UNIVERSITA' VITA-SALUTE SAN RAFFAELE

CORSO DI DOTTORATO DI RICERCA
IN NEUROSCIENZE COGNITIVE

Rem sleep Behavior Disorder: in search of neuropsychological and psychophysiological biomarkers for neurodegeneration

DoS: Dr. Andrea Galbiati

Tesi di DOTTORATO di RICERCA di

Caterina Leitner

matr. 017370

Ciclo di dottorato XXXVI°

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CONSULTAZIONE TESI DI DOTTORATO DI RICERCA

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Rem sleep Behavior Disorder: in search of neuropsychological and psychophysiological biomarkers for neurodegeneration

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DECLARATION

This thesis has been:

- composed by myself and has not been used in any previous application for a degree. Throughout the text I use both 'I' and 'We' interchangeably.
- has been written according to the editing guidelines approved by the University.

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I would like to acknowledge that the third chapter of this thesis has been previously published in Leitner, C., D'Este, G., Verga, L., Rahayel, S., Mombelli, S., Sforza, M., Casoni, F., Zucconi, M., Ferini-Strambi, L., & Galbiati, A. (2023). Neuropsychological Changes in Isolated REM Sleep Behavior Disorder: A Systematic Review and Meta-analysis of Cross-sectional and Longitudinal Studies. Neuropsychology review.

All the results presented here were obtained by myself, except for:

1)***Analyses of the Systematic Review and Meta-analysis (chapter 3)***

were performed in collaboration with Dr Giada D'Este, Vita-Salute" San Raffaele University, Milan, Italy.

2)***K-Complexes, Slow Waves and Neurodegeneration in Isolated Rem Behavior Disorder: Preliminary Data from a Multicentric Longitudinal Study (chapter 4)***

data were provided by other centers (IRCCS Fondazione Mondino, Pavia; DINOGMI, Clinical Neurology, University of Genoa; Sleep Disorder Center of the University Hospital Cagliari) but I combined and analyzed all the data, and I obtained the results by myself.

All sources of information are acknowledged by means of reference.

DEDICATION

Mi sono proiettata più volte alla fine di questo percorso, che oggi, fortunatamente, non suona come una fine ma solo come un nuovo inizio. Non mi ero certo immaginata di trovarmi a scrivere la tesi in 72 ore, ma dopo questo amaro inizio sono grata di aver potuto riprendere con calma in mano il lavoro.

Desidero esprimere la mia profonda gratitudine a coloro che hanno reso possibile la realizzazione di questa tesi di dottorato.

Innanzitutto, desidero ringraziare di cuore il mio tutor, Andrea Galbiati. Sono onorata che tu sia stato il supervisore di questo mio percorso. Penso tu abbia un dono nel trasmettere la tua passione nei confronti della conoscenza e nel promuovere la curiosità, e io ho provato a farlo mio. La tua guida è stata fondamentale per il successo di questo percorso.

Un ringraziamento speciale va a mio marito, Loris, il cui costante sostegno, fiducia e pazienza hanno reso possibile questo traguardo. Grazie per essere stato al mio fianco in ogni momento, per avermi incoraggiato quando avevo bisogno e per aver reso più leggere le lunghe giornate di lavoro. Grazie per la pazienza che hai davanti a tutti i momenti di stress e stanchezza, e grazie per aver sempre ascoltato le mie lunghissime presentazioni orali.

Desidero estendere la mia gratitudine anche ai miei cari colleghi e amici, Giada, Samantha, Elisabetta, Marco e Francesca, nonché alla nostra stimata neurologa Francesca Casoni. Il vostro contributo e il vostro sostegno hanno reso il mio percorso a Turro un'esperienza preziosa. Grazie per tutti i momenti di condivisione professionale ma anche personale e per essermi stati vicini in questo percorso di crescita reciproca.

Un ringraziamento particolare va alla mia famiglia, che ha sempre creduto in me e mi ha incoraggiato a dare il massimo in ogni circostanza. Grazie per essere stati al mio fianco, per avermi sostenuto nelle difficoltà e per avermi spronato a perseguire i miei obiettivi. Allo stesso tempo, vi ringrazio per avermi anche aiutato ad affrontare le delusioni, per avermi dato la forza di rimettermi alla prova, ricordandomi sempre l'enorme importanza dello studio, del lavoro e del sacrificio ma anche il valore della vita, che non si ferma mai, e ci presenta seconde opportunità per provare a ridimostrare il meglio. Senza di voi, questo traguardo non sarebbe stato possibile.

A Beatrice, amica preziosa e collega. Voglio ringraziarti per essere stata una costante fonte di sostegno e ispirazione durante l'ultima parte di questo mio percorso. Grazie per i tuoi preziosi consigli, per i momenti di confronto e per la tua sincera amicizia.

Infine, desidero ringraziare Viviana per aver reso il mio periodo all'estero un'esperienza indimenticabile. Grazie per avermi accolto a Cardiff con calore e per aver reso ogni giorno un'avventura unica e speciale.

A tutti voi, il mio più sincero ringraziamento per aver condiviso con me questa straordinaria avventura accademica.

Abstract

Isolated Rapid Eye Movement (REM) sleep Behavior Disorder (iRBD) is a REM sleep parasomnia, where patients experience complex behaviors due to the loss of REM sleep atonia. iRBD has been the focus of several research studies; with evidence suggesting that this disorder precedes the development of synucleinopathies. In this context, the overall aim of my PhD project is to comprehensively explore the neuropsychological, electrophysiological, and psychophysiological aspects of iRBD, evaluating them as potential sensitive biomarkers for the early detection of subsequent phenoconversion. The overall aim is addressed through the pursuit of three specific aims, each explored in three separate studies: (i) a meta-analysis to delineate the neuropsychological profile of iRBD patients, as well as to identify specific cognitive alterations that may indicate higher risk of phenoconversion; (ii) a longitudinal study exploring the association between non-REM (NREM) waveforms, namely k complexes (KC) and slow waves, and cognitive status within iRBD population, assessing their role as predictors of the phenoconversion; and (iii) a cross sectional study including heathy controls (HCs) and iRBD patients to examine diurnal emotional functioning in this disorder and explore the relationship between emotion regulation and REM sleep characteristics. Special attention is placed on REM phasic events and their involvement in the disruption of overnight emotional habituation. The meta-analytic study revealed that the neuropsychological profile of iRBD is characterized by alterations in global cognitive screening, memory, and executive functions. Additionally, we observed that executive functions, as well as the presence of mild cognitive impairment, seem to be sensitive indicators at baseline for subsequent phenoconversion. The electrophysiological study identified an association between KC density and cognitive status in iRBD patients, with a reduction in KC density at baseline being associated with subsequent phenoconversion, highlighting the potential role of KC density as a phenoconversion marker. Lastly, psychophysiological study confirmed the significant role of REM sleep in overnight emotional habituation processes in both HCs and iRBD patients, revealing disruptions in the presence of a great number of phasic events. These findings constitute a small part of a larger project investigating phenoconversion predictors in iRBD patients, potentially paving the way for pharmacological research to reduce NREM alterations and stabilize REM sleep.

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LIST OF STUDIES

Studies Published/Accepted during the course of the PhD:

1. **Leitner, C**., D'Este, G., Verga, L., Rahayel, S., Mombelli, S., Sforza, M., Casoni, F., Zucconi, M., Ferini-Strambi, L. & Galbiati, A. (2022). Neuropsychological Changes in Isolated REM Sleep Behavior Disorder: a Systematic Review and Meta-analysis of Cross-sectional and Longitudinal Studies. Neuropsychology Review, 1-26. DOI: https://doi.org/10.1007/s11065-022-09572-1 (Impact factor: 6.940) - Review Article.
2. Mombelli, S., **Leitner, C**., D'Este, G., Sforza, M., Marelli, S., Castelnuovo, A., Zucconi, M., Casoni, F., Fantini, M.L., Novellino, F., Salsone, M., Ferini-Strambi, L. & Galbiati, A. (2022). A data-driven approach to neuropsychological features in isolated REM behaviour disorder: A latent class analysis. Journal of Neuropsychology, 00, 1–19. DOI: https://doi.org/10.1111/jnp.12292 (Impact factor: 2.276) - Original Article.
3. D'Este, G., Berra, F., Carli, G., **Leitner, C**., Marelli, S., Zucconi, M., Casoni, F., Ferini-Strambi, L. & Galbiati, A. (2023). Cognitive Reserve in Isolated Rapid Eye-Movement Sleep Behavior Disorder. Brain Sciences, 13(2), 176. DOI: https://doi.org/10.3390/brainsci13020176 (Impact factor: 3.333) - Original Article.
4. Galbiati, A., Sforza, M., Fasiello, E., Casoni, F., Marrella, N., Leitner, C., Zucconi, M., & Ferini-Strambi, L. (2020). The association between emotional dysregulation and REM sleep features in insomnia disorder. Brain and cognition, 146, 105642. https://doi.org/10.1016/j.bandc.2020.105642 (Impact factor: 2.682) -Original Article.
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6. Galbiati, A., Sforza, M., **Leitner, C**., Castelnovo, A., D'Este, G., Ferini-Strambi, L., Manconi, M. & Castronovo, V. (2021). The reliability of objective total sleep time in predicting the effectiveness of cognitive-behavioral therapy for insomnia. Sleep Medicine, 82, 43-46. DOI: https://doi.org/10.1016/j.sleep.2021.03.021 (Impact factor: 4.842) - Original Article.

7. Galbiati, A., Sforza, M., **Leitner, C.,** Castelnovo, A., D'Este, G**.,** Ferini-Strambi, L., Manconi, M. & Castronovo, V. (2021). Objective total sleep time and effectiveness of cognitive-behavioral therapy for insomnia: methodological issues. Sleep medicine, 85, 105-106. DOI: https://doi.org/10.1016/j.sleep.2021.06.037 (Impact factor: 4.842) - Original Article.
8. Galbiati, A., Sforza, M., Scarpellino, A., Salibba, A., **Leitner, C**., D'Este, G., Mombelli, S., Ferini-Strambi, L. & Castronovo, V. (2021). "Thinking About Thinking" in Insomnia Disorder: The Effect of Cognitive-Behavioral Therapy for Insomnia on Sleep-Related Metacognition. Frontiers in Psychology, 3892. DOI: https://doi.org/10.3389/fpsyg.2021.705112 (Impact factor: 4.232) - Original Article.

ACRONYMS AND ABBREVIATIONS

Abbreviation	Full-length Word
AASM	American Academy of Sleep Medicine
AD	Alzheimer's Disease
ADLBV	Alzheimer's Disease with Lewy Body Pathology
aMCI	amnestic Mild Cognitive Impairment
BDI	Beck Depression Inventory
BL	Baseline
CASP	Critical Appraisal Skills Programme
CERQ	Cognitive Emotion Regulation Questionnaire
CI	Confidence Interval
DAS	Dimensional Apathy Scale
DEBs	Dream Enacting Behaviors
DERS	Difficulties in Emotion Regulation Scale
D-first	Dementia-first
DLB	Dementia with Lewy Bodies
DP	Depotentiation
EEG	Electroencephalography
EM	Eye Movements
EMG	Electromyography
EOG	Electrooculogram
ES	Effect Size
ESRS	European Sleep Research Society
Evlpo	extended part of the ventrolateral Preoptic Nucleus
FDG-PET	^{18}fluorodeoxyglucose Positron Emission Tomography
FDS	Flexor Digitorium Superficialis
fMRI	functional Magnetic Resonance Imaging
FU	Follow-Up
HCs	Healthy Controls
HR	Hazard Ratios
IADS	International Affective Digitized Sounds

IAPS	International Affective Picture System
ICSD-3	International Classification of Sleep Disorders – Third Edition
iRBD	Isolated REM sleep Behavior Disorder
IRR	Inter-Rater Reliability
JASP	Jeffreys's Amazing Statistics Program
KC	K Complex
KCd	K Complex density
LARS	Lille Apathy Ratings Scale
LC	Locus Coeruleus
LDTN	Laterodorsal Tegmental Nucleus
LPT	Lateral Pontine Tegmentum
LTP	Long Term Potentiation
MCI	Mild Cognitive Impairment
MCRF	Mesencephalic Central Reticular Formation
MMSE	Mini-Mental State Examination
MSA	Multiple System Atrophy
N1	non-REM sleep stage 1
N2	non-REM sleep stage 2
NA	Noradrenaline
NREM	Non-REM sleep
PD	Parkinson's Disease
P-first	Parkinsonism-first
PI	Prediction Intervals
PPN	Pedunculopontine Nucleus
pRBD	probable REM Sleep Behavior Disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
PSG	Polysomnography
RAVLT	Rey Auditory-Verbal Learning Test
RBD	REM Sleep Behavior Disorder
RBD1Q	RBD Single-Question Screen
RBD-I	Innsbruck RBD-Inventory

RBDQ-HK	RBD Questionnaire – Hong Kong
RBSQ	RBD Screening Questionnaire
RE	Random Effects
REM	Rapid Eye Movement
RN	Raphe Nucleus
ROCF	Rey–Osterrieth Complex Figure
RSWA	REM Sleep Without Atonia
SCWT	Stroop Color Word Test
SE	Sleep Efficiency
SFSR	Sleep to Forget, Sleep to Remember
SINP	Italian Neuropsychological Society
SL	Sleep Latency
SLD	Sublateralodorsal Nucleus
SO	Slow Oscillation
sRBD	secondary REM Sleep Behavior Disorder
SRIs	Sleep-Related Injuries
STAI	State-Trait Anxiety Inventory
STAI-Y-1	State-Trait Anxiety Inventory measuring state-anxiety
STAI-Y-2	State-Trait Anxiety Inventory measuring trait-anxiety
SW	Slow Wave
SWA	Slow Wave Activity
SWE	Slow Wave Energy
SWS	Slow Wave Sleep
TAS-20	Toronto Alexithymia Scale – 20 items
TMR	Targeted Memory Reactivation
TMT	Trial Making Test
TMT-A	Trial Making Test – part A
TMT-B	Trial Making Test – part B
TST	Total Sleep Time
UPDRS	Unified Parkinson's Disease Rating Scale
vlPAG	ventrolateral part of the Periaqueductal Gray Matter
WASO	Wakefulness after Sleep Onset

α-syn	alpha-synuclein

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1. INTRODUCTION

1.1. REM sleep Behavior Disorder

According to the third edition of the International Classification of Sleep Disorders (ICSD-3) (American Academy of Sleep Medicine, 2014) and an update on the diagnosis published in 2017 (Högl & Stefani, 2017), Rapid Eye Movement (REM) sleep Behavior Disorder (RBD) is defined as a REM sleep parasomnia characterized by the loss of muscular atonia present during REM sleep. The loss leads patients to act out their dreams through vigorous and sometimes violent behaviors and/or sleep-related vocalization. Criteria specify that these behaviors should be documented by polysomnography (PSG) to occur during REM sleep or should be presumed to occur during REM, based on previous clinical observations. To diagnose RBD, PSG evidence of REM sleep without atonia (RSWA) is also necessary. Lastly, the disturbance should not be better explained by other sleep/mental disorders, medication, or a history of substance abuse (American Academy of Sleep Medicine, 2014; Högl & Stefani, 2017).

1.2. Clinical features

The clinical features of RBD can vary in intensity based on the level of aggression displayed during sleep episodes. Once the disorder is established, it typically occurs every night with varying degrees of intensity. If the patient is awakened because of such episodes, he/she is usually aware of his/her surroundings but does not recall the nightmares he/she experienced (Santamaria *et al*, 2004). The disorder becomes more common with age and is more frequently observed in males. Symptoms generally appear between 45-61 years old, and formal diagnosis usually occurs between 52-65 years old (Kryger *et al*, 2010).

Treatment primarily focuses on preventing self-injury or harm to a bed partner during sleep. This is achieved through adjustments in the sleeping environment (Boeve, 2010) or by minimizing behaviors with the administration of clonazepam and melatonin. These medications reduce muscle activity during REM sleep but do not eliminate it (Lapierre & Montplaisir, 1992). Specifically, clonazepam primarily acts on the production of phasic movements, while melatonin reduces muscle tone without affecting phasic movements (Luppi *et al*, 2013). It is noteworthy that antidepressants can increase abnormal sleep

behaviors during REM sleep due to increased activity on electromyography (EMG), but they also reduce symptoms frequency by reducing the time spent in REM sleep stage (Iranzo *et al*, 2016).

Generally, the literature categorizes RBD clinical characteristics into three main areas, namely:

a) Abnormal Vocalizations and Sleep Talking: RBD patients often express intense emotions like anger and fear during episodes. These emotions are typically manifested through sounds like moans, screams, and wails. Of note, some patients may also show sleep talking and swearing (Iranzo *et al*, 2016).
b) Abnormal Motor Behaviors. Motor movements may start as simple actions, such as brief muscle spasms or uncontrolled limb movements; however, they often escalate to more complex behaviors, including self-defense and attempts to flee from a possible danger. These behaviors may be confined to the bed or may lead the patient to walk or run (Schenck & Mahowald, 2002). Patients may sustain injuries by falling out of bed or bumping into walls and furniture. Bed partners may also report injuries caused by kicks, punches, bites, and occasionally, attempted strangulation (Fernández-Arcos *et al*, 2016). Occasionally, patients may exhibit non-violent and complex behaviors, such as eating or reading (Oudiette *et al*, 2009).
c) Vivid Dreams. RBD patients often describe experiencing vivid dreams with highly aggressive content, which lead them to defensive actions or escape behaviors mentioned above. Only 5-10% of patients either do not remember or cannot recall the content of these dreams (Fantini *et al*, 2005). In greater detail, these dreams are typically described as vivid, intense, of short duration, and often involve only one action with elements derived from past experiences. Of note, they generally do not incorporate subject's current fears and concerns (Uguccioni *et al*, 2013).

1.3. Pathophysiology

Studies on cats and rats revealed the pivotal role of brainstem structures in REM sleep physiology. In this etiology context, the first description of a condition resembling RBD dates back to 1982 with an animal study on cats, where the pontine resection induced

motor behaviors during REM sleep (Hendricks *et al*, 1982). In humans, in the same period, the maintenance of muscle tone during REM sleep was demonstrated through the administration of a tricyclic antidepressant, clomipramine (Lacey *et al*, 1977). Current knowledge about RBD is owed to the pioneering work of Carlos Schenck and Mark Mahowald. These authors in the late 1980 published a series of clinical cases of RBD in association with neurodegenerative diseases (Schenck *et al*, 1986). Since then, interest in RBD has steadily grown, accompanied by a corresponding increase in research on it. Lu and colleagues (Lu *et al*, 2006) proposed a hypothesis involving a flip-flop switch mechanism regulating REM sleep through two distinct populations of GABAergic neurons, namely "REM-on" and "REM-off" neurons (Boeve *et al*, 2007; Boeve, 2010). The primary function of "REM-off" neurons is to inhibit REM sleep, involving structures such as the ventrolateral part of the periaqueductal gray matter (vlPAG) and the lateral pontine tegmentum (LPT). On the contrary, "REM-on" neurons promote REM sleep and encompass structures like the coeruleus-subcoeruleus complex, the sublaterodorsal nucleus (SLD), the extended part of the ventrolateral preoptic nucleus (Evlpo), the laterodorsal tegmental nucleus (LDTN), the pedunculopontine nucleus (PPN), and the raphe nucleus (RN). Physiological atonia during REM sleep occurs because GABAergic and glycinergic neurons in the ventromedial medullary formation and spinal cord inhibit trigeminal, hypoglossal, and spinal motoneurons, which typically control voluntary muscles during wakefulness (Luppi *et al*, 2013). Of note, these inhibitory neurons are activated by direct input from glutamatergic REM-on neurons located in the SLD, which, in turn, inhibit motoneurons in the spinal cord, inducing muscle atonia during REM sleep (Luppi *et al*, 2013). Discoveries related to the physiological aspects of REM sleep paved the way for research into the mechanisms responsible for RSWA in RBD. However, the underlying mechanisms of RBD in humans are not fully understood, and a substantial portion of our understanding is derived from animal studies. Soon it was realized that brainstem regions regulating REM sleep are the same areas involved in the pathophysiology of RSWA and RBD and later it has also been discovered that these brainstem structures are the same where alpha-synuclein (α-syn) pathology might begin (Boeve *et al*, 2007; Boeve, 2010; Dauvilliers *et al*, 2018).

RSWA mechanisms involve several areas, including the pontine nuclei, especially the SLD. Within SLD, two categories of REM-on neurons exist: descending neurons believed

to induce muscle atonia and ascending neurons responsible for cortical activation (Sakai *et al*, 2001). In a study of Luppi and collaborators (Luppi *et al*, 2013), it has been proposed that the occurrence of RSWA may results from either the neurodegeneration of the descending REM-on neurons in the SLD or the neurodegeneration of GABAergic/glycinergic neurons in the nucleus of raphe magnus and the ventral and alpha-gigantocellular reticular nuclei (nuclei located in ventral medulla). The pathophysiology of RBD in humans has been hypothesized to involve networks and structures similar to those observed in animal models (Boeve *et al*, 2007). The authors suggested the existence of two distinct pathways: "direct" and "indirect" routes (Boeve *et al*, 2007; Boeve, 2010). The "direct route" encompasses projections from the SLD (or a corresponding nucleus in humans) to spinal interneurons. The "indirect route" connects the projections from the SLD to spinal interneurons through the Mesencephalic Central Reticular Formation (MCRF). Degeneration of SLD neurons results in reduced inhibition of spinal motoneurons, leading to the occurrence of RSWA. However, it remains unclear whether the degeneration of these pathways alone is sufficient to cause RBD in humans (Boeve *et al*, 2007; Boeve, 2010).

Still, these are not the only areas involved in REM sleep regulation. Indeed, both the motor cortex and the cortical limbic system play a role in RBD pathophysiology. The motor cortex is involved in generating movements during dream enacting behaviors (DEBs), which might be triggered by a phasic depolarization of motoneurons caused by excitatory projections from glutamatergic neurons located in the motor cortex (Luppi *et al*, 2013). The latter, involved in emotion control, might explain why patients report recalled dreams as unpleasant and fearful(Dauvilliers *et al*, 2018).

1.4. The risk of neurodegeneration

Considering that the brainstem structures are where α-syn pathology may begin, several studies assessed the link between RBD and synucleinopathies within the framework of physiopathology. As aforementioned, RBD patients present ongoing degeneration in brainstem nuclei, with Lewy bodies and Lewy neurites in regions responsible for regulating REM sleep. Braak, analyzing postmortem Parkinson's Disease (PD) brains, hypothesized that α-syn pathology begin in brainstem and progressively develops in a caudal to rostral fashion (Braak *et al*, 2003). This progression might be

caused by cell-to-cell transmission between interconnected brain regions. Therefore, the pathological changes that begin from medulla and pons, associated with the development of RSWA, eventually ascend to more rostral structures. The staging system identified by Braak and colleagues has been described as follow (Braak *et al*, 2003, 2004):

- The first stage is defined by the neurodegeneration beginning in the medulla and involving the dorsal motor nucleus of the vagal nerve and the intermediate reticular zone.
- The second stage is characterized by the extension of the pathology to the pons, affecting the caudal RN, the MCRF, the coeruleus-subcoeruleus complex, and the olfactory bulb. These pathological changes may result in olfactory impairment and increased cardiac denervation, which are often observed in RBD patients. Indeed, when neurodegenerative changes occur in the *locus coeruleus* (LC) and MCRF structures, RBD and RSWA may become evident during this stage.
- During the third pathological stage the neurodegeneration reaches the midbrain, leading to significant damage to the substantia nigra pars compacta, the PPN, and the nucleus basalis of Meynert. At this stage, patients may show symptoms of parkinsonism.
- The fourth stage is characterized by the involvement of the temporal mesocortex and limbic structures.
- Finally, during Braak stages 5 and 6, the neurodegenerative process affects the neocortex, leading to cognitive changes that reflect the extent of the underlying pathology.

Given these premises, the reason why RBD is worldwide considered a prodromal stage of alpha-synucleinopathies is clear (Dauvilliers *et al*, 2018). Indeed, RBD cannot be investigated as a separate disease entity from synucleinopathies, but rather an early manifestation of synuclein diseases. In this context, it is necessary to make a distinction between the isolated form of RBD (iRBD) and the secondary form of RBD. According to the first form (iRBD), the disorder occurs without a confirmed link to neurological, motor, or cognitive disorders. Instead, the second form (sRBD) is associated with other neurological conditions, such as neurodegenerative diseases, narcolepsy, brainstem lesions, the use of antidepressant/beta-blocker medications, or withdrawal from alcohol

in individuals with alcoholism (Boeve, 2010; Iranzo *et al*, 2016).

Of note, most iRBD patients will develop a neurodegenerative disorder, primarily synucleinopathies such as PD and Dementia with Lewy Body (DLB) (Galbiati *et al*, 2019; Postuma *et al*, 2019). For this reason, in the literature a great effort has been made for the identification of sensitive biomarkers that might predict the possible phenoconversion of iRBD patients.

1.5. Epidemiology

The exact prevalence of iRBD in the general population is still unknown. Two main reasons for the scarcity of epidemiological data are: i) the disorder is considered uncommon, thus a large sample is needed; and ii) the diagnosis relies on PSG which is not a widely available tool; indeed, it is expensive, time consuming, should be performed by specialists, and patients must spend the night in a sleep laboratory. For this latter reason, epidemiology studies should be categorized as: questionnaires-based population studies and PSG-confirmed studies.

Questionnaire-based population studies report higher percentages compared to PSG-confirmed studies. Epidemiological studies not using PSG for RBD diagnosis estimate a prevalence between 3% and 10% (Boot *et al*, 2012). Probably, these studies overestimate the prevalence due to false positive cases, confounding RBD with other disorders, such as obstructive sleep apnea syndrome, non-REM (NREM) parasomnias, and somnambulism. Moreover, the absence of PSG confirmation can lead to false negatives too. Questionnaires are not able to detect RBD patients that are not aware of their DEBs. In the light of this, data from epidemiological studies not using diagnostic PSG must be taken with caution. Among these studies we can find the paper of Mahlknecht and collaborators (Mahlknecht *et al*, 2015). In this study, authors evaluated the prevalence of RBD in 456 subjects aged 60 years or older using two questionnaires, the RBD Screening Questionnaire (RBDSQ) and the Innsbruck RBD-Inventory (RBD-I). Based on RBDSQ, 21 participants out of 456 (4.6%) tested positive; instead, the RBD-I detected 35 probable RBD (pRBD) out of 456 (7.7%). The following year another epidemiological study was published (Wong *et al*, 2016). This community-based study considered 12,784 Chinese participants (10,556 males and 2,228 females, aged 24 years or older). They used the Chinese RBD questionnaire–Hong Kong (RBDQ-HK) in order to assess pRBD. The

prevalence reported was 5.9% for males and 4.1% for females. The last and more recent study (Ma *et al*, 2017) involved 3635 community-dwelling residents from Shanghai, aged 50 years old or older. In order to assess pRBD they used RBDSQ, leading to an estimated prevalence of pRBD of 2.70% (3.28% in men and 2.41% in women) (Ma *et al*, 2017). These two last studies highlighted a distinction based on gender; however, in the literature no clear difference was demonstrated. Sleep clinics report a strong male predominance, with an overall male-to-female ratio of 2:1 (Ju *et al*, 2011), which is probably due to a selection bias related to the fact that RBD in males is more aggressive and violent and therefore more clinically observed compared to RBD in females (Dauvilliers *et al*, 2018).

PSG-confirmed studies report an estimate that ranges from 0.5% to 2% (Galbiati *et al*, 2019). Specifically, a study conducted in Hong Kong within a community sample of 1034 elderly individuals aged 70 or older reported a RBD prevalence of 0.38% (Chiu *et al*, 2000). This study used a two-stage design to identify RBD patients: the first stage involved a question aimed at detecting sleep-related injuries (SRIs), while the second stage included an interview conducted by a sleep medicine expert and a PSG evaluation. Another longitudinal community-based study in Korea, involving 348 individuals aged over 60, found a RBD prevalence of 1.15% using PSG for the diagnosis (Kang *et al*, 2013). In a Spanish study led by Pujol and colleagues (Pujol *et al*, 2017), which involved a community sample of 539 elderly subjects aged between 74 and 82, an iRBD prevalence of 0.74% was reported. Of note, they used a single screening question for RBD diagnosis (RBD1Q) and PSG to diagnose iRBD (Pujol *et al*, 2017). Lastly, one of the most recent population-based studies was published by Haba-Rubio and collaborators (Haba-Rubio *et al*, 2018) and included a sample of 1997 participants. In this study, participants completed various sleep questionnaires, including the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, the French version of the Munich Parasomnia Screening, and then underwent PSG examination. The results indicated a RBD prevalence of 1.06% in individuals aged between 40 and 80 (Haba-Rubio *et al*, 2018).

As concerns the epidemiology of sRBD, the statistics differ significantly. The prevalence of sRBD varies according to the underlying condition. Overall, 30% to 50% of patients with PD experience RBD, whereas more than 70% of patients with DLB or multiple system atrophy (MSA) exhibit RBD (Dauvilliers *et al*, 2018).

1.6. Neuropsychological markers

Several studies demonstrated the presence of cognitive impairment in patients with iRBD. Despite this, the results from these studies exhibit heterogeneous results with a considerable variability across different cognitive domains (Ferini–Strambi et al, 2004; Fantini et al, 2011; Massicotte-Marquez et al, 2008; Marchand et al, 2017; Génier Marchand et al, 2018; Ferini-Strambi et al, 2019). This variability may be caused first by the use of a wide array of cognitive tests, each one with its sensitivity and specificity; but also factors like heterogeneity in studies' population and small sample sizes may play a role. Most cross-sectional studies agree that the most affected cognitive domains in iRBD are memory and executive functions (Massicotte-Marquez *et al*, 2008; Rolinski *et al*, 2016a, 2016b). Other studies also report poorer performance in visuospatial abilities in iRBD patients compared to healthy controls (HC) (Ferini–Strambi *et al*, 2004; Fantini *et al*, 2011). For instance, Gagnon and collaborators (Gagnon *et al*, 2009) compared 32 iRBD patients and 40 HC subjects on a comprehensive neuropsychological evaluation. The comparison revealed significant lower scores in iRBD patients compared to HCs on the following tests: Digit span, Trial Making Test part B (TMT-B), Semantic Verbal Fluency, and Rey Auditory-Verbal Learning Test (RAVLT). This study highlighted iRBD deficits in executive functions, attention, verbal memory and verbal learning. Similar results were obtained one year before from Massicotte-Marquez and colleagues (Massicotte-Marquez *et al*, 2008) who compared 14 iRBD patients with 14 age and education-matched HCs, observing that iRBD patients exhibited lower performance in tests assessing attention, executive functions, and verbal memory (Massicotte-Marquez *et al*, 2008). Moreover, studies such as those by Ferini-Strambi et al., (2004) and Terzaghi et al., (2008) highlighted deficits in visuo-constructional and visuospatial abilities in iRBD patients compared to HCs. Specifically, in the study published by Ferini-Strambi and colleagues (Ferini–Strambi *et al*, 2004), cognitive performances of 17 iRBD patients were compared with those of 17 HCs of similar ages. Both iRBD subjects and HCs underwent dementia screening tests, as well as comprehensive neuropsychological evaluations. Of note, the results revealed that iRBD patients scored lower than HCs on tests evaluating visuo-constructional (i.e., Rey–Osterrieth complex figure – ROCF) and visuospatial learning abilities (Corsi Supraspan Learning). These findings were confirmed by Terzaghi and colleagues (Terzaghi *et al*, 2008) a few years later when they

compared cognitive functioning between 23 iRBD patients and 23 HCs matched for sex, age, and education. iRBD patients exhibited significantly poorer performance on the following tests: Word Span, ROCF recall, Digit Span, and Logic Memory. However, the test that resulted most affected was the one assessing visuo-constructional learning abilities. Also some longitudinal studies have been conducted on iRBD patients to identify potential early cognitive indicators of alpha-synucleinopathies (Fantini *et al*, 2011; Youn *et al*, 2016; Marchand *et al*, 2017; Sasai-Sakuma *et al*, 2017). In the limited body of longitudinal studies available in the literature, the significant role of the executive function domain as predictor of future conversion has emerged. For instance, in a longitudinal study by Terzaghi and colleagues (Terzaghi *et al*, 2013), the authors investigated the cognitive profile of 20 iRBD patients and compared them to a group of 20 HCs. At baseline (BL), the study revealed cognitive impairments in iRBD patients across several cognitive domains, as evidenced by the poor performance found in various tests (including Word Span, Digit Span Forward, Rey 15-word test delayed recall, logical memory, Wisconsin Card Sorting Test, Attentive Matrices, Raven Colored Matrices, Semantic Fluency, and ROCF delayed recall). Subsequent follow-up (FU) assessments indicated a progression of the condition, with lower scores observed in Attentive Matrices and Raven Colored Matrices in iRBD patients compared to their BL scores (Terzaghi *et al*, 2013). A more recent study by Marchand and colleagues (Marchand *et al*, 2017) prospectively examined a large cohort of iRBD patients to identify cognitive markers for the early detection of prodromal dementia. This study involved 76 iRBD patients who underwent PSG recording, neuropsychological, and neurological assessments at both BL and after an average FU of 3.6 years. At FU, 34 out of 76 patients developed a neurodegenerative disease and categorized as follow: those with parkinsonism first (P-first, n=19) and those with dementia first (D-first, n=15). Mild Cognitive Impairment (MCI) was present in 93% of D-first patients and in 42% of P-first patients. The group with D-first showed poorer performance in executive functions and visuo-spatial abilities compared to the P-first group. Notably, two cognitive tests appeared to be particularly reliable in predicting the trajectory to D-first or P-first: the Stroop Color Word Test (SCWT) for the evaluation of inhibition interference ability, and the TMT for the assessment of divided attention and attention shifting control ability. Of note, both tests (i.e., SCWT and TMT) were included within the broad domain of executive functions

(Marchand *et al*, 2017). One year later, the same authors conducted another longitudinal study to evaluate the progression of cognitive decline in three different groups of patients, including RBD classified at their last FU as still-isolated, PD, or DLB (Marchand *et al*, 2018). Over a six-year FU period, 109 patients underwent PSG recording, neurological and neuropsychological assessments each year. Results revealed that patients diagnosed with DLB displayed attention and executive function impairments at BL which worsened over time, particularly during the last FU. Other cognitive deficits in the DLB group were observed one to two years before dementia diagnosis and involved verbal episodic learning and memory functions. In contrast, patients diagnosed with PD did not exhibit the same cognitive decline; indeed, they showed deficits only in attention and executive functions which were impaired one to two years before PD diagnosis, displaying cognitive profiles similar to those of still-isolated RBD patients. Interestingly, the TMT-B, Semantic Verbal Fluency, and RAVLT tests were found to be the most accurate predictors for dementia in iRBD patients. Based on these findings, the authors suggested that these neuropsychological tests could be useful in identifying the underlying synucleinopathy subtype; specifically, executive functions tests seemed to be one of the best predictors (Marchand *et al*, 2018).

