Probable REM Sleep Behaviour Disorder and Cognitive Impairment Specific to Parkinson's Disease: A Novel Approach Investigating Link in General Population

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List of Abbreviations

American Academy of Sleep Medicine……AASM

Internal Pallidal Segment……GPi

External Pallidal Component……GPe

Parkinson's Disease……PD

Principal Component Analysis……PCA

Rapid Eye Movement……REM

Raven's Progressive Matrices……RPM

REM Sleep Behaviour Disorder……RBD

Stop Signal Task……SST

Substantia Nigra Pars Compacta……SNc

Subthalamic Nucleus……STN

Substantia Nigra Pars Reticulata……SNr

Abstract

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease, with patients typically losing 60-80% of dopamine by the time they are diagnosed. However, subtle symptoms appear years before a diagnosis, and this prodromal phase would be a favourable window for early therapeutic interventions. In this study, we sought to identify individuals in the general population who might be in the prodromal phase and determine whether they show Parkinsonian-like symptoms. REM sleep behaviour disorder (RBD) is the most reliable predictor of PD within that prodromal window. The RBD is also strongly associated with reduced cognitive function, and we tested whether that association could be replicated. However, previous studies have not explored the relationship between RBD and more specific cognitive impairments associated with PD, namely, dysfunction of the basal ganglia, which leads to impaired reward learning and enhanced punishment learning. Hence, the second aim of this study was to determine whether this prodromal feature correlates with Parkinson's-specific cognitive decline in the general population. Participants completed the RBD Screening Questionnaire (RBDSQ) to indicate their probable RBD symptoms. General cognition and learning rate imbalance were assessed using a battery of automated tests and probabilistic reinforcement learning tasks, respectively. We found that probable RBD was a significant predictor of cognitive decline; however, this effect interacted with age. No significant results emerged for Parkinson's-specific cognitive decline. It is possible that RBD might be associated with several other neurodegenerative disorders, not necessarily PD, but determining their precise relationship remains a critical area of future study.

Keywords: Parkinson’s Disease, REM sleep behaviour disorder, RBD disorder, basal ganglia dysfunction, learning rate imbalance

Declaration

This thesis contains no material which has been accepted for the award of any other degree of diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

Contribution Statement

In writing this thesis, my supervisor and I collaborated to generate research questions of interest and design an appropriate methodology. I conducted the literature search, while the ethics application and project registration were completed by my supervisor as part of the more extensive study in which my thesis was constructed. My supervisor, other research assistants, and I collaborated in participant testing, while research assistants primarily ran recruitment as part of a more extensive study, and my supervisor provided all participation incentives. My supervisor and I collaborated to code all analyses in R. I wrote up all aspects of the thesis.

Parkinson's Disease

Approximately 6.1 million Parkinson's disease (PD) cases are diagnosed worldwide each year, making it the second most diagnosed progressive neurodegenerative disease. In the last 30 years, the incidence of PD has more than doubled, making it one of the leading causes of neurological disability (Dorsey et al., 2018; Feigin et al., 2019). PD is characterised by the pathological accumulation of intracellular protein aggregates, known as Lewy bodies, and a selective and progressive reduction of dopaminergic neurons in the brain's substantia nigra pars compacta (Dauer & Przedborski, 2003; Takahashi & Wakabayashi, 2001). Although the causes of PD remain unclear, multifactorial aetiology may be present in most cases, with genetic and environmental factors contributing to disease diagnosis and progression (Simon et al., 2020).

Parkinson's Disease Symptoms: Motor and Non-Motor

Traditionally, PD has been portrayed as a movement disorder characterised primarily by impaired motor ability functioning. In PD, typical motor symptoms include tremors (typically shaking of limbs at rest), rigidity (muscles that are too stiff to allow stretching and contraction), bradykinesia (slowed movement), and impaired mobility. These motor symptoms complicate the essential ability of PD patients to complete daily activities (Bernheimer et al., 1973; Sveinbjornsdottir, 2016). Along with motor symptoms, non-motor symptoms such as anosmia, constipation, mood disturbance, and rapid eye movement (REM) sleep behaviour disorder (RBD) are also considered part of PD (Moon et al., 2020; Si et al., 2020; Xie et al., 2019). As PD is primarily viewed as a motor disorder, less research has been conducted on its non-motor symptoms. The non-motor symptoms of PD can also be debilitating, negatively impacting the quality of life for patients (Prasuhn et al., 2017) and thus providing a compelling reason to investigate them in depth. Furthermore, as some of these non-motor symptoms emerge well before noticeable motor changes, they could be used as cues for earlier diagnosis.

The Non-Motor Prodromal Symptoms of Parkinson's Disease and Their Relevance

The current diagnostic criteria for PD allow it to be diagnosed only at an advanced stage when motor symptoms first manifest. PD patients typically experience non-motor symptoms years or decades before exhibiting motor symptoms, indicating that the pathological event leading to this disease began decades ago (Davie, 2008; Fearnley & Lees, 1991; Pfeiffer, 2016). This means that neurodegenerative degeneration is already occurring during these years, but motor symptoms are not severe enough to warrant a PD diagnosis (De La Fuente-Fernández et al., 2011; Fearnley & Lees, 1991; Greenland et al., 2019). This long latent phase of PD, which can vary from several years to decades (usually 5 to 20 years), is called the prodromal phase (Bloem et al., 2021; Postuma & Berg, 2016). In this prodromal PD phase, neurodegeneration may already have started outside SNc (Braak et al., 2003). Therefore, diagnosing PD at the prodromal stage is essential to incorporate timely therapy to mitigate further neurodegeneration (Boeve, 2013; Xie et al., 2021). Patients with prodromal PD have a wide therapeutic window and therefore are ideal for clinical trials of neuroprotective treatments (Postuma & Berg, 2016). Therefore, clinical research should prioritize finding individuals who fall within this prodromal phase.

Predictive Features of Parkinson's Disease

Drawing on an extensive range of sources, Postuma and Berg (2019) point to evidence substantiating the premise that RBD disorder, olfactory dysfunction, depression, impotence, somnolence, and constipation represent noticeable prodromal indications of PD. However, among all non-motor symptoms, idiopathic RBD (iRBD, i.e., RBD without a known cause) is a prominent indicator of PD (Iranzo et al., 2016). In general, RBD manifests itself primarily through the absence of muscle weakness (atonia), which leads people to enact their dreams during the REM phase of sleep (American Academy of Sleep Medicine [AASM], 2014).

Evidence reveals that the pathology of PD usually begins first in the area of the nervous system outside the SNc (Braak et al., 2003). As depicted in the Braak staging system and its subsequent revisions, SNc degeneration is preceded by the loss of the medullary and pontine

compositions that are affected in RBD; this occurs during stage 2 (non-symptomatic phase) of PD (Braak & Del Tredici, 2008; Braak et al., 2003). Motor symptoms of PD have been suggested to be preceded by signs of RBD at stage 3 (symptomatic phase) of the Braak model (Lin & Chen, 2018). Therefore, the Braak hypothesis supports the notion that RBD serves as an essential prognostic prodromal sign of PD. Several studies have found that RBD occurs in a significant proportion of Parkinson's patients during the prodromal stage (Hawkes et al., 2010; Postuma, 2014; Postuma et al., 2015). The substantial cross-sectional and longitudinal literature suggests that the rate of conversion of RBD to neurodegeneration (including PD) was 33.5% at five years of follow-up and that it increased to 96.6% at a 14-year follow-up. Furthermore, approximately 43% of RBD patients are estimated to convert to PD (Galbiati et al., 2019).

Considering RBD is a predictive prodromal sign of PD, examining this aspect before an official diagnosis can carry significant clinical benefit. As mentioned earlier, the progression of PD can be decelerated if people at risk of the disease are identified and treated before receiving an official symptomatic diagnosis. Therefore, it is crucial to Investigate the potential of RBD symptoms to predict parkinsonian-like subtle symptoms in the general population rather than solely focus on symptomatic patients. Given the foregoing specifics, it could be argued that timely detection of RBD could provide invaluable insight into an early intervention to prevent or delay disease diagnosis.

Relationship Between RBD and Cognitive Decline

Several neuropsychological abnormalities are associated with iRBD, even in people who have not developed PD (Van Patten et al., 2022). Previous research suggests that people with iRBD tend to perform less well on psychometric tests (Aguirre-Mardones et al., 2015; Bezdicek et al., 2018; Fantini et al., 2011; Kim et al., 2021; Li et al., 2016; Marcone et al., 2019; Massicotte-Marquez et al., 2008; Sandness et al., 2022; Youn et al., 2016). However, the results vary according to the cognitive area under scrutiny (see Table 1). Such disparities may be attributed to small sample sizes, demographic heterogeneity, and the fact that different cognitive assessments have different measurement precision (Gagnon et al., 2012). The most significant impact of iRBD manifests itself in

executive functioning, attention, linguistic memory, and visuospatial functions (see Table 1). On the other hand, response inhibition, an important aspect of executive function, has been less explored in the literature, but studies showed that iRBD patients and healthy controls did not have significantly different stop signal reaction times on Go/NoGo tasks that measure response inhibition (Delazer et al., 2012).

Furthermore, a similar relationship between RBD and cognition can be observed in people who have developed PD. Oliveira and Cardoso (2021) reported a significant association between RBD and cognitive impairment in PD patients. A meta-analysis by Mao et al. (2020) found that PD patients with confirmed RBD perform significantly worse on a range of cognitive tests such as long-term memory, language, visuospatial/constructional ability and global cognitive functioning than patients without RBD. Conclusively, a literature review revealed that RBD is associated with cognitive decline and that the effect can persist even following PD diagnosis.

Table 1

Summary of Studies on Cognitive Performance in Patients with iRBD

Study	Cognitive measure(s)	Sample size/ Participant groups	Statistical significance/Post hoc comparison
Aguirre-Mardones et al., 2015	MoCA	84 (44 iRBD, 40 HC)	MoCA (ns)
Bezdicek et al., 2018	MoCA, A, WM, EF, EM, PMS	90 (60 iRBD, 30 HC)	iRBD < HC [MoCA (*), EF ($*^{1/2}$), EM ($*^{3/3}$)] A (ns), WM (ns), PMS (ns)
Fantini et al., 2011	MMSE, M, EF, VSA,	36 (24 iRBD, 12 HC)	iRBD < HC [M ($*^{3/5}$), VSA ($*^{1/1}$)] MMSE (ns), EF (ns)
Kim et al., 2021	K-MMSE, CDR	38 (21 iRBD, 17 HC)	iRBD < HC K-MMSE (*), CDR (*)
Li et al., 2016	MoCA, MMSE, A/PS, EF, WM, VM, L, VSA	38 (21 iRBD, 17 HC)	iRBD < HC [MoCA (*), VM ($*^{5/7}$), L ($*^{1/5}$), VSA ($*^{1/4}$)] MMSE (ns), A/PS (ns), EF (ns), WM (ns)
Marcone et al., 2019	MoCA, MF, EF	58 (13 iRBD-MCI, 25 iRBD-nMCI, 20 HC)	iRBD < HC MoCA (*), EF (*), MF (*)
Massicotte-Maquez et al., 2008	A/PS, WM, EF, VM, VSA	28 (14 iRBD, 14 HC)	iRBD < HC [A/PS (*), WM ($*^{1/3}$), EF ($*^{1/2}$), VM ($*^{5/7}$)] VSA (ns)
Sandness et al., 2021	CM, VM, ViM, PS, EF, PMS, RT, CA, CF, VSA	50 (20 iRBD, 10 sRBD, 20 HC)	sRBD < iRBD < HC [PS (*), VSA ($*^{3/3}$)], sRBD < iRBD, HC [PMS (*)] CM (ns), VM (ns), ViM (ns), EF (ns), RT (ns), CA (ns), CF (ns), VSA (ns)
Youn et al., 2016	MMSE, M, EF, VSA	153 (96 iRBD, 57 HC)	iRBD < HC [MMSE (*), EF ($*^{1/5}$), VSA ($*^{2/2}$)] M(ns)

Note. MOCA and *MMSE* provide a score for general cognitive functions, *MMSE* = Mini-Mental State Examination, *MOCA* = Montreal Cognitive Assessment, *K-MMSE* = Korean version of the Mini-Mental State Exam (K-MMSE*), CDR* = Clinical Dementia Rating, *CM* = Composite Memory, *VM* = Verbal Memory, *ViM* = Visual Memory, *PS* = Processing Speed, *MF* = Memory Functioning, *EF* = Executive Function, *RT* = Reaction Time, *CA* = Complex Attention, *CF* = Cognitive Flexibility, *A* = Attention, *WM* = Working Memory, *L* = Language, *M* = Memory, *VSA* = Visuospatial Abilities, *LTM* = Long Term

Memory, *STM* = Short Term Memory, *RBD* = REM Sleep Behaviour Disorder, *iRBD* = idiopathic RBD, *pRBD+* = Probable RBD, *pRBD-* = no RBD, *iRBD-MCI* = Idiopathic RBD With Mild Cognitive Impairment, *iRBD-nMCI* = Idiopathic RBD Without Mild Cognitive impairment*, sRBD = Symptomatic RBD, HC* = Healthy Control.

*** = Denotes significant difference between RBD and HC groups. *ns* = Denotes no significant difference between RBD and HC groups. In the last column, the superscript fraction indicates the number of significant comparisons out of the total cognitive tests administered. These comparisons did not have a Bonferroni correction for multiple comparisons applied.

The Basal Ganglia: A Crucial Role in Parkinson's Disease

Although PD and RBD are associated with cognitive dysfunction, understanding the neural circuits that degenerate in PD might help us investigate cognitive dysfunction more specific to PD. The decline in cognition in PD is strongly associated with the malfunction of the basal ganglia (Blandini et al., 2000; Obeso et al., 2008). In its strictest sense, the term 'basal ganglia' refers to the interconnection of five nuclei deeply embedded in the inferior portion of the brain. These include the putamen and caudate nuclei (collectively known as the striatum), the globus pallidus (including internal (GPi) and external segments (GPe)), the substantia nigra (the pars compacta SNc and pars reticulata SNr segments), and the subthalamic nucleus (STN). The brain stem, the thalamus, and the cerebral cortex are strongly associated with these subcortical structures of the basal ganglia (Lanciego et al., 2012; Wickens, 1997). The basal ganglia and the related nuclei are collectively involved in various motor and cognitive functions (Nambu, 2008).

During the late 1980s, the direct and indirect pathways model provided a significant breakthrough in understanding the function of basal ganglia circuitry (Albin et al., 1989; Bergman et al., 1990). Figure 1 shows a simplified structural model with two parallel cortex-basal ganglia-thalamus-cortex pathways (direct and indirect) regulated by dopamine. The frontal cortex transmits motor commands to the thalamus through basal ganglia structures as per the classical model of basal ganglia function. Hence the basal ganglia act as functional intermediaries between the cortex

and thalamus by processing and organizing input signals from the cortex and generating and directing the valid output signals to the cortex through the thalamus. The thalamus functions as a facilitator or constraint of motor commands, and disinhibition is necessary for a movement to occur since the thalamus usually rests in a state of tonic inhibition from the GPi. The direct and indirect pathways connect the cortex to the thalamus, and their activity determines whether the thalamus will be disinhibited or not (Blandini et al., 2000).

