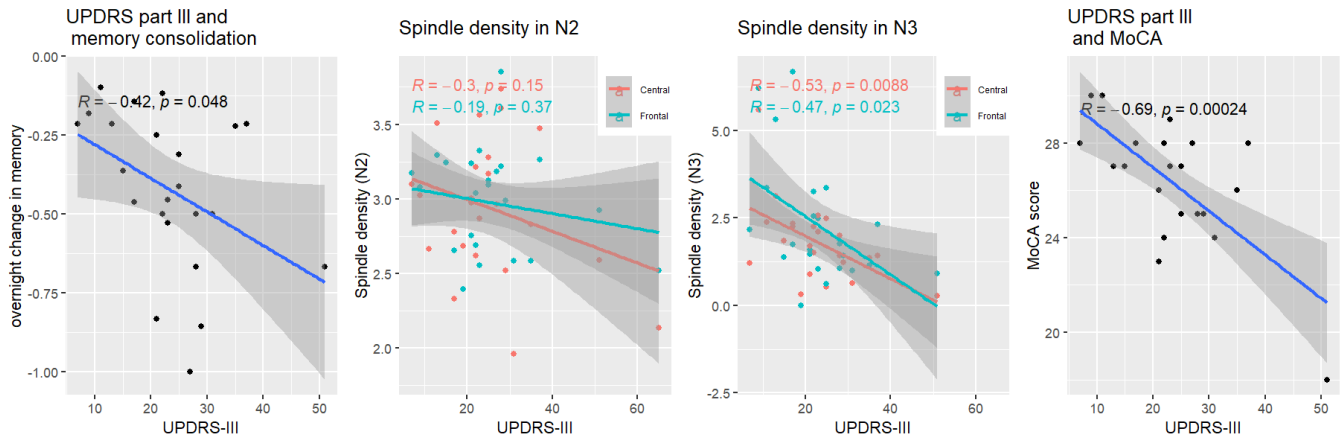

Figure S2. Association between UPDRS part III scores, overnight memory consolidation, sleep spindle density and MoCA. We found a positive relationship between UPDRS part III scores and overnight memory consolidation (R=-0.42, p =0.048), as well as with spindle density over both frontal and central leads during N3 (Central: R=-0.53, p =0.008; Frontal: R=-0.47, p =0.023) and the MoCA (R=-0.69, p =0.0002)