In summary, there have been relatively few longitudinal studies which aimed to investigate cognitive changes in iRBD patients (Fantini *et al*, 2011; Terzaghi *et al*, 2013; Marchand *et al*, 2017, 2018). However, it is noteworthy that Ferini-Strambi and colleagues (Ferini-Strambi et al, 2019) published an insightful review exploring possible biomarkers for predicting disease trajectories in iRBD patients. Their review sheds light on the involvement of multiple cognitive domains in patients with iRBD, including executive functions, attention (Massicotte-Marquez *et al*, 2008; Terzaghi *et al*, 2013) and visuospatial abilities and learning (Ferini–Strambi *et al*, 2004; Terzaghi *et al*, 2008; Marques *et al*, 2010). Longitudinal studies have identified impaired attention and executive function as the most reliable predictors of conversion, particularly for DLB (Fantini *et al*, 2011; Terzaghi *et al*, 2013; Marchand *et al*, 2017, 2018). Specifically, impairments in executive function can be observed in iRBD patients up to 6 years before a dementia diagnosis, offering an opportunity for preventive interventions (Marchand *et al*, 2018), while deficits in verbal episodic learning and memory appear to be the most suitable for monitoring changes over time (Ferini-Strambi *et al*, 2014, 2019b).

1.7. Electrophysiological markers

A relationship between electroencephalography (EEG) sleep characteristics and the progression of neurodegenerative diseases has been observed (Mander *et al*, 2015; Brazète *et al*, 2016). Various EEG characteristics, both during wakefulness and sleep, are linked to diurnal cognitive functioning in patents with iRBD (Sasai et al, 2013; Ferini-Strambi et al, 2019). Of note, several studies revealed a slowing of EEG activity during both sleep and wakefulness in iRBD (Livia Fantini *et al*, 2003; Massicotte-Marquez *et al*, 2005; Sasai *et al*, 2013; Bang *et al*, 2017). These changes can predict neurodegeneration and are associated with cognitive decline (Sasai *et al*, 2013; Brazète *et al*, 2016). Interestingly, several studies highlighted the protective role of NREM sleep in preserving the aging brain from degeneration and cognitive decline (Mander *et al*, 2015; Ju *et al*, 2017; Cordone *et al*, 2019). Notably, it has been demonstrated that a specific waveform of NREM sleep, known as K Complex (KC), plays a role in cognitive functioning. The KC is a transient and multi-component waveform that typically occurs during NREM sleep stage 2 and is more prominent in the frontal regions of the brain (Colrain, 2005). It consists of three components: a short and transient positive component in the EEG (P200), with a latency of 200ms, followed by a powerful larger negative component (N550), with a latency of 550ms, and then a final positive component (P900) with a latency of 900ms (Cash *et al*, 2009). The KC waveform is considered biphasic when the first positive component is not detectable or can be neglected (Halász, 2005), or triphasic when P200 is detectable (Cash *et al*, 2009; Amzica, 2010). The duration of KCs exceeds 0.5s with an amplitude greater than 75 µV and can occur either individually or in series. KCs can occur spontaneously or in response to sensory stimuli (Colrain, 2005). The characteristics of the wave, regarding amplitude and duration, remain unchanged whether the wave is elicited by an external acoustic stimulus or if the formation is endogenous, as the brain responds by generating a KC, whether evoked or spontaneous, indistinguishably. Spontaneous KCs are considered a precursor of slow waves, and their density tends to decrease as sleep cycles progress (De Gennaro *et al*, 2000). Slow waves, which are also characteristic waveforms of NREM sleep, play an essential role in protecting aging brain from cognitive decline as well. It has been proposed that slow wave sleep (SWS) may help counteract the accumulation of beta-amyloid and potentially α-syn, either through glymphatic

clearance or reduced production (Xie *et al*, 2013; Schreiner *et al*, 2019). In Alzheimer's Disease (AD), significant reductions in KC density have been observed compared to HCs, and a positive correlation between KC density and Mini-Mental State Examination (MMSE) scores has been noted (De Gennaro *et al*, 2017; Reda *et al*, 2017). In De Gennaro and colleagues' study (De Gennaro *et al*, 2017), 20 HC subjects and 20 AD patients were compared on PSG parameters, focusing on KC and SWS features, and neuropsychological performances. Results revealed significant differences between the two groups in terms of SWS percentage and KC density. Interestingly, KC density appeared to be more reliable in distinguishing between AD and HC than SWS, correctly classifying the 80% of subjects. Moreover, the authors also found that KC density could predict MMSE scores (De Gennaro et al, 2017). In line with this framework of research, Liu and collaborators (Liu *et al*, 2020) published a longitudinal study with 2 years of FU. The authors compared KC features between amnestic MCI (aMCI) patients and HC. Results revealed that two KC features, KC density and amplitude, were able to distinguish aMCI participants from HCs with high specificity and sensitivity. In the context of iRBD, this finding can be easily interpreted in the light of recent genetic results published by Krohn and collaborators (Krohn *et al*, 2020), indicating that iRBD seems to be a prodromal stage of synucleinopathies primarily characterized by dementia. Indeed, risk for iRBD is associated with a single-nucleotide polymorphism in the SNCA (gene coding for α-syn), which, in turn, is associated with DLB. Moreover, equally interesting, this gene is linked to a genetic variant associated with AD with Lewy body pathology (i.e., ADLBV) (Krohn *et al*, 2020). Importantly, longitudinal studies reported that the presence of MCI in iRBD subjects at BL was able to identify those patients who firstly converted into dementia at FU (Marchand *et al*, 2017; Postuma *et al*, 2019). To the best of present knowledge, only the study of Galbiati and collaborators (Galbiati et al., 2021) investigated KC features in iRBD population with MCI – according to criteria published in Peterson et al., 2014 and in Peterson et al., 2018 – in comparison to non-MCI patients (Galbiati *et al*, 2021). Specifically, 33 iRBD underwent PSG recording, comprehensive neuropsychological evaluation and 18fluorodeoxyglucose positron emission tomography (FDG-PET) scan. The authors found that KC density (the odds between the number of KCs and the minutes of N2 sleep stage) showed significant correlations with the following cognitive tests: MMSE, ROCF copy, Raven Colored Progressive Matrices,

which respectively assess global cognitive screening, visuospatial abilities, and executive functions. As concerns the comparison between patients with and without MCI, results revealed that MCI patients had a significant reduction in KCs compared to non-MCI patients (Galbiati *et al*, 2021).

In summary, these findings provide evidence regarding the relationship between alterations in sleep features and cognitive functioning. In particular, KC density might represent an early neurophysiological biomarker capable of predicting iRBD clinical trajectories.

1.8. Emotional functioning

Mood symptoms are known to precede the onset of PD and DLB (Poewe *et al*, 2017), nevertheless these symptoms have been far less assessed in iRBD. In the context of synucleinopathies, psychiatric comorbidities, mainly depression and anxiety, contribute to accelerate disability and functional morbidity, as well as to increase risk of late-stage complications, leading to poor quality of life and increasing caregiver burden (Schapira *et al*, 2017; Assogna *et al*, 2020). Despite the deep impact on life quality and cognitive functioning, mood symptoms are often under-recognized and poorly treated. An early recognition of mood symptoms is crucial in the management of neurodegenerative disorders. In this framework, iRBD – as prodromal phase – represents a unique window for the investigation of the mechanisms underlying mood symptoms long before the overtly conversion to a neurodegenerative disorder. Depressive, anxious, apathy, alexithymia symptoms have been reported to be common in patients with iRBD (Barber *et al*, 2018; Kim *et al*, 2020; Jun *et al*, 2020). In the study of Barber and colleagues (Barber et al, 2018), 88 iRBD patients with PSG-confirmed diagnosis, 65 patients with PD and 33 HCs were recruited. All the participants underwent a cognitive global screening test, Lille Apathy Ratings Scale (LARS) to assess apathy and Beck Depression Inventory (BDI) to assess depressive symptoms. Results revealed significant higher scores of BDI in iRBD patients compared to HCs. Moreover, significant differences between these two groups were also found in the total LARS score and in the following subscales: LARS intellectual curiosity score, LARS action initiation score, and LARS self-awareness score. Two years later another study evaluating mood symptoms in iRBD patients and HCs has been published (Kim *et al*, 2020). In this study (Kim *et al*, 2020), 86 iRBD patients with

PSG-confirmed diagnosis and 74 HCs were recruited. A Korean version of the BDI together with the 20-item version of Toronto Alexithymia Scale (TAS-20) were administered to evaluate respectively depression and alexithymia. iRBD patients showed significant higher scores in BDI compared to HCs, as well as in the total score of TAS-20 and in two out of three subscales. The two affected subscales involved the difficulty in identifying and describing feelings. Lastly, the same year Jun and colleagues (Jun *et al*, 2020) published a multicenter study in line with the aforementioned literature. The study included 94 iRBD patients with PSG-confirmed diagnosis and 50 HCs. The authors aimed to evaluate emotion dysregulation, which was assessed using the Cognitive Emotion Regulation Questionnaire (CERQ) and BDI. Results did not show a significant difference in BDI scores between the two groups. However, interesting findings emerged from the CERQ assessment. CERQ scale includes several subscales divided into two categories: adaptive strategy and maladaptive strategy subscales. Regarding maladaptive subscales, iRBD group scores were not significantly different from HC group scores. Instead, the two groups showed a distance concerning adaptive strategy subscales. Specifically, iRBD revealed lower scores in three adaptive strategy subscales: positive refocusing, refocusing on planning, positive reappraisal. In summary, depressive, apathy, alexithymia and emotion dysregulation symptoms have been found in iRBD patients; however, to investigate mood symptoms as a potential marker of neurodegeneration, mechanisms underlying these dysfunctions need to be explored. Phasic events disrupting REM sleep, which are considered a main feature of RBD diagnosis, may be the responsible mechanism underlying emotion dysfunctions. REM sleep in RBD population is disturbed by a high number of phasic events; indeed, RSWA is a core diagnostic feature of RBD (American Academy of Sleep Medicine, 2014; Högl & Stefani, 2017). RSWA is characterized by increased phasic or tonic muscle activity seen on EMG channels during PSG (McCarter *et al*, 2012). Wassing and collaborators coined the term “restless REM sleep” to refer to REM sleep with a high number of phasic events (Wassing *et al*, 2016). Their findings indicate that the restless REM sleep hinders the resolution of emotional distress, disrupting the correct functioning of limbic and paralimbic systems during REM phases. In fact, during wakefulness and NREM sleep, LC activity physiologically maintains high noradrenaline (NA) release levels to promote long-term potentiation (LTP). Only before and during REM sleep, LC is inhibited, causing a decreasing of NA

levels, while the cholinergic system become as or more active than during wake. These neurochemical changes during REM sleep facilitate synaptic depotentiation (DP), resulting in a bidirectional plasticity state (LTP and DP) which, together with the increase in limbic and paralimbic network activity, allows the overnight amygdala adaptation. Instead, restless REM sleep impedes the silencing of LC, hampering the bidirectional plasticity, thus resulting in the overnight amygdala maladaptation. However, Wassing and collaborators studied this phenomenon within another sleep disorder framework. Specifically, in 2019 they published a study on general population with a wide range of insomnia symptoms (Wassing *et al*, 2019). The experimental design included a night and a morning session of functional magnetic resonance imaging (fMRI), during which participants listened to their own singing out of tune and the singing of other people in tune to induce a shameful experience. Moreover, PSG was recorded between the two fMRI sessions. The authors found that the overnight decrease in amygdala reactivity is proportional to the total duration of REM episodes. Additionally, when REM interruptions were maximal the effect of REM duration on amygdala reactivity was cancelled. Furthermore, part of the sample received targeted memory reactivation (TMR), a technique in which the reactivation of memories is intentionally triggered in sleep through the re-presentation of cues previously linked to the memory in the wake (Cellini & Capuozzo, 2018). The memory reactivation helps to strengthen the memory content and at the same time to weaken the affective "blanket" of that memory (Walker, 2009; Van der Helm & Walker, 2011). In this study Wassing and collaborators used different odors as cues to associate to the shameful and control experiences. TMR boosted the effect of REM sleep duration on the overnight amygdala adaptation (Wassing *et al*, 2019).

Another recent study assessed the relationship between REM sleep characteristics and emotion dysregulation symptoms in insomnia patients (Galbiati *et al*, 2020). 23 insomnia patients and 23 HCs were enrolled and completed the Difficulties in Emotion Regulation Scale (DERS). In addition, insomnia patients underwent PSG recording. The findings showed higher scores in DERS total score in insomnia patients compared to HCs. Moreover, in insomnia patients, shorter was the REM sleep percentage higher was the emotion dysregulation (Galbiati *et al*, 2020). However, phasic events during REM sleep not only occur in RBD as well as in insomnia patients, but they are also a fundamental diagnostic criterion for RBD diagnosis. For this reason, emotion dysregulation in these

patients is highly probable. Of note, the high prevalence of depression, apathy, alexithymia, and emotion dysregulation symptoms in RBD subjects has already been reported and presented above.

Nevertheless, only few studies investigated mood symptoms in RBD patients, and more importantly only by using questionnaires (Barber *et al*, 2018; Kim *et al*, 2020; Jun *et al*, 2020). Moreover, none of them tried to directly create a relationship between RSWA and daytime emotional functioning in RBD. A task capable of capturing the emotional aspects, which until now have been explored only through questionnaires, is needed, along with a new way to explore the link between sleep and emotional functioning.

2. AIM OF THE WORK

The overall objective of my PhD work is to explore sensitive biomarkers, both neuropsychological and electrophysiological, for a timely prediction of phenoconversion to full-blown synucleinopathies in RBD patients, and to explain their daytime functioning, in particular emotional functioning.

My research plan consists of different projects. Each specific aim is research of its own, even if they are closely related in light of the overall objective.

Specific aims are listed below:

- A meta-analytic evaluation of the cognitive alterations occurring in RBD including cross-sectional and longitudinal studies. The meta-analysis has a double-aim: (i) to establish the severity and characteristics of the impaired cognitive domains in iRBD patients; (ii) to identify the cognitive profile at BL associated with the subsequent specific phenoconversion. This may lead to a validation of cognitive biomarkers of progression. (Chapter 3).
- A longitudinal multicentric study analyzing KC and SW features in RBD with the following aims: (i) to investigate differences in KC density in patients who phenoconverted or remained iRBD at FU, (ii) to investigate their correlation with cognition, and (iii) to test their role as forerunner of slow waves in deep sleep. This can provide some insights regarding the association between cortical slow waves and the development of neurodegeneration in iRBD. (Chapter 4).
- A cross-sectional study assessing the overnight modulation of emotional reactivity in HCs and iRBD patients, with the following aims: (i) to investigate the relationship between REM sleep and emotional regulation in a sample of elderly individuals HC and iRBD; (ii) to evaluate the relationship between phasic events in REM sleep and alterations in emotional regulation; (iii) to investigate emotional dysregulation in iRBD patients using questionnaires and an arousal rating task. This could provide a bridge between iRBD and mood symptoms: a clinically relevant result that might boost clinical research and treatment strategies for this disorder. (Chapter 5).

3. NEUROPSYCHOLOGICAL CHANGES IN ISOLATED REM SLEEP BEHAVIOR DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CROSS-SECTIONAL AND LONGITUDINAL STUDIES

The data are already published (Leitner *et al*., 2023).

3.1. Introduction

Cognitive impairment has been frequently observed in a large portion of iRBD patients, with longitudinal studies demonstrating that cognitive performance worsens over time. These findings suggest that neuropsychological profile could play a crucial role as prodromal marker of neurodegeneration (Massicotte-Marquez *et al*, 2008; Gagnon *et al*, 2012; Marchand *et al*, 2017, 2018; Terzaghi *et al*, 2019; Zhang *et al*, 2019). Nevertheless, results vary across studies. On one hand, the majority of cross-sectional studies agree that the most affected cognitive domains in iRBD are memory and executive functions (Massicotte-Marquez *et al*, 2008; Rolinski *et al*, 2016b, 2016a). Other studies also report poorer performance in visuospatial abilities in iRBD patients compared to HCs (Ferini–Strambi *et al*, 2004; Fantini *et al*, 2011), but this difference is not universally confirmed (Massicotte-Marquez *et al*, 2008; Terzaghi *et al*, 2008; Gagnon *et al*, 2009). On the other hand, longitudinal studies showed that only the BL performance on executive functions consistently predict the conversion into neurodegeneration, thus highlighting its role as a cognitive marker of conversion (Youn *et al*, 2016; Marchand *et al*, 2017, 2018). The cognitive deficits reported by studies in iRBD patients are similar to those observed in PD and DLB (Fantini *et al*, 2011). Indeed, executive functions (Kudlicka *et al*, 2011), verbal memory (Bohlhalter *et al*, 2009; Assogna *et al*, 2010; Galtier *et al*, 2014; Hanoğlu *et al*, 2019), and visuospatial abilities (Montse *et al*, 2001; Gullett *et al*, 2013; Chastan *et al*, 2019) are the most affected domains in PD (Curtis *et al*, 2019; Aarsland *et al*, 2021). In DLB, prominent executive and visuospatial dysfunctions are observed, with memory being affected to a variable degree (Goldman *et al*, 2014; Walker *et al*, 2015; Gomperts, 2016; Sanford, 2018). Despite accumulating evidence of cognitive impairment in iRBD, results remain highly heterogeneous. This heterogeneity might be ascribed to the use of different neuropsychological tests and the limited sample sizes of patients. Therefore, a meta-analytic evaluation of the cognitive alterations occurring in iRBD patients is required to identify a neuropsychological profile associated with subsequent phenoconversion. The present meta-analysis has two main

goals: (i) to assess cognitive impairments in iRBD patients in comparison with HC; (ii) to quantitatively estimate the risk of developing a neurodegenerative disease in iRBD patients based on the BL cognitive assessment.

3.2. Methods

The search process and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati *et al*, 2009; Moher *et al*, 2009; Radua, 2021).

3.2.1. Protocol and Registration

The research methodology and protocol for this meta-analysis was registered at the prospective register of systematic reviews (PROSPERO) with the following registration number: CRD42021253427. PRISMA Protocol was used to determine whether all the relevant items were included in the protocol (Moher *et al*, 2015).

3.2.2. Search Procedure

Cross-sectional and longitudinal published studies were searched from PubMed, Web of Science, Scopus, and Embase databases. Two researchers (C.L. and G.D.) independently carried out the systematic search, first targeting titles and abstracts, then full text reports. The systematic literature search was performed by entering the following keywords: “rapid eye movement sleep behavior disorder”, “iRBD” in combination with “cognition”, “MCI”, “mild cognitive impairment”, “neuropsychological”. These terms could appear everywhere in the manuscript. The last date of database searches was December 18, 2020. Authors were contacted when additional information from studies were needed – however, for various reasons, it was not always possible to reach the authors or access the raw data. This was done to resolve questions about eligibility, specifically regarding possible overlaps between samples of different studies. Disagreements were discussed and resolved between all authors. Only studies published in the English language were included.

3.2.3. Risk of Bias

To reduce publication bias, both publications in peer-refereed journals and conference

abstracts were considered. Specifically, special issues of journals reporting conference abstracts were searched, namely the European Journal of Neurology, Sleep, Journal of Sleep Research, Sleep Medicine, and Journal of Neurology. Then, the publication bias was assessed by funnel plot asymmetry using Egger's test (Egger *et al*, 1997). To address the multiple publication bias, when two studies provided data from the same database, the study with the highest number of patients was selected and the other was excluded. The heterogeneity between studies was assessed separately for cross-sectional and longitudinal studies using prediction intervals (PI) and I2 statistic (Higgins & Thompson, 2002; Higgins *et al*, 2003; Borenstein *et al*, 2017). The random effects (RE)-model was employed because of the considerable heterogeneity between studies (variability in the participant characteristics, variability in neuropsychological tests, variability in the FU duration, etc.).

3.2.4. Study Eligibility

The cross-sectional studies that met the following criteria were included:

- The studies had to include patients with a diagnosis of iRBD confirmed by PSG according to the standard criteria from the ICSD-3 (American Academy of Sleep Medicine, 2014).
- The studies had to include the scores of at least one neuropsychological test performed in both iRBD and HC groups; this included experimental tasks or clinical tasks that assessed at least one of the following domains: cognitive screening, language, memory, executive functions, or visuospatial abilities.

The exclusion criteria for cross-sectional studies were:

- Literature review, meta-analysis, single-case study.
- Non-iRBD patients or iRBD patients not confirmed using PSG.
- Cross-sectional studies without HC group.

The longitudinal studies that met the following criteria were included:

- The studies had to include patients with a diagnosis of iRBD confirmed by PSG according to standard criteria of the ICSD-3 (American Academy of Sleep Medicine, 2014).
- The studies had to include the BL scores of at least one neuropsychological

test for converted and still-isolated patients separately, including experimental tasks or clinical tests assessing at least one of the following domains: cognitive screening, language, memory, executive functions, or visuospatial abilities.

- The studies had to report the FU time and the phenoconversion rate of the sample.

The exclusion criteria for longitudinal studies were:

- Literature review, meta-analysis, single-case study.
- Non-iRBD patients or iRBD patients not confirmed by PSG.
- Retrospective studies investigating only RBD patients with an outcome of neurodegenerative disease, as the conversion rate would necessarily be 100%.
- Studies not reporting neuropsychological data for converted and still-isolated patients separately at BL.
- Studies not reporting the rate of phenoconversion.

3.2.5. Data Extraction

For each eligible cross-sectional study, the following information was extracted: (i) characteristics of the publication: authors, year of publication, title, journal, country; (ii) characteristics of the sample: number of iRBD patients, number of HCs, age, gender, presence/absence of iRBD patients with MCI, mean iRBD duration, age at onset of iRBD; (iii) neuropsychological tests assessing the different cognitive domains (i.e., cognitive screening, language, memory, executive functions, visuospatial abilities). The tests used to assess the different cognitive domains are reported in Table 1 for each study. The test selection for each domain followed the criteria suggested by the Italian Neuropsychological Society (SINP) (Barletta-Rodolfi *et al*, 2011). When missing, the study authors were contacted to obtain the required data.

For each eligible longitudinal study, the following information was extracted: (i) characteristics of the publication: authors, year of publication, title, journal; (ii) characteristics of the sample: number of iRBD patients who remained still isolated at FU, number of iRBD patients who converted to a neurodegenerative disease at FU and, when reported, the conversion subtype (i.e., PD, DLB, MSA, AD, other), age, gender,

presence/absence of iRBD patients with MCI, mean iRBD duration, age at onset of iRBD; (iii) mean FU duration; (iv) neuropsychological tests assessing the different cognitive domains (i.e., cognitive screening, language, memory, executive functions, visuospatial abilities). The tests used to assess the different domains are reported in Table 2 for each study. The test selection for each domain followed the criteria suggested by the SINP (Barletta-Rodolfi *et al*, 2011). Finally, study authors were contacted when the required information was missing.

Table 1. Tests used for the different domains for each cross-sectional study (in descending chronological order).

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Byun et al., 2020	MoCA; MMSE	VF; BNT	WL memory, recall, recognition; CPR; memory (MDRS)	TMT A; TMT B; attention, initiation, conceptualization (MDRS)	CP copy
Biondetti et al., 2020	MoCA; MDRS	/	/	/	/
Sasai-Sakuma et al., 2020	MoCA; ACE-R	/	/	/	/
Ehgoetz Martens et al., 2020	MMSE; MoCA	BNT; sem and ph VF	DGS-F; DGS-B; logical memory I and II; ROCF immediate and delayed recall	TMT A; TMT B	CDT
Lanza et al., 2020	MMSE	/	/	/	/
Cochen De Cock et al., 2020	MoCA	/	/	/	/
Jun et al., 2020	MoCA	/	/	/	/
Stær et al., 2020	MMSE; MoCA	/	/	/	/
Sunwoo et al., 2020	MMSE; MoCA	/	/	/	/
Kim et al., 2020	MMSE	COWAT; BNT	SVLT immediate and delayed recall, recognition	TMT A; TMT B; SCWT reading	ROCF copy

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Li et al., 2020	MMSE; MoCA	/	/	/	/
Chen et al., 2020a	MMSE	/	/	/	/
Chen et al., 2020b	MMSE; MoCA	/	/	/	/
Shin et al., 2020	MMSE	/	/	/	/
Stokholm et al., 2020	MMSE; MoCA	/	/	/	/
Ehgoetz Martens et al., 2019	MoCA	BNT; sem and ph VF	Logical memory I and II; DGS	TMT A; TMT B; SCWT 1,2,3,4	CDT
Dušek et al., 2019	MoCA	/	/	/	/
Her et al., 2019	MMSE; MoCA	Naming; language (MOCA); VF; BNT; WL recognition (CERAD)	Memory recall (MOCA); WL memory, recall, recognition; CR (CERAD)	Attention; visuospatial/executive; abstraction (MOCA); TMT A; TMT B (CERAD)	CP (CERAD)
Mollenhauer et al., 2019	MoCA	/	HVLT	SDMT; LNS	BJLO
Shin et al., 2019	MMSE	COWAT sem and ph	SVLT immediate and delayed recall, recognition	TMT-A; TMT-B; SCWT	ROCF copy
Li et al., 2019	MMSE	/	/	/	/
Lee et al., 2019	MMSE	Sem and ph COWAT; BNT	SVLT delayed recall, recognition; DGS-B	TMT A, TMT B, SCWT	ROCF copy
Campabadal et al., 2019	MMSE	BNT; sem and ph VF	RAVLT total, recall, recognition; DGS-F; DGS-B	SDMT; TMT A; TMT B; SCWT Word, C, WC	BJLO; VFD; FRT
Yoon et al., 2019	MMSE	/	/	/	/
Zhang et al., 2019	MMSE	sem VF; BNT	RAVLT sum of trials 1-5, short and long delay recall, recognition; ROCF delayed recall	SDMT; TMT A; TMT B; SCWT A, B, C, interference effect	ROCF copy; CDT

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Sunwoo et al., 2019	MoCA; MMSE	sem VF; BNT	WL Memory; WL recall; WL recognition; CPR	TMT A; TMT B	CP
Arnaldi et al., 2019	MMSE	/	/	/	/
Pereira et al., 2019	MoCA	sem VF	HVLT immediate and delayed recall, recognition	LNS; SDMT	BJLO
Liguori et al., 2019	MMSE	/	/	/	/
Yamada et al., 2019	MMSE	/	/	/	/
Marcone et al., 2019	MoCA	/	/	Executive functioning	/
Li et al., 2018a	MMSE; MoCA	Sem VF; BNT	DGS-F; RAVLT sum of trials 1–5, delayed recall, recognition; ROCF	TMT-A; TMT-B; SCWT A, C; SDMT (WAIS-RC)	ROCF copy; block design (WAIS- RC); CDT
Rahayel et al., 2018	MoCA	/	/	/	/
Li et al., 2018b	MMSE; MoCA	Sem VF; BNT	DGS-F; RAVLT sum of trials 1–5, delayed recall, recognition; ROCF	TMT-A; TMT-B; SCWT A, C; SDMT (WAIS-RC)	ROCF copy; block design (WAIS- RC); CDT
Stokholm et al., 2018	MoCA	/	/	/	/
Meles et al., 2018	MoCA	/	/	/	/
Barber et al., 2018	MoCA	/	/	/	/
Bezdicek et al., 2018	MoCA	/	RAVLT total immediate and delayed recall, recognition	TMT A; TMT B; LNS; SCWT interference condition	/
Heintz-Buschart et al., 2018	MMSE; MoCA	/	/	/	/
Byun et al., 2017	MoCA; MMSE	Naming, language (MoCA);	Memory recall (MOCA); WL memory, recall and recognition	Attention, visuospatial/executive, abstraction (MOCA);	Visuospatial/executive (MOCA); CP (CERAD)

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
		VF, BNT (CERAD)	(CERAD); CR (CERAD)	TMT-A, TMT-B (CERAD)	
Barber et al., 2017	MoCA; MMSE	Sem and ph VF	/	/	/
Sunwoo et al., 2017	MoCA	/	/	/	/
Sasai-Sakuma et al., 2017	ACE-R	Language (ACE-R); VF (ACE-R)	Memory (ACE-R)	Attention (ACE-R)	Visuospatial perception (ACE-R)
Bang et al., 2017	MMSE	Sem VF	DGS-F; DGS-B; WL recall; CPR	TMT A; TMT B; FAB; SCWT	CP; CDT
Meles et al., 2017	MoCA	/	/	/	/
Boura et al., 2017	MMSE	/	/	/	/
Li et al., 2016	MMSE, MoCA	Sem VF; BNT	RAVLT sum of trials 1 to 5, immediate and delayed recall, recognition; DGS-F; DGS-B; immediate and delayed ROCF; SDMT	TMT A; TMT B; SCWT; SDMT	ROCF copy; CDT; block design (WAIS-RC)
Ehrminger et al., 2016	MoCA	/	/	/	/
Rolinski et al., 2016a	MMSE	/	VSTM task	/	/
Rolinski et al., 2016b	MMSE, MoCA	Sem and ph VF	/	/	/
Zhang et al., 2016	MMSE, MoCA	Sem VF	RAVLT immediate and delayed recall, recognition; DGS-F; DGS-B; ROCF	TMT A; TMT B; SCWT; SDMT	ROCF copy; CDT
Aguirre-Mardones et al., 2015	MoCA	/	/	/	/
Rahayel et al., 2015	MoCA	/	/	/	/
Compta et al., 2015	MMSE	/	/	/	/
Antonell et al., 2014	MMSE	/	/	/	/

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Plomhause et al., 2014	MMSE, MDRS	Lexis picture naming test	/	/	/
Lee et al., 2014	MMSE	/	/	/	/
Sasai et al., 2013	MMSE, MoCA	/	/	/	/
Ellmore et al., 2013	MoCA	/	/	/	/
Terzaghi et al., 2013	MMSE	Sem and ph VF	Logical Memory; WL immediate, delayed recall; DGS-F; Corsi test; delayed ROCF	AM; CPM; WCST	ROCF copy
Videnovic et al., 2013	MMSE	/	/	/	/
Delazer et al., 2012	/	/	/	IGT, IST, IED, OTS, Go-NoGo Task	/
Sasai et al., 2012	/	/	/	IGT	/
Vendette et al., 2012	MMSE	Sem and ph VF	RAVLT sum of trials 1–5, list B, immediate recall, delayed recall, recognition; DGS-F	SCWT; TMT B	ROCF copy; block design (WAIS-III); bells test
Nardone et al., 2012	MMSE, MDRS	Sem and ph VF	/	/	/
Hanyu et al., 2012	MMSE	/	/	/	/
Fantini et al., 2011	MMSE	Sem and ph VF	DGS-F; DGS-B; Corsi test; story recall; Corsi supraspan learning test; delayed recall of ROCF	AM; CPM; SCWT interference Test; TMT A; TMT B; TMT B/A	ROCF copy
Marques et al., 2010	MMSE, MDRS	Sem and ph VF	DGS-F; DGS-B; WL Learning and Recall Test	SCWT; SDMT	/
Gagnon et al., 2009	/	Sem and ph VF	RAVLT sum of trials 1 to 5, list B, immediate and	TMT B; SCWT	ROCF copy; block design; bells test

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
			delayed recall, recognition; DGS		
Postuma et al., 2009	MMSE	/	/	/	/
Massicotte-Marquez et al., 2008	MMSE	Sem and ph VF; similarity subtest (WAIS-III)	RAVLT total words of trial 1–5, list B, retention, delayed recall, correct recognitions, false positive recognitions; DGS-F; DGS-B	TMT A; TMT B; SCWT Interference condition, flexibility condition; SDMT	ROCF copy; block design (WAIS-III)
Terzaghi et al., 2008	MMSE	Sem and ph VF	DGS-F; WL immediate and delayed recall; Corsi's Test; logical Memory; delayed recall of ROCF	AM; CPM; WCST	ROCF copy
Raggi et al., 2007	MMSE	/	/	AM	/
Postuma et al., 2006	MMSE	/	/	/	/
Ferini-Strambi et al., 2004	MMSE	Sem and ph VF	DGS-F; DGS-B; Corsi block-tapping task; Corsi supraspan learning; logical memory	AM; SCWT interference condition; CPM; TMT A; TMT B	ROCF copy

ACE-R: Addenbrooke Cognitive Examination-Revised; AM: Attentive Matrices; BJLO: Benton Judgment of Line Orientation; BNT: Boston Naming Test; CDT: Clock-Drawing Test; CERAD: Consortium to Establish a Registry for Alzheimer's disease; COWAT: Controlled Oral Word Association Test; CP: Constructional Praxis; CPM: Raven's Coloured Progressive Matrices; CPR: Constructional Praxis Recall; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; FAB: Frontal Assessment Battery; FRT: Facial Recognition Test; HVLT: Hopkins Verbal Learning Test; IED: Intra/Extra Dimensional Shift; IGT: Iowa Gambling Task; IST: Information Sampling Task; LNS: Letter-Number Sequencing Test; MDRS: Mattis Dementia Rating Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; OTS: One Touch Stockings of Cambridge; RAVLT: Rey Auditory Verbal Learning Test; VSTM: Visual Short-Term Memory; ROCF: Rey Complex Figure; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; SVLT: Seoul Verbal Learning Test; TMT: Trail Making Test; VF: Verbal Fluency (Ph VF: Phonemic Verbal Fluency; Sem VF: Semantic Verbal Fluency); VFD: Visual Form Discrimination; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card-Sorting Test; WL: Word List.