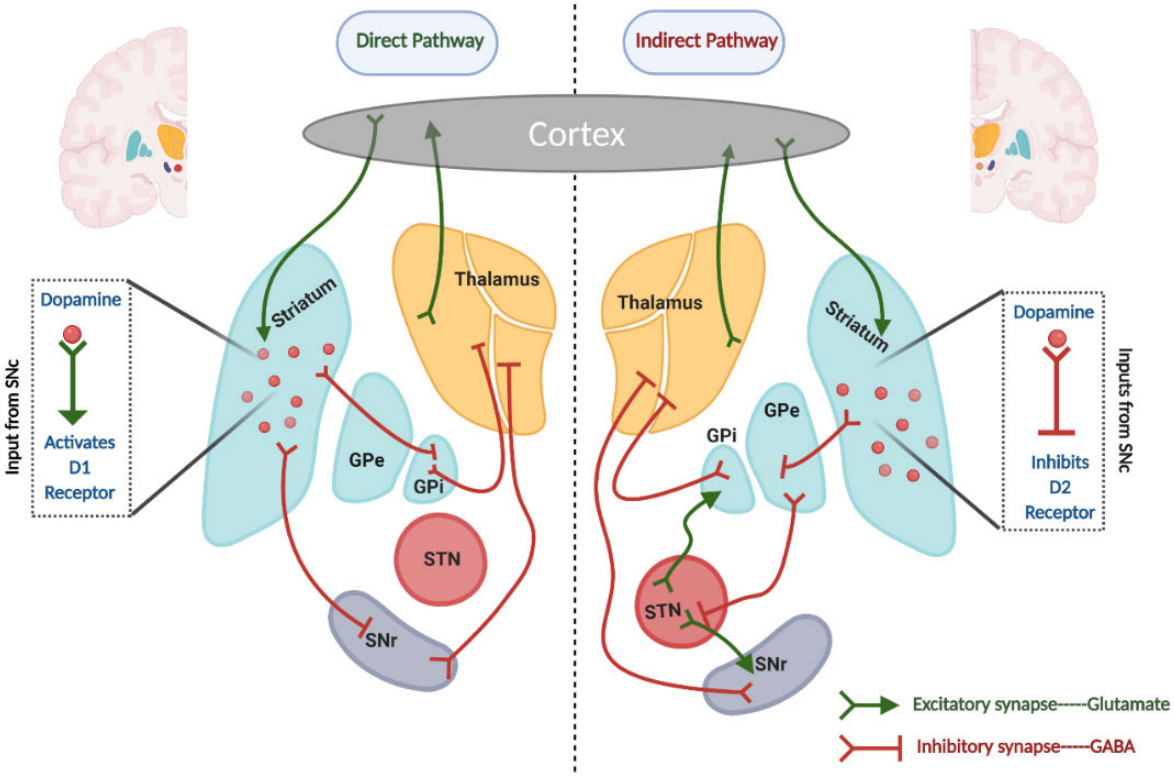
The net effect of increased activity in the direct pathway is to disinhibit the thalamus, facilitating movement initiation (see Figure 1). The net effect of indirect pathway activity is to generate further inhibition of the thalamus, thereby suppressing movements by strengthening the inhibition of thalamo-cortical activity (Alexander & Crutcher, 1990; DeLong, 1990; Nambu, 2004). These two pathways operate opposite to allow only certain motor plans to be performed and inhibit alternative ones. Direct pathway activation permits desired motor commands, while indirect pathway activation inhibits undesirable movements or motor commands that are not likely to be followed by positive feedback (Galvan & Smith, 2010).

As shown in Figure 2A, dopamine contributes to the normal functioning of the basal ganglia circuitry by promoting direct pathway activity and inhibiting indirect pathway activity simultaneously (Obeso et al., 2008). The tonic level of dopamine and the activity of the D1 and D2 receptors affect the plasticity of the synapses on direct and indirect pathways, respectively (Shen et al., 2008). D1 receptors require high dopamine levels to become active, so the loss of dopamine in PD primarily affects the direct pathway (Kreitzer & Malenka, 2008; Meredith et al., 1992). This inadequacy of neuron activation leads to imbalances in processing extrinsic output from the striatum to GPe and GPi, which further leads to hyperactivity of the STN. Hyperactivation of STN leads to an increase in efficiency of the indirect pathway, which requires low dopamine levels to be active, and a decrease in efficiency of the direct pathway circuit, as shown in Figure 2 (Albin et al., 1989; DeLong, 1990; Parker et al., 2016). This loss of dopamine in PD leads to a hyperactive indirect pathway, leading to

global inhibition of the motor cortex, which in turn leads to cardinal motor symptoms (Neumann et al., 2018).

Figure 1

Cortico–Basal Ganglia–Thalamo–Cortical Circuits and Their Interactions



Note. For ease of reference, several networks within these basal ganglia have been excluded from this figure. The left panel illustrates the "Direct Pathway" connections, and the right panel illustrates the "Indirect Pathway" connections. The red and green arrows indicate inhibitory and excitatory connections, respectively. D1 and D2 refer to dopamine receptor subtypes; *GPi* = internal pallidal segment; *GPe* = external pallidal component; *SNr* = substantia nigra pars reticulata; *SNc* = substantia nigra pars compacta; STN = subthalamic nucleus.

Basal Ganglia: A Crucial Component of Cognition

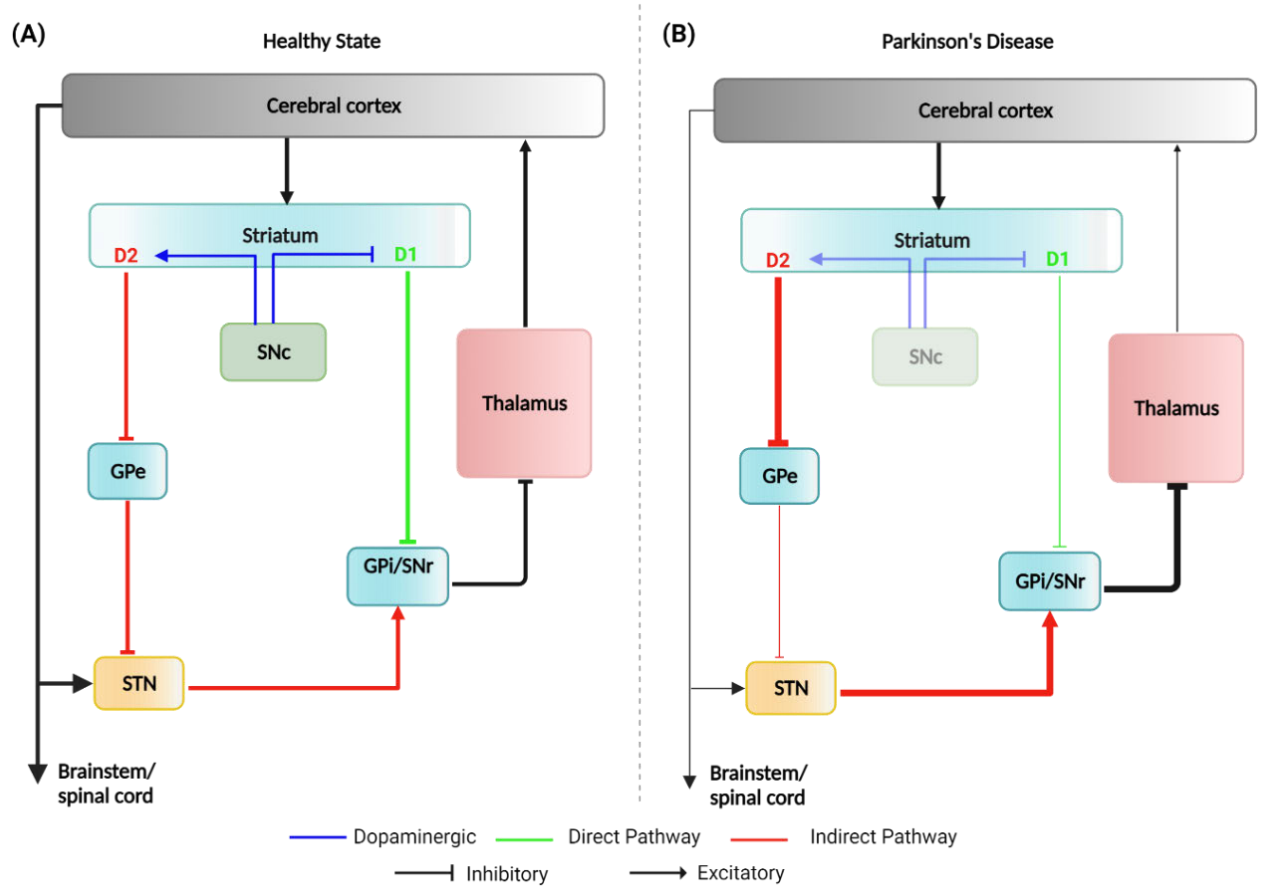
Previously, it was assumed that the basal ganglia were primarily involved in motor control. However, the role of basal ganglia in cognitive functions is now well established (Leisman et al., 2014; MacDonald et al., 2014; Middleton & Strick, 2000). The basal ganglia modulate cognition by

regulating cognitive processes in the cortex, such as reinforcement learning through the direct pathway and inhibitory control through the indirect pathway, further affecting decision-making capacity (Frank, 2005). As a result, the loss of dopamine in PD leads to decision-making deficits. A chronically low amount of striatal dopamine in PD may lead to impaired reward learning and improved punishment learning (Delgado et al., 2005; Frank, 2005; Frank et al., 2004; Niv & Rivlin-Etzion, 2007; Shohamy et al., 2006).

The role of dopamine in decision-making is further supported by other experiments, which showed that PD patients on dopaminergic medications learn better from rewards than punishments. In contrast, patients off dopaminergic medication exhibited the opposite bias (Bodi et al., 2009; Frank et al., 2004; Kobza et al., 2012; Mathar et al., 2017; McCoy et al., 2019; Moustafa et al., 2008; Palminteri et al., 2009; Rutledge et al., 2009; Vo et al., 2018). An explanation of this behaviour is that learning to repeat rewarded actions relies on D1-mediated neuroplasticity in the direct pathway, and learning to avoid punishment relies on D2-mediated neuroplasticity in the indirect pathway (Kravitz et al., 2012). So, the activation of neurons expressing dopamine D1 receptors promotes behaviours that have previously led to rewarding outcomes, while activation of neurons expressing dopamine D2 receptors suppresses decisions that have previously led to punishing outcomes (Bahuguna et al., 2015; Frank & Fossella, 2011). In PD patients, neurons expressing dopamine D1 receptors are deactivated due to dopamine loss, resulting in impaired reward learning (see Figure 2). The reason for deactivation is that D1 receptors rely on high dopamine levels, whereas D2 receptors do not, resulting in more severe impairment in reward learning than punishment learning (Kravitz et al., 2010; Kravitz et al., 2012).

Figure 2

The Variation in the Cortico–Basal Ganglia–Thalamo–Cortical Circuit in a Healthy State vs PD



Note. For ease of reference, several networks within the basal ganglia have been excluded from this figure. Panel A illustrates the basal ganglia circuits in the "normal" state, and panel B illustrates the changes in the basal ganglia model associated with PD. Abbreviations: D1 and D2 refer to dopamine receptor subtypes; *GPi* = internal pallidal segment; *GPe*, external pallidal component; *SNr*, substantia nigra pars reticulata; *SNc*, substantia nigra pars compacta; STN, subthalamic nucleus. Thicker or thinner arrows in the right panel indicate that the projections have increased (thicker arrows) or decreased (thinner arrows) relative to normal. Green arrows indicate projections specific to direct pathways, while red arrows indicate those specific to indirect pathways. The lighter green colour of *SNc* (on panel B) indicates that dopaminergic neurons have degenerated due to PD.

As we age, we lose dopamine as well (Bohnen et al., 2009), and trends such as losing the ability to learn from rewards have also been observed in healthy older adults (Eppinger & Kray, 2011; Frank & Kong, 2008; Samanez-Larkin & Knutson, 2014; Simon et al., 2020). However, few studies contradict this view, showing that aging impairs punishment and reward learning (Lighthall et al., 2013; Samanez-Larkin et al., 2014; Sojitra et al., 2018). These inconsistencies may be because ageing is associated with dopamine loss, as well as loss of both dopamine D1 and D2 receptors (Rinne et al., 1993; Wang et al., 1998). Combined with dopamine loss, reward learning deteriorates more quickly with age than punishment learning. Therefore, studying these patterns in people without PD is crucial because they may begin to show stronger trends towards losing their ability to learn from rewards than others, which may indicate later PD diagnosis. Furthermore, if RBD can predict PD, it should correlate with these learning patterns in people without a PD diagnosis. These learning patterns can be assessed using the probabilistic reinforcement learning task (Frank et al., 2007; Frank et al., 2004).

The probabilistic learning task has been widely applied to understand learning patterns in PD patients and to assess how learning from positive versus negative feedback is altered by dopamine levels (Frank et al., 2007; Frank et al., 2004; Grogan et al., 2017; Palminteri et al., 2009; Shiner et al., 2012). The probabilistic reinforcement learning task involves participants making informed decisions based on either positive feedback (i.e., learning from rewards) or negative feedback (i.e., learning from punishment). Hence allowing us to examine the extent to which learning that relies on the basal ganglia is imbalanced by subtracting the punishment learning score from the reward learning score. A probabilistic reinforcement learning task might be more sensitive to detecting cognitive decline that relies on the basal ganglia than other general cognitive tests used in previous studies.

The Current Study in the Context of Current Knowledge Gaps

According to existing research, RBD has been associated with reduced cognitive functioning (see Table 1) and is a predictive feature of PD. Nonetheless, some limitations remain; firstly, in some studies, the sample size is small, making it difficult for authors to accurately estimate the size of the

effects (Aguirre-Mardones et al., 2015; Bezdicek et al., 2018; Fantini et al., 2011; Kim et al., 2021; Li et al., 2016; Marcone et al., 2019; Marques et al., 2010; Massicotte-Marquez et al., 2008; Sandness et al., 2022). Secondly, many previous studies have used arbitrary cut-off points to split continuous variables into categories (see Table 1), which is not an accurate approach to utilize. A continuous variable provides greater power to the study and may provide more accurate and sensitive data for analysis than a categorical variable (Altman, 2014; Bennette & Vickers, 2012; MacCallum et al., 2002).

Therefore, we designed our first hypothesis to extend the study related to the role of RBD in cognitive decline by using a much larger sample size than previously available. This study will also address the issue concerning the dichotomous nature of the data in previous studies by treating the measure of RBD as a continuous variable. Thus, we intend to contribute meaningfully to expanding the evidence base by conducting our study. The first hypothesis of this study is that possible symptoms of RBD in the general population should predict general cognitive decline.

Moreover, previous studies did not investigate the relationship between RBD and more specific cognitive impairments associated with PD, namely, dysfunction of the basal ganglia, which leads to impaired reward learning and enhanced punishment learning. Hence to evaluate this dysfunction of the basal ganglia, which leads to learning rate imbalance, it is necessary to use specific cognitive tests that assess basal ganglia function, such as probabilistic reinforcement learning tests. So, the second hypothesis of this study is that the possible symptoms of RBD in the general population should predict learning rate imbalance (lower reward than punishment learning). To the best of my knowledge, this work offers one of the first investigations to scrutinise the relationship between RBD and cognitive impairment related to the functioning of the direct and indirect pathways of the basal ganglia, potentially providing more substantial evidence that RBD could be used as an early marker of increased PD risk.

Method

Participants

The experiment protocol was approved by the Human Research Ethics Committee of the University of Adelaide (ethics approval number H-2020-017). In this study, data were collected as part of a broader research project aimed at assessing the impact of aging on cognitive ability. Data was collected from April 2021 to August 2022. Participants were recruited mainly through Facebook ads. Additionally, physical flyers and posters were distributed, and participants were recruited through the researchers' networks. In the experiment, seven hundred and thirty adults (*mean age* = 50.92*, SD* = 18.17*, range* = 18-86) participated; of these, 500 were females, 1 was intersex, and 229 were males. We only analysed data from participants aged 50 years and older (*n* = 443) because 50 years of age represent the minimum diagnosis age for idiopathic PD, whereas a diagnosis before the age of 50 represents young-onset PD presents differently and is assumed to result from genetic causes (Mehanna et al., 2014; Schrag et al., 2003). Among these four hundred and forty-three participants, 50 participants were excluded from the study because they did not identify as either male or female (*n*=1), had missing data (*n*=9), and their performance on some of the cognitive tasks reflected anticipatory responses or inattention (*n*= 40; see details in Appendix A). The final sample (*N* = 393; 264 female and 129 male; *mean age* = 63.30, *SD* = 8.25 years) consisted of healthy adults aged 50-86 who have self-identified as fluent in English, not taking medications that interfere with neurological function for at least six months; not experiencing a neurological condition or a history of brain injury; not having a learning disability; no uncorrected visual or auditory impairment; not being drug or alcohol dependent, currently or previously; and, not smoking more than five cigarettes per day.

Procedure

Participants were asked to complete a series of online survey questionnaires (30 minutes) and to attend an in-person research session at the University of Adelaide (2.5 hours). The online questionnaires collected demographic information, including age, sex (male, female, intersex), and

medical history covering various medical conditions. The REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ) was also completed as part of an online questionnaire collection. Before completing online surveys, participants received an overview of the study (see Appendix B), along with information about biobanking, which detailed how certain types of data will be stored (see Appendix C). All the information received above, including the consent form (see Appendix D), was signed by the participants in person when they attended their in-person session. Each participant received a $50 Coles/Myer gift card to thank them for participating in the study.

Measures

REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ)

As an extensively used instrument, the RBDSQ assesses the self-reported presence and severity of RBD disorder symptoms in the general population (Stiasny-Kolster et al., 2007). This questionnaire assesses the main characteristics of RBD according to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association, 2013). Scale administration usually takes five minutes, and the scale is in the public domain.