Appendix C: Supplementary Material for Chapter 4

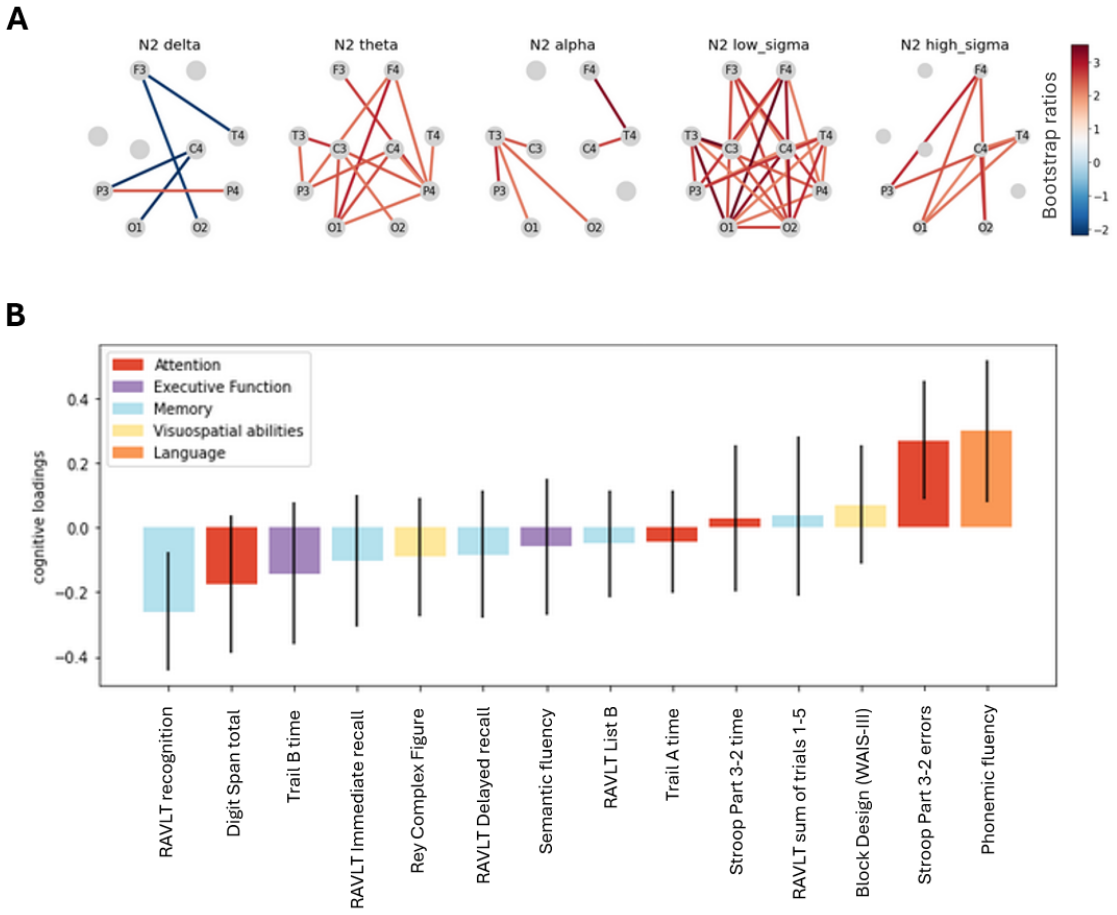

Figure S1. Latent Variable 3 of the NREM-2 PLS. The third latent variable identified in NREM-2 explained 14% of the covariance between connectivity and cognition (p=0.015). A) Connectivity pattern associated with cognition. Visible edges represent edges with bootstrap ratios thresholded at 2.58 ($p < 0.1$), colors indicate the values of the edge's bootstrap ratio. B) Cognitive variables and their correlation coefficient with the connectivity pattern. Variables that are not greyed out have a 95% confidence interval that does not cross zero. As such, these significantly contribute to the connectivity pattern.

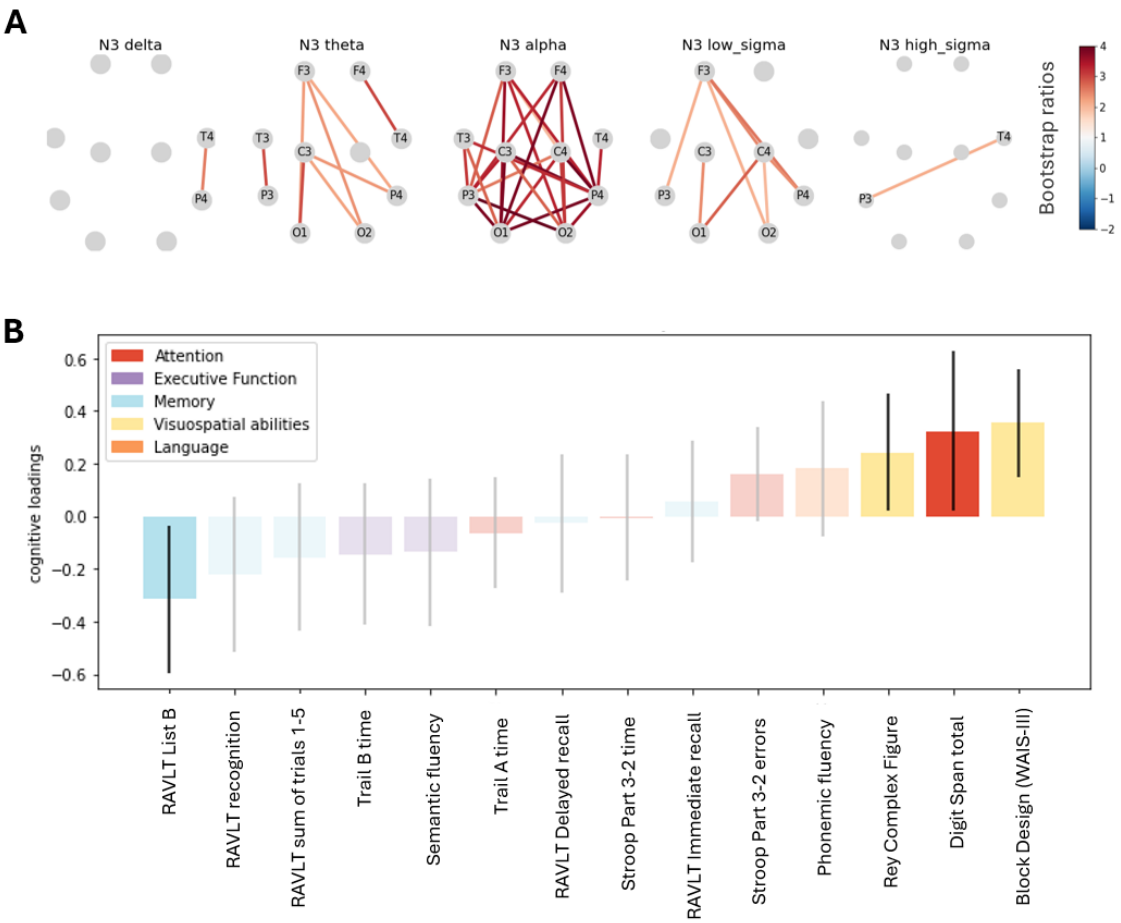

Figure S2. Latent Variable 1 of the NREM-3 PLS, including only participants with at least 5 minutes of time spent in NREM-3. A) Connectivity pattern associated with cognition. Visible edges represent edges with bootstrap ratios thresholded at 2.58 ($p < 0.1$), colors indicate the values of the edge's bootstrap ratio. B) Cognitive variables and their correlation coefficient with the connectivity pattern. Variables that are not greyed out have a 95% confidence interval that does not cross zero. As such, these significantly contribute to the connectivity pattern.