Table 2. Tests used for the different domains for each longitudinal study (in descending chronological order).

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Arnaldi et al., 2021	/	Sem and ph VF	RAVLT immediate, delayed recall; DGS; Corsi Span	SCWT; TMT A; TMT B; SDMT	CDT
Kogan et al., 2020	MoCA	/	/	/	/
Campabadal et al., 2020	/	/	/	/	/
Feng et al., 2020	MoCA	/	/	/	/
Miyamoto et al., 2020	MMSE	/	/	/	/
Kim et al., 2020	MMSE	Sem and ph COWAT, BNT	SVLT immediate recall, delayed recall, recognition	TMT A; TMT B; SCWT	ROCF copy
Terzaghi et al., 2019	MMSE	Sem VF	DGS-F; Corsi test; WL immediate and delayed recall; logical memory; ROCF delayed recall	AM; Weigi's sorting test; FAB; CPM	ROCF copy; CP
Pereira et al., 2019	MoCA	Sem VF	HVLT immediate recall, delayed recall, recognition	LNS; SDMT	BJLO
Nepozitek et al., 2019	MoCA	/	/	/	/
Marchand et al., 2018	MMSE	Sem VF	DGS-F; DGS-B; WL recall test; CPR	TMT A; TMT B;	CP; CDT
Youn et al., 2016	MMSE, MoCA	Sem and ph VF	DGS; RAVLT sum of trials 1–5, list B, immediate and delayed recalls, recognition	TMT A; TMT B; FAB; SCWT	ROCF copy, block design; bells test

AM: Attentive Matrices; BNT: Boston Naming Test; BJLO: Benton Judgment of Line Orientation; CDT: Clock-Drawing Test; COWAT: Controlled Oral Word Association Test; CP: Constructional Praxis; CPM: Raven's Coloured Progressive Matrices; CPR: Constructional Praxis Recall; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; FAB: Frontal Assessment Battery; FRT: Facial Recognition Test; HVLT: Hopkins Verbal Learning Test; LNS: Letter-Number Sequencing Test; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey Complex Figure; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; SVLT: Shiraz Verbal Learning Test; TMT: Trail Making Test; VF: Verbal Fluency (Sem VF: Semantic Verbal Fluency; Ph VF: Phonemic Verbal Fluency); VFD: Visual Form Discrimination; WCST: Wisconsin Card-Sorting Test.

3.2.6. Quality Check

To assess the quality of the studies, the Critical Appraisal Skills Programme (CASP) checklist for cohort studies was assessed independently by two raters (C.L. and G.D.). In this study, the following points were investigated: clarity of the focused issue (question 1); cohort recruitment (e.g., accuracy of inclusion and exclusion criteria) (question 2), bias selection (e.g., validated and standardized measures and diagnostic criteria) (question 3), outcome measures (e.g., measure similarity between HC and iRBD, for cross-sectional studies, and between BL and FU, for longitudinal studies (Question 4), confounding factors (e.g., control or adjust for education and years of illness) (Question 5, a &b), FU completeness and length (only for longitudinal studies) (Question 6a & b), relevance of the results (e.g., presence of considerable differences between the groups: HC VS iRBD for cross-sectional studies and converted VS non converted for longitudinal studies) (Question 7); precision/accuracy of the results (e.g., the type of provided data: mean and standard deviations or other statistics) (Question 8); credibility of the results (e.g., study design, check for confounding factors, use of standardize and validated measures, effect sizes) (Question 9), applicability of the results (e.g., reliability of inclusion, exclusion criteria and sample size) (Question 10), fitness of the results within other available evidence (Question 11), and lastly practice implications (e.g., completeness and reliability of neuropsychological data) (Question 12). Each study could reach a maximum value of 14, reflecting the highest methodological quality. The scores between raters were compared and disagreements were solved by discussion.

3.2.7. Specific Methods for Meta-analysis

Data analyses were performed using the software R studio supporting R version 4.0.5 (Team, 2020). For cross-sectional analyses, effect sizes (ES) were calculated for each cognitive domain to quantify the difference in cognitive performance between iRBD patients and HCs. A RE-model was used for the analyses. The metafor package was used for these analyses (Viechtbauer, 2010). For the analyses of longitudinal studies, to estimate the survival function for the different phenoconversion trajectories, the survival package (Therneau, 2015) was used in R. Specifically, a Kaplan–Meier survival analysis with stratification factors, which indicated the different types of conversion (i.e., PD, DLB, MSA, AD, other), was applied. A dichotomous variable was used to describe the

status of the patients at FU (0: still-iRBD patients; 1: patients who converted) and the mean FU time was used as the timing variable. To identify a BL neurocognitive profile associated with phenoconversion, the cognitive performance of iRBD patients and the rate of phenoconversion at FU time were analyzed. As for cross-sectional studies, ES were calculated using the metafor package. Moreover, a Cox proportional hazards analysis using simulated data was performed to evaluate how cognitive status predicted the development of a neurodegenerative disease (survival package). This analysis required a time variable (FU time), a dichotomous status variable (0: still-iRBD patients; 1: patients who converted), and a factor, which in this case was represented by the simulated neuropsychological score for each cognitive domain, given the impossibility of getting access to single-subject data. The runuran R package (Leydold et al, 2012) was used to simulate single-subject data since these were necessary to perform the survival analyses. Specifically, the function urnorm was used to generate a normal distribution of random numbers with means and standard deviations equal to those provided by the different longitudinal studies. Furthermore, we also used a Cox proportional hazards analysis to investigate the presence of MCI at BL as a predictor of phenoconversion. This analysis was conducted using the three studies (Nepozitek *et al*, 2019; Terzaghi *et al*, 2019; Arnaldi *et al*, 2021) that provided information on the number of patients that presented with MCI at BL, and whether they converted or not at FU. Taken together, these studies included 163 iRBD patients, of which 40 were iRBD patients with MCI. Finally, additional analyses were conducted to probe whether our criteria to select tests and define the cognitive domains may have influenced our results. More specifically, we noticed domain inconsistencies in the neuropsychological tests reported by some studies, for example in two cross-sectional studies (Li *et al*, 2018; Zhang *et al*, 2019) verbal fluency tests were used to assess language ability, whereas in other two cross-sectional studies (Gagnon *et al*, 2009; Ehgoetz Martens *et al*, 2020) verbal fluency tests were used to assess attention and executive functions. Therefore, we modified the domains to which these tests were assigned and calculated additional ES for language and executive domains. More specifically these modifications targeted those neuropsychological tests where the included studies showed domain inconsistencies. Specifically, phonemic Controlled Oral Word Association Test and phonemic Verbal Fluency tests were moved from the language to the executive domain. The tests used to evaluate the two modified

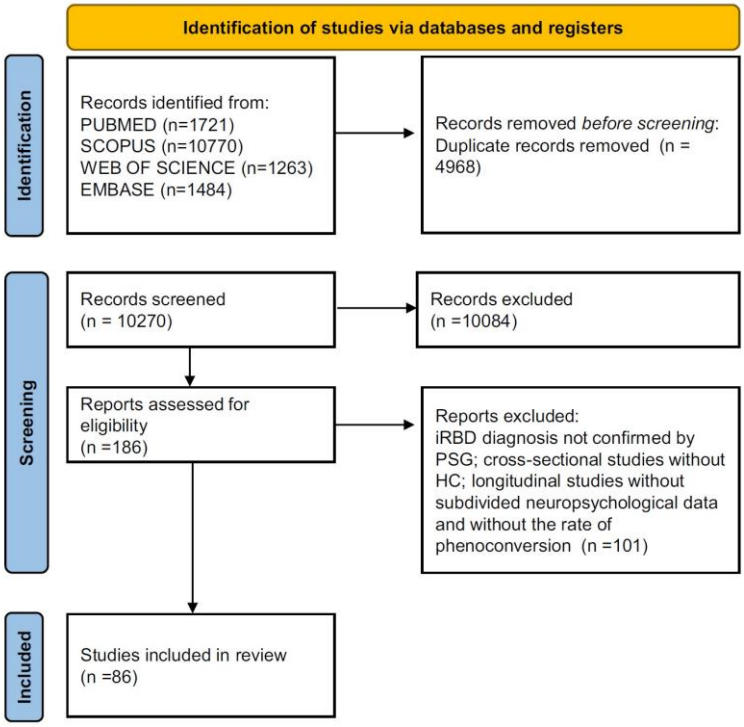
domains are reported in Supplementary Table 2. In addition, because of the heterogeneity inherent to the executive domain, we analyzed attention and processing speed separately. This latter analysis was only performed on the cross-sectional studies given the limited number of longitudinal studies available for secondary analyses of cognitive domains.

3.3. Results

3.3.1. Study Selection

Figure 1 shows the flow diagram according to the PRISMA statement summarizing the selection procedure.

Figure 1. PRISMA flow diagram summarizing the selection procedure.



HC: healthy controls; iRBD: isolated Rapid Eye Movement (REM) sleep behaviour disorder; PSG: polysomnography.

3.3.2. Systematic Review Results

The systematic review analyzed 75 cross-sectional studies. These studies assessed the cognitive performance of 2,398 HCs (1,397 males, 941 females; mean age 65.66±3.28) and 2,460 iRBD patients (1,867 males, 562 females; mean age 66.80±3.06). A total of 61

out of 75 cross-sectional studies reported either the mean age of iRBD symptoms onset (59.67 ±3.33), the mean RBD duration from symptoms onset (6.47±2.67), or the mean RBD duration from PSG diagnosis (2.99±1.20). The selected cross-sectional studies were conducted in 16 different countries: South Korea (14 studies), Italy (10 studies), China (nine studies), Canada (seven studies), Japan (six studies), France (five studies), United Kingdom (four studies), Spain (four studies), Germany (three studies), United States (three studies), Australia (two studies), Czech Republic (two studies), the Netherlands (one study), Austria (one study), and Sweden (one study). The samples of three studies were composed of patients from both Denmark and Spain. These results are presented in Table 3. The systematic review analyzed 11 longitudinal studies, including 495 patients (non-converted n=356; converted n=139). The descriptive data for each group were provided in every study but one (Marchand *et al*, 2018). The 10 longitudinal studies that provided sociodemographic data included 370 males and 90 females, with a mean age of 67.57±1.88 years. The mean FU of all 11 longitudinal studies was 3.2±1.45 years (1.6–6.7 years). All studies provided the type of phenoconversion except one, which provided BL iRBD cognitive performance scores separated between those who converted to PD versus DLB at FU (Marchand *et al*, 2018). Four studies (Youn *et al*, 2016; Terzaghi *et al*, 2019; Campabadal *et al*, 2020; Kogan *et al*, 2021) provided the mean age of iRBD symptoms onset (61.59±1.19). The mean RBD duration from symptoms onset was 9.85±4.72 (seven studies, presented in Table 4), whereas the mean RBD duration from PSG diagnosis was respectively 2.7±3.5 and 1.2±1.2 in the two studies that reported this information (Feng *et al*, 2020; Miyamoto *et al*, 2020). Furthermore, one study reported the age at onset of neurodegenerative disease (73.8±7.6) (Feng *et al*, 2020). The selected longitudinal studies were conducted in 9 different countries: South Korea (two studies), Italy (two studies), Spain (one study), China (one study), Japan (one study), Sweden (one study), Czech Republic (one study), and Canada (one study). Lastly, one study was a collaboration between the Netherlands and Germany. Specifically, in the last study, the patients were provided by both countries. These results are presented in Table 4.

Table 3. Cross-sectional studies characteristics (in descending chronological order).

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Byun et al. 2020	KOR	37 (12 F)	67.7 ± 7.1	/	6.8 ± 3.8	/	15 (6 F)	68.3 ± 3.3
Biondetti et al., 2020	FRA	42 (5 F)	67.7 ± 5.2	/	/	/	38 (21 F)	59.9 ± 9.3
Sasai-Sakuma et al., 2020	JPN	35 (10 F)	75.45 ± 0.95	/	/	/	11 (7 F)	69 ± 1.3
Ehgoetz Martens et al., 2020	AUS	30 (6 F)	66.7 ± 7.2	/	/	/	28 (14 F)	65.6 ± 8.1
Lanza et al., 2020	ITA	14 (3 F)	65.5	/	2.5 ± 0.89	/	14 (5 F)	65
Cochen De Cock et al., 2020	FRA	21 (4 F)	68.7 ± 6.9	/	11.4 ± 11.2	/	38 (7 F)	69.1 ± 7.2
Jun et al., 2020	KOR	94 (41 F)	67.6 ± 7.3	/	5.9 ± 4.6	/	50 (26 F)	65.4 ± 6
Stær et al., 2020	DNK and ESP	19 (2 F)	66.6 ± 6.3	62.2 ± 6.3	3.7 ± 3.5	/	27 (7 F)	65.55
Sunwoo et al., 2020	KOR	16 (2 F)	65.4 ± 6.6	/	3.7 ± 2	/	10 (3 F)	62.3 ± 7.5
Kim et al., 2020	KOR	30 (11 F)	68.6 ± 5.9	/	5.1 ± 4.5	/	12 (6 F)	67.9 ± 4.6
Li et al., 2020	CHN	15 (6 F)	64.27 ± 1.87	/	/	/	15 (6 F)	64.8 ± 1.83
Chen et al., 2020°	CHN	15 (5 F)	64.33 ± 12.16	/	4.33 ± 2.19	/	20 (5 F)	61.1 ± 8.04
Chen et al., 2020b	CHN	27 (5 F)	65.89 ± 8.54	/	11.09 ± 11.24	/	33 (13 F)	68.25 ± 7.8
Shin et al., 2020	KOR	39 (17 F)	69.37 ± 5.77	/	4.83 ± 3.63	/	19 (11 F)	69.38 ± 5.06
Stokholm et al., 2020	DNK and ESP	17 (2 F)	65.3 ± 6.3	/	3.5 ± 3.3	/	9 (0 F)	64.3 ± 6.9
Ehgoetz Martens et al., 2019	AUS	24 (6 F)	66.9 ± 7.6	/	/	/	14 (6 F)	67.4 ± 10.1
Dušek et al., 2019	CZE	74 (8 F)	67.5 ± 6.3	/	6.5 ± 5.8	/	39 (7 F)	65.2 ± 8.2
Her et al., 2019	KOR	15 (3 F)	64.94 ± 6.92	/	/	/	19 (5 F)	63.47 ± 7.37
Mollenhauer et al., 2019	USA	32 (6 F)	69.3 ± 4.83	/	/	/	173 (63 F)	60.9 ± 11.3

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Shin et al., 2019	KOR	25 (12 F)	69.6 ± 5.8	/	4.2 ± 3	/	13 (8 F)	68.8 ± 5.2
Li et al., 2019	CHN	83 (19 F)	67.87 ± 7	/	7.3 ± 6.16	/	79 (21 F)	66.65 ± 7.04
Lee et al., 2019	KOR	31 (14 F)	70.5 ± 5.9	/	4.3 ± 3	/	19 (12 F)	70.1 ± 4.8
Campabadal et al., 2019	ESP	20 (6 F)	71.3 ± 7.8	/	3.1 ± 3.5	/	27 (14 F)	66.4 ± 9.9
Yoon et al., 2019	KOR	28 (14 F)	69.8 ± 5.6	/	4.4 ± 3.9	/	24 (17 F)	69.5 ± 4.3
Zhang et al., 2019	CHN	15 (8 F)	64.93 ± 1.81	/	5.77 ± 1.4	/	23 (13 F)	63.39 ± 2.14
Sunwoo et al., 2019	KOR	13 (2 F)	66.3 ± 6.5	/	4 ± 2.1	/	10 (3 F)	62.3 ± 7.5
Arnaldi et al., 2019	ITA	36 (4 F)	64.1 ± 6	/	/	/	79 (26 F)	65.6 ± 9
Pereira et al., 2019	SWE	27 (5 F)	68.9 ± 5.5	/	/	/	31 (11 F)	58.5 ± 11
Liguori et al., 2019	ITA	54 (13 F)	69.75 ± 8.89	/	5.75 ± 2.57	/	35 (16 F)	67.89 ± 4.95
Yamada et al., 2019	JPN	23 (11 F)	71.5 ± 3.8	/	5.01 ± 3.33	/	20 (9 F)	70.7 ± 3.6
Marcone et al., 2019	ITA	38 (10 F)	67.7 ± 8.45	/	4.39 ± 4.45	/	20 (15 F)	65.3 ± 8.5
Li et al., 2018°	CHN	42 (10 F)	70.88 ± 8.29	/	8.81 ± 12.01	/	45 (33 F)	69.36 ± 10.04
Rahayel et al., 2018	CAN	52 (10 F)	65.5 ± 6.6	/	11.7 ± 11.9	1.6 ± 2.2	41 (16 F)	63.2 ± 8.2
Li et al., 2018b	CHN	28 (7 F)	72.32 ± 7.22	/	9.87 ± 13.59	/	21 (14 F)	69.81 ± 10.24
Stokholm et al., 2018	DNK and ESP	21 (3 F)	66.2 ± 6.3	/	/	3.6 ± 3.4	29 (8 F)	65.7 ± 4.8
Meles et al., 2018	DEU	21 (3 F)	61.9 ± 5.4	55 ± 7.1	5.88 ± 1.13	/	19 (10 F)	62.4 ± 7.5
Barber et al., 2018	GBR	88 (5 F)	66.9 ± 7.62	/	8.5 ± 6.7	3 ± 2.5	33 (18 F)	68.4 ± 8.94
Bezdicek et al., 2018	CZE	60 (5 F)	68.08 ± 7.91	/	4.49 ± 5.33	/	30 (4 F)	66.63 ± 7.43

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Heintz-Buschart et al., 2018	DEU	21 (9 F)	66.1 ± 7.9	/	/	/	78 (32 F)	68.4 ± 6.7
Byun et al., 2017	KOR	14 (4 F)	62.5 ± 6.5	/	4.9 ± 4.1	/	14 (3 F)	64 ± 5.5
Barber et al., 2017	GBR	171 (20 F)	64.7 ± 9	/	7.07 ± 6.3	/	296 (151 F)	64.9 ± 10.2
Sunwoo et al., 2017	KOR	16 (5 F)	64.3 ± 7.4	/	4.8 ± 3.7	/	16 (3 F)	62 ± 6.9
Sasai-Sakuma et al., 2017	JPN	202 (58 F)	66.8 ± 8	/	6.8 ± 7.1	/	46 (14 F)	64.7 ± 5.8
Bang et al., 2017	KOR	57 (24 F)	66 ± 6.09	/	5.66 ± 8.45	/	33 (15 F)	63.88 ± 5.61
Meles et al., 2017	NLD	21 (3 F)	61.9 ± 5.4	55 ± 7.1	6.9 ± 5.4	/	19 (10 F)	62.4 ± 7.5
Boura et al., 2017	DEU	14 (2 F)	65.6 ± 7	/	6.8 ± 4.7	/	27 (16 F)	63.7 ± 11.5
Li et al., 2016	CHN	23 (4 F)	72.48 ± 6.78	/	6.89 ± 8.1	/	23 (4 F)	72.52 ± 6.72
Ehrminger et al., 2016	FRA	21 (6 F)	67.4 ± 7.6	/	5.9 ± 3.8	/	21 (5 F)	67.6 ± 6.3
Rolinski et al., 2016°	GBR	21 (2 F)	66 ± 9	/	/	2.7 ± 1.9	26 (8 F)	66 ± 7
Rolinski et al., 2016b	GBR	26 (4 F)	67 ± 7.7	/	6.3 ± 3.2	5.3 ± 3.01	23 (NA)	NA
Zhang et al., 2016	CHN	15 (4 F)	61.7 ± 12.7	/	12.4 ± 14.5	/	36 (17 F)	62.7 ± 8.1
Aguirre-Mardones et al., 2015	ESP	44 (9 F)	70.89 ± 6.12	61.16 ± 8.08	9.64 ± 6.25	/	40 (11 F)	70.13 ± 6.08
Rahayel et al., 2015	CAN	24 (4 F)	64.2 ± 7	/	9.3 ± 9	2.1 ± 3.1	42 (14 F)	63.3 ± 7.1
Compta et al., 2015	ESP	23 (7 F)	70.33	/	10.65	/	13 (6 F)	71.5
Antonell et al., 2014	ESP	12 (1 F)	69 ± 5.6	/	/	/	43 (31 F)	61.6 ± 7.6
Plomhause et al., 2014	FRA	15 (1 F)	66.7 ± 5.9	/	/	/	20 (5 F)	64.8 ± 7.6
Lee et al., 2014	KOR	15 (5 F)	62.8 ± 7.41	/	5.93 ± 3.22	/	20 (8 F)	59.95 ± 6.41

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Sasai et al., 2013	JPN	31 (7 F)	67 ± 7.5	/	5.4 ± 3.9	/	17 (NA)	59.5 ± 5.6
Ellmore et al., 2013	USA	10 (4 F)	57 ± 2.7	/	/	/	10 (6 F)	57 ± 2.4
Terzaghi et al., 2013	ITA	20 (1 F)	66.1 ± 7.1	60 ± 9.1	7 ± 8.5	/	20 (NA)	NA
Videnovic et al., 2013	USA	10 (4 F)	61.5 ± 8.6	58.5 ± 9.3	1.3 ± 0.9	/	10 (2 F)	62.7 ± 11.5
Delazer et al., 2012	AUT	16 (3 F)	65.2 ± 7.6	/	8.9 ± 7.1	/	45 (23 F)	63.9 ± 9.6
Sasai et al., 2012	JPN	38 (7 F)	64 ± 4.8	/	5.2 ± 3.7	/	34 (13 F)	66.4 ± 7.6
Vendette et al., 2012	CAN	20 (8 F)	67.06 ± 6.97	/	/	/	20 (5 F)	67.35 ± 6.38
Nardone et al., 2012	ITA	10 (0 F)	64.6 ± 7	/	1.23 ± 0.46	/	15 (0 F)	63.7 ± 6.4
Hanyu et al., 2012	JPN	20 (3 F)	68 ± 7	/	6 ± 5	/	18 (9 F)	71 ± 8
Fantini et al., 2011	ITA	24 (6 F)	69.5 ± 7.3	/	7.6 ± 7.3	/	12 (3 F)	69.3 ± 6.3
Marques et al., 2010	FRA	10 (2 F)	59 ± 2.4	/	4.5 ± 1.7	/	8 (3 F)	64 ± 2
Gagnon et al., 2009	CAN	32	65.69 ± 8.52	/	11.27 ± 8.56	/	40 (19 F)	65.78 ± 8.82
Postuma et al., 2009	CAN	68 (15 F)	68 ± NA	/	9.3 ± 1.1	2.6 ± 0.62	36 (8 F)	65.8
Massicotte-Marquez et al., 2008	CAN	14 (0 F)	66.6 ± 7.7	/	11.2 ± 6.7	/	14 (0 F)	65.6 ± 6.5
Terzaghi et al., 2008	ITA	23 (2 F)	67 ± 7	61.2 ± 5.9	6.6 ± 3.6	/	23 (2 F)	67 ± 6
Raggi et al. 2007	ITA	16 (3 F)	66.37 ± 6.14	/	3.43 ± 2.58	/	16 (3 F)	67.56 ± 5.25
Postuma et al., 2006	CAN	25 (3 F)	69.2 ± NA	/	10.5 ± 7	/	25 (3 F)	69.2
Ferini-Strambi et al., 2004	ITA	17 (4 F)	70 ± 7.3	64.31 ± 7.45	5.69 ± 5.31	/	17 (3 F)	69.5 ± 7.1

Table 4. Longitudinal studies characteristics (in descending chronological order).

First Author and Year	Country	N of Patients (Gender)	Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of Non-Converted (Gender)	Mean Age and sd Non-Converted	N of Converted (Gender)	Mean Age ± sd Converted	Mean FU Time	MCI Included/Excluded
Arnaldi et al., 2021	ITA	44 (6 F)	69 ± 6.95	41.06 ± 16.94	/	/	34 (4 F)	68.09 ± 7.54	10 (2 F)	69.9 ± 6.12	2.21	1
Kogan et al., 2020	NLD and DEU	20 (2 F)	66,37 ± 5.17	56.64 ± 6.7	6.02 ± 2.48	/	16 (2 F)	66.86 ± 4.58	4 (0 F)	64.4 ± 6.19	3.7	NA
Campabadal et al., 2020	ESP	13 (3 F)	70.1 ± 6.9	65.65 ± 7.5	4.5 ± 3.4	/	13 (3 F)	NA	0	NA	1.6	0
Feng et al., 2020	CHN	88 (17 F)	69.8 ± 7.7	/	/	2.7 ± 3.5	66 (18 F)	70.9 ± 7.5	22 (6 F)	72.1 ± 7.6	2	1
Miyamoto et al., 2020	JPN	24 (3 F)	65.4 ± 5.5	/	7.3 ± 6.2	1.2 ± 1.2	13 (1 F)	67.1 ± 4.2	11 (2 F)	63.5 ± 6.3	2.3	0
Kim et al., 2020	KOR	30 (11 F)	68.6 ± 5.9	/	5.1 ± 4.5	/	22 (6 F)	67.6 ± 6	8 (5 F)	71.3 ± 5.1	3.4	0
Terzaghi et al., 2019	ITA	63 (8 F)	66.46 ± 6.83	62.43 ± 8.32	14.54 ± 19.05	/	33 (2 F)	66.09 ± 7.48	30 (6 F)	66.87 ± 6.13	6.7	1
Pereira et al., 2019	SWE	27 (5 F)	68.9 ± 5.5	/	/	/	21 (3 F)	69.2 ± 5.9	6 (2 F)	67.8 ± 4.1	2.8	1
Nepozitek et al., 2019	CZE	55 (5 F)	65.7 ± 9.1	/	9.9 ± 9.3	/	46 (NA)	65 ± 9.5	9 (NA)	68.9 ± 6.5	2.3	1
Marchand et al., 2018	CAN	47 (NA)	NA	/	/	/	26 (NA)	NA	21 (NA)	NA	4	1
Youn et al., 2016	KOR	84 (30 F)	65.41 ± 5.83	60.75 ± 8.32	/	/	66 (18 F)	64.98 ± 7.21	18 (8 F)	65.83 ± 4.45	4.24	1

3.3.3. Risk of Bias within Studies

To evaluate the publication bias, a funnel plot for each cognitive domain, for both cross-sectional and longitudinal studies, was inspected. Plots showed few asymmetries, which appears consistent with the inference of publication bias, except for the longitudinal study domain of cognitive screening. Plots are reported in Supplementary Fig. 1. PI and I2 statistics were calculated to assess the heterogeneity across studies. Cross-sectional studies showed considerable heterogeneity levels (I2 values from 65 to 100%) in every cognitive domain. Specifically, ranked by the extent of heterogeneity (I2), cognitive screening came first (I2=79.02%, PI=–1.7395 0.3563), followed by executive functions (I2= 78.58%, PI = –1.6327 0.6254), visuospatial abilities (I2=65.39%, PI=–1.1656 0.3896), language (I2= 64.40%, PI = –1.1024 0.3401), and memory (I2=62.13%, PI=–1.4122 0.1225). Longitudinal studies showed different heterogeneity levels across domains, ranging from low heterogeneity levels, such as for cognitive screening (I2=11.64%, PI=–0.5759 0.0615) and visuospatial (I2=32.03%, PI=–0.7392 0.2070) domains, to considerable heterogeneity values, such as for language (I2=91.41%, PI=–3.3743 1.8179), memory (I2=85.69%, PI=–2.0882 0.9665), and executive (I2=87.17%, PI=–2.4378 1.0192) domains.

3.3.4. Quality Assessment

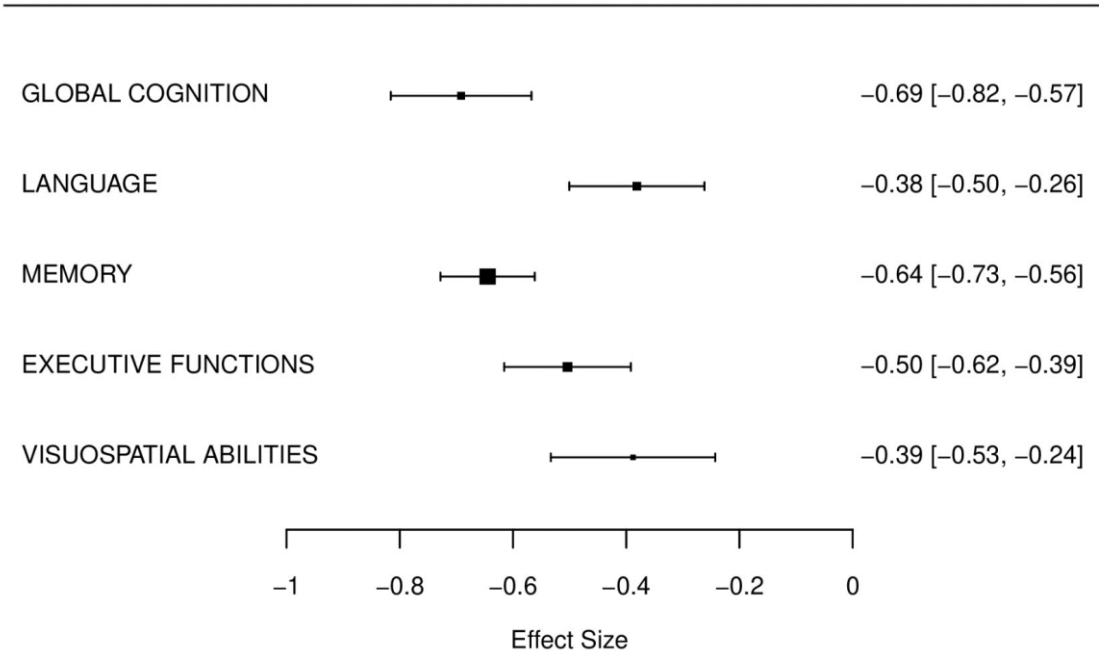
In terms of quality assessment of the studies, the agreement between the two raters was high (Cohen's K =0.855, z=14.2, p-value<0.001; inter-rater reliability (IRR)=89%). All the cross-sectional studies reached a cut-of score≥10 on the CASP checklist, whereas the longitudinal studies reached a cut-of score≥11. In other words, no studies were excluded based on quality ratings.