RBDSQ measures different events related to RBD, including the attributes of eye and body movements during sleep, sleep quality, and the connections between dreams and behaviours. Different topics are included to assess sleep quality from different perspectives (Li et al., 2017). The 10-item self-report scale is used to determine the most noteworthy clinical characteristics of RBD: items 1 to 4 assess the rate of recurrence and content of dreams and their association to nocturnal movements and behaviour; item 5 assesses self-inflicted injuries and injuries to bed partners; item 6 consists of four subsections, each addressing a particular aspect of nocturnal motor behaviour, such as vocalisations, abrupt limb movements, complex movements, and objects falling from bedsides; items 7 and 8 assess waking up in the middle of the night; item 9 assesses restless sleep in general, and item 10 asks about any neurological impairment. Answers to each item are yes/no choices. RBDSQ scores range from 0 to 13, with higher scores indicating more RBD-related features (Stiasny-Kolster et al., 2007).

The RBDSQ has demonstrated excellent psychometric properties. Cronbach's alpha of 0.77-0.89 indicates the scale has high internal consistency (Stiasny-Kolster et al., 2007; Wang et al., 2015). The intraclass correlation coefficients of 0.84–0.95 indicate that the scale has good test-retest reliability (Miyamoto et al., 2009; Tarı Cömert et al., 2016). Through a meta-analysis, Li et al. (2017) assessed the effectiveness of the RBDSQ in diagnosing RBD. A cut-off point of 5 yielded a pooled sensitivity of 0.91, a specificity of 0.77, and a diagnostic odds ratio of 34. These values indicate an impressive diagnostic performance for RBD screening using the RBDSQ, showing high accuracy in classifying patients with RBD.

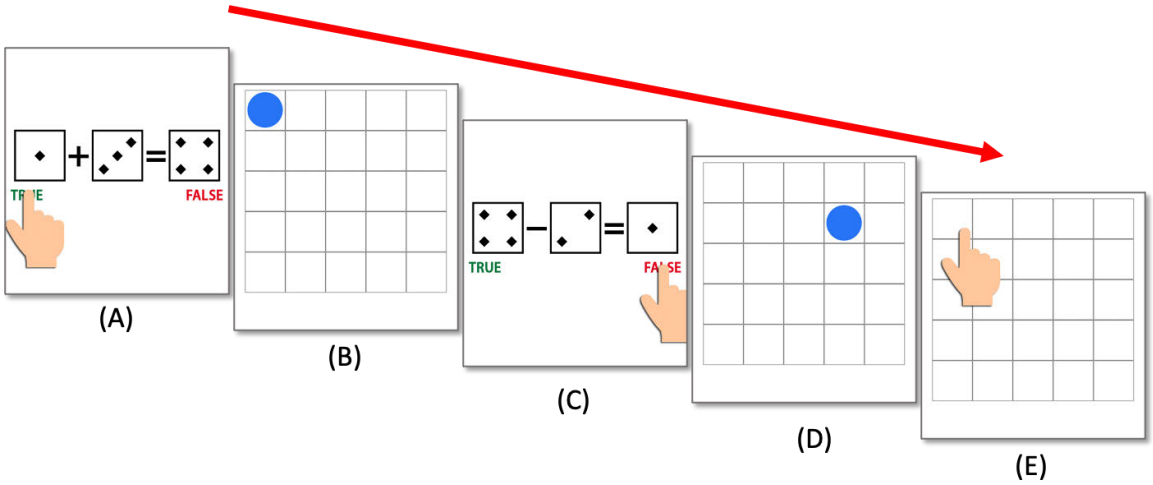
General Cognition and Learning Rate Imbalance Measures

The tasks of general cognition ability (visual-spatial working memory, verbal working memory, visual processing speed, reasoning ability, and response inhibition) and learning rate imbalance were administered on an Apple iPad Pro 10.2-inch (Apple Inc., Cupertino, California, USA) and programmed in Xojo software (Xojo Inc., version 3, 2019, Austin, Texas; Cavanagh et al., 2011). Apart from the verbal working memory task that the research assistant administered, all other tasks were self-administered by participants. At the start of each task, the participants were guided by written instructions (see Appendix E) and pre-recorded verbal instructions and animations on the iPad.

Visual-Spatial Working Memory. The dot matrix task was adapted from a task published by Law et al. (1995) that assesses visual working memory. The task measured the storage capacity and resistance to interference of working memory (Law et al., 1995; Miyake et al., 2001). In this task, participants were asked to memorize the position of the sequence of dots (storage capacity) presented on a 5x5 grid while providing their response to a simple math question, with participants given 4 seconds to answer “True” or “False” (see Figure 3). There were 16 unique items in the task, with 4 items per level. Increasing levels require recalling more dots, starting with 2 to a maximum of 5. Participants proceeded to the next level only if they identified the dot locations correctly more than 75% of the time. Each correct recall of a dot was worth one point.

Figure 3

Dot Matrix Task



Note. An example of a Dot Matrix item for level 2 dots: (A) Basic math problem; (B) Presenting location of the first dot (dot appears for 1.5 seconds); (C) Second elementary math problem; (D) Presenting location of the second dot; and (E) choosing points on an empty grid to indicate the previously seen dot locations from (B) and (D).

Verbal Working Memory. The digit span task was designed to measure storage capacity and the effects of manipulation of information. A design was adapted from the original version for the digit span task (Hebb, 1961; Monaco et al., 2013). For the digit span forward items, acoustic recordings read out a list of digits at one digit per second with a steady pitch, and upon hearing the sequence, participants were asked to repeat it in the same order. As shown in Figure 4, the forward digit span was divided into 8 levels ranging from two to nine digits per sequence, with each level consisting of two items of the same length. Testing discontinues if both items associated with each level (number of digits per sequence) were incorrectly recalled. For each correctly recalled sequence, one point was awarded. Digit span backward was conducted similarly, although participants must recall the sequence of digits in reverse order, with the most extended list consisting of eight items. The backwards digit span was divided into 7 levels ranging from 2 to 8 digits per sequence, with each level consisting of two items of the same length (see Figure 4). The

total score is based on the number of sequences correctly repeated in forwarding order for the forward digit span task and reverse order for the backward digit span task.

Figure 4

Digit Span Task

(A)

Digit Span Forward
1, 7
6, 3,
5, 8, 2
6, 9, 4
6, 4, 3, 9
7, 2, 8, 6
4, 2, 7, 3, 1
7, 5, 8, 3, 6
6, 1, 9, 4, 7, 2
3, 9, 2, 4, 8, 7
5, 9, 1, 7, 4, 2, 8
4, 1, 7, 9, 3, 8, 6
5, 8, 1, 9, 2, 6, 4, 7
3, 8, 2, 9, 5, 1, 7, 4
2, 7, 5, 8, 6, 2, 5, 8, 4
7, 1, 3, 9, 4, 2, 5, 6, 8

(B)

Digit Span Backward
2, 4
5, 8,
6, 2, 9
4, 1, 5
3, 2, 7, 9
4, 9, 6, 8
1, 5, 2, 8, 6
6, 1, 8, 4, 3
5, 3, 9, 4, 1, 8
7, 2, 4, 8, 5, 6
8, 1, 2, 9, 3, 6, 5
4, 7, 3, 9, 1, 2, 8
9, 4, 3, 7, 6, 2, 5, 8
7, 2, 8, 1, 9, 6, 5, 3

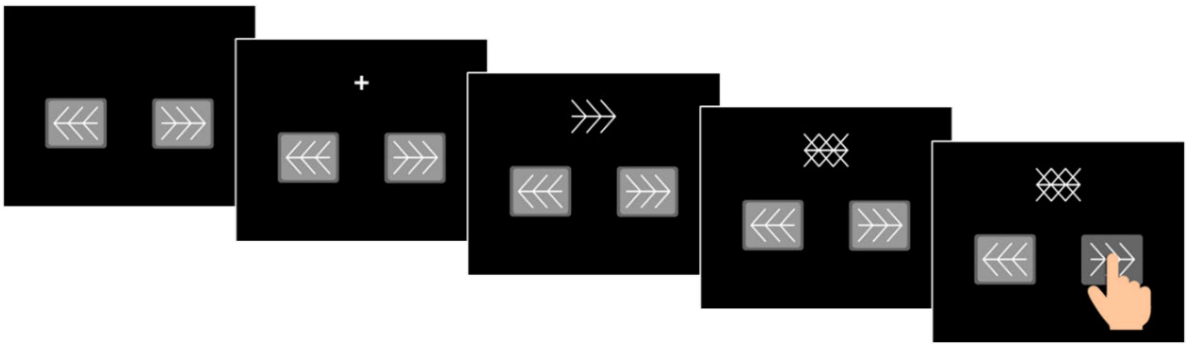
Note. (A) Digit span forward task comprising 16 items ranging from two to nine digits per sequence), and (B) Digit span backward task comprising 14 items from two to eight digits per sequence.

Visual Processing Speed. The inspection time task was designed based on an original version (Vickers et al., 1972) and measured visual processing speed using inspection time (*i.e.* exposure time needed to differentiate or identify a relatively simple stimulus). Participants were first shown an arrow pointing left or right, then covered by a mask. Participants must indicate the arrow's direction before it was masked, though responses were not timed (see Figure 5). A total of 90 trials were conducted, half displaying a left arrow and the other half displaying a right arrow. To achieve a 75% correct response rate, the Bayesian algorithm lengthens stimulus duration if excessive numbers of incorrect responses are encountered and shorten stimulus duration if excessive numbers of correct responses are encountered. The 30 easy trials were shortened to 0.45 seconds to alleviate

frustration. Process speed can be measured using this task without motor or learning confounding outcomes. Visual processing speed was measured in milliseconds (the minimum duration of arrow presentation that allows an individual to detect its direction with 75% accuracy), with lower values indicating faster processing.

Figure 5

Inspection Time

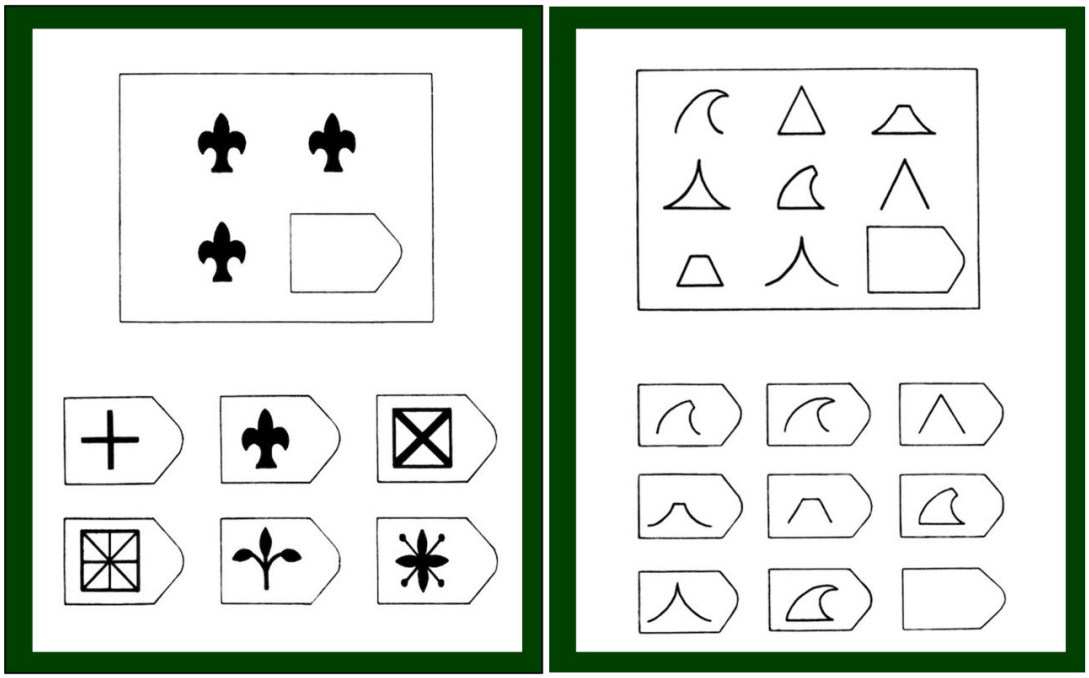


Note. An example of an inspection time sequence displays the arrow's onset before the mask covers the original stimulus' direction. Participants use two buttons to indicate the arrow's direction.

Reasoning Ability. A computerised, abbreviated version of Raven's Progressive Matrices (RPM) was used for measuring higher-order reasoning abilities (Raven et al., 2003). Participants were presented with 18 items of progressively increasing difficulty in which they must select which element best completes a matrix pattern. Each matrix contained four or nine target images that form a pattern sequence along each row or column, with the bottom-right grid piece blank (see Figure 6). This test requires participants to select the best matching option to complete the pattern. Correct selections earn one point. The task timed out after 15 minutes. The intraclass correlation coefficients of 0.82 indicated that this test has good test-retest reliability (Bors & Stokes, 1998).

Figure 6

Raven's Progressive Matrix Task



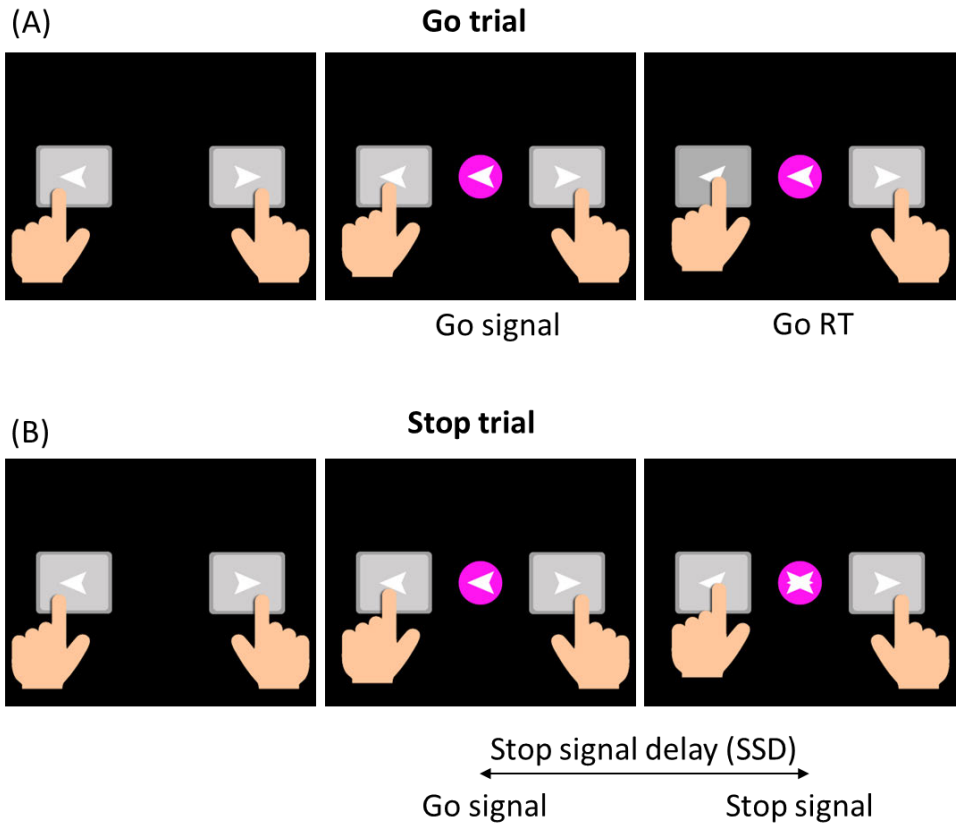
Note. Examples of Raven's Progressive Matrix items, where the top square contains three images (on the left), or eight (on the right) repeated a pattern in every row or column. The bottom-right grid piece was blank. The bottom six (on the left) and nine (on the right) shapes show participants' options to complete the pattern.

Response Inhibition. Response inhibition was measured using a Stop Signal Task (SST), where two arrow buttons were shown to participants on each trial. The participants were required to indicate if an arrow points to the left or right using a speeded response. As shown in Figure 7, one trial was the “Go trial”, where one arrow stayed the same (Go signal), and the participants had to press the button as quickly as possible on the side of the arrow pointed. The second was the "Stop trial", during which one arrow appeared and was immediately covered by another arrow (Stop signal), and participants had to withhold their response. A random mix of 120 Go trials and 60 Stop trials was used. Using a Bayesian algorithm, the duration of the interval between the Go and Stop signals on Stop trials was optimized to ensure that 50% of trials result in successful inhibitions (the critical Stop Signal Delay, SSD). The duration of delay can range from 50ms to 550ms. Response

inhibition ability can be assessed through an individual's Stop Signal Reaction Time (SSRT), calculated as the difference between their average Go reaction time on Go trials and their critical Stop Signal Delay (Livesey & Livesey, 2016). Shorter SSRT indicate faster response inhibition.