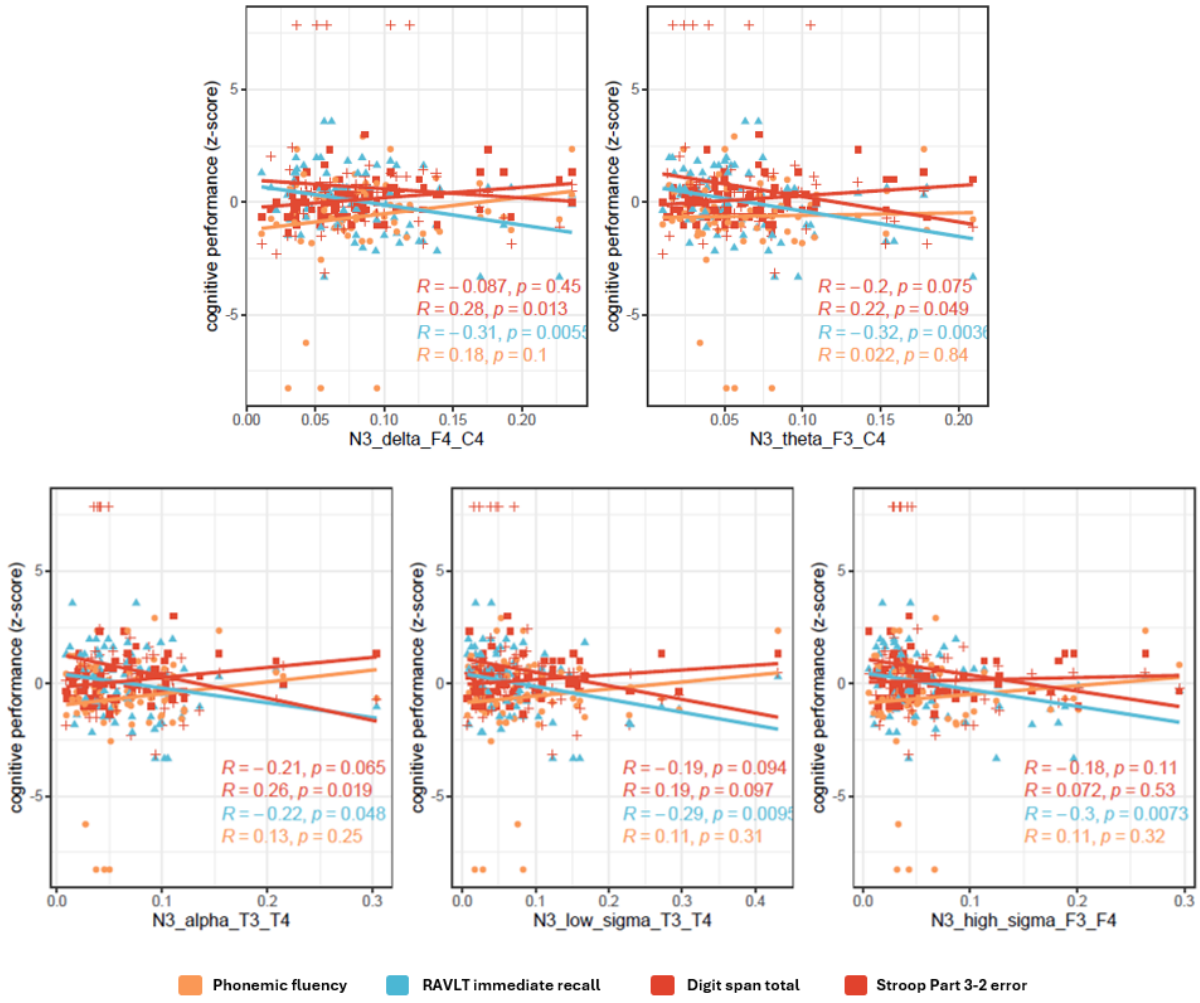

Figure S3. Association between significant edges identified by NREM-3 PLS and cognition. For each frequency band of interest, the edges with the highest bootstrap ratio, identified through PLS, were selected and their imaginary coherence was correlated with cognitive performance on the four tests identified in our NREM-3 PLS. Colors denote the cognitive domain: red represents attention, blue represents memory and orange represents language.