3.3.5. Meta-analytic Results

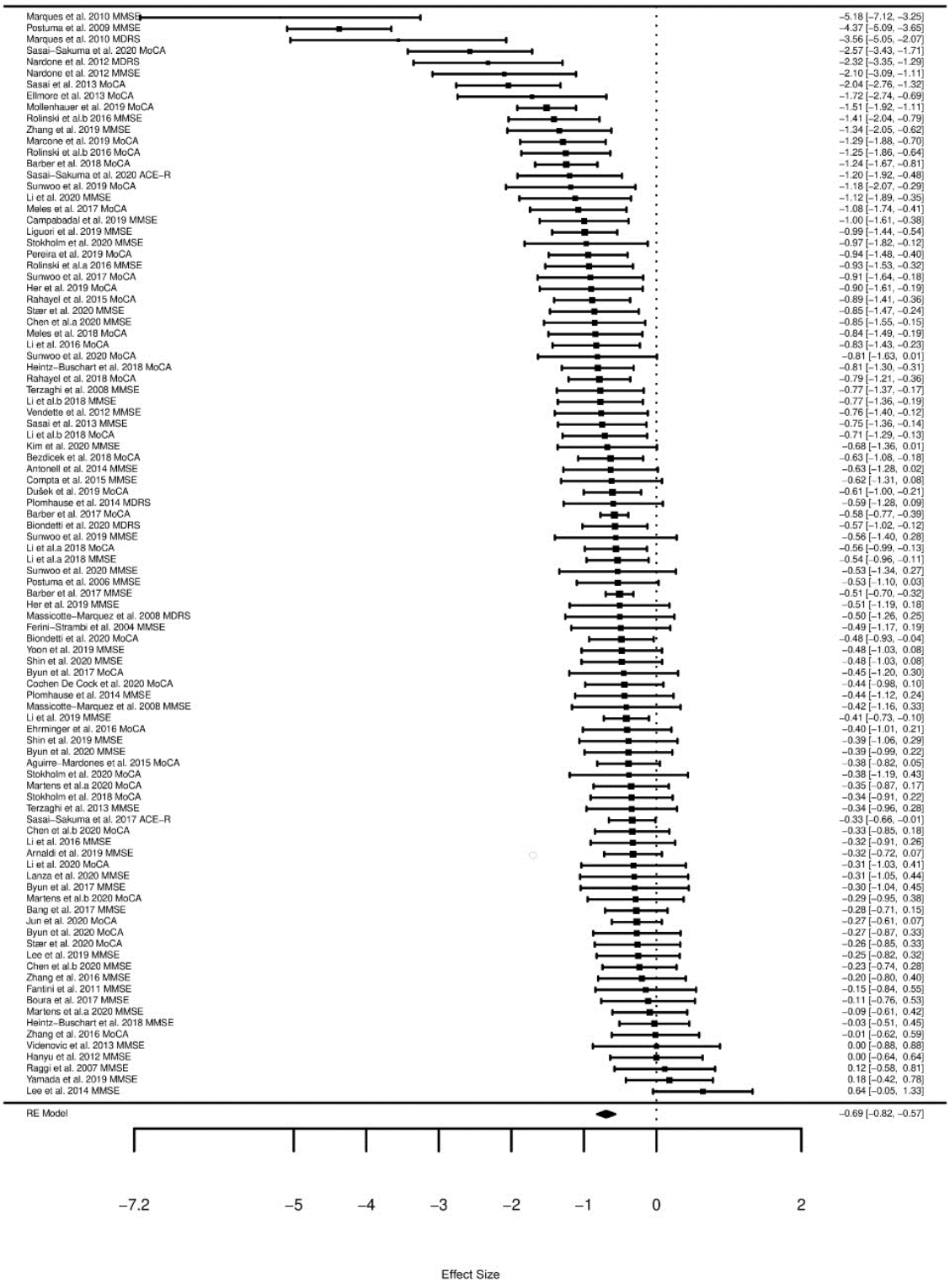
With regards to the cross-sectional meta-analysis, the largest ES was found for cognitive screening (RE model=–0.69 [95% confidence interval (CI) −0.82, −0.57]), followed by memory (RE model = –0.64 [95% CI −0.73, −0.56]), and executive functions (RE model = –0.50 [95% CI −0.62, −0.39]). Smaller differences between iRBD patients and HCs were found for language (RE model=–0.38 [95% CI –0.50, –0.26]) and visuospatial abilities (RE model=−0.39 [95% CI−0.53, −0.24]). This suggests that iRBD

patients performed significantly worse compared to HCs on every cognitive domain, but more so on cognitive screening, memory, and executive functions. These results are presented in Fig. 2. No differences were found between the ES above reported and the ES calculated for domains where tests were re-attributed (i.e., modified language domain with RE model=–0.37 [95% CI –0.50, –0.23] and modified executive function domain (RE model=–0.50 [95% CI –0.60; –0.39]).

Figure 2. Graphical representation of the main results for cross-sectional studies.
(Fig.2a) Cognitive domains summary forest plot for cross-sectional studies.

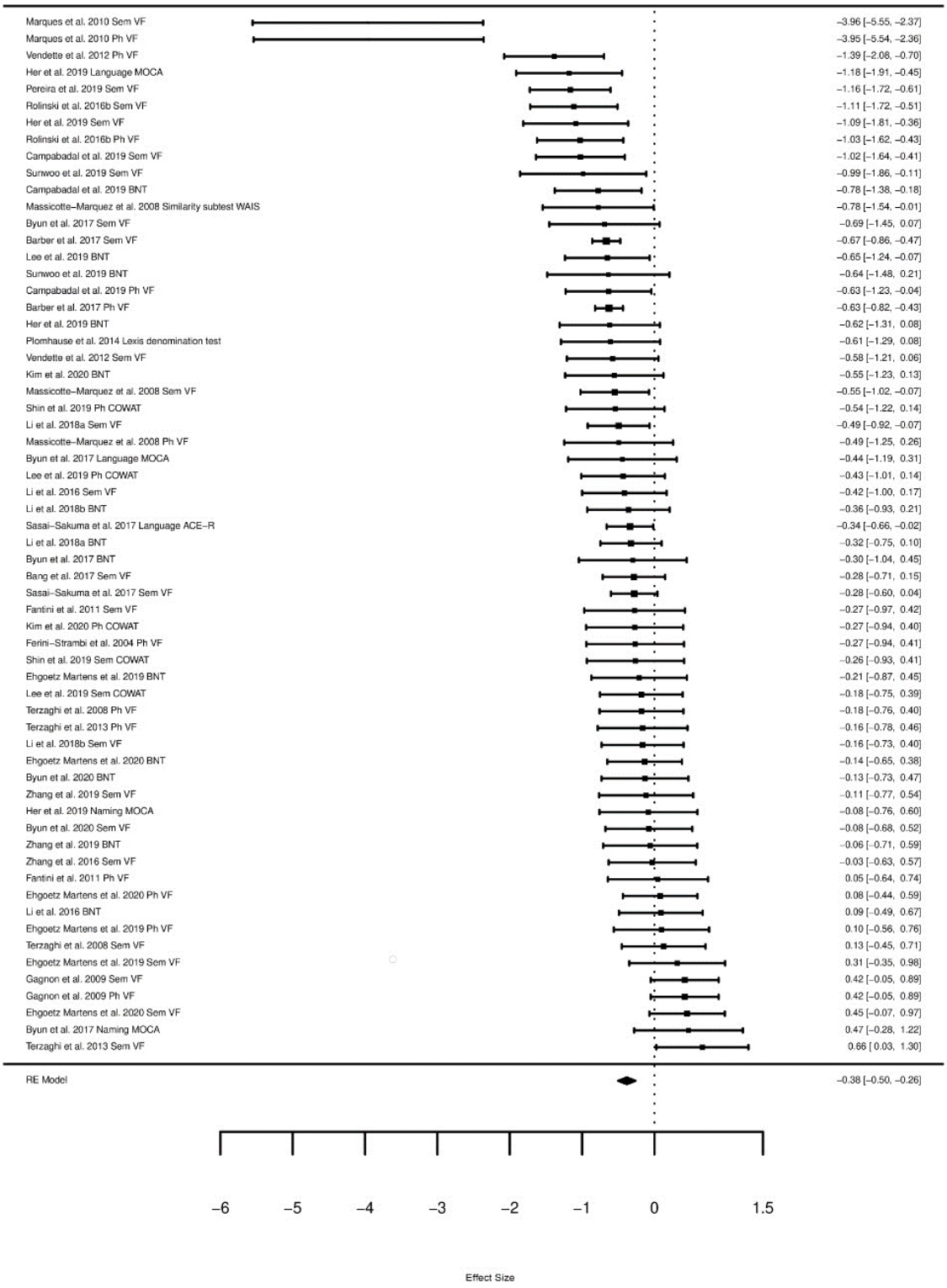


(Fig.2b) Cognitive screening forest plot for cross-sectional studies.



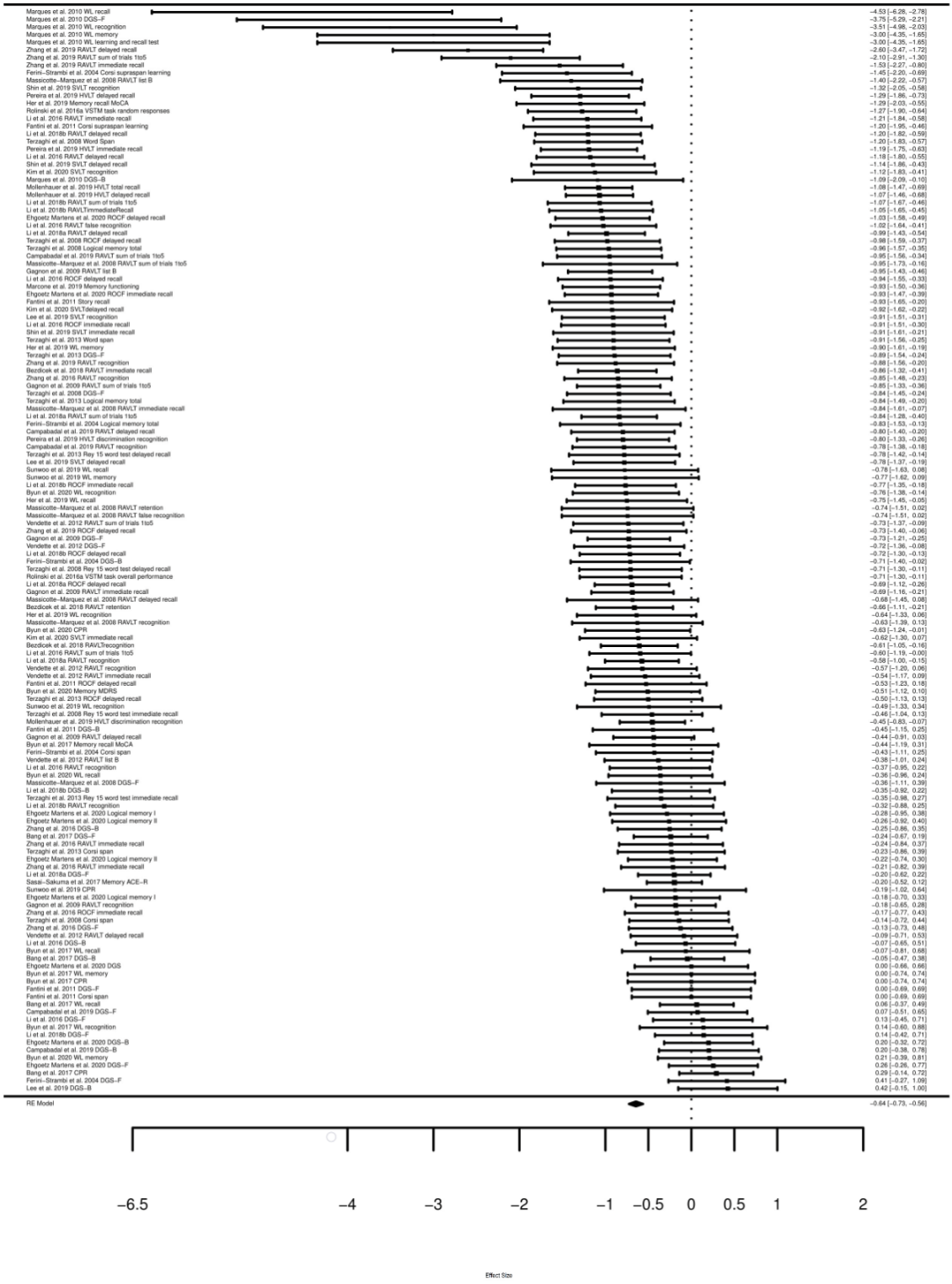
ACE-R: Addenbrooke Cognitive Examination-Revised; MDRS: Mattis Dementia Rating Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

(Fig.2c) Language forest plot for cross-sectional studies.



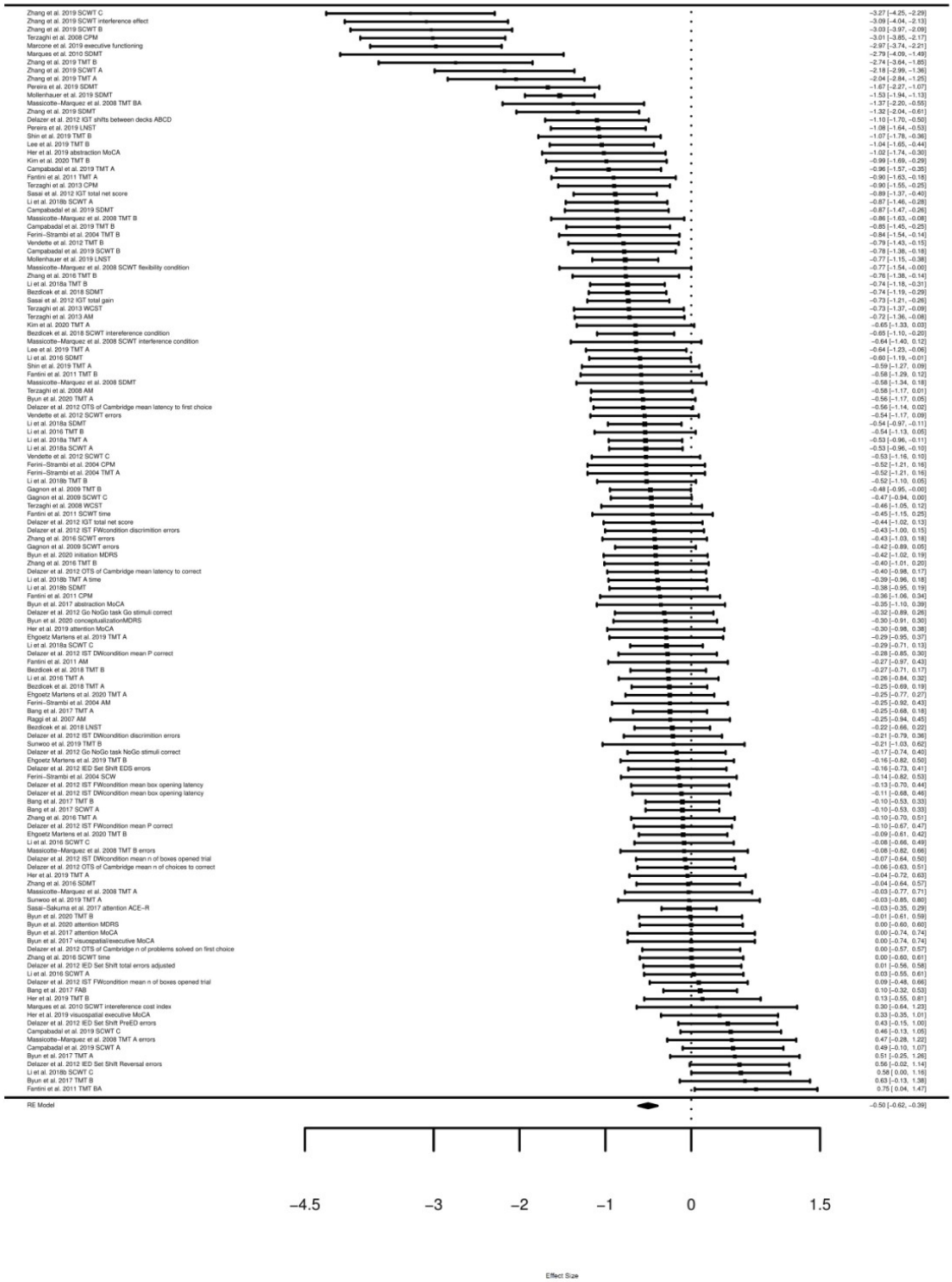
BNT: Boston Naming Test; COWAT: Controlled Oral Word Association Test; Ph VF: Phonemic Verbal Fluency; Sem VF: Semantic Verbal Fluency; WAIS: Wechsler Adult Intelligence Scale.

(Fig.2d) Memory forest plot for cross-sectional studies.



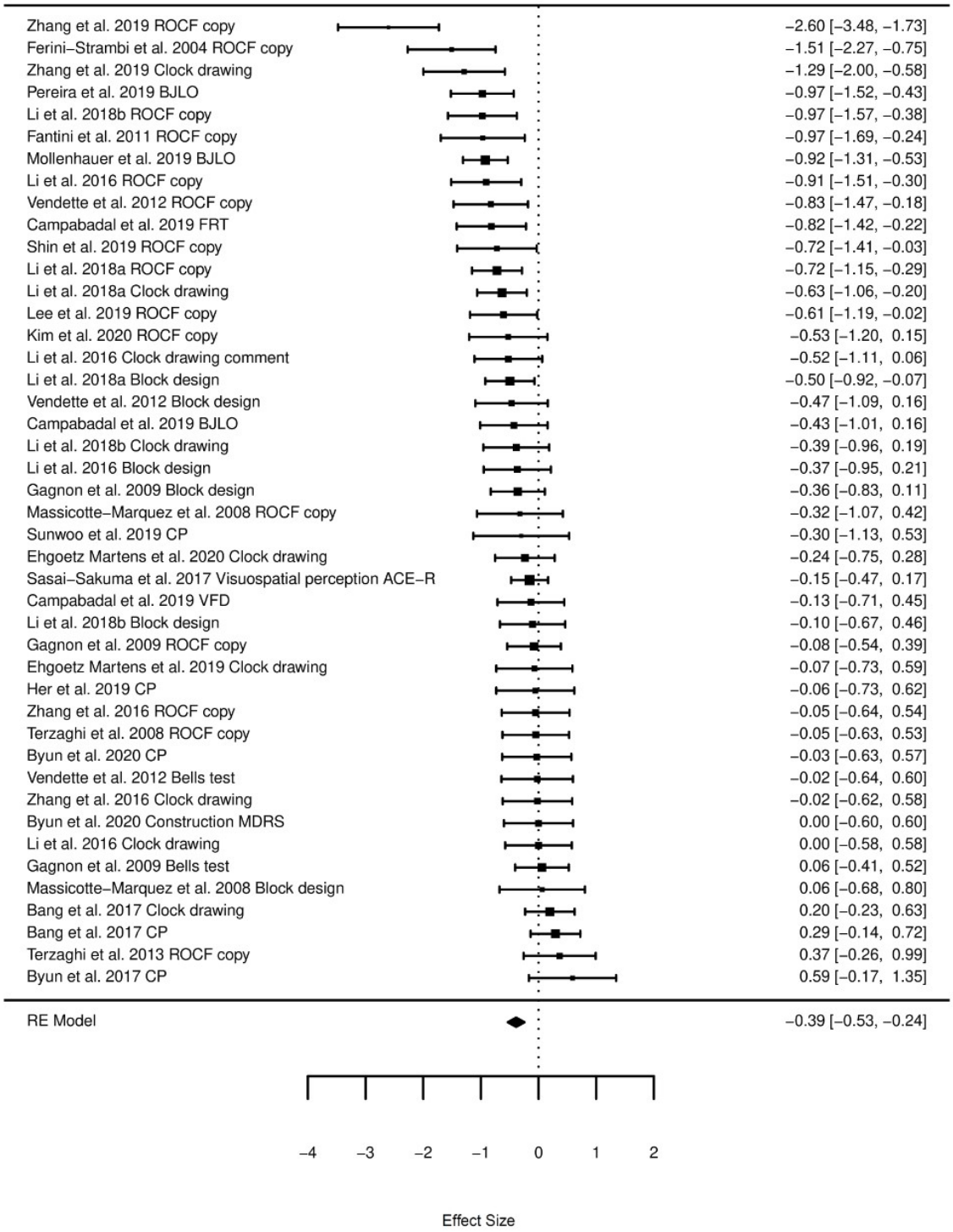
CPR: Constructional Praxis Recall; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; HVLT: Hopkins Verbal Learning Test; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey Complex Figure; SVLT: Shiraz Verbal Learning Test; WL: Word list.

(Fig.2e) Executive function forest plot for cross-sectional studies.



CPM: Raven's Colored Progressive Matrices; FAB: Frontal Assessment Battery; IED: Intra/Extra Dimensional Shift; IGT: Iowa Gambling Task; IST: Information Sampling Task; LNST: Letter-Number Sequencing Test; OTS: One Touch Stockings of Cambridge; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WCST: Wisconsin Card-Sorting Test.

(Fig.2f) Visuospatial abilities for cross-sectional studies.



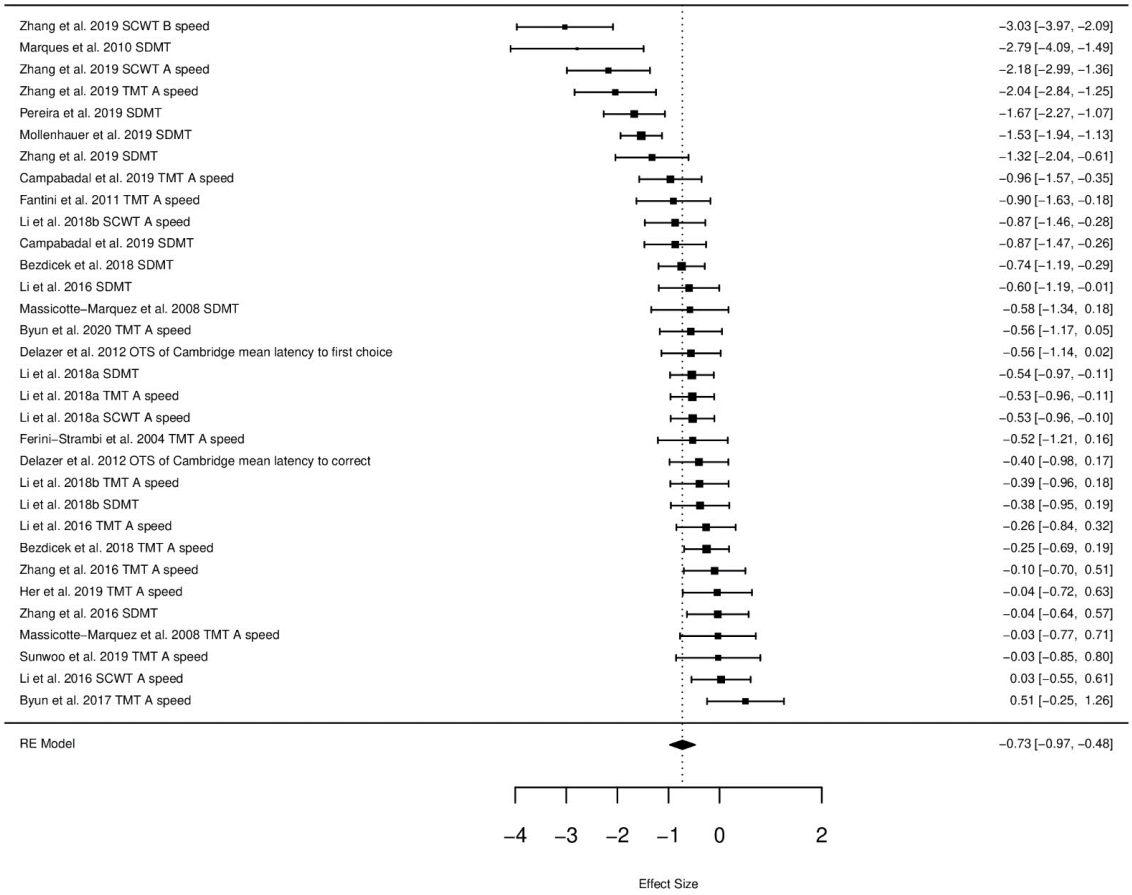
BJLO: Benton Judgment of Line Orientation; CP: Constructional Praxis; FRT: Facial Recognition Test; ROCF: Rey Complex Figure; VFD: Visual Form Discrimination.

In terms of the analyses of executive subdomains, processing speed showed the largest ES (RE model =–0.73 [95% CI−0.97, −0.48]), while a minor difference between HCs and

iRBD patients was found in the attention subdomain (RE model=−0.25 [95% CI−0.40, −0.10]). These results are presented in Fig. 3.

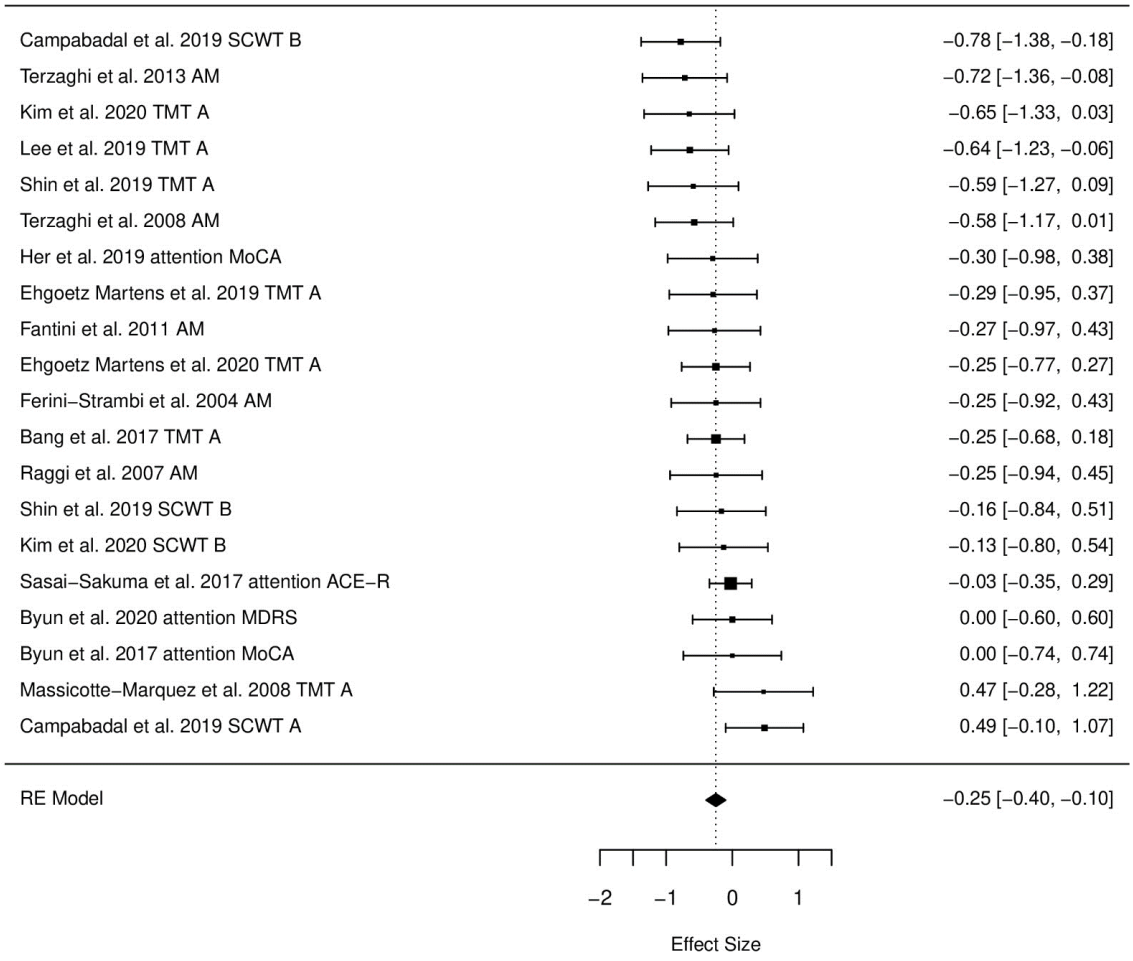
Figure 3. Graphical representation of the executive functions subdomains results for cross-sectional studies.

(Fig.3a) Speed processing forest plot for cross-sectional studies.



OTS: One Touch Stockings of Cambridge; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test.

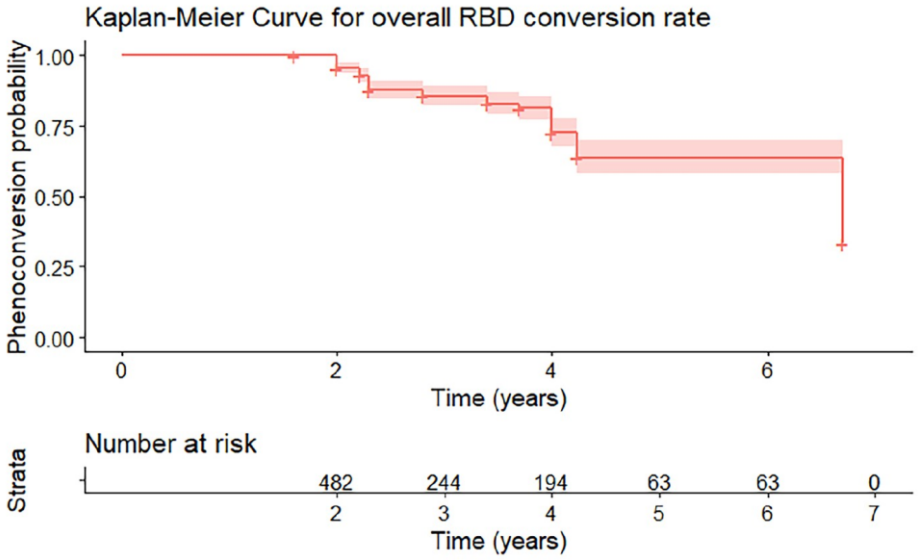
(Fig.3b) Attention forest plot for cross-sectional studies.



ACE-R: Addenbrooke Cognitive Examination-Revised; AM: Attentive Matrices; MDRS: Mattis Dementia Rating Scale; MoCA: Montreal Cognitive Assessment; SCWT: Color Word Stroop Test; TMT: Trail Making Test.

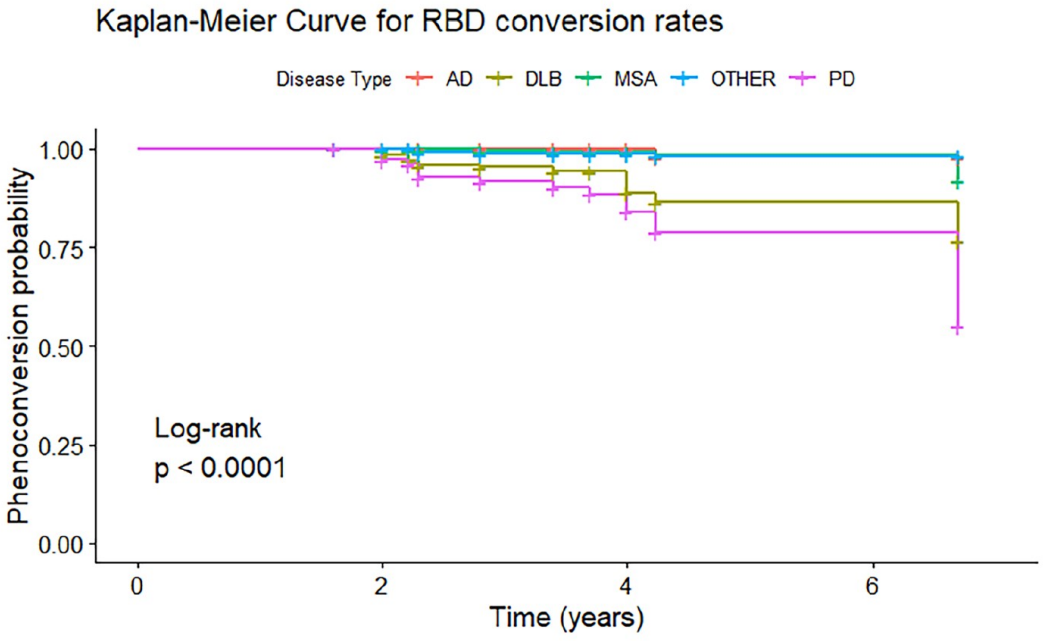
With regards to the longitudinal meta-analysis, the Kaplan–Meier survival analysis estimated a hazard rate of 73.7% after 7 years of FU (Fig. 4).

Figure 4. Kaplan–Meier Analysis plotting disease-free survival in iRBD patients.



The most frequent conversion phenotype was represented by PD (56.83%), followed by DLB (31.65%), MSA (5.75%), other neurodegenerative diseases (i.e., non-specific parkinsonism, pure autonomic failure, spinocerebellar ataxia) (3.60%), and AD (2.16%) (Fig. 5).

Figure 5. Kaplan–Meier analysis stratified for disease type.