Figure 7

The Stop Signal Task



Note. The Stop Signal Task trials consisted of two trials: (A) "Go trial", participants were required to choose a direction in response to the appearance of a single arrow; (B) In the "Stop trial", Participants inhibited their response upon seeing the superimposed arrow.

Learning Rate Imbalance Measure. The probabilistic reinforcement learning task was used to measure reinforcement learning. The purpose of the task was to examine participants' learning from positive (reward) and negative (punishment) feedback, which is assumed to rely on the basal ganglia's direct and indirect pathways, respectively (Frank et al., 2004). The learning rate imbalance was determined based on the difference between these two feedbacks. In contrast to fear-based

assessment designs that tend to hide individual differences due to ceiling effects, learning was assessed in a non-fear-based manner, using mild rewards and punishment in the form of performance feedback to capture and represent slight individual variances (Lissek et al., 2005). Probabilistic reinforcement learning consists of repeated, two-alternative forced-choice decisions. There was a set chance that each cue would elicit positive feedback if chosen. The task consists of two successive stages, a training phase and then a testing phase (Figure 8). Both phases involved choices, but only the training phase provided feedback.

In the training phase, 16 randomly intermixed trials were conducted for each of the six sets. There were two pairs of stimuli, each presented 8 times within a set, and each associated with different probabilities of yielding correct feedback. The stimuli in the first pair, S1 and S2, had a 100% and 0% chance of generating correct feedback, respectively. The stimuli in the other pair, S3 and S4, had a 75% and 25% chance of generating correct feedback, respectively. Participants were instructed to tap one of the stimuli within four seconds. Darkened borders were displayed for 300 ms to emphasize their selection; then feedback was shown for 1 second. Correct feedback ("Correct") appears in blue font; incorrect feedback ("Incorrect") appears in red font. Failure to respond within 4 seconds resulted in the message "No response detected" appearing in red for 1 second, followed by the next trial.

Participants' reward and punishment learning strategies were examined using *win-stay* and *lose-shift* scores. *Win-stay* scores were calculated based on the proportion of trials in which participants chose the same stimulus after receiving positive feedback in the preceding trial. The *lose-shift* score was calculated as the proportion of times participants learned not to repeat the previous unsuccessful choice after receiving negative feedback, i.e., the proportion of trials on which they switched their response after receiving negative feedback (Frank & Kong, 2008).

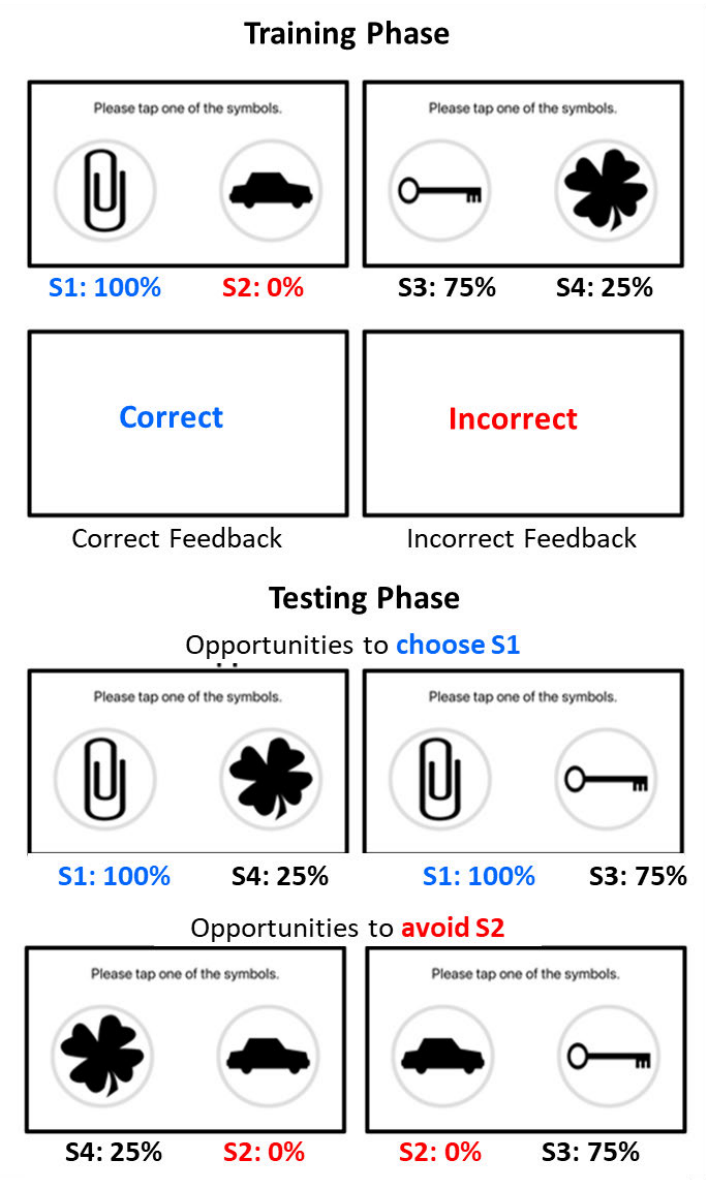
In the testing phase, including 16 randomly intermixed trials, participants were instructed to choose the stimulus that felt most "correct" in each pair based on the information gained during the

trial. The responses in the test phase generated a second pair of measures of the participants' learning. This phase of testing assumed that the choice of stimulus S1 (which had a 100% chance of being correct during training) was due to learning from positive feedback while avoiding stimulus S2 (which had a 0% chance of being correct during training) indicated learning from negative feedback. The variables *choose-S1* and *avoid-S2* correspond to the proportions of participants' choices to choose S1 and avoid S2 during the testing phase, respectively.

All the four measures (*win-stay*, *lose-shift*, *choose-S1* and *avoid-S2)* were averaged for all six sets, and the *win-stay* and *choose-S1* measures were assumed to reflect learning from rewards, which should rely on the direct pathway, whereas *lose-shift* and *avoid-S2* measures were assumed to reflect learning from punishment, which should rely on the indirect pathway.

Figure 8

Probabilistic Reinforcement Task



Note. During the training phase, two pairs of stimuli were shown to the participants, each with a unique chance of generating correct feedback. After selecting a stimulus, each participant received one second of feedback on their choice. In the testing phase, new combinations of stimuli were presented to the participants. Participants did not receive feedback regardless of their choice. The participants' choose-S1 score was determined by the proportion of times they chose stimulus S1 during the test, while their avoid-S2 score was determined by the proportion of times they avoided stimulus S2 during the test

Statistical Analysis

The statistical analyses of the present study were performed using R Statistical Software (v4.2.1; R Core Team, 2022). Principal component factor analysis (PCA) and descriptive statistical analysis were run using the 'psych' R package (v2.2.5; Revelle, 2022). The Shapiro-Wilk test was used to test the normality using the 'stats' R package (v4.2.1; R Core Team, 2022). Spearman correlation coefficient was used to evaluate the correlations among the age, RBDSQ scores, and performance measures, and it was run using the 'stats' R package (v4.2.1; R Core Team, 2022). The significance level was set at $p < 0.05$. Assumptions of linear regression models were checked using the 'car' and 'caret' packages. The assumption of normality, linearity, independence of error, homoscedasticity, and multicollinearity was checked using Q-Q plots, component plus residual plots, Durbin–Watson test, ncvTest (score test for non-constant error variance), and variance inflation factor (VIF), respectively (Fox & Weisberg, 2019; v6.0-93; Kuhn, 2022).

Data was also screened for outliers, high-leverage, and influential observations using the 'olsrr' R package to ensure robust regression analysis results (Hebbali, 2020). The multiple and robust linear regression was conducted using the 'stats' and 'robustbase' R package, respectively (v0.95-0; Maechler et al., 2022). A relative importance test was conducted in R using the package 'relaimpo' (v2.2-6; Grömping, 2006). The interaction plots between age and RBDSQ were plotted using the 'interactions' package in R (v1.1.0; Long, 2020). The additive and interaction models were compared using anova () function using the 'stats' R package. Post-hoc power analysis was conducted using R's 'pwr' package (v1.3-0; Champely, 2020).

Results

Descriptive Statistics

Table 2 presents descriptive statistics for participants' age, scores on the RBDSQ questionnaire, general cognition, and learning measures derived from the probabilistic reinforcement learning task. The win-stay and RPM scores were negatively skewed, whereas the SST, RBDSQ, digit span, and inspection time scores were positively skewed.

Table 2

Descriptive Statistics for Study Variables

Variable	*M*	*SD*	Skewness	Kurtosis	Range
Age	63.30	8.25	0.21	-0.70	50.00 - 86.00
RBDSQ	3.09	2.29	0.92	0.88	0.00 - 11.00
		General Cognition Measure			
RPM	14.98	2.52	-1.32	2.40	3.00 - 18.00
SST	262.30	57.31	0.79	3.42	118.02 - 603.13
Dot Matrix	27.13	13.59	0.53	-0.98	4.00 - 55.00
Digit Span	17.54	3.81	0.63	0.50	8.00 - 30.00
Inspection Time	62.20	30.37	2.17	8.74	25.00 - 272.19
		Learning Measure			
Training Phase					
Win-stay	0.86	0.12	-1.62	3.03	0.26 - 1.00
Lose-shift	0.61	0.12	0.17	-0.20	0.29 – 0.91
Testing Phase					
Choose-S1	0.74	0.14	-0.36	-0.29	0.27 - 1.00
Avoid-S2	0.76	0.15	-0.38	-0.44	0.23 - 1.00

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *RPM* = Raven's Progressive Matrices, *SST* = Stop Signal Task.

Principal Components Analysis: General Cognition and Learning Rate Imbalance

General cognition was assessed via five measures (RPM, SST, Dot Matrix, Digit Span and Inspection Time). All measures were intercorrelated as expected, consistent with an underlying general factor of intelligence (see Appendix F, Table F1; Spearman, 1904; Deary, 2000). A PCA was used to identify the commonality between these variables, taken to reflect general cognition, as recommended by Jensen (1998). As a way of fitting planes using orthogonal least squares, PCA relies on analysing and partitioning covariance to capture the most critical patterns in data and reduce the number of variables to a small number of essences (Pearson, 1901). The PCA solution for the first unrotated component is summarized in Table 3. This component had an eigenvalue of 1.89 and accounted for 38% of the variance in the five cognition measures. The participants' component scores (from now on, referred to as GC-scores) were used as a measure of general cognition.

Table 3

Principal Component Analysis for General Cognition Measure

Measure	Loading
RPM	.68
SST	-.49
Dot Matrix	.72
Digit Span	.66
Inspection Time	-.48

Note. RPM = Raven's Progressive Matrices, *SST* = Stop Signal Task. Lower scores for inspection time and SST indicate better general cognition (faster processing speed and more efficient response inhibition, respectively). In contrast, higher scores on the other tasks indicate better general cognition.

Learning from rewards was assessed by two measures (win-stay and choose-S1). As expected, these two measures showed a positive correlation, indicating that both were rooted in some underlying tendency to learn from rewards (see Appendix F, Table F2). A PCA was used to

estimate reward learning based on the two measures. Table 4 summarises the PCA solution for the first unrotated component. This component had an eigenvalue of 1.47 and accounted for 74% of the variance in the two learning from reward measures. The participants' component scores (from now on, referred to as RL-scores) were used to measure learning from rewards.

Similarly, learning from punishment was assessed by two measures (lose-shift and avoid-S2). There was also a positive correlation between these measures, indicating the possibility of underlying punishment-related learning (see Appendix F, Table F2). A PCA was used to estimate punishment learning based on the two learning from punishment measures (see Table 4). This first unrotated component had an eigenvalue of 1.24, accounting for 62% of the variance in the two learning from punishment measures. The participants' component scores (starting now referred to as PL-scores) were used as a measure of learning from punishments. Learning rate imbalance (hereinafter referred to as LRI-scores) was obtained by subtracting the PL-scores from the RL-scores. Negative LRI-scores reflect a greater dominance of the indirect pathway than the direct pathway.

Table 4

Principal Component Analyses on Reward and Punishment Learning Measures

Measure	Loading
Reward Learning	
Win-stay	.86
Choose-S1	.86
Punishment Learning	
Lose-shift	.79
Avoid-S2	.79

Correlations between Age, RBDSQ and Performance Measures

Kurtosis and skewness scores for GC-scores and LRI-scores displayed perfectly symmetric distributions for both outcome variables (see Appendix G). The Normal Q-Q plot and Shapiro-Wilk normality test of GC-scores and LRI-scores indicated no significant departure from normality (see Appendix H, Figure H1, Table H1). However, The Normal Q-Q plot and Shapiro-Wilk normality test for Age and RBDSQ indicated a significant departure from normality (see Appendix H, Figure H1, Table H1). Therefore, the nonparametric Spearman correlation test was used to investigate the relationship between the predicting variables age and RBDSQ scores and the different performance measures (GC-scores and LRI-scores). As expected, age exhibited a significant moderate negative correlation with GC-score, indicating that with age, an individual's general cognition declines (see Table 5). However, there was no significant correlation between the RBDSQ scores and GC-scores, which contradicts previous findings that RBD disorders are associated with lower cognitive abilities. Figure 9A depicts the relationship between GC-scores and LRI-scores as a function of age. Similarly, **i**n Figure 9B, the relationship between GC-scores and LRI-scores was plotted as a function of RBDSQ scores.

Table 5

Spearman Correlations Between Age, RBDSQ Scores, General Cognition, and Learning Rate Imbalance

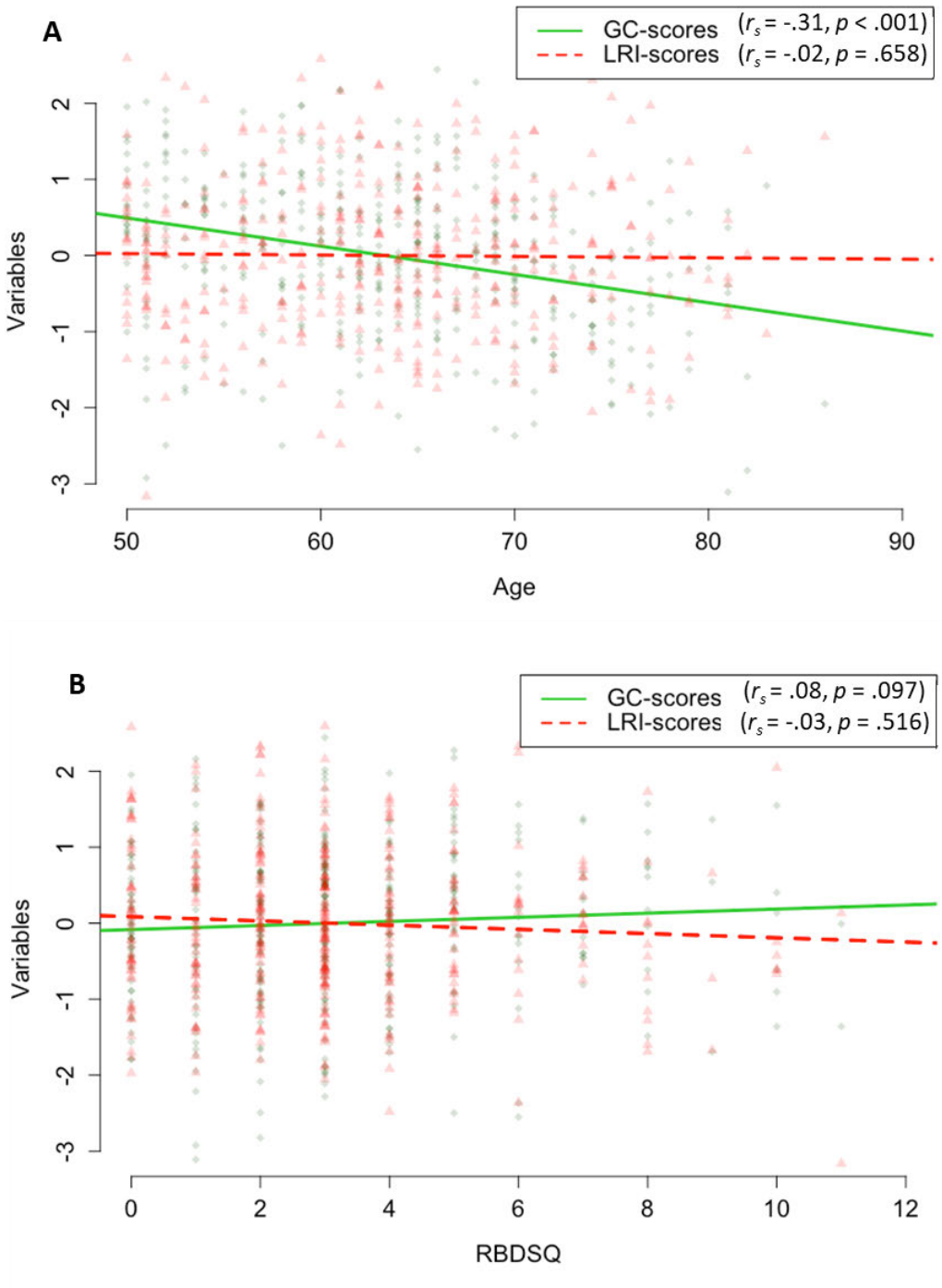
Variable	Age	RBDSQ	GC-scores	LRI-scores
Age	—			
RBDSQ	-.15**	—		
GC-scores	-.31***	.08	—	
LRI-scores	-.02	-.03	-.02	—

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *GC-scores* = General Cognition Scores, *LRI-scores* = Learning Rate Imbalance Scores.