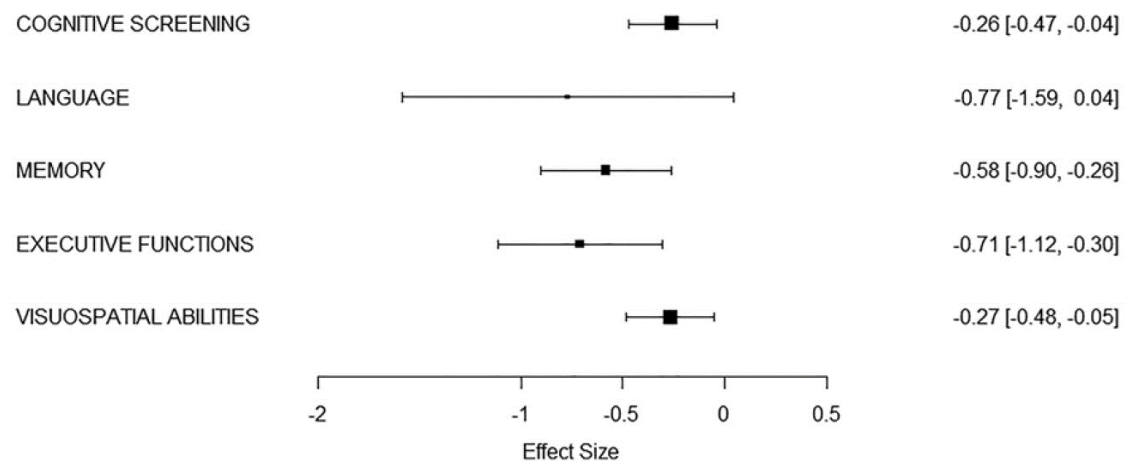
AD: Alzheimer's disease; DLB: dementia with Lewy bodies; MSA: multiple system atrophy; PD: Parkinson's disease

Of note, 6 of the 11 longitudinal studies had a FU duration shorter than three years. The largest difference (i.e., ES) at BL between patients who converted at FU and those

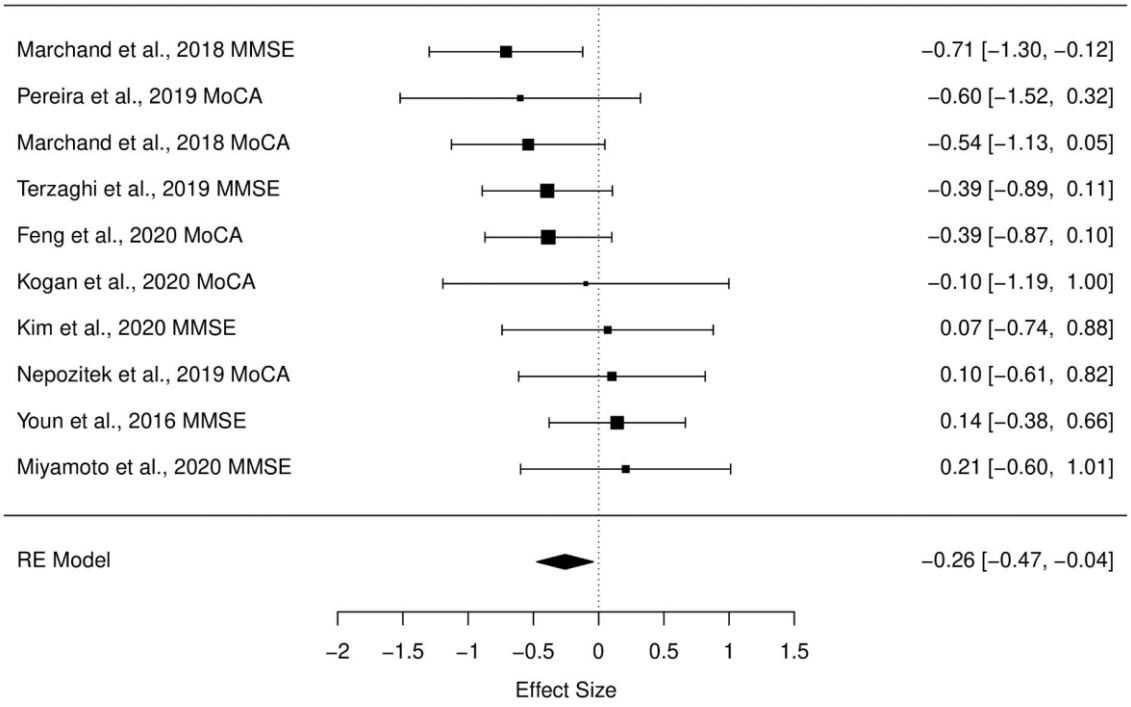
who remained still isolated was found in the executive function domain (RE model=–0.71 [95% CI –1.12, –0.30]). Of note, language was close to significance (RE model=–0.77 [CI –1.59, 0.04]). Smaller differences between patients who converted at FU and those who remained still-isolated were found for memory (RE model=–0.58 [95% CI –0.90, –0.26]), visuospatial abilities (RE model=−0.27 [95% CI−0.48, −0.05]), and cognitive screening (RE model=–0.26 [95% CI –0.47, –0.04]). These results were presented in Fig. 6. No relevant differences were found between the ES above reported and the ES calculated for domains with re-attributed tests: the modified executive domain showed, as above, a large and significant difference between converters and non-converters (RE model=–0.78 [95% CI –1.17, –0.38]. As found previously, the modified language domain was not significant (RE model 95% CI –1.61, 0.44).

Figure 6. Graphical representation of the main results for longitudinal studies.

(Fig.6a) Cognitive domains summary forest plot for longitudinal studies.

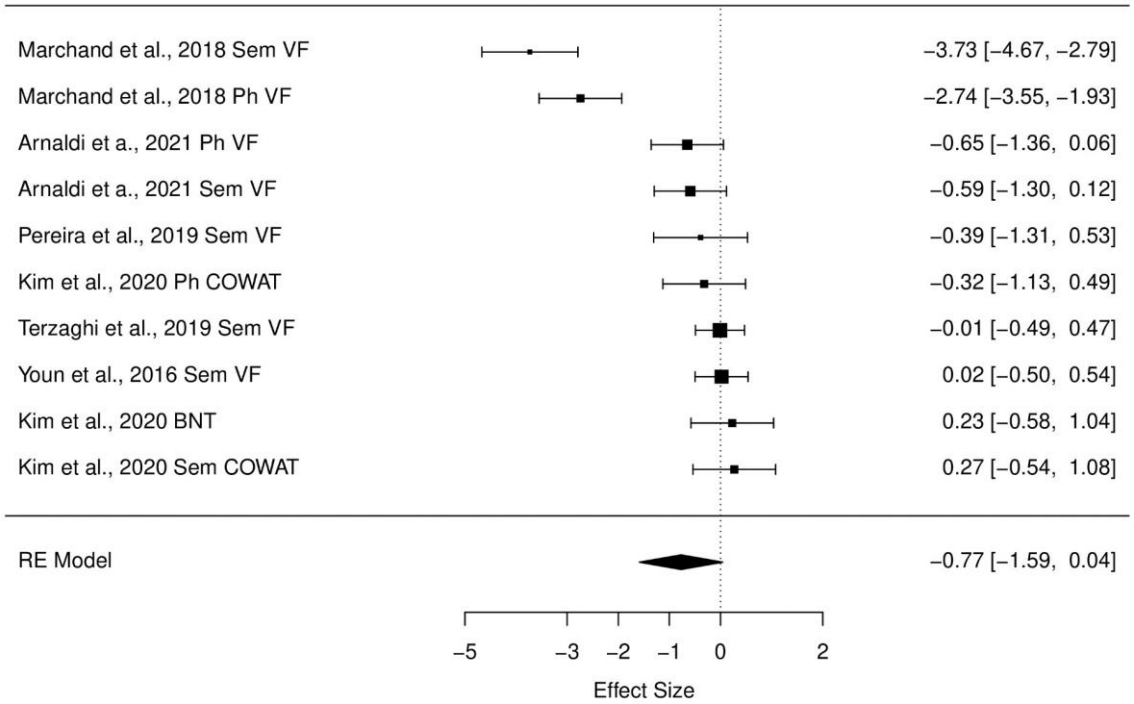


(Fig.6b) Cognitive screening forest plot for longitudinal studies.



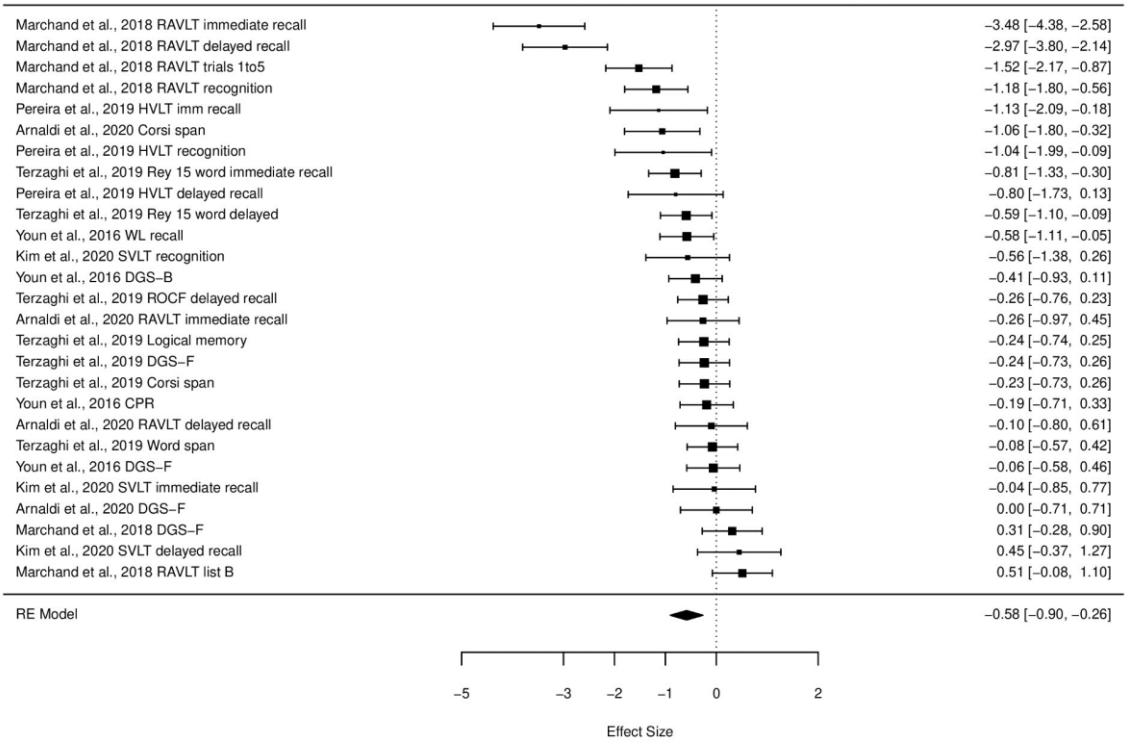
MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

(Fig.6c) Language forest plot for longitudinal studies.



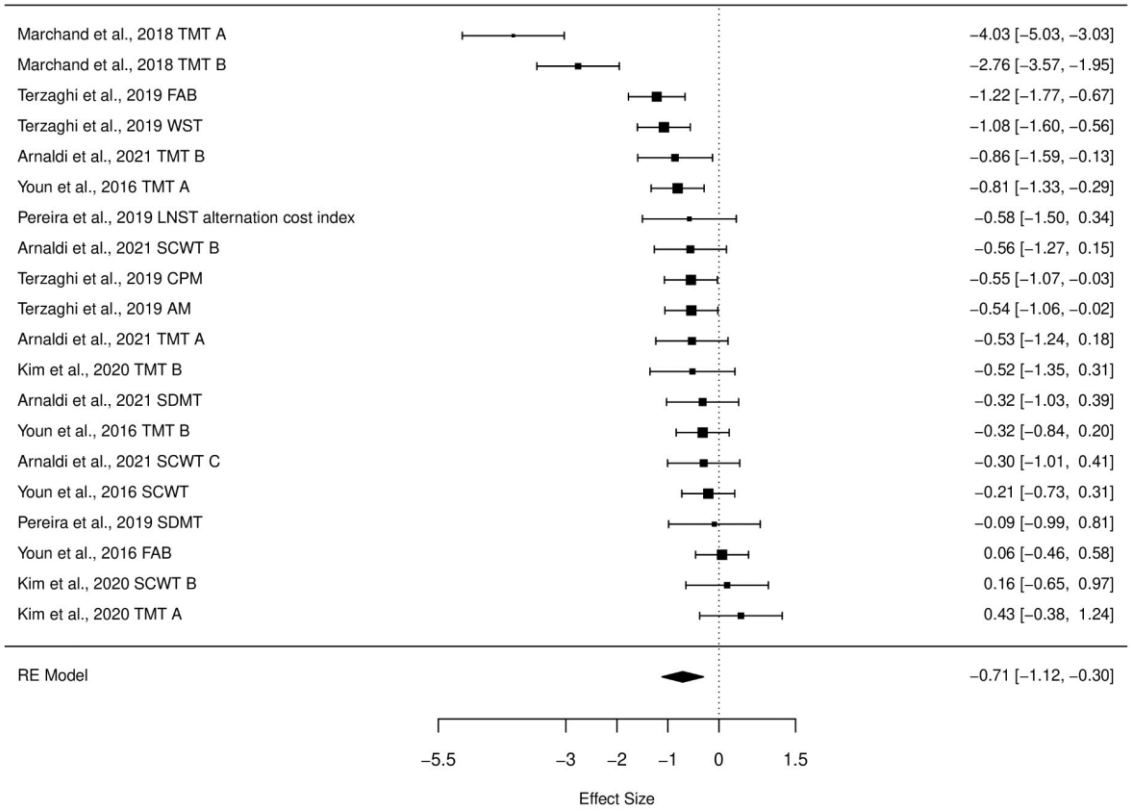
BNT: Boston Naming Test; COWAT: Controlled Oral Word Association Test; Ph VF: Phonemic Verbal Fluency; Sem VF: Semantic Verbal Fluency.

(Fig.6d) Memory forest plot for longitudinal studies.



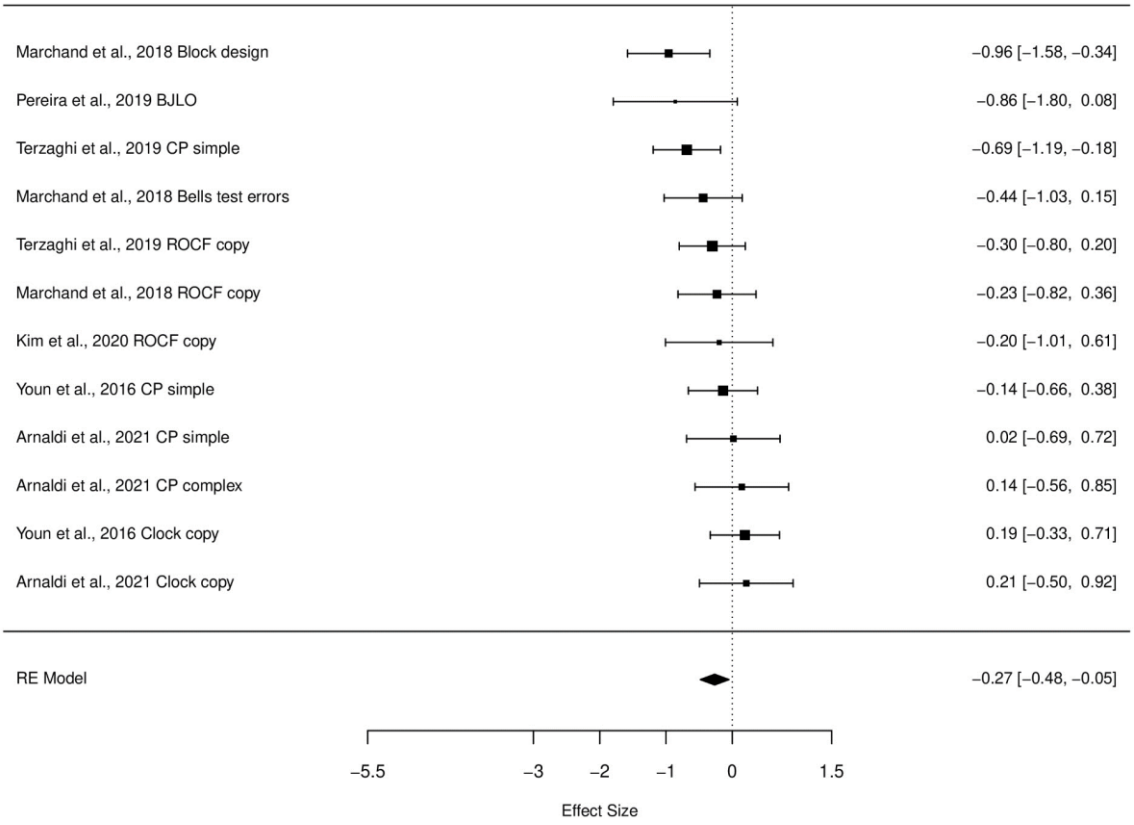
CPR: Constructional Praxis Recall; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; HVLT: Hopkins Verbal Learning Test; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey Complex Figure; SVLT: Shiraz Verbal Learning Test; WL: Word list.

(Fig.6e) Executive function forest plot for longitudinal studies.



AM: Attentive Matrices; CPM: Raven's Colored Progressive Matrices; FAB: Frontal Assessment Battery; LNST: Letter-Number Sequencing Test; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WST: Wisconsin Card-Sorting Test.

(Fig.6f) Visuospatial abilities forest plot for longitudinal studies.



BJLO: Benton Judgment of Line Orientation; CP: Constructional Praxis; ROCF: Rey Complex Figure.

The Cox proportional hazards analysis showed that the domains that best predicted phenoconversion (i.e., the highest and significant hazard ratios (HR)) were executive functions and language. Each reduction of one unit in executive function performance (expressed in z-scores) increased the hazard by a factor of 0.4, equal to 60% (HR=0.3992; 95% CI 0.309, 0.5157; p-value = 0.000) for the conversion to a neurodegenerative disorder, followed by language with a hazard of 0.7, corresponding to 24% (HR=0.7628; 95% CI 0.6136, 0.9483; p-value=0.01). Of note, memory was slightly above statistical significance threshold with a hazard of 0.64 (HR = 0.6379; 95% CI 0.3999, 1.018; p-value=0.0592). There was no significant predictive value of either cognitive screening (p-value=1) or visuospatial abilities (p-value=0.47). The Cox proportional hazards analysis that assessed MCI as a predictor of conversion showed that a patient with iRBD and MCI had a three-fold chance of converting compared to a patient with iRBD but no MCI (HR=2.957; 95% CI 1.681, 5.201 p value=0.001).

3.4. Discussion

This meta-analysis aimed at evaluating the presence of cognitive impairment in iRBD patients in comparison with HCs and at quantitatively estimating the risk of phenoconversion in iRBD patients based on their neuropsychological assessment.

The meta-analysis of cross-sectional studies showed that the most impaired cognitive domains in iRBD patients were cognitive screening, memory, and executive functions, which were associated with "medium" ES (Cohen, 1992; Vacha-Haase *et al*, 2000). These results are partly in line with the previous literature. Indeed, the cognitive domains generally reported as most affected in iRBD are memory and executive functions (Ferini–Strambi *et al*, 2004; Massicotte-Marquez *et al*, 2008; Terzaghi *et al*, 2008; Gagnon *et al*, 2009; Li *et al*, 2016, 2018). Some studies have also reported poorer performance in visuospatial abilities in iRBD patients compared to HCs (Ferini–Strambi *et al*, 2004; Fantini *et al*, 2011; Youn *et al*, 2016), but this was not always observed (Massicotte-Marquez *et al*, 2008; Terzaghi *et al*, 2008; Gagnon *et al*, 2009). Here, we confirmed memory and executive functions as two of the most impaired domains in iRBD patients compared to HCs. Since executive functions represent a broad and highly heterogeneous cognitive domain, we additionally performed an analysis based on its subdomains, showing that the most severe impairments within this category were specific to processing speed. This is in line with the slowness in information processing previously reported in DLB patients, which has been shown to be both a marker useful for differentiating synucleinopathy from AD and normal aging, as well as a marker of progression from MCI to DLB (McKeith *et al*, 2017). Moreover, speed processing alterations have been found in PD, even from the initial stages of the disease (Johnson *et al*, 2016). The PD literature coined two different terms to refer to speed processing alterations: "bradyphrenia" and "slowness in information processing" (Shipley *et al*, 2002; Johnson *et al*, 2016). Remarkably, a study of Arroyo and collaborators (Arroyo *et al*, 2021), which investigated the nature of this slowness, assessed different components of these processes in a stimulus–response pathway (i.e., motor, perceptual-alertness, response strategy-inhibition, decisional, visual search, and control of interference). They found an impairment in PD patients compared to HCs in the simplest stages of processing, particularly in the motor and perceptual-alertness components. The results of our meta-analysis support this finding and revealed the presence of speed processing impairment

already in the prodromal stage of synucleinopathies. This result is important as it means that speed processing may play a role in the prediction of phenoconversion. Future longitudinal studies should investigate more in-depth speed processing and its components as potential phenoconversion biomarkers. We also found a large and unexpected difference in cognitive screening performance between iRBD patients and HCs, which may be ascribed to several factors. One possible explanation is that studies including a comprehensive neuropsychological assessment generally do not discuss findings on cognitive screening, but rather insist on more specific, and consequently more informative, cognitive tests (Sasai-Sakuma *et al*, 2017; Campabadal *et al*, 2019; Her *et al*, 2019; Marcone *et al*, 2019). Second, cognitive changes based on screening tests in iRBD are subject to conflicting results in the literature due to the inclusion (Dušek *et al*, 2019; Mollenhauer *et al*, 2019; Sasai-Sakuma *et al*, 2020) or exclusion (Bang *et al*, 2017; Sunwoo *et al*, 2017; Campabadal *et al*, 2019) of iRBD patients with MCI. Future studies should investigate this issue more closely. Since MCI may be in some cases a reversible condition (Koepsell & Monsell, 2012; Postuma *et al*, 2012; Lin & Chen, 2018; Saredakis *et al*, 2019), it may be questionable to exclude MCI patients from iRBD samples; instead, it would be more appropriate to report the number of iRBD with concomitant MCI, if any. For example, in the cross-sectional studies included in our meta-analysis, the number of MCI patients included at BL was often not reported (Sasai-Sakuma *et al*, 2017; Her *et al*, 2019; Pereira *et al*, 2019; Cochen De Cock *et al*, 2020). Another factor that may have led to conflicting results are the differences in the clinical characteristics of iRBD samples, especially the time passed since diagnosis. Given that cognitive performance worsens over time in iRBD (Marchand *et al*, 2017, 2018; Terzaghi *et al*, 2019; Zhang *et al*, 2019), the time that has passed since the diagnosis of iRBD is an important factor to consider. Yet, several of the cross-sectional studies in our meta-analysis did not specify the years since diagnosis (Vendette *et al*, 2012; Ellmore *et al*, 2013; Her *et al*, 2019; Pereira *et al*, 2019). Furthermore, none of the longitudinal studies provided information about the average age of symptoms onset for iRBD subjects who converted to a D-first versus a P-first phenotype during FU. Future studies should provide a more detailed clinical characterization of patients that convert to the different phenotypes. The second part of this study focused on longitudinal studies. First, we aimed to quantitatively estimate the phenoconversion risk in iRBD patients. The Kaplan–Meier survival analysis

revealed an estimated hazard rate of 73.7% after 7 years of FU. The most frequent conversion phenotype was PD (56.83%), followed by DLB (31.65%), which is in line with a previous meta-analysis (Galbiati *et al*, 2019). Second, we aimed to evaluate the risk of phenoconversion based on neuropsychological assessment. In agreement with previous studies (Youn *et al*, 2016; Marchand *et al*, 2017, 2018; Terzaghi *et al*, 2019), our results showed that converted patients had lower scores at BL in the executive domain compared with patients who did not yet convert. This may suggest a predictive role played by executive functions as a marker of progression. Another consideration regards cognitive screening, which despite the lower performance found in cross-sectional studies, did not allow to distinguish between converted and still-isolated patients at FU. Several studies found no significant changes from BL to FU in cognitive screening in iRBD patients (Youn *et al*, 2016; Pereira *et al*, 2019; Campabadal *et al*, 2020; Kogan *et al*, 2021). This may be due to a possible test–retest effect on the major cognitive screening tests. Of note, 2 of the 11 longitudinal studies reported a positive trend from BL to FU in the cognitive screening scores (Youn *et al*, 2016; Kogan *et al*, 2021). The lack of prediction from the cognitive screening tests may also be due to the fact that cognitive screening assessment is not sensitive enough to detect changes taking place over time on the alpha-synuclein spectrum. Importantly, some studies reported an association between the presence of MCI at BL and the future development of a neurodegenerative disease, particularly the dementia-first phenotype (Terzaghi *et al*, 2013; Marchand *et al*, 2017; Postuma *et al*, 2019; Arnaldi *et al*, 2021; Rahayel *et al*, 2021). In this study, we therefore aimed to assess the role of MCI as a predictor of conversion. Only 3 of 11 longitudinal studies provided information about the number of MCI patients at BL between those who converted to a manifest synucleinopathy during FU versus those who remained disease-free (Nepozitek *et al*, 2019; Terzaghi *et al*, 2019; Arnaldi *et al*, 2021). These 3 studies tested 163 iRBD patients, of which 40 had concomitant MCI. Importantly, because of the small sample size, our results should be interpreted with caution until more studies with larger sample sizes become available. In our analysis, we found that iRBD patients with MCI had a three-fold increased risk of phenoconverting compared to patients without MCI. MCI therefore represents a risk factor for phenoconversion, in line with the previous literature (Marchand *et al*, 2017; Postuma *et al*, 2019; Terzaghi *et al*, 2019; Arnaldi *et al*, 2021). Of note, only 2 of the 3 studies (Postuma *et al*, 2019; Arnaldi *et al*, 2021) adopted

the same criteria for MCI, based on the guidelines from the Movement Disorder Society Task Force for the diagnosis of MCI (Litvan *et al*, 2012); the study by Nepozitek and collaborators instead used a MoCA cutoff for diagnosing MCI based on Czech normative data (Kopecek *et al*, 2017). Future work should aim at applying similar diagnostic criteria in order to ease comparability of findings between studies. When considering longitudinal studies, one issue was the impossibility to compare patients who converted to a P-first versus those who converted to a D-first phenotype since only two studies provided values for the conversion subtypes (Marchand *et al*, 2018; Terzaghi *et al*, 2019). The inability to assess conversion phenotypes separately may have prevented us from observing a differential pattern of cognitive impairments in those who developed DLB versus PD. An impairment in visuospatial and visuoperceptive abilities in iRBD patients, which have been observed along the spectrum of α-synucleinopathies, has been reported in several cross-sectional studies (Ferini–Strambi *et al*, 2004; Fantini *et al*, 2011; Plomhause *et al*, 2014; Ehgoetz Martens *et al*, 2020). In particular, DLB patients show lower performance on this cognitive domain (Beretta *et al*, 2019; Salmon *et al*, 2020). It is therefore possible that visuospatial deterioration may represent a specific feature of prodromal DLB but not of prodromal PD and that the inability to distinguish between the two groups may have explained the lack of an association between visuospatial performance and phenoconversion. Future studies should report separate data for the type of conversion in order to identify neuropsychological measures able to predict D-first and P-first patients. Moreover, the use of the same updated criteria for the definition of prodromal PD or DLB is of the utmost importance. Indeed, the longitudinal studies included in our meta-analysis employed different criteria to establish the type of phenoconversion: two out of ten longitudinal studies, including converted patients at FU, did not report the criteria used to assess the conversion (Youn *et al*, 2016; Pereira *et al*, 2019); the remaining eight studies applied different criteria for the parkinsonism diagnosis. In five studies (Marchand *et al*, 2018; Terzaghi *et al*, 2019; Feng *et al*, 2020; Kim *et al*, 2020; Kogan *et al*, 2021) parkinsonism was diagnosed according to the United Kingdom PD Society Brain Bank criteria (Gibb & Lees, 1988; Hughes *et al*, 1992). Finally, only three studies (Nepozitek *et al*, 2019; Miyamoto *et al*, 2020; Arnaldi *et al*, 2021) applied more recent PD criteria of the Movement Disorder Society (Postuma *et al*, 2015). Meanwhile, for the diagnosis of DLB all eight studies used the fourth consensus report of the DLB Consortium (McKeith

et al, 2017). Therefore, in order to improve the accuracy of the diagnosis of PD and to obtain comparable data, future studies should apply up to date diagnostic criteria. Another relevant aspect would have been the assessment of neuropsychological performance changes over time (from BL to FU), separately for still-isolated patients, patients who converted first to PD, and those who converted first to DLB. Indeed, this would have been important in order to separate patients with similar neuropsychological profiles at BL but with a different progression of cognitive impairment, which may have led to different phenoconversions. However, given that only one study provided this information (Marchand *et al*, 2018), neuropsychological trajectories could not be drawn. The assessment of methodological quality and of risk of bias revealed some above-mentioned important aspects that we have considered to discuss our results: the variability in the inclusion/exclusion of MCI condition, the employment of different criteria to establish the type of phenoconversion, the incompleteness of clinical characterization of iRBD samples, especially concerning the time passed since diagnosis, and the use of different neuropsychological measures–probably the factor that caused the most heterogeneity. Indeed, the cognitive screening domain for longitudinal studies was the domain with the lowest value of heterogeneity and it was characterized by the highest level of homogeneity between neuropsychological questionnaires. This meta-analysis had a statistical limitation to consider: to evaluate how cognitive status may predict the development of a neurodegenerative disease, we performed a Cox proportional hazards analysis using simulated data. Specifically, the use of artificially generated data comes with some disadvantages, because it can only approximate real-studies results. For this reason, a difference between real data and simulated data should be taken into account (see supplementary materials Table 1 for further details). Finally, the present meta-analysis focused on the cognitive alterations occurring in Irbd patients. However, there are also many non-cognitive markers and risk factors related to phenoconversion in iRBD. A multicenter study published in 2019 (Postuma *et al*, 2019) tested 19 potential non-cognitive predictors. Of these, abnormal quantitative (adjusted HR=3.16) and standardized (adjusted HR=3.03) motor testing, olfactory impairment (adjusted HR=2.62), erectile dysfunction (adjusted HR=2.13), motor symptoms (adjusted HR=2.11), abnormal DaT scan (adjusted HR= 1.98), color vision abnormalities (adjusted HR=1.69), constipation (adjusted HR=1.67), RSWA (adjusted HR=1.54) and advanced

age (adjusted HR=1.54) were all associated with an increased risk of conversion during FU (Postuma *et al*, 2019). Additionally, a recent multicenter FU study explored the role of several environmental and life-style risk factors for phenoconversion in 281 PSG-confirmed iRBD patients. The authors concluded that only advanced age (adjusted HR=1.05) and nitrate derivatives use (adjusted HR=2.18) were associated with an increased risk of conversion at FU (Zhang *et al*, 2022). In both studies, patients who converted first to PD and those who converted first to dementia showed similar risk profiles (Postuma *et al*, 2019; Zhang *et al*, 2022), with the only difference being found for cognition (Postuma *et al*, 2019). Efforts have been made towards the identification of highly sensitive and specific markers that predict conversion phenotypes in iRBD, including electrophysiology (i.e., RSWA quantification, sleep micro- and macro-structure, wakefulness EEG activity), neuroimaging (i.e., 123I-FP-SPECT, 18F-FDG-PET, MRI), motor (i.e., motor scales, upper extremity alternate tap-test, gait dysfunction, speech abnormalities) and autonomic (i.e., autonomic questionnaires, 123I-MIBG-SPECT) functioning, olfactory (i.e., odor identification tests) and ocular (i.e., optical coherence tomography, pupillometry) functions, genetic (i.e., GBA variants, SNCA variants), biofluids (i.e., CSF RT QuIC, nasal swabs RT QuIC, serum neuronal exosomal a-synuclein) and tissue biopsy (i.e., colon biopsy, tissue biopsy, major and minor salivary glands) (for a comprehensive review see (Ferini-Strambi et al, 2019) and (Miglis *et al*, 2021)). The identification of both cognitive and non-cognitive risk factors and markers of conversion is crucial to monitor disease progression and to timely predict its future clinical trajectories. In conclusion, our meta-analysis on cross-sectional studies identified lower cognitive performance in iRBD patients compared to HCs in cognitive screening and memory. In longitudinal studies, iRBD patients who converted to a neurodegenerative disorder showed reduced performances in executive function at BL. Moreover, our results highlighted the role of MCI at BL as predictor of future conversion. Thus, iRBD patients with reduced performances in executive functions, as well as those with MCI, should be closely monitored because of their high conversion risk, as already suggested in previous studies (Youn *et al*, 2016; Marchand *et al*, 2017, 2018; Terzaghi *et al*, 2019). Further longitudinal studies reporting comprehensive neuropsychological assessment both at BL and FU are needed to evaluate changes over a long time period in large cohorts of iRBD patients. This, together with a detailed characterization of iRBD

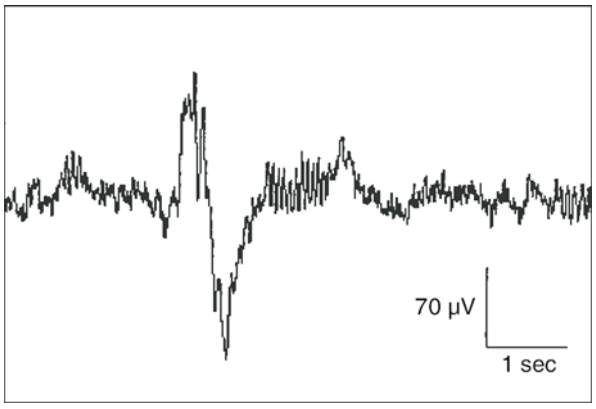
samples, can provide a crucial insight into the dynamic of the neuropsychological changes that occur over time and their association with the future progression to a specific neurodegenerative disease.