*p<.05, **p<.01, ***p<.001

Figure 9

Changes in Performance Measures as a Function of Age and RBDSQ Scores



Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *GC-scores* = General Cognition Scores, *LRI-scores* = Learning Rate Imbalance Scores.

Regression Analyses

There was a significant but negative correlation between RBDSQ and age, meaning that younger individuals had higher RBDSQ scores than older individuals (see Table 5). This might explain the unexpected lack of correlation between RBDSQ and GC-scores. Also, there was a strong male predominance in PD, with men twice as likely to develop PD as women (Cerri et al., 2019). Therefore, regression models controlling for age and sex would be more effective in assessing the effect of RBD symptoms. A series of multiple regression analyses were conducted, adjusted for age and sex, in which RBDSQ was a predictor of (a) GC-scores and (b) LRI-scores. Assumptions testing revealed that influential values exist for both GC-Scores and LRI-scores regression models; therefore, robust linear regression was used to verify all the results.

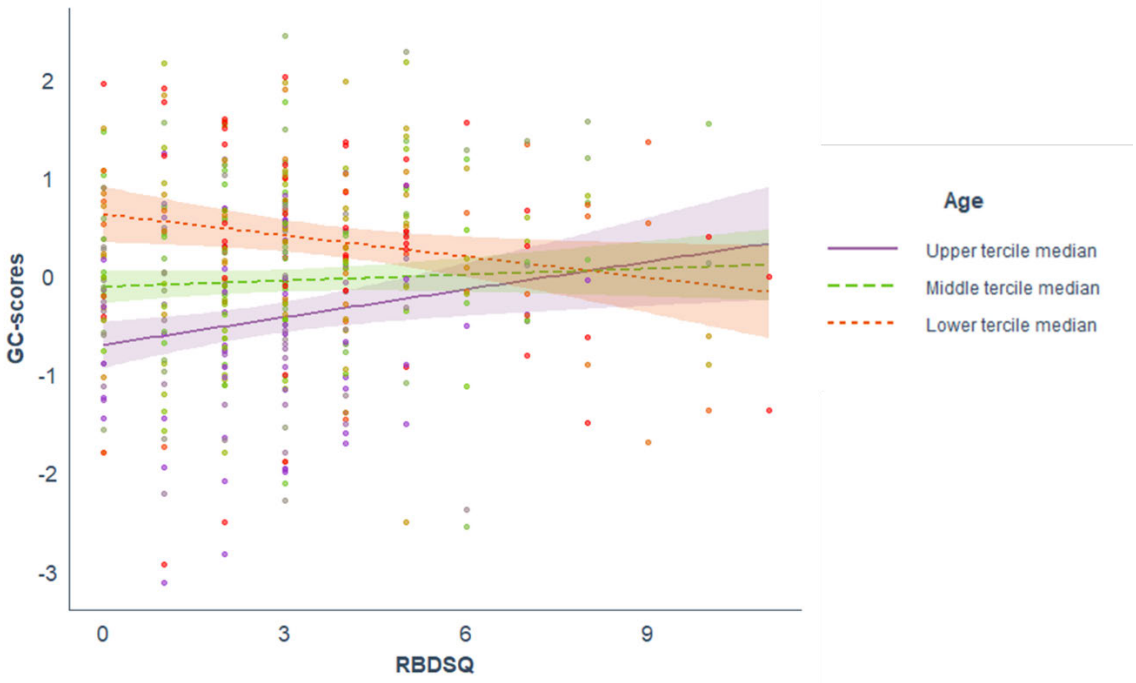
Hypothesis 1: Testing Whether RBDSQ Scores Predicted GC-Scores

Multiple linear regression was conducted with age, sex, and RBDSQ scores as GC-scores predictors. Overall, the regression model was significant (F (3, 389) = 15.92, p < .001) and accounted for 10.93% of the variance in GC-scores. Being younger and male sex was a significant predictor of higher general cognition. RBDSQ scores did not significantly predict general cognition (see Table 6). Our sample might have had some age-dependent selection bias, explaining the negative correlation between RBDSQ scores and age. This negative correlation means older adults with RBDSQ symptoms might have already developed a neurodegenerative disorder, which would have made them ineligible for our study. So, the older adults we recruited might have been more likely to experience RBDSQ symptoms for other reasons, perhaps unrelated to neurodegeneration. We, therefore, also tested whether the interaction between the two variables could explain individual differences in GC-scores. A second regression model that included the interaction between RBDSQ scores and age was also significant (F (4, 388) = 14.38, p < .001), accounting for 12.91% of the variance in GC-scores. All four variables (age, sex, RBDSQ, and interaction term coefficient (age x RBDSQ)) were significant predictors of general cognition. Younger age, lower RBDSQ score and being male predicted higher general cognition (Table 6). The interaction model accounted for more variance in GC scores than

the additive model that included only main effects (F (389,1) = 8.80, p = .003). The interaction term is illustrated in Figure 10. In contrast to younger participants, who showed a decline in GC-scores with an increase in RBDSQ scores, older participants showed the opposite trend.

Figure 10

Interaction Between Age and RBDSQ predicting GC-Scores



Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *GC-scores* = General Cognition Scores. Individuals were grouped into three groups according to their RBDSQ scores for illustration purposes. Medians of each tercile of age were 54, 64 and 72.

Table 6

Summary of Linear Regression Analyses for RBDSQ as a Predictor of General Cognition, Controlling for Age and Sex

Variable	R^2	*B*	*SE B*	β	*t*	*p*
Additive model predicting GC-scores						
	.11					
Constant		2.41	0.39		6.12	<0.001
RBDSQ		-0.00	0.02	-0.00	-0.00	0.997
Age		-0.04	0.01	-0.33	-6.61	<0.001
Sex (Male)		0.26	0.10	0.12	2.57	0.010
Interaction model predicting GC-scores						
	.13					
Constant		3.96	0.65		6.08	<0.001
RBDSQ		-0.48	0.16	-1.11	-2.94	0.003
Age		-0.06	0.01	-0.53	-6.27	<0.001
Sex (Male)		0.25	0.10	0.12	2.41	0.016
Age x RBDSQ		0.01	0.00	1.10	2.97	0.003

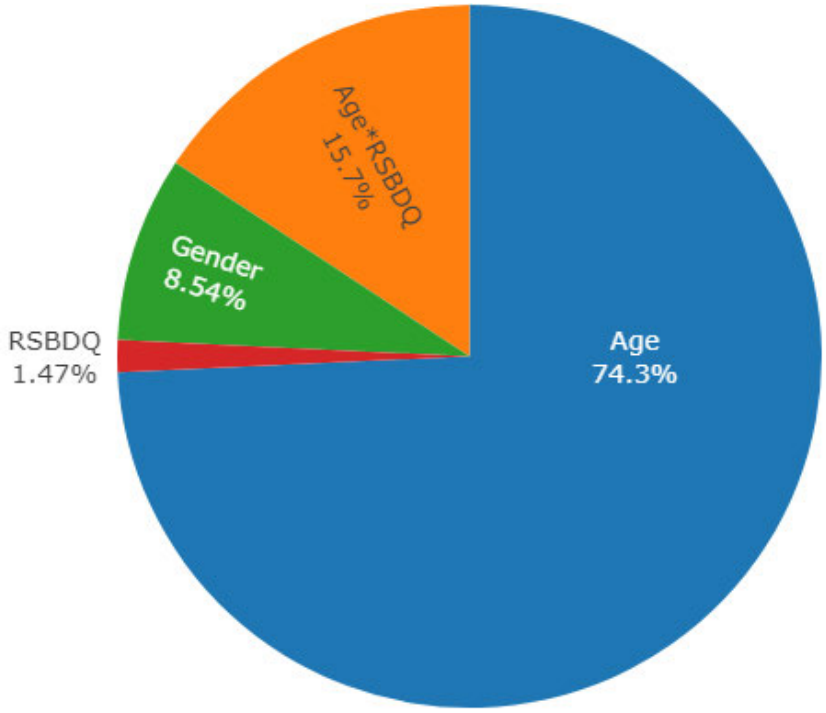
Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *GC-scores* = General Cognition Scores.

For both additive and interaction models, robust linear regression demonstrated similar results to our standard linear regression models, except that robust linear regression (R^2 = 14.43%; R^2 = 17.28%, respectively) accounted for slightly more of variance in GC-scores than standard linear regression (R^2 = 10.93%; R^2 = 12.91%, respectively; see Appendix I). Relative importance regression was used to determine which predictors contributed the most to explaining the variance in GC-scores. Out of the total 12.91% of the variance in GC-scores that the interaction regression model

explained, age accounted for the most variance, followed by the age x RBDSQ interaction, sex, and RBDSQ (see Figure 11).

Figure 11

Relative Proportion of Variance Explained by Predictors Age, Age x RBDSQ, Sex, and RBDSQ for Change in General Cognition Functioning



Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire.

Hypothesis 2: Testing Whether RBDSQ Scores Predicted LRI-Scores

We ran multiple regression analyses to examine whether RBDSQ predicted learning rate imbalance whilst controlling for age and sex. Overall, the regression model was non-significant (F (3, 389) = 0.67, p = 0.571, R^2 = .00; Table 7). Similarly, a second regression model that included the interaction between RBDSQ scores and age was also non-significant (F (4, 388) = 0.58, p = 0.673, R^2 = .01; Table 8). We ran a robust linear regression analysis to verify these findings, and the results were consistent with the findings of multiple linear regression (see Appendix I).

Table 7

Summary of Linear Regression Analyses for RBDSQ as a Predictor of Learning Rate Imbalance Controlling for Age and Sex

Variable	R^2	*B*	*SE B*	β	*t*	*p*
	Additive Model Predicting Learning Rate Imbalance					
	.00					
Constant		0.31	0.41		0.76	0.450
RBDSQ		-0.03	0.02	-0.07	-1.37	0.171
Age		-0.00	0.01	-0.03	-0.58	0.566
Sex (Male)		0.03	0.11	0.01	0.29	0.774
	Interaction Model Predicting Learning Rate Imbalance					
	.01					
Constant		0.63	0.69		0.92	0.359
RBDSQ		-0.13	0.17	-0.30	-0.75	0.452
Age		-0.01	0.01	-0.07	-0.81	0.421
Sex (Male)		0.03	0.11	0.01	0.25	0.802
Age: RBDSQ		0.00	0.00	0.23	0.58	0.561

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *LRI-scores* = Learning Rate Imbalance Scores.

Discussion

Current Study Findings

Probable RBD as a Predictive Feature of General Cognitive Decline

In the first hypothesis of the present study, the probable RBD is investigated in relation to general cognitive functioning in individuals living in the general population but controlling for age and sex differences. The general cognition regression model results show that being younger and being male are significant predictors of higher general cognition. These results are in agreement with the past research that ageing affects mental functions like processing speed, reasoning, working memory, and executive functioning (Cappell et al., 2010; Deary et al., 2009). Tests used in the current study, such as Raven progressive matrices, Dot matrix, and Inspection time, are mostly related to testing of visuospatial abilities, and it has been reported that these abilities are typically better exhibited by males in some tests (Moore et al., 2010; Upadhayay & Guragain, 2014; Voyer et al., 2017; Yuan et al., 2019).

However, the results of the current study contradict the first hypothesis as RBD is not a significant predictor of general cognition, unlike past research that consistently suggested that higher RBD was associated with cognitive decline (see the introduction, Table 1). One of the possible reasons behind the evidential absence of a direct relationship between RBD and general cognition could be the selection bias based on the age in choosing participants for the study. Due to strict inclusion criteria (not taking medications that interfere with neurological function for at least six months; not experiencing a neurological condition or a history of brain injury), only a healthy population that ages well was eligible for participation in this study. Additionally, there is a significantly weak negative correlation between RBDSQ and age. This is surprising, as past research suggested that elderly individuals are more likely to suffer from RBD (AASM, 2014; Iranzo et al., 2016; Trotti, 2010).

For the reasons mentioned above, exploring the interaction between age and RBDSQ may provide more information that might explain the unpredicted results. Cognitive decline with RBD is

only noticeable in younger participants (median 52 years old). This means that when people exhibit higher RBDSQ scores at an older age, it may mean different things compared to when they do so at a younger age. For example, on the one hand, a younger population with higher RBDSQ scores may later develop neurodegenerative diseases such as PD, dementia with Lewy bodies, and multiple system atrophy (Galbiati et al., 2018; Li et al., 2018; Zhang et al., 2020). On the other hand, a healthy older population (which in our sample may have been selected in such a way that these individuals are not fully representative of older populations because they lived for a long time without any neurodegeneration) with a very high RBDSQ score may have iRBD that occurs without any neurological disease (Fulda, 2011; Keir & Breen, 2020). Therefore, the healthy older population of the current study has even lower chances of being in the prodromal phase of PD compared to the younger healthy population of this study, which could develop parkinsonian symptoms at a later stage of their life. This notion also supports our unexpected findings that older populations are less impacted by RBD than younger populations (Iranzo et al., 2016; Trotti, 2010).

Probable RBD as a Predictive Feature of Dysfunction of the Basal Ganglia

The second hypothesis is that probable RBD would be predictive of more specific cognitive impairments associated with PD, namely, dysfunction of the basal ganglia, leading to impaired reward learning and enhanced/or preserved punishment learning. For this, RBD is investigated in relation to the learning rate imbalance in individuals living in the general population but controlling for age and gender differences. The results reveal that probable RBD does not significantly influence the learning rate imbalance of the basal ganglia. The results are contrary to our expectations, as RBD is well known to be a solid predictive feature of PD (Iranzo et al., 2016), and patients with PD exhibit learning deficits (Ashby et al., 2003; Foerde et al., 2013; Shohamy et al., 2004). The results also demonstrate that even age does not influence the learning rate imbalance of basal ganglia, which again contradicts past studies, which have shown a significant association between learning rate imbalance and age (Frank & Kong, 2008; Lerner et al., 2018; Simon et al., 2010; Sojitra et al., 2018).

The first cause behind the contradiction in the results where no association is found between probable RBD and learning rate imbalance could be due to the lack of power to detect relatively small differences in our data which could lead us to erroneously accept the null hypothesis (i.e., type 2 error). So, to rule out type 2 errors, post hoc power analysis was conducted, and the results demonstrate that with a sample size of 393 and three predictors (age, sex and RBDSQ), even effects as small as 0.03 could be detected with a power of 80%. Hence, the true effect size might be smaller than 0.03, or there is no effect.

The second possible reason for the absence of an effect is that perhaps our learning rate imbalance measures were not optimal and did not adequately assess learning. So, we analysed the learning from reward and punishment separately (see Appendix J; Table J1 and J2) and tested whether they were at least sensitive to ageing individual differences, which would replicate previous studies (Eppinger & Kray, 2011; Frank & Kong, 2008; Lighthall et al., 2013; Samanez-Larkin & Knutson, 2014; Simon et al., 2010; Sojitra et al., 2018). As with the learning rate imbalance, RBD did not influence either reward learning or punishment learning. However, age plays a significant role in both the reward and punishment learning regression models. The results showed that older age is associated with deficits in learning from rewards and punishments (see Appendix K, Table and Figure K1). These findings are expected as the dopamine system is vulnerable to aging, and dopamine levels decline monotonically as individuals age (Berry et al., 2016; Van Dyck et al., 2002) which results in reinforcement learning impairments (Eppinger & Kray, 2011; Samanez-Larkin et al., 2014). Hence the measures (probabilistic reinforcement learning task) used in this study are sensitive enough to variables (RBDSQ and age) associated with dopamine loss. Our learning rate imbalance measures are, therefore, unlikely to be suboptimal.

The third possibility is that RBD in the given population sample is not entirely specific to PD-related neurodegeneration but may be associated with other synucleinopathy neurodegenerative diseases, such as dementia with Lewy bodies, multiple system atrophy, as well as non-synucleinopathy neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, and

amyotrophic lateral sclerosis (Galbiati et al., 2018; Zhang et al., 2020). Past literature demonstrated that participants with Alzheimer's and Huntington's disease showed no impairment in reward-related decision-making specific to basal ganglia dysfunction, but the inferior performance was associated with impairments in other cognitive domains (Delazer et al., 2012; Sinz et al., 2008). Despite the lack of extensive research on reward and punishment-based learning in amyotrophic lateral sclerosis, one study has demonstrated intact probabilistic reversal learning (Meier et al., 2010). Hence the findings of the present study solidify previous studies showing that RBD is strongly related to other neurodegenerative diseases besides PD.

Methodological Factors: Strengths and Weaknesses

Approaches to Analyses

Using PCA, regression analyses of broad constructs in general cognition are simplified as we obtained a more stable estimate of cognition using a composite measure derived from several cognitive tests. The current study's multivariate approach may allow more extensive conclusions to be drawn at a lower risk of overgeneralization than previous studies using single variable measures (see Introduction, Tables 1 & 2). However, it may be argued that PCA should be abandoned in favour of multiple regression models when utilizing a multivariate approach. Nevertheless, since regression equations are complex, individually analysing each outcome variable would have resulted in running several regressions, introducing the issue of controlling for multiple comparisons, and relying on single measures to assess each construct, which might result in more measurement error than a composite measure (Gelman et al., 2012)

Choice of Study Design and Sample Characteristics

Rather than a high-risk population, this cross-sectional study used a general population, which can draw conclusions that could be generalized to different populations, leading to a less biased assessment of the prodromal marker utility to predict PD. (Postuma & Berg, 2016). With 393 participants, the current study addresses the issue of low power using a larger sample size. To my knowledge, this is the largest sample size of similar studies performed in the past (see the

introduction, Table1). Given the apparent subtlety of the learning differences that are considered, adequate power must be applied to detect such differences (Balasubramani et al., 2014).

However, there is concern that the present sample's characteristics could limit the results' generalizability. Selection bias is one of the significant drawbacks of the current study. The selection bias is more potent for older individuals than younger ones since older individuals would have had more time to develop diseases that would have excluded them from the study. For this reason, we also had difficulty recruiting comparable samples of different ages. Using advertisements led to the self-selection of participants, resulting in nonrepresentative distributions for ages and sexes of the general population.

Furthermore, the larger research project in which this study is a small part imposed several eligibility criteria on participants, which may have influenced the sample's composition. These exclusion criteria included smoking more than five cigarettes a day and suffering or having suffered from alcohol or drug dependence. In previous research studies, chronic and acute use of alcohol, cannabis, cocaine and opiates has been shown to contribute to RBD, confirming their high comorbidity with RBD (Angarita et al., 2016; Postuma et al., 2012; Yao et al., 2019). Excluding individuals with drug, smoking or alcohol dependence was designed to reduce confounding effects on learning and general cognition, but it may have also prevented some subsets of people with RBD from participating in this study. Additionally, a gender bias in our sample could have limited the scope of our study. Compared to the male population, females constitute twice the sample size in our study. According to well-established research, women are affected half as often as men by PD (Cerri et al., 2019; Haaxma et al., 2007). So again, this could have led to a sample population that does not suffer from PD-related neurodegeneration.

Measurement of RBD symptoms

A strength of this study is the use of RBDSQ scores as a continuous variable, which provided more accurate and sensitive information for analysis than could be obtained from categorizing RBDSQ scores (MacCallum et al., 2002). Continuous variables in a study are statistically more

powerful, and data can be described more effectively with fewer parameters. Furthermore, it is more informative since it presents a more straightforward interpretation of the magnitude of the relationship between one continuous variable and another in terms of unit changes (Lazic, 2008). Moreover, arbitrary cut-off points may fail to capture some subtle differences that are crucial, especially for those without a diagnosis, as in this study (Altman, 2014; Bennette & Vickers, 2012).

From an economical and practical standpoint, strength is the ability to screen for probable RBD (without confirmation of diagnosis) in the general population using simple questionnaires. However, the positive predictive value of this questionnaire could be less than 10% (Berg et al., 2015). A prodromal PD measure, polysomnography, can address this limitation of the questionnaire. As the most specific and reliable measure of RBD, polysomnography is necessary to confirm the diagnosis of RBD (Berg et al., 2015). In addition, compared to people with probable RBD, people with confirmed RBD could be tempting targets for neuroprotective trials and future treatments. In fact, a meta-analysis by Mao et al. (2020) also revealed that probable RBD patients only showed a cognitive decline in global cognitive function and shifting compared to confirmed RBD patients, who demonstrated worse performance on a broader range of cognitive tests. However, using. However, using polysomnography on larger samples is impossible due to its complexity and cost, so its practical application is limited (Frauscher et al., 2012; Postuma & Berg, 2016). In this context, the development of a novel RBD predictor with improved predictive power and accessibility, such as RBDSQ, is a necessity of the moment.

Other Improvements and Future Directions

In addition to the possible improvements described above, this study's results could have been strengthened by including additional prodromal predictors of PD, such as olfactory dysfunction, impotence, somnolence, constipation, and other psychopathologies such as depression and anxiety disorders (Iranzo et al., 2016). Previous studies indicated that single markers are limited in predictive value and are easily influenced by multiple factors, including acquired diseases, diet, physical activities (lifestyle), and genetic heterogeneity. Also, combining predictive markers could

result in higher sensitivity and specificity of predictions (Iijima et al., 2021; Zhou et al., 2019). Hence, this study may benefit from considering above mentioned prodromal markers in conjunction with the other variables of interest, as they may enhance understanding of how these factors interact.

We calculated the learning rate imbalance of the basal ganglia by subtracting punishment learning scores from reward learning scores. However, a better way to capture the imbalance between learning reward and punishment is to use measures such as the "learning rate imbalance" (LRI) and the "learning rate disparity" (LDR) index using a computational methodological approach that might be more sensitive and better capture learning individual differences. These techniques calculate the basal ganglia imbalance by normalizing the difference between the reward and punishment learning rates assessed using a computational model (Lerner et al., 2018; Sharot & Garrett, 2016). It is beyond the scope of this thesis to use these methods to calculate LRI, but future research could use computational modelling to provide a more accurate measure of learning.

Moreover, the general cognition scores were estimated using several measures, making it far more reliable than the learning rate imbalance measure, which was measured using only a probabilistic reinforcement learning task. The measurement of reward and punishment learning could also be improved by incorporating a variety of learning tasks. Consequently, the excessive noise associated with single measurement tasks may explain the lack of association between RBD and basal ganglia dysfunction. The future scope of this study can be further improved by using a multi-measure approach. When it comes to psychopathology assessment, using multiple measures can be very helpful in uncovering subtle differences that cannot be identified with just one measure alone (Kagan et al., 2002).

The sampling issue in the cross-sectional study can be addressed using a longitudinal study, which would help with the sample characteristic problem we encountered. The attrition issue that we faced in the cross-sectional study, where participants were not eligible to participate due to any neurological condition, will no longer be a problem in the longitudinal study that would recruit a middle-aged cohort. Middle-aged individuals are unlikely to have been diagnosed with

neurodegenerative disorders yet, so one could examine whether those who later developed PD had higher RBDSQ and LRI scores when they enrolled in the study, which may indicate early subtle neurodegeneration. The longitudinal method can better identify cognitive impairment than cross-sectional research and provide a time course of how cognitive and health constructs change over time (McQuail et al., 2021). Other advantages of longitudinal study design include obtaining a more accurate understanding of aetiology and patterns of disease progression (Markopoulou et al., 2020).

Practical Implications

This study is designed to examine the importance of the prodromal phase of PD as it offers a unique window of opportunity for early detection of PD. Such early detection could allow better prognostic counselling and open the door to opportunities for novel neuroprotective therapies at a stage when treatment might be most effective (Postuma & Berg, 2016). Also, the importance of this finding lies in the fact that simple screening instruments such as the ones used in the current study might be able to predict cognitive decline. However, these results need to be replicated and interpreted cautiously because this relationship is only observed in younger people. Furthermore, this knowledge may aid investigators in selecting individuals suited for inclusion in disease-modifying trials, thus contributing to developing new therapies. For example, neuropsychological deviations associated with RBD can be detected early, further supporting the notion that it can serve as a predictor of dementia or other neurodegenerative conditions (Massicotte-Marquez et al., 2008; Postuma & Montplaisir, 2009). Furthermore, as discussed above, a combination of prodromal markers of PD that could be screened cheaply in the clinic might help identify individuals who are most at risk of developing a neurodegenerative disorder. Future clinical trials can be conducted to delay the onset, modify the course, or prevent Alzheimer's disease, Huntington's disease, or amyotrophic lateral sclerosis from developing disabling manifestations.

Conclusion

This study investigated the relationship between probable RBD and general cognitive function and found that probable RBD might be related to the deterioration of cognitive ability,

thereby contributing to the expanding literature on this subject matter. However, the cognitive decline associated with RBD was evident only in younger individuals. A further investigation of the interaction between RBD and age is therefore warranted. Also, to our knowledge, our study is the first to examine the relationship between RBD and cognitive impairment in relation to the direct and indirect pathways of the basal ganglia. However, we did not find such a relationship. This might be because RBD could be predictive of neurodegeneration that could lead to several disorders other than PD, including synucleinopathy and non-synucleinopathy neurodegenerative diseases. Thus, as our findings do not provide unequivocal evidence for the role of RBD in basal ganglia dysfunction specific to PD, explicating the precise relationship between these two remains an important area for future study.

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Appendix A

Exclusion of Participants Reflected Anticipatory Responses and Inattention

1. For the inspection time task, we exclude individuals who scored less than 75% correct on easy catch trials and those with ITs > 300ms (*n* = 7).
2. For the dot matrix task, we exclude individuals with 10 or more errors on the True/False statements (*n* = 1).
3. For the stop signal task, we remove subjects with faster correct Go RT > incorrect NoGo RT and remove subjects with > 20% (>24) omission errors on Go trials (*n* = 31; Verbruggen et al., 2019).
4. For probabilistic reinforcement learning task, extremely low reinforcement learning avoid-S2 accuracy <0.07, indicating inattention (*n* = 1).

Appendix B

Information Sheet

Cognitive function across the lifespan
Participant Information Sheet

Investigators

Human Research Ethics Committee Approval Number	H-2020-017
Location	The University of Adelaide, North Terrace Campus / Western Sydney University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. Please read the information contained in this document carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

This project will examine how general cognitive function (for example, decision-making, reasoning ability, working memory, processing speed) changes with age. We know that many aspects of cognitive function are to some extent genetically determined. Genes (DNA) that affect the expression of certain chemicals and receptors in the brain seem to influence the ability to perceive and process information in our environment, form new memories, and make decisions. This project will try to understand genetic influences on cognitive performance across the lifespan. This project could lead to a deeper understanding of how cognitive function evolves in healthy ageing, and could provide a tool based on genetic scores to predict an individual's trajectory of cognitive function. This could help identify individuals who are at risk for cognitive decline, which could then inform better interventions.

In addition, depending on your demographics, your results may also be used in a study investigating genetic predictors of cognitive performance in patients with Parkinson's disease

(University of Adelaide ethics approval number H-2016-219) or in individuals with traumatic brain injury (University of Adelaide ethics approval number H-2021-120). Given that we need to compare the patients' performance to that of healthy individuals, your results may be included in this study's healthy control group. Given that we need to ensure that our patient and healthy control groups are similar in terms of age, gender distribution and education levels, the inclusion of your data in the healthy control group will depend on the demographics of our recruited patient groups.

3 What does participation in this research involve?

For this study, we are seeking participants who are:

1. aged 18-80 years
2. fluent English speakers
3. not suffering from a neurological disorder and no history of brain injury
4. not suffering from a drug or alcohol dependency, either a current or previous condition
5. not smoking more than 5 cigarettes per day
6. not using medication that affects neurological function (e.g., sedatives, antipsychotics)
7. not suffering from an uncorrected visual disorder
8. not diagnosed with a learning disability.

You will be asked to attend a testing session, which will take approximately 2.5-3 hours in total, with breaks given as required. Refreshments will be available during needed breaks. The testing session will take place at the University of Adelaide, North Terrace Campus, or at Flinders University, Bedford Campus. You will also be asked to complete a series of surveys using an online link that will be sent to you via email or text message. If you are having difficulty accessing or completing the surveys online, please let us know and we will organise for you to complete them in person during the testing session.

Questions and tests will include:

1. Questions regarding demographic information (age, gender, disease history)
2. Questions regarding vascular risk factors (high blood pressure, tobacco use, weight, history of diabetes, physical inactivity, poor diet, history of high cholesterol/lipids)
3. The Montreal Cognitive Assessment
4. Short questionnaires that assess mood, personality, and history of adverse life events, including childhood abuse.
5. A series of tests that assess your reasoning ability, processing speed, working memory, executive function, and general vocabulary.
6. Tests that assess your ability to learn to select correct actions and inhibit incorrect actions.
7. Short tests that assess motor function (for example, tremor).

In order to investigate whether there is a relationship between target genotypes and cognitive performance, we will ask you to provide a saliva sample from which your DNA will be analysed. The genetic code of our DNA varies between people, with these changes called a variant, or a mutation. This variation exists for a number of reasons and can contribute to the many things that make us different from one another. In addition to physical factors such as hair, and eye colour, they can contribute to behaviour and how we learn and make decisions. We know that different DNA variants affect cognitive performance, and we would like to compare your DNA with that of other participants, to identify potential genetic pathways that are related to differences in cognitive performance. The genetic variation we will investigate is likely to have small effects on performance. This could, nevertheless, be useful in the future for developing more accurate diagnoses for a number of disorders that are characterised by loss of cognitive function, along with other pieces of information, such as motor, cognitive and mood assessments.

We wish to store your DNA and collected data in a biobank, a database that contains your de-identified information (preserving your anonymity) so that other researchers could use this data to answer other research questions. Please see the attached Biobank Information Sheet and Consent Form for more information about this.

To thank you for your participation in the study, you will receive a $50 Coles/Myer gift card at the end of the testing session.

4 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign, as well as the Biobank Information Sheet and Consent Form, and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your opportunity to take part in future studies.

5 What are the possible benefits of taking part?

The results of this research project will not provide you with any direct benefit. However, the current study will advance our understanding of brain functions, which has potential implications for detection and treatment of cognitive impairment in a number of disorders, including Parkinson's disease.

6 What are the possible risks and disadvantages of taking part?

Mood questionnaires
You will be asked to complete questionnaires that assess levels of depression, anxiety and stress. The questionnaires are not diagnostic tools and cannot be used to diagnose depression or anxiety. However, we will recontact all of our participants to provide information about available resources for coping with psychological problems should they need them.

Montreal Cognitive Assessment
We will use the Montreal Cognitive Assessment to screen for possible cognitive impairment. Scores below 23/30 are considered abnormal, and we may contact you if your score is below 23 to inform you of the outcome of the test, as an early diagnosis of cognitive impairment could help planning treatment. Please note that this is not a diagnostic test. Mild cognitive impairment is not dementia, and it does not always lead to dementia. It is defined as a noted problem with cognition or brain processing that is unusual for a person's age or education. Mild cognitive impairment does not usually cause any interference with the person's daily level of activities. Although the cause of the syndrome is not fully known, it is possible that it could be triggered by stress or illness. So someone can score below the cutoff score because of temporary illness, fatigue, or other reasons. Furthermore, a good number of people who score below the cutoff at some point seem to recover their cognitive function and score in the normal range when retested. For these reasons, this test cannot be used to diagnose an illness such as dementia. Such a diagnosis would require further testing.

Genetic analyses
Finally, even though results do not have clinical utility at this stage and individual results will not be returned, statutory or contractual duties may require us or you to disclose the results of genetic tests or analysis to third parties (for example, insurance companies, employers, financial

and educational institutions), particularly where results provide information about health prospects.

7 Will I be given the results of the research project?

We have developed new cognitive tests to assess cognitive performance more precisely. However, because these tests are novel, they have not been standardised. This means although one can compare scores of different individuals, it is difficult to interpret these differences in a meaningful way (for example, a given score on a test does not necessarily indicate cognitive decline). For this reason, we will not give you feedback on your results on the cognitive tests. We can only give you feedback on the Montreal Cognitive Assessment, which is a standardised test.