4. K-COMPLEXES, SLOW WAVES AND NEURODEGENERATION IN ISOLATED REM BEHAVIOR DISORDER: PRELIMINARY DATA FROM A MULTICENTRIC LONGITUDINAL STUDY

4.1. Introduction

The KC is the largest waveform observable during night sleep, specifically during NREM sleep stage 2 (N2). It can occur in association with another typical EEG element of NREM sleep, the sleep spindle. The KC was first described over 70 years ago by Loomis (Loomis *et al*, 1938). Since its physiological mechanisms and impact on nocturnal sleep have been extensively investigated in many studies. KC is a characteristic wave clearly detectable in frontocentral EEG derivations and characterized by a short and transient surface-positive peak immediately followed by a slower surface-negative complex at around 350ms and 550ms, with a final positivity peaking near 900ms. According to the American Academy of Sleep Medicine (AASM) for the scoring of sleep and associated events, KC must have a total duration ≥ 0.5s (Berry *et al*, 2012). Even if no clear recommendations are provided for peak-to-peak amplitude criterion, some works have reported a minimum peak-to-peak amplitude that must be above 75 μV. An example of a KC is shown in figure 7 (De Gennaro et al., 2000).

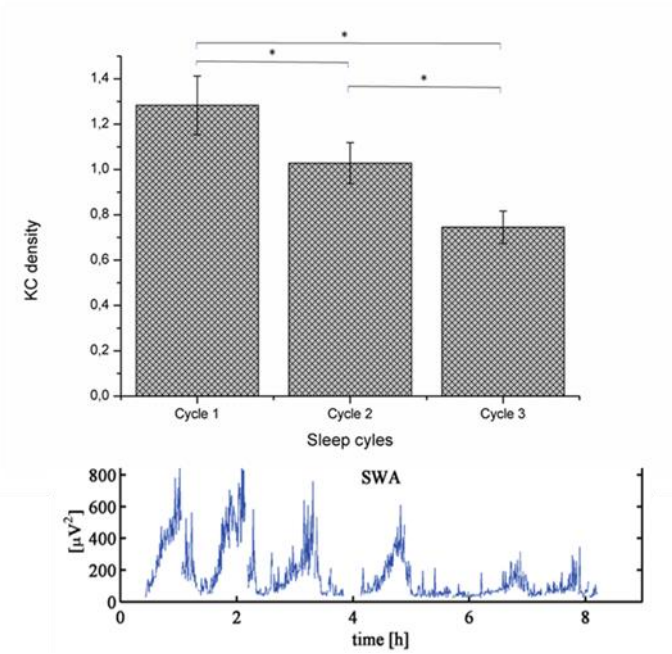
Figure 7. KC followed by a sleep spindle.



KCs can occur spontaneously, in which case they are referred to as endogenous KCs, or they can be the result of external sensory stimulation, in which case they are termed

elicited or exogenous KCs. The density of KC (KCd) can vary throughout the night, in particular it is observable a decrease in function of sleep cycles that may follow the decrease observed for slow wave activity (SWA) (see figure 8).

Figure 8. Decay of KC density in function of sleep cycles and its association with SWA. Adapted from (Galbiati *et al*, 2021).



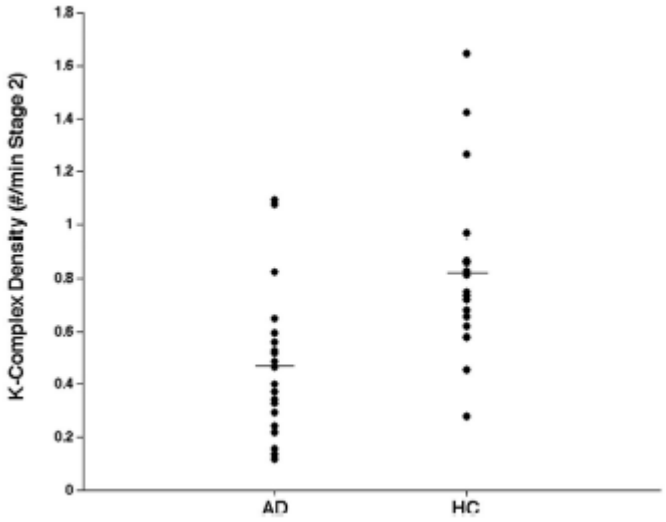
KC: K complex; SWA: Slow Wave Activity

In literature, several works underlined the importance of NREM sleep, and in particular SWS, in protecting aging brain from degeneration and cognitive decline, not only in patients with dementia but also in the context of progression of motor symptoms in PD (Mander *et al*, 2015; Ju *et al*, 2017; Schreiner *et al*, 2019). The study protocol of Mander and colleagues involved [11C] Pittsburgh compound B PET scan, PSG night, and a sleep-dependent memory task, revealing significant interrelations among these factors in 26 HC subjects. Specifically, they observed a negative correlation between Aβ deposition in the medial prefrontal cortex with NREM SWA and NREM slow wave density (0.6–1 Hz). Additionally, they showed that increased NREM SWA is associated with better overnight memory retention in the sleep-dependent memory task (Mander *et al*, 2015). Later, Schreiner and colleagues investigated the potential predictive role of SWA and slow wave energy (SWE), defined as the accumulated power in the SWA band

summed across all epochs of N2 and NREM sleep stage 3 (N3), on changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores in a longitudinal study involving 129 patients with PD. The results indicated that the higher was SWE, the slower was the progression of axial motor symptoms, as assessed by UPDRS III (Schreiner *et al*, 2019). Given the potential relationship between SWS and KCs, as underlined by evidence suggesting that KCs might act as forerunner of deep sleep, several works specifically focused on the impact of KC alterations on cognitive decline and neurodegenerations.

In this context, De Gennaro and collaborators investigated KCs in a cross-sectional study comparing 20 patients affected by AD and 20 age-matched HCs hypothesizing that (i) the density of KCs might better discriminate AD patients from healthy elderly in comparison to SWA comprised between 0.6–1 Hz, and (ii) the decreased density of spontaneous KCs in subjects affected by dementia may be associated to the severity of cognitive impairment, evaluated throughout the MMSE (De Gennaro *et al*, 2017). These authors found a decrease in KCd in patients affected by AD in comparison to HCs in frontal derivation (see figure 9), whereas no significant difference was found between the two groups regarding SWA. Furthermore, only KCd but not SWA showed a significant and positive correlation with MMSE scores highlighting a specific association between KCs and cognitive decline.

Figure 9. Reduction of KCd in patients with AD compared to HCs. Adapted from (De Gennaro et al, 2017).

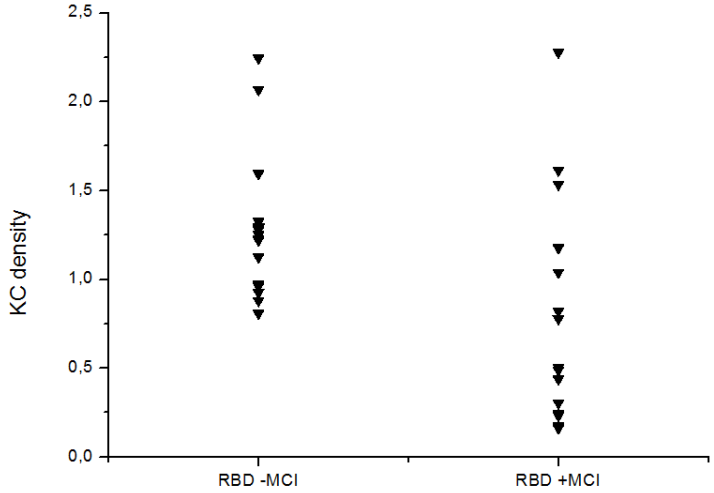


AD: Alzheimer's Disease; HC: healthy control

Recently, the same group aimed to evaluate KC measures in 12 aMCI patients who consequently converted to AD, compared with 12 HCs and 12 stable aMCI patients. The authors reported a reduced parietal KCd in aMCI patients successively converted to AD compared with stable aMCI patients and HCs, with no difference in morphology and overnight modulation. Interestingly, both aMCI groups exhibited diminished SWS percentage compared to HCs, however no significant differences concerning SWA were found between all groups. Once again, these findings confirm that KC alterations occur without any significant power changes in the slow oscillations (SO) range in patients with cognitive decline (Gorgoni *et al*, 2023). Starting from this evidence regarding an involvement of KC alterations in AD and MCI patients, our group, in collaboration with the sleep laboratory of Rome, investigated this issue in patients affected by iRBD. In a first cross-sectional study still unpublished but presented at the 26th Congress of the European Sleep Research Society (ESRS) in Athens (Greece) in 2022 and reported in the abstract supplement issue on Journal of Sleep Research (Gorgoni *et al*, 2023), we aimed to evaluate for the first time disruption of KCd in iRBD patients compared to HCs. Visually scored KCs were detected during N2 in frontal, central and parietal derivations by an independent scorer blind to subjects' diagnosis. KCd was assessed in 31 patients with iRBD (27 males and females; age: 68.64 ± 6.67 years) and 31 HCs (23 males and 8 females; age: 69.03 ± 6.12 years). A comparison between the two groups concerning KCd and a correlational analysis between this index and performance in global cognitive function and performance in neuropsychological measures were performed. The results confirmed a significant reduction in KCd in iRBD patients in the frontal, central and parietal derivations in comparison to HCs. Taking into account the whole sample, KCd detected in the midline central derivations positively correlated with MMSE scores. Moreover, in the iRBD group the midline central KCd index was also positively correlated with scores in attentional matrices and Raven Colored Progressive Matrices, two neuropsychological tests assessing executive functions. These findings described for the first time a clear reduction in KCd in iRBD patients. Moreover, these results further support the relationship between KCs and specific cognitive domains, considered crucial for the prediction of phenoconversion into α-synucleinopathies. A second study (Galbiati *et al*, 2021), always conducted by our group, further explored the functional role and

neural correlates of KCs in iRBD by means of a multimodal approach. Indeed, combining PSG, multivariate molecular imaging (FDG-PET) and a comprehensive neuropsychological evaluation, the study aimed to provide crucial insights regarding KCs role in the prodromal stages of synucleinopathies. 33 iRBD patients (28 male patients, mean age 68.82 ± 6.81 years, mean education 10.64 ± 4.14 years) diagnosed according to current clinical criteria defined by the AASM (American Academy of Sleep Medicine, 2014) underwent a whole night PSG evaluation, a comprehensive neuropsychological evaluation and FDG-PET scan during wakefulness in resting state conditions. As reported in figure 10, a significant decay of KCd was found in function of sleep cycle, with this decrement that seems to parallel those observed in SWA throughout the night. No effect of sleep cycle was observed in the amplitude of KCs thus suggesting its "all-or-none" nature. Remarkably, KCd was significantly associated with cognitive functioning in iRBD patients. Indeed, patients with MCI showed a decreased KCd in N2 in comparison to patients without MCI.

Figure 10. KCd comparison between RBD patients with (RBD+MCI) and without MCI (RBD-MCI). Adapted from (Galbiati *et al*, 2021).



KC: K-Complex; MCI: Mild Cognitive Impairment

Furthermore, KCd displayed significant positive correlations with MMSE performance and two other neuropsychological functions, namely visuo-spatial abilities and executive functions. This result is of relevance since these two domains are recurrently impaired in iRBD patients, and also because these neuropsychological domains are relevant for the prediction of converting into overt synucleinopathies, namely

DLB or PD. By means of a voxel-wise whole brain regression analysis aimed to evaluate the association between cortical metabolism and the index of KCd, results showed an association between KC activity and brain metabolism in the right superior medial frontal cortex. Moreover, decreased KCd was associated with a severe alteration of metabolic connectivity in the Anterior Default Mode Network, suggesting an association between the generation of this particular type of slow waves and the integrity of the anterior brain network (Galbiati *et al*, 2021).

In the light of these considerations and since up to now no longitudinal study investigated KCs in the context of neurodegeneration in iRBD patients, the aims of the present study are (i) to investigate differences in KCd in patients who phenoconverted or remained iRBD at FU, (ii) to investigate their correlation with cognition, and (iii) to test their role as forerunners of slow waves in deep sleep.

4.2. Methods

4.2.1. Participants

In this multicentric study, we enrolled 60 iRBD patients (51 male patients, mean age = 67.69 ± 7.81 years, mean education = 10.93 ± 4.43 years) from three different centers in Italy (IRCCS Fondazione Mondino, Pavia; DINOGMI, Clinical Neurology, University of Genoa; Sleep Disorder Center of the University Hospital Cagliari) who underwent an overnight video-PSG, a clinical assessment, a comprehensive neuropsychological assessment at BL, as well as a FU only involving a clinical evaluation. All patients were diagnosed according to current clinical criteria defined by AASM (American Academy of Sleep Medicine, 2014) with a clinical interview and a video-PSG evaluation. Exclusion criteria were the presence of dementia as diagnosed by expert neurologist, another sleep disorder, mental disorder, medication, or substance use.

4.2.2. PSG evaluation

Every iRBD patients underwent a PSG assessment in a sound-attenuated sleep laboratory room. Patients were medication-free at the time of the evaluation. Based on patients' typical bedtime, lights out-time ranged from 21.30 to 23.30. Following the AASM manual for sleep and associated events, sleep scoring was based on the following

electrophysiological signals: EEG (F3, C3 referred to the contralateral mastoids), electrooculography (EOG), electromyography (EMG) of the sub-mentalis muscle. Sleep staging was performed according to standard criteria on 30-sec epochs (Berry *et al*, 2012). However, given the multicentric nature of this study, we chose not to use the original sleep scoring provided by each center, but we preferred to homogenize them by using an automated algorithm running on Python (https://raphaelvallat.com/yasa/build/html/generated/yasa.SleepStaging.html#yasa.SleepStaging) (Vallat & Walker, 2021). Sleep macrostructure measures comprised: Sleep Latency (SL) to NREM sleep stage 1 (N1), N2, N3; Total Sleep Time (TST); Sleep Efficiency (SE) (expressed as TST divided by the time spent in bed * 100); N1; N2; N3; REM sleep, all expressed as percentages of TST; Wakefulness after Sleep Onset (WASO).

4.2.3. K Complexes, Slow Waves and Slow Oscillations detection

As described in the introduction section of this thesis, KCs were defined as a dynamic and multicomponent event with a large and well-delineated negative sharp wave, immediately followed by a positive polarity component with a maximum amplitude at frontal derivations, a minimum duration of 0.5s and a maximum duration of 3s and a minimum amplitude of 75 µV. KCs were automatically detected by means of a validated algorithm (Lechat *et al*, 2020) on frontal and central (F3 and C3) derivations during artifact free N2 epochs. The proposed algorithm is based on a deep neural network and Gaussian process, which gives the input waveform a probability of being a KC ranging from 0% to 100%. The algorithm was trained on half a million synthetic KCs derived from manually scored N2 KCs from the Montreal Archive of Sleep Study containing 19 healthy young participants. Algorithm performance was subsequently assessed on 700 independent recordings from the Cleveland Family Study using N2 and N3 data. KCd index was calculated as the number of KCs divided by the minutes of N2. SWs (frequency range 1 to 4 Hz) and SOs (frequency range 0.3 to 1) both with a minimum peak-to-peak amplitude of 75 µV were automatically detected on artifact free N3 epochs by means of a validated algorithm (https://raphaelvallat.com/yasa/build/html/generated/yasa.sw_detect.html?highlight=sw#yasa.sw_detect). The density of SWs and SOs was calculated as the total number of

these specific waveforms divided by the minutes of N3.

4.2.4. Neuropsychological evaluation

Each iRBD patients underwent a comprehensive neuropsychological examination, including evaluation of global mental status (i.e., MMSE), language (i.e., Token test), verbal and visuo-spatial memory (i.e., Digit Span Forward, immediate and delayed recall of RAVLT, ROCF recall, Corsi block tapping test), attention and executive functions (i.e., Attentional Matrices, Raven Colored Progressive Matrices; Digit Span Backward; verbal fluency with phonemic, and semantic cue – animals, fruits, car brands]), and visuospatial abilities (i.e., ROCF copy). Subsequently, we calculated z-scores for each individual test and then for each neuropsychological domain.

4.3. Results

60 iRBD patients were followed for 35.47±22.97 months. After this evaluation 49 patients were considered "still iRBD" whereas 11 patients converted into an overt neurodegenerative disease (PD or DLB). Table 5 depicts the characteristics of the sample divided into patients who converted at FU and those who remained still isolated. Table 6 illustrates the sleep macrostructure of RBD participants categorized into "still iRBD" and "converted" groups.

Table 5. Characteristics of the sample divided into patients who at FU converted and those who remained still isolated.

	Sex		**Age**		**Years of Education**	
	Still iRBD	Converted	Still iRBD	Converted	Still iRBD	Converted
Valid	49	11	48	10	48	11
Frequency / Mean	43 M	8 M	67.62	68	11.10	10.18
St. Dev.	-	-	7.97	7.39	4.43	4.58

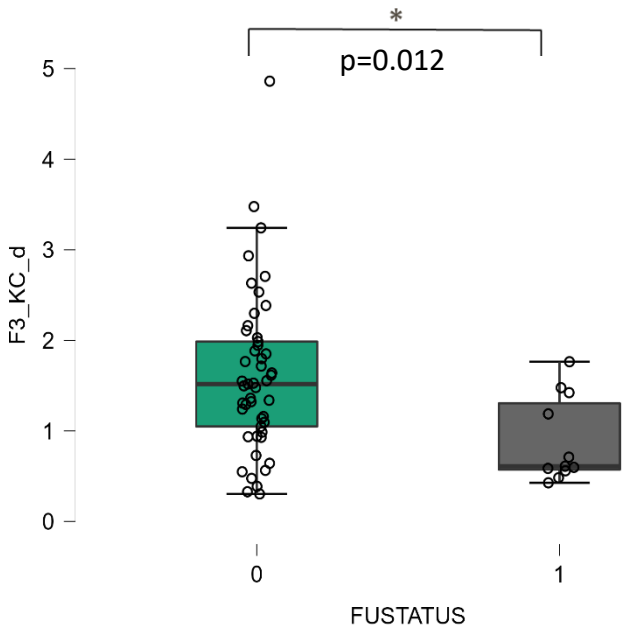
Table 6. Sleep macrostructure of RBD participants categorized into "still iRBD" and "converted" groups.

	% N1		**% N2**		**% N3**		**% REM**		**TST**	
	Still iRBD	Converted	Still iRBD	Converted	Still iRBD	Converted	Still iRBD	Converted	Still iRBD	Converted
Valid	49	11	49	11	49	11	49	11	49	11

Mean	8.54	7.13	57.20	62.31	18.63	19.03	15.63	11.52	332.66	323.36
St. Dev.	4.57	3.63	9.52	10.91	10.76	9.73	7.59	8.66	77.58	61.01
	WASO		**N1 latency**		**N2 latency**		**N3 latency**			
	Still iRBD	Converted	Still iRBD	Converted	Still iRBD	Converted	Still iRBD	Converted		
Valid	49	11	49	11	49	11	49	11		
Mean	119.48	126.54	37.51	86.54	36.20	66.27	68.68	92.95		
St. Dev.	68.95	63.20	41.12	83.68	36.63	45.65	68.07	46.48		

The mean KCd measured on F3 was 1.61±0.88 in “still iRBD” patients (n=49) at FU vs. 0.89±0.47 in patients who converted (n=11) (p=0.012) with no effect of age, FU duration, and ’UPDRS (figure 11).

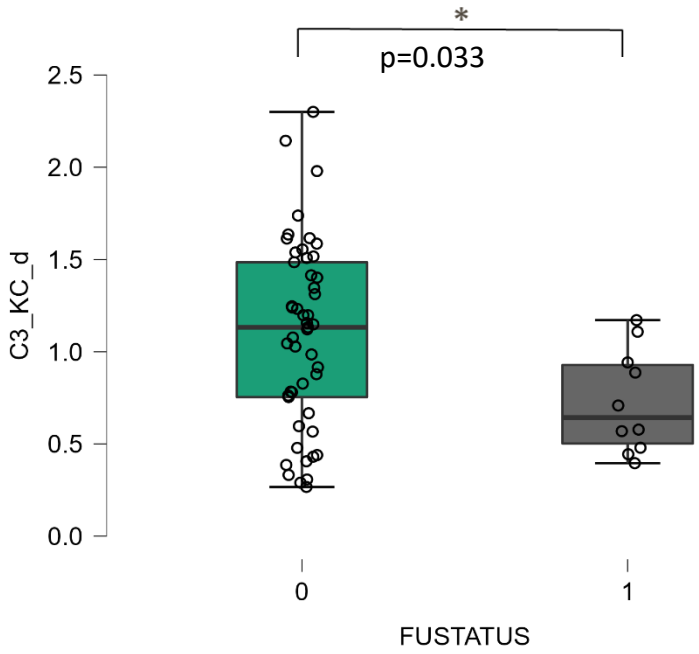
Figure 11. KCd comparison between patients who were still iRBD at FU or who converted into an overt neurodegenerative disease. KC detection performed on F3.



The difference was less pronounced on C3 with a KCd of 1.09±0.50 in “still iRBD” patients at FU versus 0.73±0.28 in patients who converted (p=0.033) (figure 12).

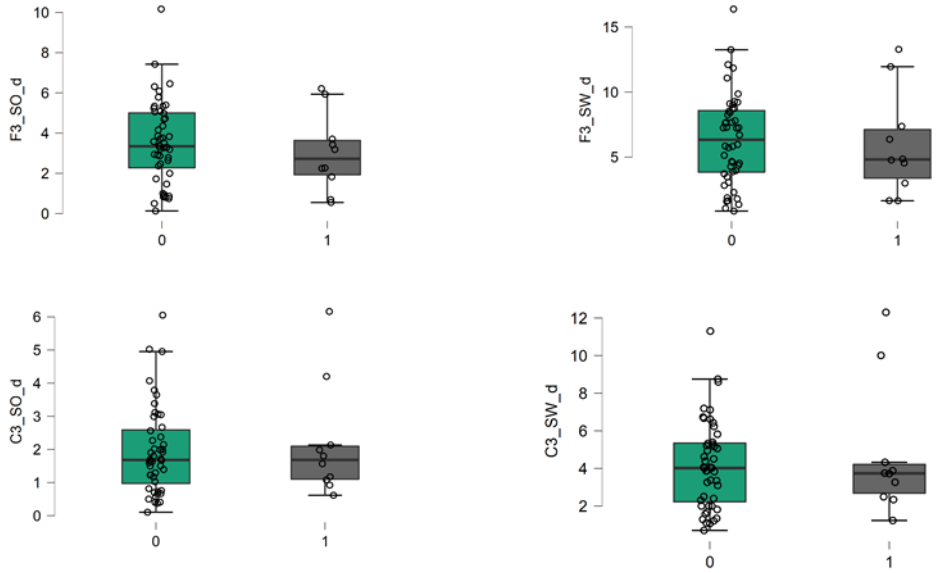
Figure 12. KC density comparison between patients who were still iRBD at FU or who

converted into an overt neurodegenerative disease. KC detection performed on C3.



In contrast with the findings concerning KCd, no significant differences were found for SWs and Sos in central or frontal sites (figure 13).

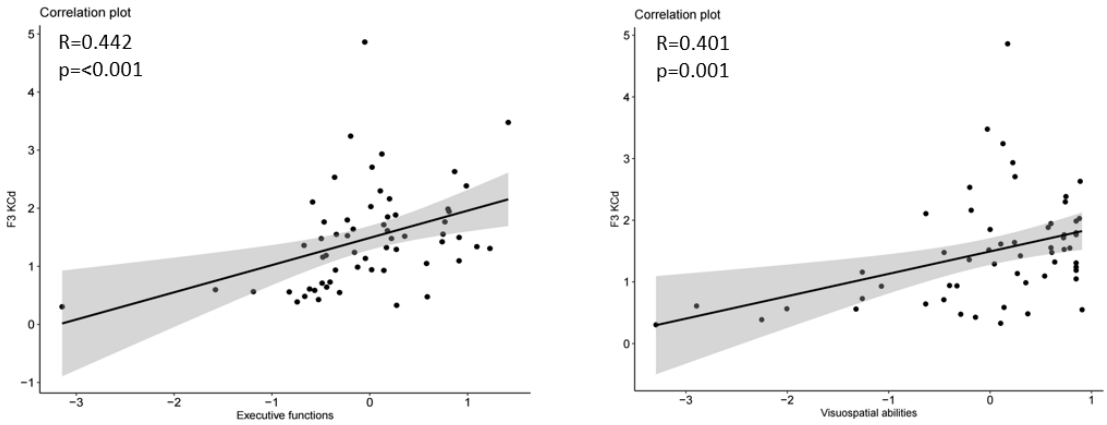
Figure 13. Comparison concerning SOs and SWs between patients who remain "iRBD" (=0) and who converted (=1) at FU detected on F3 and C3.



F3_SO_d: Slow Oscillation density in frontal channel; F3_SW_d: Slow Wave density in frontal channel; C3_SO_d: Slow Oscillation density in central channel; C3_SW_d: Slow Wave density in central channel

Regarding the association between the density of KCs and neuropsychological functioning, we found that KCd on frontal derivation showed a significant association with performance across all neuropsychological domains, with a more pronounced effect observed in visuospatial abilities and executive functions (figure 14).

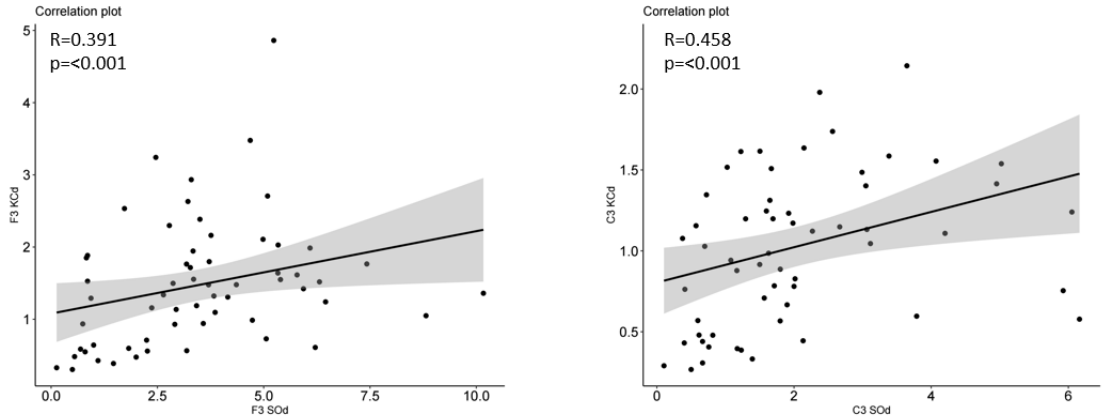
Figure 14. Association between KCd on F3, executive functions performances (left panel) and visuo-spatial abilities performances (right panel) in the whole sample.



Following the association between KCd on frontal derivation and performances in visuospatial abilities and executive functions, we also report, in descending order of correlation coefficient, the significant correlations with the remaining cognitive domains: memory (r=0.338, p=0.005), Language (r=0.296, p=0.012), and Global Cognition (r=0.234, p=0.039) domains.

Finally, we observed again a positive association between KCd in N2 and SO density in N3 both in frontal and central derivations (figure 15).

Figure 15. Association between KCd in N2 on F3 and C3, and SO density in N3 detected on the same derivations.



4.4. Discussion

The aim of this study was to evaluate differences in KCs in patients who phenoconverted or remained iRBD at FU, to confirm their correlation with cognition, and to test their role as forerunners of slow waves in deep sleep. KCd in patients who phenoconverted to parkinsonism/dementia at FU showed a reduction in comparison to patients remaining iRBD over time, mainly in frontal channel but also in central channel. At the same time, we did not find a significant difference between these two groups in terms of SO and SW density, nor in frontal neither in central sites. This underlines a possible association between KCs sand the development of neurodegeneration, even in iRBD. This result is consistent with the study conducted by De Gennaro and colleagues (De Gennaro *et al*., 2017), where the authors observed a significant difference in KCd between AD patients and HCs, while SWA failed to differentiate between the two groups. In our multicentric study, KCd was also associated with cognitive functioning in iRBD patients, in particular with visuo-spatial abilities and executive functions. This finding is of particular relevance for two main reasons: (i) it replicates the findings observed in a previous study (Galbiati *et al*, 2021) and (ii) because these two neuropsychological domains are known to specifically deteriorate in iRBD patients who phenoconverted but also characterize the cognitive profile of patients with DLB and PD. Finally, we found a significant association between KCd in N2 and SO density in N3, supporting the view of KC as forerunner of slow waves in deep sleep. These results should be cautiously considered in light of some limitations. First, although this study is multicentric, the sample size might be considered relatively small. Secondly, the unbalanced

representation of patients who phenoconverted in comparison to still iRBD at FU significantly affects the interpretability of the findings. Third, the lack of conversion subtypes (DLB vs PD) due to the small number of phenoconverters also limits our results since it does not allow to compare these two phenotypes. Future studies should also consider the topographical characterization of KCs, SWs and SOs in iRBD patients, also evaluating their dynamic throughout the night. Furthermore, combining these neurophysiological data with imaging techniques might provide important insight on ongoing neuropathological mechanisms in these patients.

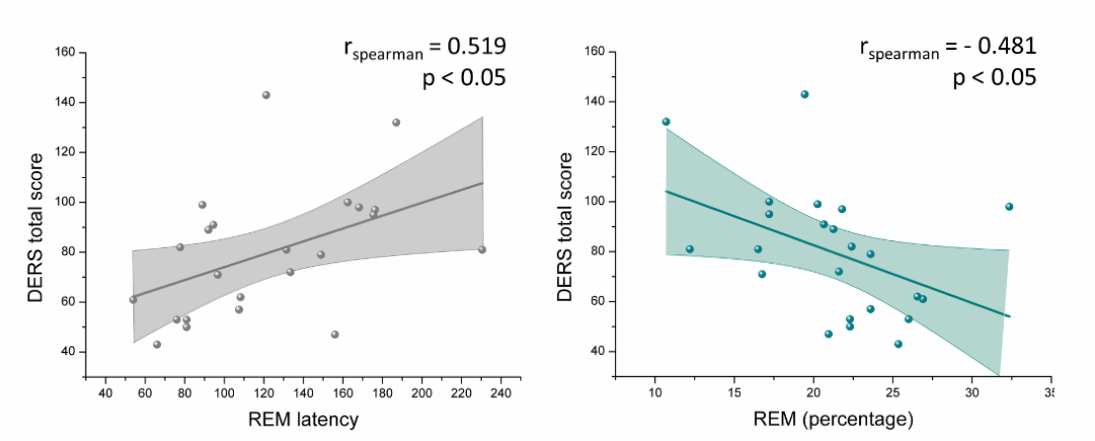
Taken together, these findings suggest the involvement of KCs in the underlying pathological processes of RBD patients, providing insights into their association with cognitive functioning and SWS.

5. ASSESSMENT OF AROUSAL RESPONSE IN HEALTHY CONTROLS AND IRBD PATIENTS

5.1. Introduction

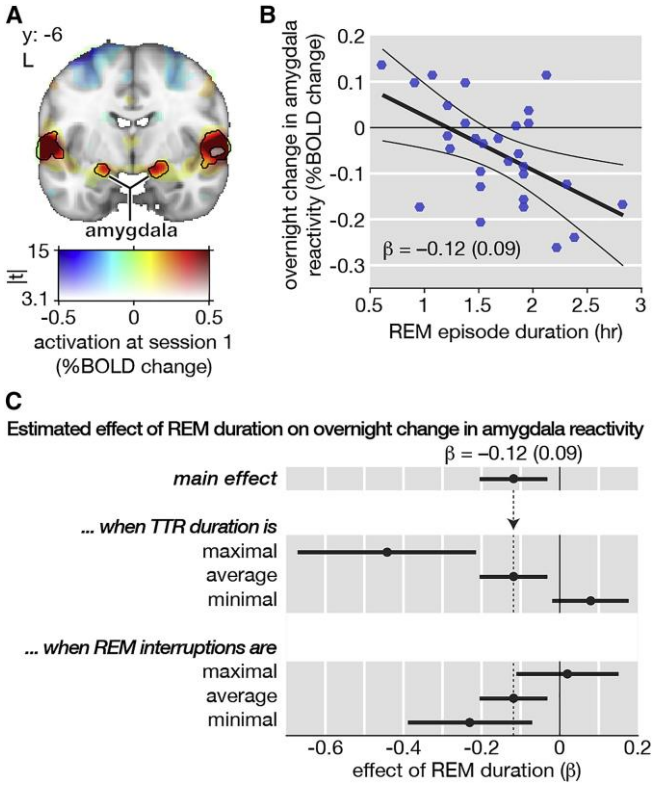
Sleep provides a time window for reactivation and reorganization of the neuronal circuits that were activated during the diurnal emotional experience (Wassing *et al*, 2019). The Sleep to Forget, Sleep to Remember (SFSR) (Walker, 2009) hypothesis posits that the content of emotional memories is strengthened over time while the affective responses associated with their recall are attenuated across multiple night of sleep. This parallel process of content strengthening and affective envelope attenuation is made possible by memory reactivation, which is the re-emergence of the pattern of brain activity elicited while learning during sleep, a naturally occurring phenomenon. Moreover, the SFSR hypothesis also suggests that REM sleep, because of its unique biology, represents a particular brain state for the consolidation and modulation of emotional memories, and several studies have confirmed this hypothesis (Groch *et al*, 2013, 2015; van der Helm & Walker, 2010; Hutchison *et al*, 2021). Emotional memory reactivation during REM sleep underlies sleep-dependent habituation of emotionally salient memories. A relationship between REM features and emotion regulation has been found (Galbiati *et al*, 2020; Wassing *et al*, 2019). A study conducted by our group (Galbiati *et al*, 2020) assessed the relationship between REM sleep characteristics and emotion dysregulation symptoms in insomnia patients. 23 insomnia patients underwent PSG recording and completed the DERS questionnaire. The findings showed that the shorter the REM sleep percentage, the higher the emotion dysregulation, and the longer the REM sleep latency, the higher the emotion dysregulation (Galbiati *et al*, 2020) (figure 16).