Part 2 How is the research project being conducted?

8 What will happen to information about me?

A unique ID number will be given to all your samples and data in place of your name, in order to prevent anyone from identifying you from your samples or data. These ID numbers **will not** correspond to any names, emails, addresses or phone numbers that may be used to identify you. A document linking your name to your unique ID will be kept by the Principal Investigator, [redacted], who will store this securely on a computer at the University of Adelaide. In general, your samples and data will not be released for any use without your prior consent, unless required by law or by the ethics committee that approved this project. It may also be used to re-contact you in the future to ask for your participation in a follow-up study if you have consented to be re-contacted for that purpose, or to convey the results of the Montreal Cognitive Assessment, as explained in Section 6.

Only average results from all participants will be reported in future publications and presentations. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, maintaining your confidentiality.

Please note that publication and funding requirements may require submission of data or information to controlled access repositories that meet international security and safety standards for sharing with researchers globally. Any data (including genetic and cognitive testing data) shared via such repositories will be de-identified, protecting your anonymity.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact a study team member named at the end of this document if you would like to access your information.

9 Who is organising and funding the research?

Please note that you will not benefit financially from your involvement in this research project even if, for example, knowledge acquired from analysis of your saliva sample and other information collected from you prove to be of commercial value to the institutions with which the investigators are affiliated.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

10 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the University of Adelaide.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project, you can contact the principal

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2020-017). Please contact the Human Research Ethics Committee's Secretariat on phone +61 8 8313 6028 or by email to hrec@adelaide.edu.au if you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

12 If I want to participate, what do I do?

Following your reading of this Participant Information sheet, if you wish to participate, please contact

Mental Health Resources

We understand that some of the questionnaires included in this study might cause feelings of distress or might remind you of events or circumstances that cause you to feel anxious. Should you need to speak to someone immediately regarding your psychological difficulties, please contact your GP or health professional. There are also a number of services that you can access to help you with any difficulties you might experience.

The Australian Government provides access to information and digital resources, as well as information about other free or low-cost counselling and support services for mental health. Please visit **www.headtohealth.gov.au** for more information. In particular, please take note of the following services:

Mental Health Assessment and Crisis Intervention Service: provides immediate help in regard to a crisis in your health or living circumstances.
13 14 65

Lifeline Australia: a crisis support service that provides short-term support at any time for people who are having difficulty coping or staying safe.
www.lifeline.org.au
13 11 14

Beyond Blue: provides support on a range of mental health issues and is available by phone, online chat or email.
www.beyondblue.org.au
1300 22 4636

Suicide Call-Back Service: anyone considering suicide, living with someone who is considering suicide, or bereaved by suicide, can access the Suicide Call-Back Service.
www.suicidecallbackservice.org.au
1300 659 467

MensLine Australia: a telephone and online counselling service for men.
www.mensline.org.au
1300 78 99 78

Open Arms – Veterans and Families Counselling: provides current serving armed forces personnel, veterans and their families free and confidential counselling, group treatment programs, and community and peer networks.
www.openarms.gov.au
1800 011 046

Kids Helpline: a free, private and confidential phone and online counselling service for young people aged 5 to 25 years old.
www.kidshelpline.com.au
1800 55 1800

eheadspace: free online and telephone support and counselling for young people aged 12 to 25 years old, their families and friends.
headspace.org.au/eheadspace
1800 650 890

Blue Knot Foundation Helpline (formerly Adults Surviving Child Abuse)
The Blue Knot Helpline provides information and short term counselling nationally for adult survivors of childhood trauma.
www.blueknot.org.au
email: helpline@blueknot.org.au
1300 657 380, 7 days a week 9am to 5pm AEST.

Appendix C

Bio Bank Form

WESTERN SYDNEY UNIVERSITY Flinders UNIVERSITY THE UNIVERSITY of ADELAIDE

A biobank for genomic, cognitive and motor function data
Participant Information Sheet

Investigators

Human Research Ethics Committee Approval Number	H-2020-016
Location	The University of Adelaide, North Terrace Campus / Western Sydney University

Part 1 What does my participation involve?

1 Introduction

You will be asked to donate a sample of saliva which will be used for genetic research. Please read the information contained in this document carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Biobank Information Sheet and Consent Form to keep.

2 What is genetic research?

Genes are made of DNA – the chemical structure carrying your genetic information that determines many human characteristics such as the colour of your eyes and hair. Researchers study genes in order to understand the link between our biological makeup and our behaviour, or our risk for different diseases. For example, genetic research can be used to understand why some people have a certain condition, such as Parkinson's disease, or why some people's cognitive function is better preserved as they age.

3 What is the purpose of this research?

We know that many aspects of motor and cognitive function are to some extent genetically determined. Genes (DNA) that affect the expression of certain chemicals and receptors in the brain seem to influence the ability to perceive and process information in our environment, form new memories, and make decisions. This biobank will provide a tool to help us understand genetic influences on behaviour. This could help identify individuals who are at risk for cognitive decline, which could then inform better interventions.

4 What does participation in this research involve?

In order to investigate whether there is a relationship between target genotypes and behaviour, we will ask you to provide a saliva sample from which your DNA will be analysed. The genetic code of our DNA varies between people, with these changes called a variant, or a mutation. This variation exists for a number of reasons and can contribute to the many things that make us different from one another. In addition to physical factors such as hair, and eye colour, they can contribute to behaviour and how we learn and make decisions. We know that different DNA variants affect cognitive performance, and we would like to compare your DNA with that of other participants, to identify potential genetic pathways that are related to differences in cognitive performance. The genetic variation we will investigate is likely to have small effects on performance. This could, nevertheless, be useful in the future for developing more accurate diagnoses for a number of disorders that are characterised by loss of cognitive function, along with other pieces of information, such as motor, cognitive and mood assessments.

5 What are the possible risks and disadvantages of taking part?

Genetic testing involves the study of genetic material (typically DNA), which you share with your blood relatives. Genetic research is undertaken for many reasons, including discovering more accurate ways of predicting disease within a group of people. It is important to note the current study **is not** employing genetic testing. That is, we will not intentionally test whether you carry genetic material that is known to cause a disease. Instead, we will perform genetic analyses that identify patterns in the DNA that are linked to small differences in brain function and behaviour between individuals. Although these genetic differences may cause changes in behaviour, they are not currently used to diagnose disorders. Our primary analyses focus on single point mutations in the genome. So given that we are not screening for clinical disorders in this study, we will not return your individual genetic results.

Please be aware that the impact of genomic information may change over time as new knowledge is gained. We will not be revisiting your genomic data in the context of medical advancements as this is indefinite.

6 What will happen to my test samples?

We would like to store your saliva sample in a biobank for use in any future research studies that may or may not be related to the original research project. Further information can be found in this document's section on banking. Any such studies would require additional ethical clearances through our ethics committees.

7 Will I be given the results of the research project?

If you wish to find out the aggregate results of the study as they might appear in professional publications, please feel free to follow A/Prof. Cohen-Woods' laboratory's official Facebook page linked below. Please note that these publications will not include any information that can identify any individual.
Behavioural GEMs Facebook page: https://www.facebook.com/bGEMslab/

8 Banking (long term storage of samples and data)

"Banking" is storing health information and biological samples for future research studies. A "bank" is the place where the health information and samples are stored. Your saliva will be securely stored as re-identifiable specimen(s) by A/Prof. Cohen-Woods, currently at the Flinders Centre for Innovation in Cancer (FCIC). The health information will be the responses to the questionnaires and your performance on the cognitive and motor function tests, as well as your diagnosis, and will be stored securely on computers at the University of Adelaide and Flinders University. New information is constantly being published in relevant scientific fields, and we would like to take the opportunity to contribute to future research where relevant with your samples. We are not currently able to specify what these studies in the future may be, however we seek permission to store and analyse your samples in the future for such analyses. We request you to consider taking part in this bank due to the potential benefits of ongoing research in this area. Other researchers may also have access to a de-identified database including your saliva, DNA and cognitive test results, which may allow them to answer research questions that we have or could not answer. When data and samples are shared with other researchers and/or deposited in a repository, the data and samples are de-identified.

Your saliva, DNA, and data will be stored in the bank using a means that ensures your confidentiality and anonymity. The only people with access to identifying information are the professionals who need to check the project data. These people are limited supervisors of the project and/or inspectors from the ethics committee. They may view your name and other collected information but have no right to reveal this information to anyone else.

Your saliva sample will be stored to be re-identifiable. This means that your identity is not linked within the bank, data, or in analyses, however it can be re-linked for purposes of follow-up studies. Therefore it is re-identifiable. You can have your sample removed and destroyed from

Please note that if you choose to withdraw your data, including your saliva sample, your saliva sample and/or DNA will be disposed of according to biohazard management policies of the University, but this will not affect any de-identified (i.e., anonymous) data already shared with other researchers, or data previously analysed. This will result in your data being deleted and excluded in future analyses, but will not influence analyses and/or data sharing retrospectively.

9 What are the possible benefits of banking my saliva?

There is no direct benefit to you. Other people might benefit if researchers learn more by using your banked saliva sample and other information collected during this study.

10 What are the possible risks and disadvantages of banking?

This procedure forms part of the main research project. There is no extra physical risk to you as part of the research.

Your saliva will be stored in the bank using a means that ensures your confidentiality and anonymity. The only people with access to identifying information are professionals who need to

check the project data. These people are limited to the research team and/or inspectors from the ethics committee. They may view your name and associated information but have no right to reveal this information to anyone else.

11 Will I be informed of results of future research using my biospecimen?

The aggregate results of this and other studies that have used your saliva sample and other data will likely appear on A/Prof. Cohen-Woods' laboratory's official Facebook page (https://www.facebook.com/bGEMslab/). Please note that these publications will not include any information that can identify any individual.

Although genomic information may change over time as new knowledge is gained, we will not be revisiting your genomic data in the context of medical advancements as this is indefinite. Therefore, you will not be informed of the results of future research.

12 Banking of Health Information

The health information we will collect and store in a bank for this research project consists of your responses to the questionnaires and your performance on the cognitive and motor function tests, as well as your answers to the demographic and health-related questions.

We will not use your personal health information for a different research project without the permission of a Human Research Ethics Committee. Once all personal identification is removed, the information might be used or released for other purposes without asking you. Results of the research project may be presented in public talks or written articles, but information will not be presented that identifies any participant.

Part 2 How is the research project being conducted?

13 What will happen to information about me?

All genetic and other biological samples will be de-identified; a unique ID number will be given to all your samples in place of your name, in order to prevent anyone from identifying you from your samples. These ID numbers **will not** correspond to any names, emails, addresses or phone numbers that may be used to identify you. A document linking your name to your unique ID will be kept by the Principal Investigator, [redacted], who will store this securely on a computer at the University of Adelaide. She will be the only one able to access this information. This information will only be accessed in the case that a) we find medically significant information, and b) you have requested that we inform you of said information. In general, your samples and data will not be released for any use without your prior consent, unless required by law, by an insurance agency, or by the ethics committee that approved this project. It may also be used to re-contact you in the future to ask for your participation in a follow up study if you have consented to be re-contacted for that purpose.

Only average results from all participants will be reported in future publications and presentations. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, maintaining your confidentiality.

Please note that publication and funding requirements may require submission of data or information to controlled access repositories that meet international security and safety standards for sharing with researchers globally. Any data (including genetic and cognitive testing data) shared via such repositories will be de-identified, protecting your anonymity.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Please note that you will not benefit financially from your involvement in this research project even if, for example, knowledge acquired from analysis of your saliva sample and other information collected from you prove to be of commercial value to the institutions with which the investigators are affiliated.

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the University of Adelaide.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project, you can contact the principal

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2020-016). Please contact the Human Research Ethics Committee's Secretariat on phone +61 8 8313 6028 or by email to hrec@adelaide.edu.au if you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

ID: _____

A biobank for genomic, cognitive and motor function data

Participant Consent Form

Investigators

Human Research Ethics Committee Approval Number	H-2020-016
Location	The University of Adelaide, North Terrace Campus / Western Sydney University

Declaration by Participant

I have read the Participant Information Sheet

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with any answers I have received.

I understand that I will be given a signed copy of this document to keep.

I give permission for the use of my data and DNA and/or tissue for the purposes of **(choose one)**:

- **The research project associated with this study only** ☐
- **This research project associated with this study, and any future research projects that may or may not be related to the aims of this research project** ☐

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project by contacting the researchers listed in the information sheet, and that withdrawal will not affect my future health care.

I understand that should I choose to withdraw, I can request for my data (including questionnaire answers and genetic information) be omitted from research, and my biological samples destroyed.

Name of Participant (please print): _____

Signature: _____ Date: _____

Declaration by Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood all the necessary information contained in the information sheet required for their informed consent.

Name of Researcher (please print): _____

Signature: _____ Date: _____

Note: All parties signing the consent section must date their own signatures.

Appendix D

Consent Form

Cognitive function across the lifespan
Participant Consent Form

Investigators

Human Research Ethics Committee Approval Number	H-2020-017
Location	The University of Adelaide, North Terrace Campus / Western Sydney University

Declaration by Participant

- I have read the Participant Information Sheet.
- I understand the purposes, procedures and risks of the research described in the project.
- I have had an opportunity to ask questions and I am satisfied with any answers I have received.
- I understand that I will be given a signed copy of this document to keep.

I consent to being recontacted in the future if I am eligible to participate in other studies and/or to provide further biological samples: **Yes** ☐ **No** ☐

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project by contacting the researchers listed in the information sheet, and that withdrawal will not affect my future health care.

I understand that should I choose to withdraw, I can request in writing for my data (including questionnaire answers and genetic information) be omitted from research, and my biological samples destroyed.

Name of Participant (please print): _____

Signature: _____ Date: _____

Declaration by Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood all the necessary information contained in the information sheet required for their informed consent.

Name of Researcher (please print): _____

Signature: _____ Date: _____

Note: All parties signing the consent section must date their own signatures.

Appendix E

Task instructions

Dot Matrix Task

Initial Instructions

In this task, you will be asked to verify simple visual equations while remembering dot locations on a grid. The aim is to remember as many dot locations as you can. Tap the 'Begin animation' button to see an animated explanation of this task. You will first see a matrix equation like the one below. You will have to indicate whether the equation is True or False. Then a grid containing a dot will be shown. Try to remember the location of the dot. Then another matrix will be shown, and another dot on the grid to remember. In the end, you will be asked where the dots had been shown. Tap the locations you remember and submit your answer.

Final Instructions

There will be several item questions. The items will start with 2 dot locations to remember, and the number of dot locations will gradually increase. If you don't remember a location, you can guess its approximate location, but don't choose more locations than the number of dots you have seen. Tap the 'Begin' button to begin the task or tap the 'Replay animation' button to watch the instructions again.

Digit Span Task

Digit Span Forward

I am going to say some numbers. Listen carefully, and when I am finished, say them right after me, in the same order that I have said them. For example, if I say 7-1-9, what would you say? And if I say 3-4-8, what would you say?

Digit Span Backward

I am going to say some numbers. Listen carefully, and when I am finished, say them right after me, in the reverse order that I have said them. For example, if I say 7-1-9, what would you say?

Inspection Time Task

In this task, you will be shown several arrows. Each arrow will be shown briefly, followed by a mask like this. Your task is to indicate whether the arrow is pointed left or right by pressing the corresponding button. Some arrows will be shown for a very short time, so it may be difficult to determine whether they are pointed left or right. But don't worry if this happens. Just take a guess. This task will last about four minutes. Tap the 'Replay' button to watch these instructions again or tap the 'Start' button to begin.

Raven's Progressive Matrix Task

You will be shown 18 images, one at a time. An example image is shown below. Each image illustrates a larger matrix at the top from which a part is missing. The smaller patterns below the matrix are possible parts that might complete the matrix. For each image, you will have to choose the part that you think best completes the matrix.

[animation plays automatically]

Stop Signal Task

In this task, you will see two buttons. Press the left arrow button if an arrow pointing left appears or the right arrow button if an arrow pointing right appears. You should try to respond as quickly as you can, so keep your hands near the buttons. However, try your best not to respond when you see two overlapping arrows. Stopping a response can be difficult, so try not to get too frustrated if you sometimes can't do it. Tap the 'Replay' button to watch these instructions again or tap the 'Start' button to begin.