Figure 16. Correlation between emotion dysregulation, indicated by DERS total score, and REM features, on the left REM sleep latency, on the right REM sleep duration percentage. Adapted from (Galbiati *et al*, 2021).



Also, Wassing and collaborators studied this relationship within insomnia framework (Wassing *et al*, 2019). Specifically, in 2019, they published a study on the general population with a wide range of insomnia symptoms (Wassing *et al*, 2019). The experimental design included a night and a morning session of fMRI, during which participants listened to their own singing out of tune and the singing of other people in tune to induce a shameful experience. Moreover, PSG was recorded between the two fMRI sessions. The authors found that the overnight decrease in amygdala reactivity is proportional to the total duration of REM episodes. Additionally, when REM interruptions were maximal, the effect of REM duration on amygdala reactivity was cancelled (figure 17).

Figure 17. Association between REM sleep duration and overnight change in amygdala reactivity (B); the effect of the REM interruptions (moderating variable) on association between REM sleep duration and overnight change in amygdala reactivity. Adapted from (Wassing *et al*, 2019).



Therefore, they demonstrated that restless REM sleep, i.e., REM sleep with a high number of phasic events, interferes with the overnight resolution of emotional distress. In their study published in 2016 (Wassing *et al*, 2016), they considered arousals and eye movements as phasic events; later, in 2019 (Wassing *et al*, 2019), eye movements were not anymore considered as phasic events, but arousals and stage transitions. Higher was the percentage of these phasic events occurring in REM sleep, more restless was considered. Restless REM sleep disrupts the proper functioning of limbic and paralimbic system, not allowing correct overnight resolution of emotional distress (see Chapter 1, Paragraph 1.8.). However, phasic events during REM sleep not only occur in RBD as well as in insomnia patients, but they are also a fundamental diagnostic criterion for RBD diagnosis. This may explain the higher percentage of mood symptoms in iRBD, but no study until now tried to directly create a relationship between phasic events and emotion

dysregulation in iRBD population (Barber *et al*, 2018; Kim *et al*, 2020; Jun *et al*, 2020). Research on emotional functioning in iRBD patients represents the third pillar of my PhD project. As we have seen in the introduction, mood symptoms are known to precede the onset of PD and DLB (Poewe *et al*, 2017). Nevertheless, these symptoms have been far less assessed in iRBD. In the context of synucleinopathies, psychiatric comorbidities, mainly depression and anxiety, contribute to accelerate disability and functional morbidity, as well as to increase risk of late-stage complications, leading to poor quality of life and increasing caregiver burden (Assogna *et al*, 2020; Schapira *et al*, 2017). Early recognition of mood symptoms is crucial in the management of neurodegenerative disorders. In this framework, iRBD – as prodromal phase – represents a unique window for the investigation of the mechanisms underlying mood symptoms long before the overtly conversion to a neurodegenerative disorder. However, only few studies have investigated mood symptoms in RBD patients, and more importantly, they have only relied on questionnaires (Barber *et al*, 2018; Kim *et al*, 2020; Jun *et al*, 2020). Moreover, none of them tried to directly establish a relationship between RSWA and daytime emotional functioning in RBD. A task capable of capturing the emotional aspects, which until now have been explored only by questionnaires, is needed. In light of these considerations, the aims of this study are: (i) to assess emotion dysregulation in iRBD using, along with mood questionnaires, a computer-based task, (ii) to assess the relationship between REM sleep and emotion regulation in an elderly sample including HCs and iRBD patients, (ii) to investigate the relationship between phasic events occurring in REM sleep and emotion dysregulation.

5.2. Methods

5.2.1. Participants

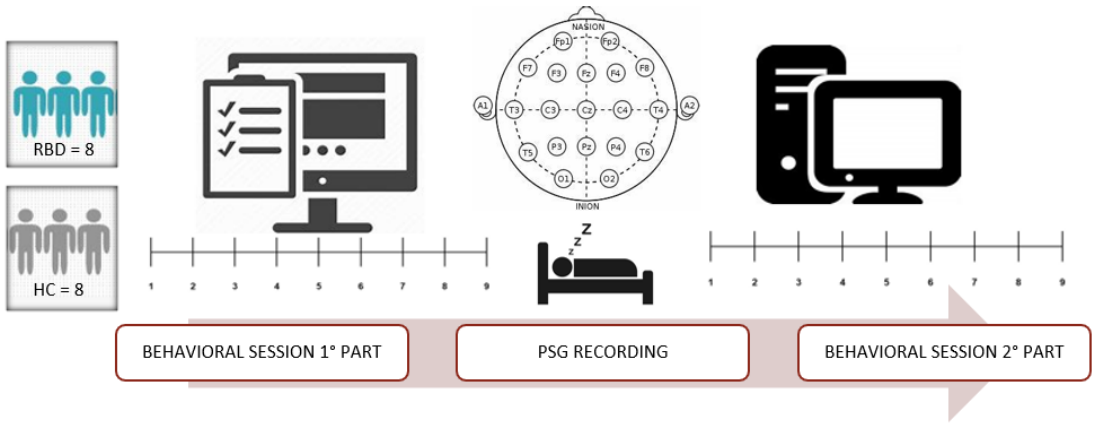
We enrolled 9 HC volunteers (4 male subjects, mean age 60 ± 6.63 years) and 8 iRBD patients (7 male patients, mean age 68.25 ± 5.12 years). HC and iRBD were recruited in two different centers. I recruited HC participants during my abroad PhD period in UK (Cardiff University Brain Research Imaging Centre (CUBRIC), Cardiff); meanwhile the acquisition of iRBD patients took place in Italy (Sleep Disorders Center, Vita-Salute San Raffaele University, Milan). Of note, one HC participant was excluded due to a

headphone malfunctioning during the task. HC participants underwent a screening questionnaire to exclude history of psychiatric, psychological or sleep disorders. Additionally, HC participants were not under the influence of any medication or substance that could directly affect sleep. All iRBD patients were diagnosed according to current clinical criteria defined by AASM (American Academy of Sleep Medicine, 2014). Moreover, they underwent both a clinical interview and a video-PSG recording. Exclusion criteria were the presence of dementia as diagnosed by expert neurologist, another sleep disorder, mental disorder, medication, or substance use.

5.2.2. Experimental design

The experimental design consisted of a single overnight session. In the evening, participants performed several questionnaires assessing mood functioning and an emotional task (evening session part). Then they got a normal night of sleep with PSG recording. In the morning, participants were asked to perform again the emotional task (morning session part). Figure 18 illustrates the experimental design.

Figure 18. Experimental design.



5.2.3. Behavioral session

Participants filled out: (i) BDI, (ii) State-Trait Anxiety Inventory (STAI), (iii) DERS, (iv) Dimensional Apathy Scale (DAS). Along with questionnaires evaluation, participants performed an arousal rating task. A detailed description of the various questionnaires is provided below:

i. BDI: a self-report measure with 21 items to assess depressive symptoms. The total

score ranges from 0 to 63, with higher scores indicating higher levels of depressive symptomatology (Beck *et al*, 1988).

ii. STAI-Y: this version of STAI questionnaire consists of two 20-items scales, one measuring state-anxiety (STAI-Y-1) and one measuring trait-anxiety (STAI-Y-2). For both scales, total score spans from 20 to 80, with higher scores indicating greater levels of anxiety (Tenenbaum *et al*, 1985).

iii. DERS: 36 items questionnaire to assess emotional regulation difficulties in the adult population. Scores range from a minimum of 36 to a maximum of 180, with higher scores reflecting greater difficulties in emotion regulation. It is divided into 6 subscales: Non-acceptance of negative emotions (Non acceptance), Inability to engage in goal-directed behaviors when experiencing negative emotions (Goals), Difficulty controlling impulsive behaviors when experiencing negative emotions (Impulse), Limited access to effective emotion regulation strategies (Strategies), Lack of awareness of one's own emotions (Awareness), Lack of understanding of the nature of one's emotional responses (Clarity) (Gratz & Roemer, 2004; Sighinolfi *et al*, 2010).

iv. DAS: in this multidimensional scale apathy in divided in three factors: demotivation associated with planning, organization, or attention (Executive apathy), indifference or emotional neutrality (Emotive Apathy), and self-generation of thoughts and/or actions (Initiation Apathy). The maximum total score is 72, with higher scores reflecting greater levels of apathy (Radakovic & Abrahams, 2014; Santangelo *et al*, 2017).

The arousal rating task is a computer-based task implemented in PsychoPy. Participants observed 40 emotionally negative and 40 neutral pictures. Each picture was presented for 1s with a semantically related sound. Each sound was trimmed to a 3s duration and volume normalization was performed on all sounds using Audacity. Pictures were chosen from the International Affective Picture System (IAPS), while semantically associated sounds were sourced from either the International Affective Digitized Sounds (IADS) database or freely accessible online resources.

Between each picture there was a dark grey central fixation cross on a white background followed by a black screen. Then participants rated how arousing the image-sound pairs were from 1 to 9. From the two repetitions of this task, the one in the evening

and the one in the morning, we extracted an overnight habituation index, calculated as the average difference between the evening score and the morning score separately for negative and neutral image-sound pairs. More positive results are associated with greater levels of overnight habituation.

5.2.4. PSG evaluation

All participants, both iRBD patients and HC subjects, underwent PSG assessment in a sound-attenuated sleep laboratory room. Patients were medication-free at the time of the evaluation. During the night, a full PSG montage was applied to record EEG activity (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, all EEG channels were referred to the average of the two mastoids), eyes' activity (EOG) and muscle activity for chin, tibialis, and flexor digitorum superficialis (FDS) (EMG). We manually scored sleep stages according to the AASM standard criteria on 30s epochs (Berry *et al*, 2012).

5.2.5. REM sleep microstructure parameters

The eye movements were manually analyzed, following the guidelines in the AASM manual. REMs and other eye movements (Ems) were separately detected, considering mini epochs of 3s at a time. REMs were identified as conjugate, irregular, and having a peak with an initial deflection lasting less than 500ms. All other movements with an initial deflection lasting more than 500ms were defined as Ems. EM density and REM density were separately computed by dividing the total number of Ems and REMs by the duration of REM sleep in minutes. We also detected arousals in REM sleep, which are defined as a sudden change in EEG frequency, including alpha, theta, and/or >16 Hz (except spindles), lasting for at least 3s, with at least 10s of stable sleep preceding the event, accompanied by concomitant increases in submental EMG amplitude lasting at least 1s (Berry *et al*, 2012). In addition to the arousal definition, the following guidelines were also considered: when the level of EMG in REM sleep appeared fluctuating, the increase in EMG in the presumed arousal area had to exceed the background level of fluctuations. We applied the same rule to EEG, we determined the onset of arousal when a defined change in background EEG was observed. Furthermore, we assessed the number of awakenings occurring in REM sleep. REM arousal index is calculated as the number of

arousals in REM sleep divided by the minutes spent in this sleep stage. REM arousals and awakenings index is calculated as the ratio of the total arousals and awakenings over the duration of REM sleep.

5.2.6. Statistical analyses

We conducted statistical analyses using Jeffreys's Amazing Statistics Program (JASP, Amsterdam, NL) software. Given that our data did not meet the assumptions of normally distributed data required for parametric tests and considering the limited sample size, we performed non-parametric tests. To assess the differences in overnight habituation, REM sleep features (duration, latency), number of arousals in REM sleep, density of REMs and Ems, and mood questionnaires between iRBD patients and the HC group, we utilized Mann-Whitney U tests. Then, to explore the relationship between overnight habituation and REM sleep features (duration and latency), as well as between overnight habituation and REM sleep phasic indices (REM density, arousals, and arousal and awakenings index), we performed Spearman's correlations.

5.3. Results

We finally analysed the data of 8 HC volunteers (4 male subjects, mean age 60.62 ± 6.8 years) and 8 iRBD (7 male patients, mean age 68.25 ± 5.12 years). The two groups do not significantly differ in terms of gender and age, although the latter is very close to the significance level. PSG sleep parameters for each group, both for HC and patients, are reported in Table 7. The comparison of PSG sleep parameters between the two groups revealed significant differences: for macrostructure, REM sleep latency is longer in iRBD patients compared to HCs (figure 19); for microstructure, the density of REMs and the number of arousals in REM sleep are higher in iRBD patients than in HCs (figure 20).

Table 7. PSG sleep parameters for the HC and patients' groups.

PSG sleep parameters	Group	Mean	SD	p
%N1	HC	17.08	8.65	0.645
	iRBD	21.77	10.70	
%N2	HC	57.88	8.99	0.161
	iRBD	50.33	9.80	

%N3	HC	7.21	10.26	0.563
	iRBD	5.21	8.67	
%REM	HC	17.82	4.00	0.195
	iRBD	22.69	8.33	
REM latency	HC	99.50	47.01	**0.041**
	iRBD	182.81	102.13	
REM density	HC	3.224	1.460	**<0.001**
	iRBD	8.601	2.850	
REM arousal index	HC	0.235	0.099	**0.036**
	iRBD	0.353	0.110	
REM arousals and awakenings index	HC	0.295	0.125	0.140
	iRBD	0.385	0.118	

Figure 19. REM sleep latency in HC and iRBD groups.

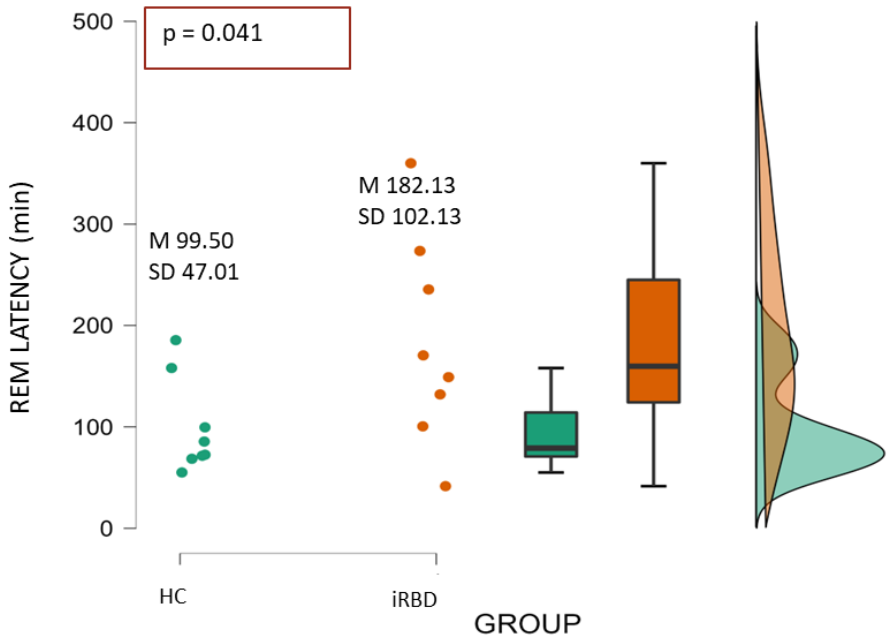


Figure 20. REM density and REM arousal index in HC and iRBD groups.

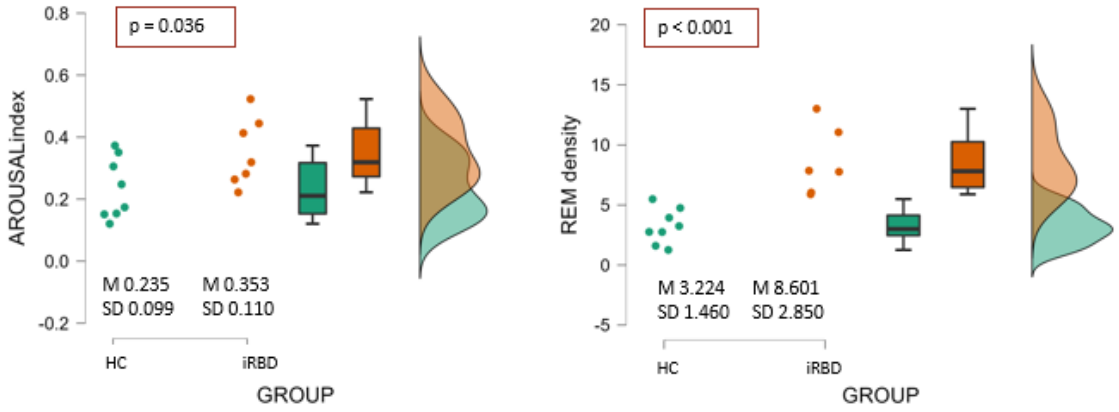


Table 8 displays the comparison of the mood questionnaire scores between the two groups. No mood questionnaires were found to be significant; however, a tendency was observed in three subscales of the DERS: non acceptance, impulsiveness, strategies.

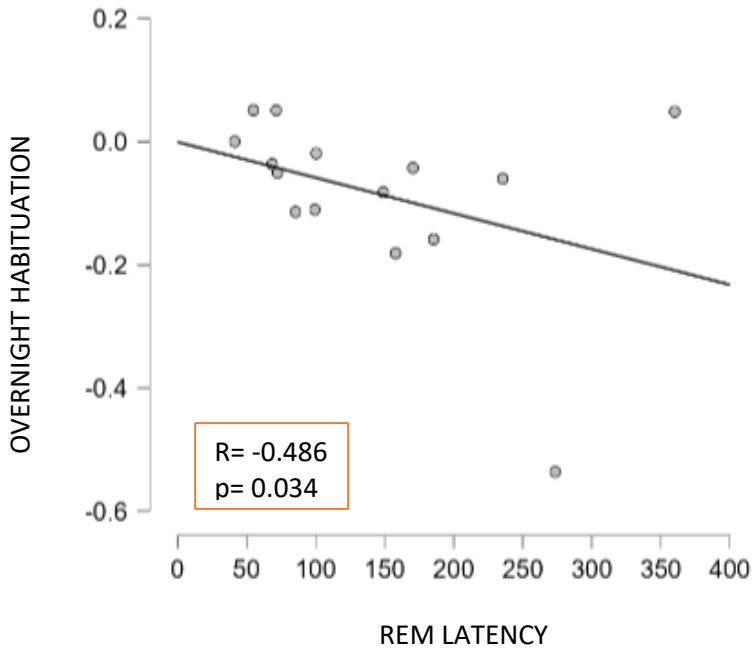
Table 8. Mood questionnaires scores in HC and iRBD groups.

Mood Questionnaires	Group	Mean	SD	p
DERS_TOTAL	HC	70.37	17.83	0.282
	iRBD	76.75	17.55	
DERS_NONACCEPTANCE	**HC**	10.00	3.25	**0.069**
	iRBD	13.00	3.89	
DERS_GOALS	HC	13.87	5.38	0.830
	iRBD	11.50	2.73	
DERS_IMPULSNESS	**HC**	9.50	4.21	**0.076**
	iRBD	13.37	5.10	
DERS_AWARENESS	HC	14.62	5.34	0.816
	iRBD	12.12	5.36	
DERS_STRATEGIES	**HC**	14.37	4.69	**0.070**
	iRBD	17.75	4.68	
DERS_CLARITY	HC	8.00	2.51	0.500
	iRBD	8.87	4.61	
BDI	HC	5.37	5.34	0.282
	iRBD	6.00	2.39	
STAI	HC	29.37	8.42	0.215
	iRBD	34.57	13.38	
STAI2	HC	32.37	12.12	0.185
	iRBD	34.25	7.46	
DAS_EXECUTIVE	HC	7.62	4.81	0.978

	iRBD	3.62	1.92	
DAS_EMOTIONAL	HC	7.37	4.63	0.437
	iRBD	7.37	3.20	
DAS_BEHAVIORCOGNITION	HC	9.25	3.99	0.787
	iRBD	6.62	4.14	
DAS_TOTAL	HC	24.25	7.05	0.959
	iRBD	17.62	7.11	

Finally, in the comparison between the two groups, we did not observe a significant difference in the overnight habituation index assessed with the task. After evaluating the differences between the two groups, we explored the association between the overnight habituation index and the PSG sleep parameters. The analysis of REM macrostructure revealed that overnight habituation is significantly associated with REM sleep latency ($r=-0.486$, $p<0.034$; figure 21) but not with REM sleep duration in the whole sample. Notably, when considering only the HC group, we found a positive correlation between REM sleep duration and overnight habituation ($r=0.67$, $p=0.042$).

Figure 21. Association between overnight habituation and REM sleep latency, expressed in minutes.

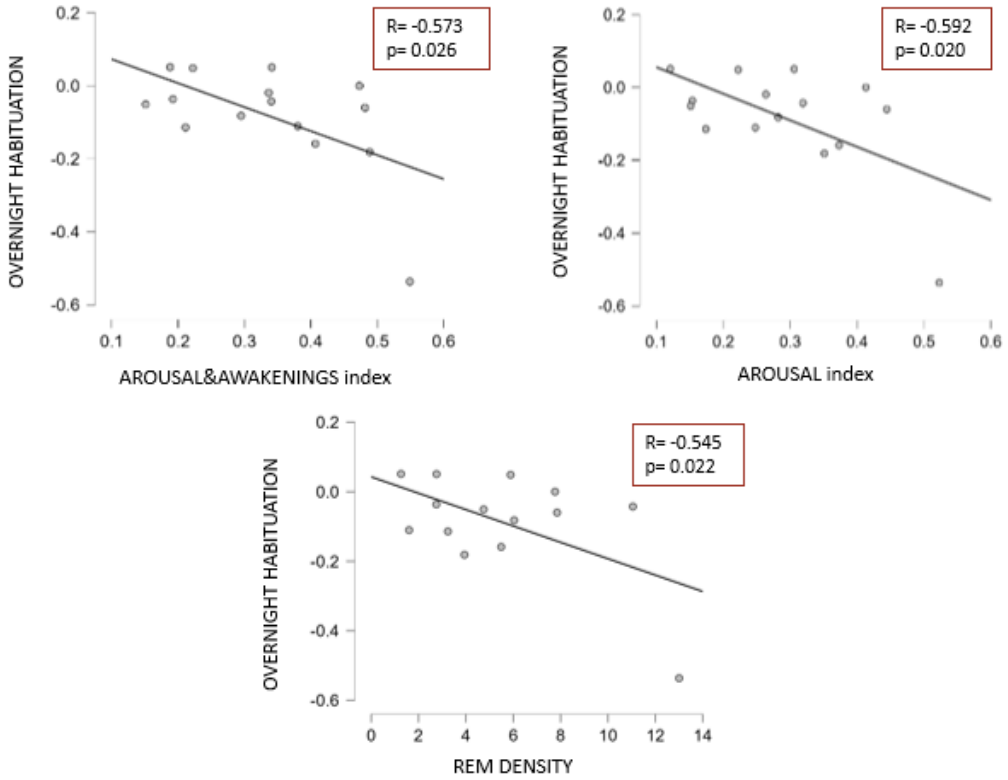


In addition to REM sleep parameters, we also observed a significant positive

correlation between N2 and overnight habituation (r=0.53, p=0.022), while no significant correlation was found between N3 and overnight habituation.

As regards REM microstructure, we found negative correlations between overnight habituation and phasic events occurring in REM sleep, i.e., rem density (r=-0.54, p=0.022), arousal index (r=-0.59, p=0.020), arousals and awakenings index (r=-0.57, p=0.026) (figure 22).

Figure 22. Association between overnight habituation and REM microstructure.



The relationship between emotion dysregulation and phasic events was also confirmed using questionnaires to assess emotional dysregulation, not only relying on the emotion dysregulation index provided by the task. Specifically, we found significant positive correlations between the DERS non acceptance subscale score and REM density (r=0.53, p=0.024), as well as between the DERS strategies subscale score and all REM phasic indices, including REM density (r=0.52, p=0.028), REM arousal index (r=0.55, p=0.017), REM arousals and awakenings index (r=0.48, p=0.034).

5.4. Discussion

Results showed that overnight habituation is modulated by the number of REM arousals and awakenings as well as REM density. REM sleep latency negatively correlated with the overnight habituation. Of note, when considering only the HC group, REM sleep duration positively correlated with the overnight habituation. Our results highlight the role of REM sleep in emotional processing, in line with previous results (Galbiati *et al*, 2020; Wassing *et al*, 2019). Specifically, Wassing and colleagues (Wassing *et al*, 2019), in a sample with a wide range of insomnia symptoms, found that REM sleep duration was positively associated with the overnight amygdala adaptation, while REM interruptions cancelled the beneficial effects of REM duration on the overnight adaptation. This result could potentially explain why we found a significant beneficial effect of REM sleep duration on overnight habituation in the HC group but not when considering both groups together. Indeed, the significantly higher number of phasic events present in REM sleep among our iRBD patients may have obscured the significant correlation between REM sleep duration and overnight habituation. Moreover, the finding on REM sleep latency partially aligns with a previous study of Nishida and colleagues on HCs (Nishida *et al*, 2009). Authors assessed the consolidation of neutral and negative emotional memories through the use of a nap paradigm. In their findings, better was the performance in emotional negative memories, minor was the REM sleep latency. Also, the study of Hutchison and collaborators (Hutchison *et al*, 2021) highlighted the crucial role of REM sleep in the overnight habituation process to negative stimuli. In their study, the authors assessed whether REM or SWS is the sleep stage that allows the decoupling process of the memory contents from their emotional charge. To test this, they applied the TMR paradigm in two conditions: REM (HC n=15) and SWS (HC n=18). TMR in REM but not in SWS contributed to increase overnight habituation to negative emotional stimuli. As in the study just reported, we also did not find a relationship between SWS and overnight habituation, but we found it instead with REM sleep. However, we cannot ignore that we found a positive correlation between N2 and overnight habituation. It is known that N2 includes sleep spindles that play a fundamental role in neural plasticity and in memories consolidation and modulation. Future studies should further investigate the role of N2 in the specific field of emotional memories, with specific analyses on this type of waveforms.

Differences between HC and iRBD groups in terms of task (overnight habituation) were not found, nor were they found in the overnight habituation index provided by the mood questionnaires. However, a tendency was observed in three subscales of the DERS questionnaire: non acceptance, impulsiveness, strategy subscales. The first one indicates difficulty in accepting the negative emotion experienced, the second one relates to controlling impulsive behaviors when experiencing negative emotions, while the last one indicates limited access to emotion regulation strategies that are considered efficient. Although not statistically significant, this last trend is in line with the study of Jun and colleagues (Jun *et al,* 2020). Authors evaluated emotion dysregulation with the use of CERQ, a different measure, but also in this case a significant difference in adaptive strategies subscales between iRBD and HC was found.

The present pilot study has various limitations: along with the small sample size, an objective measure for overnight habituation is missing. Future studies should consider the evaluation of physiological parameters, such as heart rate and skin conductance. Additionally, the beneficial effect of REM sleep duration on the modulation of emotional memories has been found to be more consistent after multiple nights of sleep. Such that, conflicting results have emerged in the literature regarding overnight habituation after the first night of sleep following the emotional event.

Given our interest in RBD, characterized by REM disruptions and the presence of mood alterations, this experiment is grounded in the SFSR hypothesis (van der Helm & Walker, 2010; Walker, 2009) due to the importance attributed to REM sleep in the consolidation and modulation of emotional memories within this hypothesis. Our results highlight the fundamental role of REM sleep in the modulation of emotional memories. These results emerged from correlation analyses between sleep parameters and overnight habituation index, which indicates the distance between the mean score given in the evening for negative images and that given in the morning for negative images. However, in our study, we did not find a statistically significant average decrease from evening to morning in subjective arousal scores for negative images. This latest finding seems to align more with another type of theory. The SFSR is not the only one; alternative, more recent accounts have proposed more integrated and complex views, such as the Emotional Salience Consolidation Account (Baran et al., 2012; Werner et al., 2015; Werner et al., 2021). According to this hypothesis,

emotional experiences are processed and consolidated during sleep through a process that firstly may increases the emotional salience of such experiences. Essentially, this model suggests that during REM sleep, emotional experiences are reactivated and reprocessed, and their emotional salience is increased or at least is not decreased but maintained in the short term. However, in the long term, these emotional experiences are reprocessed and integrated into long-term memory, which may result in a decrease in their emotional salience. This hypothesis may explain the reason for the many conflicting results in the literature regarding the role of REM sleep in the habituation of emotional memories. Future studies that further investigate the role of REM sleep in the short and long term are essential. Therefore, it is crucial to mention, among the limitations, the use of a single experimental night.

Finally, in a future study an experimental manipulation should be considered. The application of TMR paradigm in the iRBD context may lead to results with important clinical implications. A finding regarding the role of TMR on overnight emotional adaptation in iRBD could pave the way for the use of TMR in clinical contexts.

In conclusion, our finding concerning the relationship between REM sleep and emotion regulation in iRBD may provide new insights on the presence of daytime mood impairment in iRBD driven by REM sleep. The potential underlying this finding is that it may break the ground for new clinical research evaluating the effects of pharmacological approaches affecting REM sleep on emotion regulation. Furthermore, the early recognition of mood symptoms in iRBD may guide the choice of specific life planning changes and different therapeutic options to better handle disability, improve quality of life, and decrease caregiver burden.

6. CONCLUSIONS

The overall objective of my PhD work was to profile RBD in terms of their neuropsychological, electrophysiological, and psychophysiological aspects. Meanwhile, in a longitudinal framework, the aim was to evaluate these aspects as biomarkers for a prediction of phenoconversion to synucleinopathies. For this purpose, I divided this work into three parts, each one is research of its own, but they are closely related considering the overall aim. (i) To establish a neuropsychological profile of iRBD and to determine the BL cognitive status associated with the future development of synucleinopathies, I performed a meta-analysis. I included cross-sectional studies reporting neuropsychological testing in HCs and PSG-confirmed RBD patients and longitudinal studies reporting BL neuropsychological testing separately for converted and still isolated patients (chapter 3). (ii) To explore RBD electrophysiological functioning and its role in predicting phenoconversion, I combined BL data from different centers on NREM waveforms, i.e., KCs and SWs, and neuropsychological testing in iRBD, along with FU clinical data about the presence of phenoconversion (chapter 4). (iii) To investigate the psychophysiological profile of iRBD, I assessed the role of REM sleep alterations in RBD emotion dysregulation. Thus, I performed a pilot cross-sectional study evaluating the overnight modulation of emotional reactivity in HCs and RBD patients, then I assessed the association between the overnight modulation of emotional reactivity and REM features (chapter 5). Neuropsychological research identified cognitive screening, memory, and executive functions alterations as the most common in iRBD. Meanwhile, alterations in executive functions at BL, as well as the presence of MCI, were the most capable of predicting future phenoconversion. The main result of the electrophysiological study is that iRBD patients with a reduction in KCs density at BL have a higher risk of conversion at FU. Moreover, this study confirmed an association between KCs and the neuropsychological profile. Finally, the last psychophysiological study concerning the emotional functioning of iRBD patients underlined the crucial role of REM sleep in emotion regulation. Notably, REM sleep phasic events were associated with a reduction in overnight emotional adaptation to negative stimuli. In summary, iRBD patients, years before an overt phenoconversion, often show already NREM sleep physiological alterations, cognitive and emotional deficits. The reported association between cognitive functioning and KC alterations break ground for the research of medications able to

reduce KC alterations and consequently slow down the cognitive decline. In the meantime, it is crucial to intervene also on REM sleep alterations to avoid the escalation of mood symptomatology and the subsequent acceleration of neurodegenerative processes. It is clear that iRBD represents a model, it is a perfect window to study prodromal stages of synucleinopathies. Nevertheless, it is also a complex model with various and heterogenous trajectories over time. iRBD patients may remain still-isolated for years or they may convert to PD or DLB or MSA and other neurodegenerative diseases. Future studies should not only investigate sensitive biomarkers for phenoconversion, but also identify those sensitive biomarkers which are best able to distinguish between the different clinical trajectories of iRBD patients.