Learning Rate Imbalance Task Instructions

Initial Task Instructions

"In this task, you'll be presented with different pairs of pictures. For every pair you're presented with, you'll need to tap one of the two pictures like this. Once you do, you'll find out whether your response was correct or incorrect. This feedback will help you make the right choices more often. You'll only have 4 seconds to make a response, so don't waste too much time making a

decision. Remember, your task is to discover which pictures are more likely to be correct and to maximise how many correct choices you make. Tap the 'Replay' button to watch these instructions again or tap the 'Start' button to begin."

Instructions Before Each Test Phase

"It's time to test what you've learnt! During this set of trials, you will NOT receive feedback ('Correct!' or 'Incorrect') to your responses. If you see new combinations of pictures, please choose the picture that 'feels' more correct based on what you have learnt so far. If you're not sure which one to pick, just go with your gut instinct. Please remember to continue responding even though you will no longer receive feedback. Tap the 'Start' button to begin."

Instructions Before Each New Set

"In the next phase of this task, you will be presented with entirely new pairs of pictures. On every trial, you will have to choose one of the pictures by tapping it. Like before, you will be informed whether your response was correct or incorrect. Your task is to discover which pictures are more likely to be correct and to maximise how many correct choices you make. Tap the 'Start' button to begin."

Appendix F

Correlations Matrices for General Cognition, Reward and Punishment Learning Measures

Table F1

Correlations Between General Cognition Measures

Measure	RPM	SST	Dot Matrix	Digit Span	Inspection Time
RPM	-				
SST	-.21***	-			
Dot Matrix	.34***	-.20***	-		
Digit Span	.29***	-.09	.40***	-	
Inspection Time	-.17**	.13*	-.13*	-.15**	-

Note. RPM = Raven's Progressive Matrices; *SST* = Stop Signal Task.

*p<.05, **p<.01, ***p<.001

Table F2

Correlations Between Reward and Punishment Learning Measures

Measure	Win-stay	Choose-S1	Lose-shift	Avoid-S2
Win-stay	-			
Choose-S1	.42***	-		
Lose-shift	.19***	.16**	-	
Avoid-S2	.43***	.46***	0.24***	-

Note. *p<.05, **p<.01, ***p<.001

Appendix G

Skewness and Kurtosis Statistics

Table G1

Skewness and Kurtosis Statistics for GC-Scores, RL-Scores, PL-Scores and LRI-Scores.

Variable	Skewness	Kurtosis	Range
RL-scores	-0.95[a]	0.68	-3.47 – 1.76
PL-scores	-0.03	-0.37	-2.66 – 2.51
GC-scores	-0.34	-0.03	-3.11 - 2.44
LRI-scores	0.14	-0.16	-3.16 - 2.59

Note. RL-scores = Reward Learning Scores, *PL-scores* = Punishment Learning Scores, *GC-scores* = General Cognition Scores, *LRI-scores* = Learning Rate Imbalance Scores.

[a] Distribution was negatively skewed for RL-scores

Appendix H

Shapiro-Wilk Test and Q-Q plots for Study Variables

Table H1

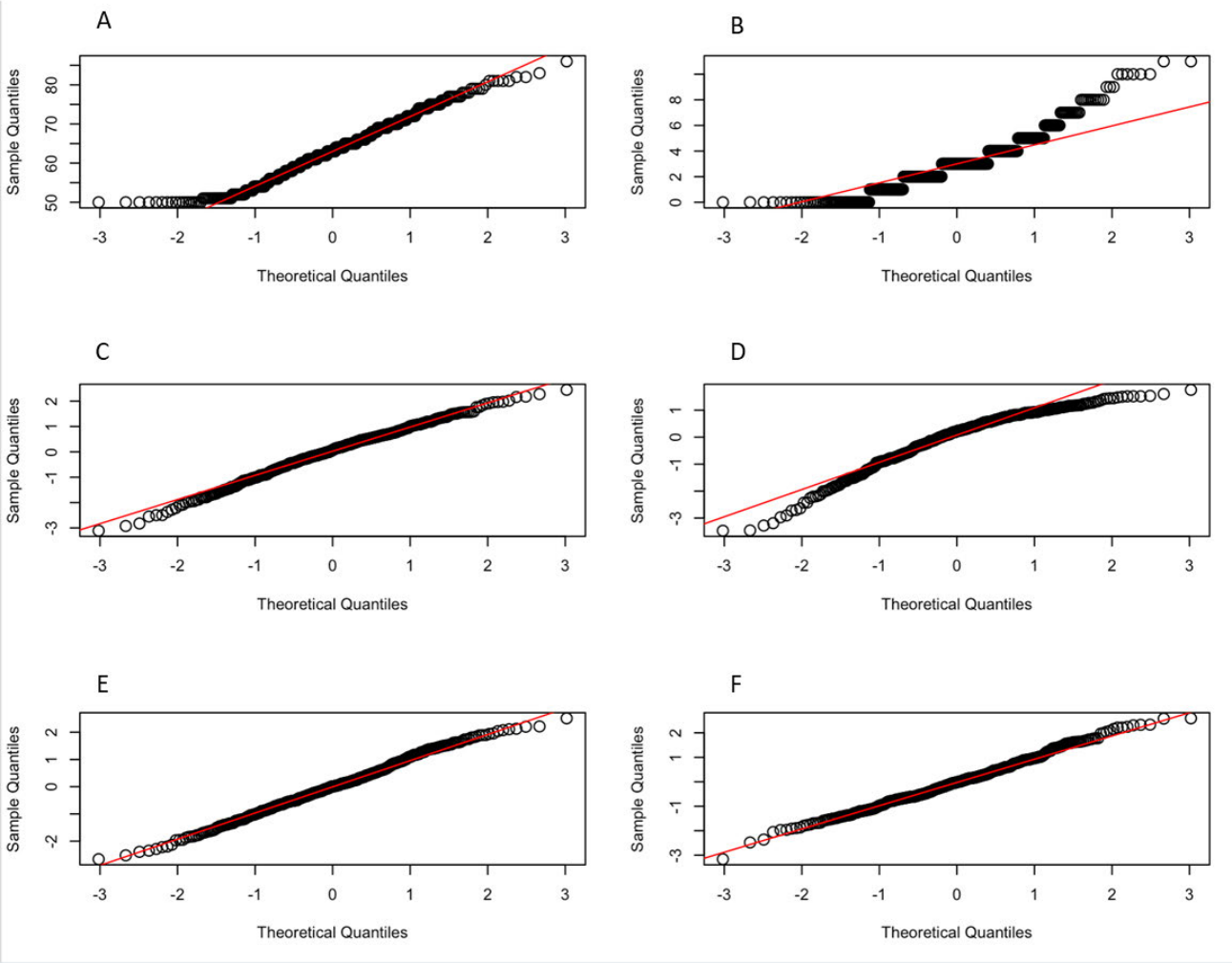
Test of Normality (Shapiro-Wilk)

Variable	W	*p*
Age	0.97	<0.001
RBDSQ	0.92	<0.001
RL-scores	0.94	<0.001
PL-scores	0.99	0.297
GC-scores	0.99	0.021
LRI-scores	0.99	0.273

Note. Significant results suggest a deviation from normality; Significant values are with p<.001.

Figure H1

Normal Q-Q Plots



Note: The graphs demonstrated normal Q-Q plots of participants (A) Age, (B) RBDSQ scores, (C) GC-scores, (D) RL-scores, (D) PL-scores, and (E) LRI-scores against the expected normal distribution of adult participants. *RL-scores* = Reward Learning Scores, *PL-scores* = Punishment Learning Scores, *GC-scores* = General Cognition Scores, *LRI-scores* = Learning Rate Imbalance Scores.

Appendix I

Summary of Robust Linear Regression Analyses for General Cognition and Learning Rate Imbalance

Table I1

Summary of Robust Linear Regression Analyses for RBDSQ as a Predictor of General Cognition and Learning Rate Imbalance Controlling for Age and Sex

Variable	R^2	*B*	*SE B*	*t*	*p*
Additive Model Predicting General Cognition (GC-scores)					
	.14				
RBDSQ		-0.00	0.02	-0.11	0.910
Age		-0.04	0.01	-6.86	<0.001
Sex (Male)		0.33	0.10	3.15	0.002
Interaction Model Predicting General Cognition (GC-scores)					
	.17				
RBDSQ		-0.57	0.18	-3.24	0.001
Age		-0.07	0.01	-6.51	<0.001
Sex (Male)		0.29	0.10	2.80	0.005
Age x RBDSQ		0.01	0.00	3.30	0.001
Additive Model Predicting Learning Rate Imbalance (LRI-scores)					
	.00				
RBDSQ		-0.02	0.02	-1.01	0.314
Age		-0.00	0.01	-0.54	0.592
Sex (Male)		0.04	0.10	0.36	0.718
Interaction Model Predicting Learning Rate Imbalance (LRI-scores)					
	.00				
RBDSQ		-0.08	0.18	-0.45	0.655
Age		-0.01	0.01	-0.54	0.590
Sex (Male)		0.04	0.10	0.35	0.729
Age x RBDSQ		0.00	0.00	0.32	0.750

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *GC-scores* = General Cognition Scores; *LRI-scores* = Learning Rate Imbalance Scores.

Appendix J

Summary of Regression Analyses for Reward and Punishment Learning

Table J1

Summary of Linear Regression Analyses for RBDSQ as a Predictor of Reward Learning and Punishment Learning, Controlling for Age and Sex

Variable	*B*	*SE B*	β	*t*	*p*
Additive Model Predicting Reward Learning (F (3, 389) = 4.20, p = .002, R^2 = 0.04)					
RBDSQ	-0.03	0.02	-0.06	-1.21	0.226
Age	-0.02	0.01	-0.19	-3.79	<0.001
Sex (Male)	0.11	0.11	0.05	0.98	0.328
Interaction Model Predicting Reward Learning (F (4, 388) = 3.72, p = 0.005, R^2 = 0.04)					
RBDSQ	-0.09	0.17	-0.22	-0.55	0.584
Age	-0.03	0.01	-0.22	-2.50	0.013
Sex (Male)	0.10	0.11	0.05	0.95	0.341
Age x RBDSQ	0.00	0.00	0.15	0.40	0.692
Additive Model Predicting Punishment Learning (F (3, 389) = 3.62, p =.01, R^2 = 0.03)					
RBDSQ	0.00	0.02	0.01	0.16	0.873
Age	-0.02	0.00	-0.16	-3.20	0.002
Sex (Male)	0.07	0.11	0.03	0.69	0.491
Interaction Model Predicting Punishment Learning (F (4, 388) = 2.71, p =.03, R^2 = 0.03)					
RBDSQ	0.04	0.17	0.08	0.20	0.838
Age	-0.02	0.01	-0.15	-1.69	0.092
Sex (Male)	0.08	0.11	0.04	0.70	0.486
Age x RBDSQ	-0.00	0.00	-0.07	-0.19	0.853

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *RL-scores* = Reward Learning Scores, *PL-scores* = Punishment Learning Scores.

Table J2

Summary of Robust Linear Regression Analyses for RBDSQ as a Predictor of Reward Learning and Punishment Learning, Controlling for Age and Sex

Variable	R^2	*B*	*SE B*	*t*	*p*
Additive Model Predicting Reward Learning (RL-scores)					
	.04				
RBDSQ		-0.02	0.03	-0.61	0.544
Age		-0.02	0.01	-3.76	<0.001
Sex (Male)		0.07	0.10	0.73	0.469
Interaction Model Predicting Reward Learning (RL-scores)					
	.04				
RBDSQ		0.03	0.22	0.14	0.892
Age		-0.02	0.01	-1.56	0.119
Sex (Male)		0.07	0.10	0.74	0.458
Age x RBDSQ		-0.00	0.00	-0.21	0.831
Additive Model Predicting Punishment Learning (PL-scores)					
	.03				
RBDSQ		0.00	0.02	0.26	0.793
Age		-0.02	0.01	-3.07	0.002
Sex (Male)		0.08	0.11	0.78	0.435
Interaction Model Predicting Punishment Learning (PL-scores)					
	.03				
RBDSQ		0.03	0.18	0.14	0.888
Age		-0.02	0.01	-1.53	0.127
Sex (Male)		0.08	0.11	0.78	0.433
Age x RBDSQ		-0.00	0.00	-0.11	0.916

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *RL-scores* = Reward Learning Scores, *PL-scores* = Punishment Learning Scores.

Appendix K

Changes in Reward Learning and Punishment Learning as a Function of Age and RBDSQ Scores

Table K1

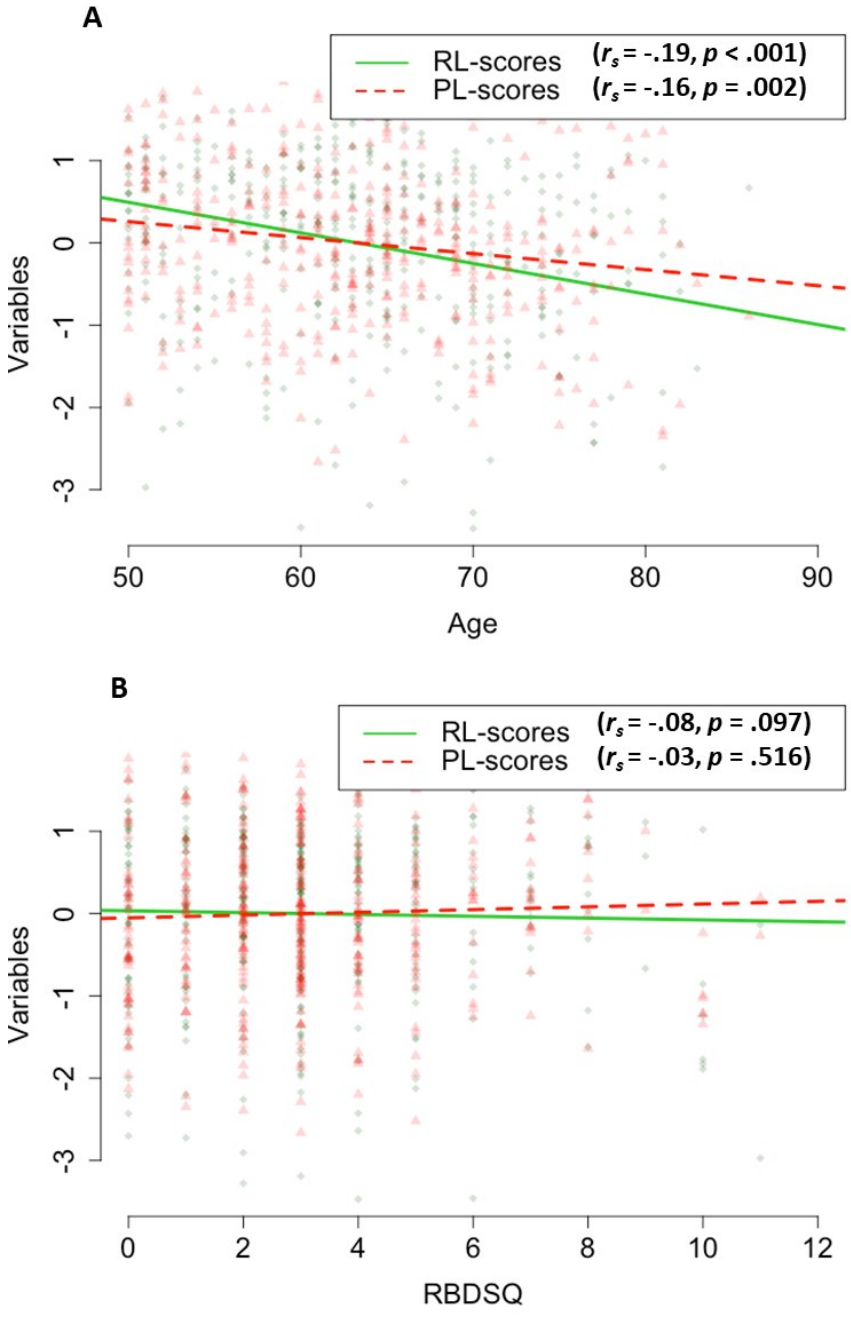
Spearman Correlations Between Age, RBDSQ scores, General Cognition, Reward Learning and Punishment Learning

Variable	Age	RBDSQ	RL-scores	PL-scores
Age	—			
RBDSQ	-.16**	—		
RL-scores	-.19***	.01	—	
PL-scores	-.16**	.05	.46***	—

Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *p<.05, **p<.01, ***p<.001, *RL-scores* = Reward Learning Scores, *PL-scores* = Punishment learning scores.

Figure K1

Changes in Reward Learning and Punishment Learning as a Function of Age and RBDSQ Scores.



Note. RBDSQ = REM Sleep Behaviour Disorder Screening Questionnaire, *RL-scores* = Reward Learning Scores, *PL-scores* = Punishment Learning Scores.