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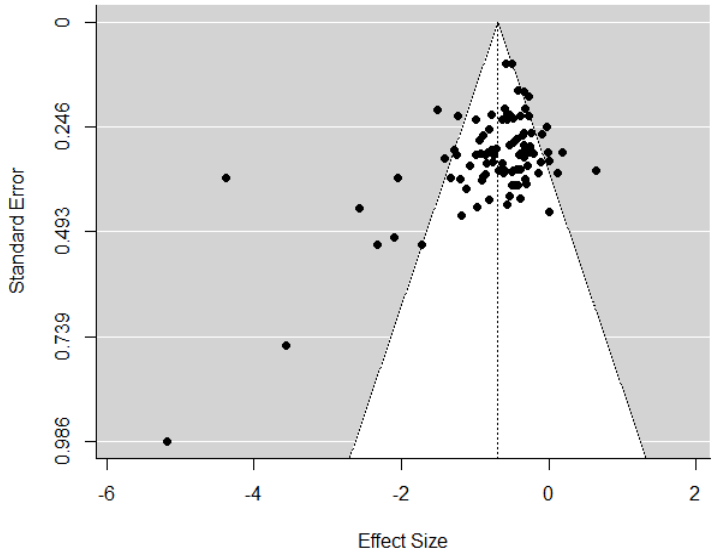
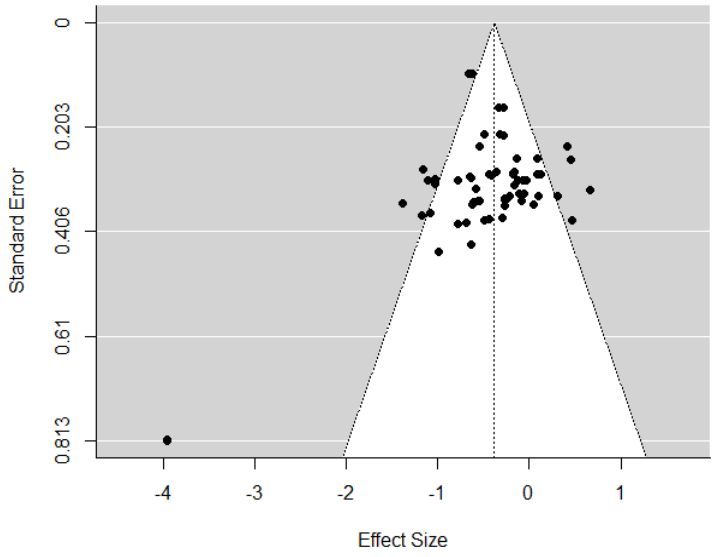
8. APPENDICES

Figure 1 Supplementary Materials. Publication bias assessment by funnel plot for each cognitive domain for both cross-sectional (a-e) and longitudinal studies (f-j).

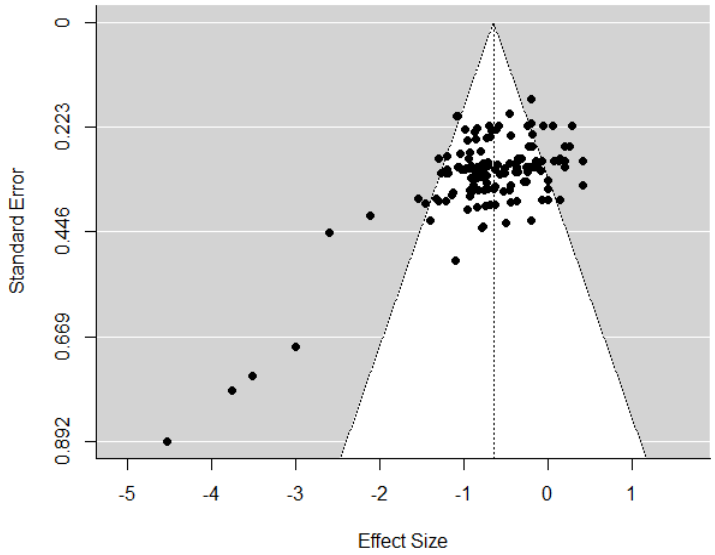
(Supplementary Fig.1a) Cognitive screening, cross-sectional studies.



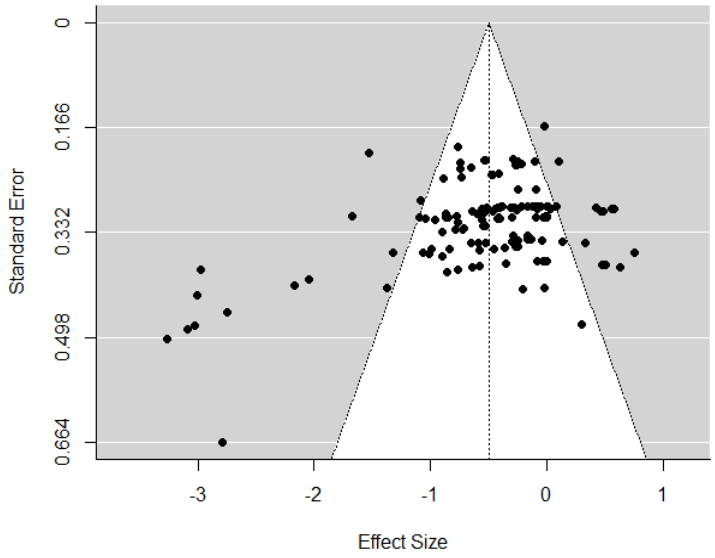
(Supplementary Fig.1b) Language, cross-sectional studies.



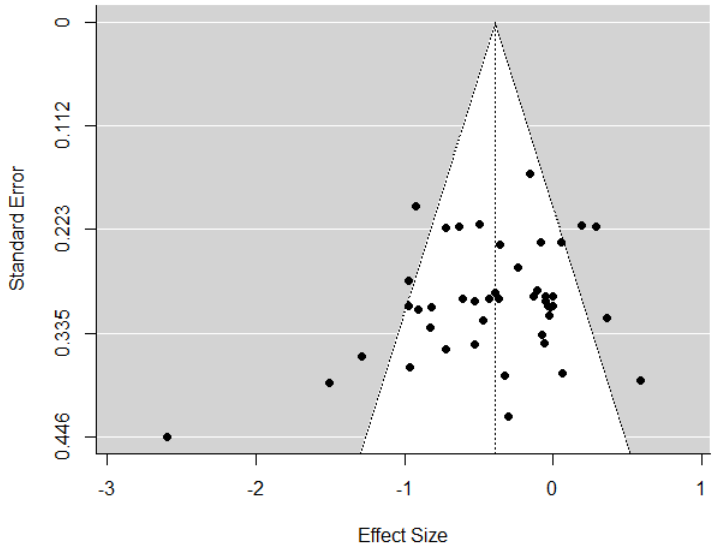
(Supplementary Fig.1c) Memory, cross-sectional studies



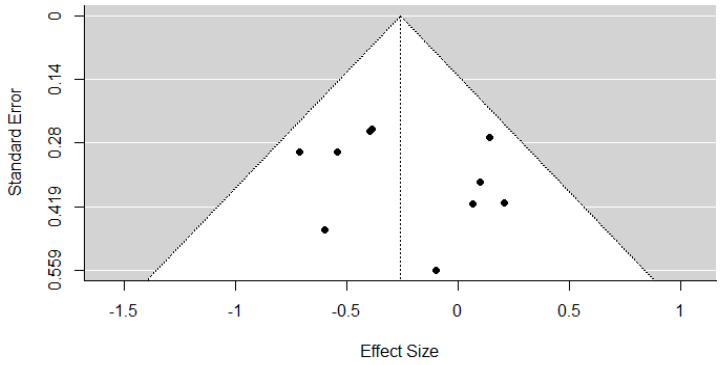
(Supplementary Fig.1d) Executive functions, cross-sectional studies



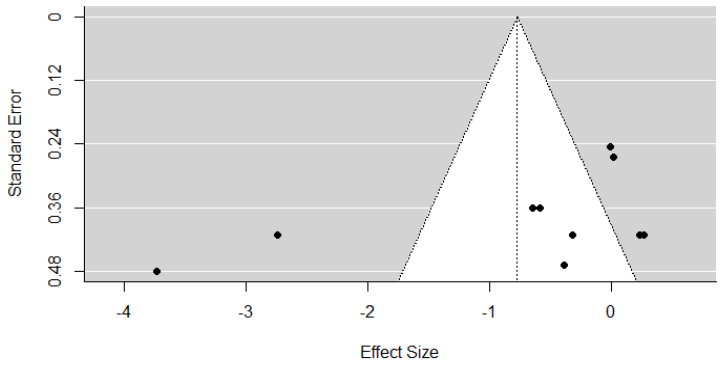
(Supplementary Fig.1e) Visuospatial abilities, cross-sectional studies.



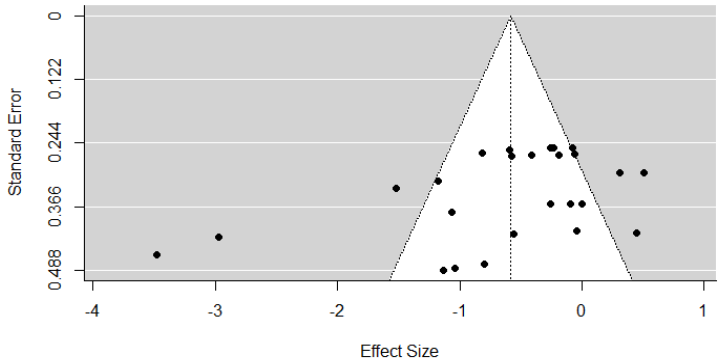
(Supplementary Fig.1f) Cognitive screening, longitudinal studies.



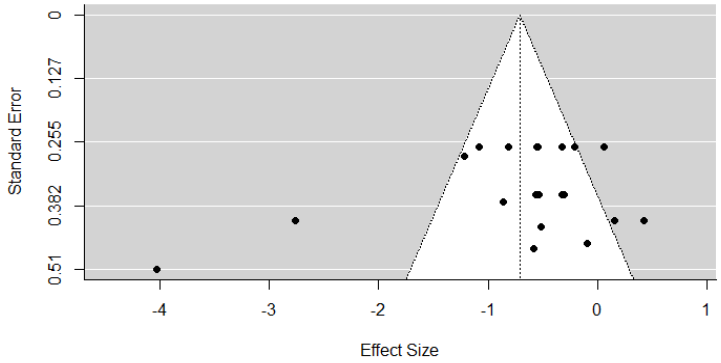
(Supplementary Fig.1g) Language, longitudinal studies.



(Supplementary Fig.1h) Memory, longitudinal studies.



(Supplementary Fig.1i) Executive functions, longitudinal studies.



(Supplementary Fig.1j) Visuospatial abilities, longitudinal studies.

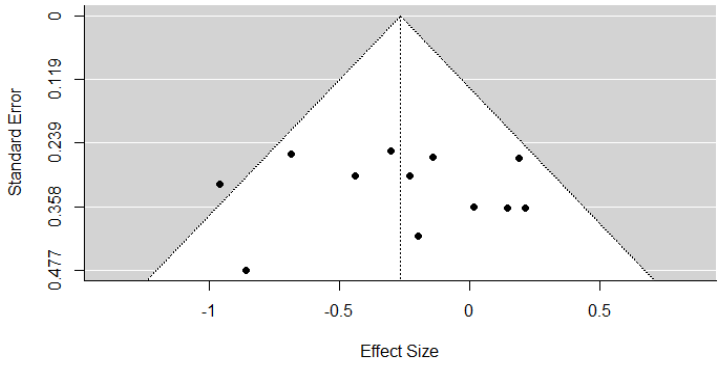


Table 1 Supplementary Materials. The Comparison between Real Data and Simulated Data in each Cognitive Domain: (a) Cognitive Screening, (b) Language, (c) Memory, (d) Executive Function, and (e) Visuospatial Abilities

(Supplementary Tab.1a) Cognitive Screening. Comparison between Real Data and Simulated Data (in descending chronological order)

First Author and Year	Test	N Non-Converted	Non-Converted Real Mean	Non-Converted Real sd	Non-Converted Estimated Mean	Non-Converted Estimated sd	N Converted	Converted Real Mean	Converted Real sd	Converted Estimated Mean	Converted Estimated sd	Real p-value	Estimated p-value
KOGAN et al, 2020	MOCA	16	26.94	1.95	26.21	2.07	4	26.75	1.92	25.56	2.03	0.86	0.58
CAMPABADAL et al., 2020	MMSE	13	27.9	1.7	27.44	1.66	NA	NA	NA	NA	NA	NA	NA
FENG et al., 2020	MOCA	66	24.9	3.3	24.98	3.4	22	23.5	4.5	23.38	3.84	0.25	0.068
MIYAMOTO et al., 2020	MMSE	13	28.2	2.1	27.68	2.25	11	28.6	1.7	29.19	1.35	0.735	0.065
KIM et al., 2020	MMSE	22	26.8	3.1	26.64	2.4	8	27	2.1	27.35	2.16	0.909	0.469
TERZAGHI et al., 2019	MMSE	33	26.66	2.45	26.57	2.59	30	25.62	2.84	26.75	2.37	0.176	0.775
PEREIRA et al., 2019	MOCA	21	25.9	4	25.78	3.94	6	23.2	6.1	26.06	6.13	0.422	0.893
NOPOZITEK et al., 2019	MOCA	46	24	3	23.7	3.02	9	24.3	2.6	23.6	3.54	0.749	0.93
MARCHAND et al., 2018	MOCA	26	25.75	2.86	24.79	2.54	21	24.36	2.12	24.59	2	0.071	0.77
MARCHAND et al., 2018	MMSE	26	28.7	1.29	28.77	1.28	21	27.72	1.48	27.71	0.93	0.019	0.003
YOUN et al., 2016	MMSE	66	26.17	NA	26.12	0.99	18	25.61	NA	25.9	1.04	0.601	0.411

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

(Supplementary Tab.1b) Language Domain Comparison between Real Data and Simulated Data (in descending chronological order)

Study	Test	N Non-Converted	Non-Converted Real Mean	Non-Converted Real sd	Non-Converted Estimated Mean	Non-Converted Estimated sd	N Converted	Converted Real Mean	Converted Real sd	Converted Estimated Mean	Converted Estimated sd	Real p-value	Estimated p-value
ARNALDI et al., 2021	SEM VF	34	40	9.42	42.43	11.41	10	34.33	9.95	36.69	7.75	0.106	0.144
ARNALDI et al., 2021	PH VF	34	32.26	10.94	31.43	9.94	10	25.38	8.83	27.29	10.62	0.076	0.261
CAMPABADAL et al., 2020	SEM VF	13	15	5.1	15.44	3.97	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	PH VF	13	12.9	5.7	14.07	4.22	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	BNT	13	13.2	0.9	13.57	0.72	0	NA	NA	NA	NA	NA	NA
KIM et al., 2020	BNT	22	-0.05	1.19	-0.24	1.18	8	0.22	1.14	-0.34	0.8	0.518	0.827
KIM et al., 2020	SEM COWAT	22	-0.36	0.99	-0.18	0.84	8	-0.08	1.1	-0.64	0.68	0.153	0.176
KIM et al., 2020	PH COWAT	22	-0.62	1.02	-0.35	1.18	8	-0.93	0.82	-0.86	0.85	0.566	0.274
TERZAGHI et al., 2019	SEM VF	33	26.43	15.62	26.26	14.33	30	26.33	16.38	21.27	15.54	0.98	0.19
PEREIRA et al., 2019	SEM VF	21	45.1	9.4	44.88	8.96	6	41.5	8.6	43.18	10.94	0.429	0.699
MARCHAND et al., 2018	SEM VF	26	-0.75	0.12	-0.86	0.13	21	-1.47	0,21	-1,43	0.18	0	0
MARCHAND et al., 2018	PH VF	26	-38	0.15	-0.3	0.16	21	-0.96	0.27	-1	0.32	0	0
YOUN et al., 2016	SEM VF	66	29.52	NA	29.52	1.06	18	28.94	NA	29.09	0.98	0.954	0.125

BNT: Boston Naming Test; COWAT: Controlled Oral Word Association Test; PH VF: Phonemic Verbal Fluency; SEM VF: Semantic Verbal Fluency.

(Supplementary Tab.1c) Memory Domain Comparison between Real Data and Simulated Data (in descending chronological order)

Study	Test	N Non-Converted	Non-Converted Real Mean	Non-Converted Real sd	Non-Converted Estimated Mean	Non-Converted Estimated sd	N Converted	Converted Real Mean	Converted Real sd	Converted Estimated Mean	Converted Estimated sd	Real p-value	Estimated p-value
ARNALDI et al., 2021	RAVLT IMM RECALL	34	34.88	9.05	36.77	7.04	10	32.4	10.97	31.66	12.53	0.47	0.1
ARNALDI et al., 2021	RAVLT DEL RECALL	34	7	2.68	6.35	2.43	10	6.7	4.19	6.25	2.89	0.79	0.91
ARNALDI et al., 2021	DGS-F	34	5.56	1.05	5.42	1.16	10	5.56	0.73	6.14	0.64	1	0.07
ARNALDI et al., 2021	CORSI SPAN	34	4.94	1.07	5.31	1.24	10	3.89	0.6	4.37	0.59	0.01	0.03
CAMPABADAL et al., 2020	RAVLT SUM 1-5	13	39.8	7.2	38.24	6.34	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	DGS-F	13	5.3	1.8	5.63	1.15	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	DGS-B	13	4.2	0.9	4.06	1.29	0	NA	NA	NA	NA	NA	NA
KIM et al., 2020	SVLT IMM RECALL	22	-0.26	1.05	-0.3	0.87	8	-0.3	0.79	-0.4	0.72	0.98	0.77
KIM et al., 2020	SVLT DEL RECALL	22	-0.83	1.11	-0.81	1	8	-0.33	1.13	-0.34	0.87	0.26	0.25
KIM et al., 2020	SVLT RECOG	22	-0.38	1.15	-0.06	1.2	8	0.21	0.66	0.42	0.7	0.28	0.3
TERZAGHI et al., 2019	DGS-F	33	4.65	0.62	4.6	0.52	30	4.51	0.56	4.56	0.57	0.35	0.77
TERZAGHI et al., 2019	CORSI SPAN	33	4.35	0.69	4.38	0.64	30	4.19	0.68	4.21	0.57	0.36	0.27
TERZAGHI et al., 2019	ROCF DEL RECALL	33	13.71	6.82	12.19	5.92	30	12	6.17	12.05	4.64	0.3	0.92
TERZAGHI et al., 2019	LOGICAL MEMORY TOT	33	10.83	4.22	11.23	4.05	30	9.81	4.13	10.17	4.26	0.34	0.32
TERZAGHI et al., 2019	REY 15 WT IMM RECALL	33	40.36	7.85	40.81	8.46	30	33.98	7.84	33.19	8.82	0	0
TERZAGHI et al., 2019	REY 15 WT DEL RECALL	33	8.17	2.95	9.01	3.05	30	6.33	3.28	5.34	3.29	0.02	0
TERZAGHI et al., 2019	WORD SPAN	33	3.87	0.61	3.93	0.61	30	3.82	0.69	3.71	0.73	0.76	0.2
PEREIRA et al., 2019	HVLT IMM RECALL	21	21.9	5.1	22.96	5.33	6	16.3	4.3	17.56	3.79	0.03	0.03
PEREIRA et al., 2019	HVLT DEL RECALL	21	7.3	2.6	8	2.73	6	5	3.8	5.05	4.69	0.06	0.06
PEREIRA et al., 2019	HVLT RECOG	21	10.7	1.3	10.7	1.42	6	9.3	1.5	8.66	1.37	0.04	0
MARCHAND et al., 2018	RAVLT SUM 1-5	26	0.13	0.22	0.14	0.25	21	-0.33	0.38	-0.25	0.43	0	0
MARCHAND et al., 2018	RAVLT_LISTB	26	-0.71	0.21	-0.68	0.15	21	-0.57	0.34	-0.56	0.34	0.09	0.11
MARCHAND et al., 2018	RAVLT IMM RECALL	26	0.01	0.18	0	0.16	21	-0.81	0.29	0.73	0.34	0	0
MARCHAND et al., 2018	RAVLT DEL RECALL	26	0.18	0.19	0.17	0.17	21	-0.58	0.32	-0.64	0.39	0	0
MARCHAND et al., 2018	RAVLT RECOG	26	0.07	0.21	0.1	0.2	21	-0.25	0.33	-0.12	0.29	0	0
MARCHAND et al., 2018	DGS-F	26	-0.27	0.14	-0.26	0.17	21	-0.21	0.24	-0.07	0.25	0.03	0
YOUN et al., 2016	DGS-F	66	6.48	NA	6.54	1.21	18	6.22	NA	6.49	1.02	0.84	0.87
YOUN et al., 2016	DGS-B	66	4.4	NA	4.44	0.96	18	3.83	NA	4.11	1.26	0.13	0.23
YOUN et al., 2016	WLR	66	6.06	NA	6.08	1.08	18	5.06	NA	4.8	0.99	0.04	0
YOUN et al., 2016	CPR	66	7.6	NA	7.34	0.99	18	6.72	NA	6.97	0.85	0.49	0.15

CPR: Constructional Praxis Recall; DEL: delayed; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; HVLT: Hopkins Verbal Learning Test; RAVLT: Rey Auditory Verbal Learning Test; RECOG: recognition; ROCF: Rey Complex Figure; SVLT: Shiraz Verbal Learning Test; WLR: Word List Recall; WT: Word test.

(Supplementary Tab.1d) Executive Functions Comparison between Real Data and Simulated Data (in descending chronological order)

Study	Test	N Non-Converted	Non-Converted Real Mean	Non-Converted Real sd	Non-Converted Estimated Mean	Non-Converted Estimated sd	N Converted	Converted Real Mean	Converted Real sd	Converted Estimated Mean	Converted Estimated sd	Real p-value	Estimated p-value
ARNALDI et al., 2021	SCWT B	34	40.91	10.17	39.76	9.06	10	34.7	13.99	40.46	16.05	0.13	0.86
ARNALDI et al., 2021	SCWT C	34	16.48	7.3	14.79	6.79	10	14.2	9.04	15.02	9.53	0.42	0.93
ARNALDI et al., 2021	SDMT	34	30.53	12.98	32.34	12.41	10	26.4	13.39	25.93	14.97	0.38	0.18
ARNALDI et al., 2021	TMT A	34	60.29	21.92	66.06	21	10	73.6	35.17	75.97	37.26	0.15	0.28
ARNALDI et al., 2021	TMT B	34	159.68	107.44	174.83	96.48	10	263.4	160.06	263.5	94.74	0.02	0.01
CAMPABADAL et al., 2020	SCWT A	13	84.6	17.6	82.69	22.01	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	SCWT B	13	54.7	12	44.92	8.23	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	SCWT C	13	30	11.3	31.79	12.78	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	SDMT	13	35.5	12.6	41.44	13.23	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	TMT A	13	52.6	14.1	49.64	15.12	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	TMT B	13	161.3	76.6	155.18	85.28	0	NA	NA	NA	NA	NA	NA
KIM et al., 2020	SCWT B	22	-0.93	1.06	-0.55	0.99	8	0.76	1.02	-0.52	0.84	0.44	0.94
KIM et al., 2020	TMT A	22	-0.64	1.09	-0.54	1.48	8	-0.18	1.02	-0.74	1.29	0.17	0.74
KIM et al., 2020	TMT B	22	-0.83	1.64	-1.3	1.87	8	-1.88	2.84	-2.11	2.14	0.35	0.32
TERZAGHI et al., 2019	AM	33	48.25	6.99	46.36	7.78	30	44.09	8.29	39.23	11.25	0.03	0
TERZAGHI et al., 2019	FAB	33	16.86	1.37	16.83	1.39	30	13.73	3.42	14.09	2.84	0	0
TERZAGHI et al., 2019	PCM	33	26.35	4.07	27	4.86	30	23.76	5.28	23.28	4.75	0.03	0
TERZAGHI et al., 2019	WS	33	10.11	3.36	10.38	3.86	30	6.69	2.92	6.99	2.98	0	0
PEREIRA et al., 2019	LNST	21	9	3.3	8.97	4.03	6	7.2	2.1	7.42	2.2	0.7	0.38
PEREIRA et al., 2019	SDMT	21	31.2	10	31.39	9.47	6	32	6.1	36.51	3.88	0.8	0.21
MARCHAND et al., 2018	TMT A	26	-0.44	0.28	-0.5	0.33	21	-1.98	0.48	-2	0.38	0	0
MARCHAND et al., 2018	TMT B	26	-0.95	0.53	-0.99	0.58	21	-2.87	0.86	-2.62	0.7	0	0
YOUN et al., 2016	FAB	66	15.59	NA	15.55	1.02	18	15.44	NA	15.39	0.8	0.81	0.54
YOUN et al., 2016	SCWT	66	38.77	NA	38.87	0.93	18	41.06	NA	41.23	0.72	0.45	0
YOUN et al., 2016	TMT A	66	57.16	NA	57.27	1.1	18	84.28	NA	84.4	0.71	0	0
YOUN et al., 2016	TMT B	66	160.05	NA	159.97	0.95	18	204.17	NA	204.81	1.16	0.24	0

AM: Attentive Matrices; FAB: Frontal Assessment Battery; LNST: Letter-Number Sequencing Test; PCM: Raven's Coloured Matrices; SCWT: Stroop Color Word Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WS: Weigi's Sorting Test.

(Supplementary Tab.1e) Visuospatial Abilities Comparison between Real Data and Simulated Data (in descending chronological order)

Study	Test	N Non-Converted	Non-Converted Real Mean	Non-Converted Real sd	Non-Converted Estimated Mean	Non-Converted Estimated sd	N Converted	Converted Real Mean	Converted Real sd	Converted Estimated Mean	Converted Estimated sd	Real p-value	Estimated p-value
ARNALDI et al., 2021	CLOCK	34	13.06	2.9	12.58	2.89	10	13.7	3.47	12.11	2.7	0.56	0.65
ARNALDI et al., 2021	PRAXIA	34	8.97	1.99	8.57	1.6	10	9	1.05	9.46	1.31	0.96	0.12
ARNALDI et al., 2021	PRAXIA guiding	34	66.09	5.95	65.72	5.31	10	66.9	4.2	68.19	7.63	0.4	0.25
CAMPABADAL et al., 2020	BJLO	13	22.4	4.9	23.93	5.3	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	VFD	13	29.3	2.8	29.27	2.27	0	NA	NA	NA	NA	NA	NA
CAMPABADAL et al., 2020	FRT	13	21.4	2.4	21.35	2.83	0	NA	NA	NA	NA	NA	NA
KIM et al., 2020	ROCF	22	-1.86	1.75	-2.54	2.05	8	-1.53	1.41	-1.38	0.95	0.8	0.14
TERZAGHI et al., 2019	ROCF	33	33.03	6.32	32.4	6.15	30	31.21	5.69	31.21	5.68	0.24	0.43
TERZAGHI et al., 2019	PRAXIA	33	13.26	1.4	13.51	1.83	30	12.06	2.07	11.87	1.76	0.01	0
PEREIRA et al., 2019	BJLO	21	11.8	1.7	11.58	1.77	6	10.2	2.4	10.9	1.81	0.08	0.42
MARCHAND et al., 2018	BELLS	26	-0.09	0.19	-0.05	0.15	21	0.02	0.31	-0.02	0.42	0.31	0.74
MARCHAND et al., 2018	BLOCKD	26	0.18	0.15	0.2	0.16	21	-0.03	0.28	0	0.3	0	0.01
MARCHAND et al., 2018	ROCF	26	-0.02	0.2	0	0.24	21	-0.08	0.33	-0.1	0.29	0.45	0.2
YOUN et al., 2016	CLOCK	66	14.48	NA	14.58	0.97	18	14.5	NA	14.36	0.95	0.49	0.39
YOUN et al., 2016	PRAXIA	66	10.29	NA	10.42	1	18	10	NA	10.28	0.92	0.61	0.59

BJLO: Benton Judgment of Line Orientation; BLOCKD: Block Design; FRT: Facial Recognition Test; ROCF: Rey Complex Figure Copy; VFD: Visual Form Discrimination.

Table 2 Supplementary Materials. Tests used for the modified cognitive domains for cross-sectional studies (A: language, B: executive functions) and for longitudinal studies (C: language, D: executive functions) (in descending chronological order)

(Supplementary Tab.2A) Modified language domain (cross-sectional studies)

Byun et al. 2020	Sem VF, BNT
Ehgoetz Martens et al., 2020	Sem VF, BNT
Kim et al. 2020	BNT
Ehgoetz Martens et al., 2019	Sem VF, BNT
Her et al. 2019	Sem VF; BNT; naming, language (MOCA)
Shin et al. 2019	Sem COWAT
Lee et al. 2019	BNT; sem COWAT
Campabadal et al. 2019	Sem VF; BNT
Zhang et al. 2019	Sem VF; BNT
Sunwoo et al. 2019	Sem VF; BNT
Pereira et al. 2019	Sem VF
Li et al. 2018a	Sem VF; BNT
Li et al. 2018b	Sem VF; BNT
Byun et al. 2017	Sem VF; BNT; naming, language (MOCA)
Barber et al. 2017	Sem VF
Sasai-Sakuma et al. 2017	Sem VF
Sasai-Sakuma et al. 2017	Language (ACE-R)
Bang et al. 2017	Sem VF
Li et al. 2016	Sem VF; BNT
Rolinski et al. 2016b	Sem VF
Zhang et al. 2016	Sem VF
Plomhause et al. 2014	Lexis picture naming test
Terzaghi et al. 2013	Sem VF
Vendette et al. 2012	Sem VF
Fantini et al. 2011	Sem VF
Marques et al. 2010	Sem VF
Gagnon et al. 2009	Sem VF
Massicotte-Marquez et al. 2008	Sem VF; similarity subtest (WAIS-III)
Terzaghi et al. 2008	Sem VF

BNT: Boston Naming Test; sem COWAT: semantic Controlled Oral Word Association Test; sem VF: semantic Verbal Fluency.

(Supplementary Tab.2B) Modified executive functions domain (cross-sectional studies)

Byun et al. 2020	TMT A; TMT B; attention, initiation, conceptualization (MDRS)
Ehgoetz Martens et al. 2020	TMT A; TMT B; ph VF
Kim et al. 2020	TMT A; TMT B; ph COWAT
Her et al. 2019	TMT A; TMT B; attention, executive, abstraction (MOCA)
Mollenhauer et al. 2019	SDMT; LNS
Shin et al. 2019	TMT A; TMT B; ph COWAT
Ehgoetz Martens et al. 2019	TMT A; TMT B; ph VF
Lee et al. 2019	TMT A; TMT B; ph COWAT
Campabadal et al. 2019	SCWT A, B, C; TMT A; TMT B; SDMT; ph VF
Zhang et al. 2019	SCWT A, B, C, interference effect; TMT-A; TMT-B; SDMT
Sunwoo et al. 2019	TMT A; TMT B
Pereira et al. 2019	SDMT; LNS
Marcone et al. 2018	Executive functioning
Li et al. 2018a	TMT-A; TMT-B; SCWT A, C; SDMT (WAIS-RC)
Li et al. 2018b	TMT-A; TMT-B; SCWT A, C; SDMT (WAIS-RC)
Bezdicek et al. 2018	TMT A; TMT B; LNS; SCWT interference condition
Byun et al. 2017	Attention, visuospatial/executive, abstraction (MOCA); TMT-A, TMT-B
Sasai-Sakuma et al. 2017	Attention (ACE-R)
Barber et al. 2017	Ph VF
Bang et al. 2017	TMT A; TMT B; FAB; SCWT
Li et al. 2016	SCWT A, C, TMT-A; TMT-B; SDMT
Zhang et al. 2016	TMT A; TMT B; SCWT; SDMT
Rolinski et al., 2016b	Ph VF
Terzaghi et al. 2013	AM; CPM; WCST; ph VF
Delazer et al. 2012	IGT, IST, IED, OTS, Go-NoGo Task
Sasai et al. 2012	IGT

Vendette et al. 2012	SCWT C; TMT-B; ph VF
Fantini et al. 2011	AM; CPM; SCWT interference Test; TMT A; TMT B; TMT B/A; ph VF
Marques et al. 2010	SCWT; SDMT; ph VF
Gagnon et al. 2009	SCWT; TMT B; ph VF
Massicotte-Marquez et al. 2008	TMT A; TMT B; SCWT Interference condition, flexibility condition; DSMT; ph VF
Terzaghi et al. 2008	AM; CPM; WCST; ph VF
Raggi et al. 2007	AM
Ferini-Strambi et al. 2004	AM; SCWT interference condition; CPM; TMT A; TMT B; ph VF

ACE-R: Addenbrooke Cognitive Examination-Revised; AM: Attentive Matrices; CPM: Raven's Coloured Matrices; FAB: Frontal Assessment Battery; IED: Intra/Extra Dimensional Shift; IGT: Iowa Gambling Task; IST: Information Sampling Task; LNS: Letter-Number Sequencing test; MDRS: Mattis Dementia Rating Scale; OTS: One Touch Stockings of Cambridge; ph COWAT: phonemic Controlled Oral Word Association Test; ph VF: phonemic Verbal Fluency; SCWT: Stroop Color Word Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WCST: Wisconsin Card Sorting Test; WS: Weigi's Sorting Test.

(Supplementary Tab.2C) Modified language domain (longitudinal studies)

Arnaldi et a., 2021	Sem VF
Kim et al., 2020	Sem COWAT; BNT
Terzaghi et al., 2019	Sem VF
Pereira et al., 2019	Sem VF
Marchand et al., 2018	Sem VF
Youn et al., 2016	Sem VF

Sem VF: semantic Verbal Fluency; BNT: Boston Naming Test; sem COWAT: semantic Controlled Oral Word Association Test.

(Supplementary Tab.2D) Modified executive functions domain (longitudinal studies)

Arnaldi et al., 2021	SCWT; TMT A; TMT B; SDMT; ph VF
Kim et al., 2020	TMT A; TMT B; SCWT; ph COWAT
Terzaghi et al., 2019	AM; WS; FAB; CPM
Pereira et al., 2019	SDMT; LNS
Marchand et al., 2018	TMT A; TMT B; ph VF
Youn et al., 2016	TMT A; TMT B; FAB; SCWT

AM: Attentive Matrices; CPM: Raven's Coloured Matrices; FAB: Frontal Assessment Battery; LNS: Letter-Number Sequencing test; ph COWAT: phonemic Controlled Oral Word Association Test; ph VF: phonemic Verbal Fluency; SCWT: Stroop Color Word Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WS: Weigi's Sorting Test.