Isolated REM Sleep Behavior Disorder: Cognitive, Psychiatric, and Genetic Predictors of Phenoconversion

Lucy Honeycutt

Integrated Program in Neuroscience

McGill University

Montreal, Quebec

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Abstract

REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of muscle atonia during REM sleep. It has been shown to be a part of the prodromal stage of neurodegenerative diseases such as Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB), that is, a stage that precedes the onset of motor symptoms. As such, it is of interest to study other aspects of the disease that may occur before motor symptoms and to track how these disease aspects change over time and as a result of phenoconversion. As part of this thesis, we focused on three main aspects of RBD in a longitudinal cohort: genetic mutations, cognition, and depression and anxiety. Each of these disease aspects was assessed at baseline and at phenoconversion in order to look for potential disease predictors and to see how disease presentation changes over time. In Chapter 1, we found that *GBA* mutations are associated with 3.3-fold higher phenoconversion rate to parkinsonism and dementia but did not represent a distinct clinical subtype at baseline or at time of phenoconversion. Chapter 2 focuses on cognition in RBD and demonstrates that patients with RBD make false noise errors on the pareidolia test and that these errors are associated with poorer overall cognition, attention/executive function, memory, and visuospatial function, and may be associated with higher phenoconversion to DLB. Finally, in Chapter 3 we found that RBD patients have worse baseline depression and anxiety symptoms as measured by the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) in terms of overall scores, individual scores, and SPSS-derived factor scores. Total BAI but not BDI scores change over time but neither predict rate of phenoconversion. SPSS-derived factor scores show subtle differences, though this assessment may be limited by small sample size. Taken together, these results demonstrate that using a longitudinal cohort of RBD patients is effective in order to compare various aspects of the

disease over time, and that viewing the progression of these disease aspects may provide insight to potential predictors of neurodegenerative disease.

Résumé

Le trouble comportemental du sommeil paradoxal (TCSP) est une parasomnie caractérisée par une perte d'atonie musculaire pendant le stade de sommeil paradoxal. Il a été démontré que le TCSP fait partie de la phase prodromale des maladies neurodégénératives, tel que la maladie de Parkinson (MP) et la démence à corps Lewy (DCL) ; cette phase précède l'apparition de symptômes moteurs. Donc, il est d'intérêt d'étudier d'autres aspects de la trouble du sommeil pouvant survenir avant des symptômes moteurs et de suivre l'évolution de ceux-ci au fil du temps et en fonction de la phénoconversion. Pour cette thèse, nous nous sommes concentrés sur trois aspects centraux du TCSP dans une cohorte longitudinale: les mutations génétiques, la cognition, et la dépression et l'anxiété. Chaque aspect du TCSP a été évaluée lors de l'évaluation initiale et au moment de la phénoconversion afin de rechercher des prédicteurs potentiels des maladies neurodégénératives et d'observer la présentation du TCSP au fil du temps. Dans le premier chapitre, nous avons constaté que les mutations *GBA* sont associées à un taux de phénoconversion 3,3 fois plus élevé pour le parkinsonisme et la démence, mais ne représentaient pas un sous-type clinique distinct, ni initialement, ni au moment de la phénoconversion. Le deuxième chapitre porte sur la cognition dans le TCSP et démontre que les patients atteints de TCSP font des erreurs sur le test de paréidolie et que ces erreurs sont associées à une pire cognition globale, une pire attention ou fonction exécutive, une pire mémoire et une fonction visio-spatiale plus faible, et peuvent être associées à une phénoconversion plus élevée à la DCL. Enfin, au troisième chapitre, nous avons constaté que les patients TCSP présentent lors de l'évaluation clinique initiale des symptômes de dépression et d'anxiété plus graves, mesurés par l'Inventaire de dépression de Beck (IDB) et l'Inventaire d'anxiété de Beck (IAB) en terme de scores globaux, de scores individuels et de scores factoriels

dérivés par SPSS. Les scores IAB varient avec le temps mais ne prédisent pas la phénoconversion. Les scores IDB ne varient pas avec le temps ou en raison de la phénoconversion. Des changements subtils dans les scores factoriels ont été observés au fil du temps. La subtilité des changements dans les scores factoriels peut être expliquée par la petite taille de l'échantillon. Ensemble, ces résultats démontrent que l'utilisation d'une cohorte longitudinale de patients atteints de TCSP est efficace pour comparer divers aspects de ce trouble du sommeil au fil du temps, et que la visualisation de la progression de ces aspects du TCSP peut fournir un aperçu des prédicteurs potentiels de maladies neurodégénératives.

Contribution of Authors

Chapter 1: Glucocerebrosidase mutations and phenoconversion of REM sleep behavior disorder to parkinsonism and dementia

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Authors: [1]Lucy Honeycutt, [2,3]Jacques Y Montplaisir MD, PhD, [2,4]Jean-François Gagnon PhD, [7]Jennifer Ruskey, [2,5]Amélie Pelletier PhD, [6,7]Ziv Gan-Or MD, PhD*, [1,2,5]Ronald B. Postuma MD, MSc*

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada, [2]Centre d'études avancées en médecine du sommeil, CIUSSS-NÎM-Hôpital du Sacré-Cœur de Montréal, Montreal, Canada, [3]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada, [4]Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada, [5]Department of Neurology, The Research Institute of the McGill University Health Centre, Montreal, Canada,[6]Department of Human Genetics, McGill University, Montreal, Canada,[7]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Canada

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Authors: [1]Lucy Honeycutt, [2,3]Jean-François Gagnon PhD, [2,4]Amélie Pelletier PhD, [2,3]Jessie De Roy, [2,5]Jacques Y Montplaisir MD, PhD, [1,2,4]Ronald B. Postuma MD, MSc*

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada, [2]Centre d'Études Avancées en Médecine du Sommeil, CIUSSS-NÎM-Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada, [3]Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada, [4]Department of Neurology, The Research Institute of the McGill University Health Centre, Montreal, Canada, [5]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada

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Authors: [1]Lucy Honeycutt, [2,3]Jean-François Gagnon PhD, [2,4]Amélie Pelletier PhD, [2,5]Jacques Y Montplaisir MD, PhD, [1,2,4]Ronald B. Postuma MD, MSc*

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada, [2]Centre d'Études Avancées en Médecine du Sommeil, CIUSSS-NÎM-Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada, [3]Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada, [4]Department of Neurology, The Research Institute of the McGill University Health Centre, Montreal, Canada,[5]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada

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Introduction

REM sleep behavior disorder (RBD) is a parasomnia that has become well recognized as a precursor to neurodegenerative disease, such as Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB). However, research is still ongoing to understand differences in clinical presentation in patients with RBD. For example, it is of interest to understand how genetic mutations may affect clinical presentation and disease progression or how cognitive symptoms may vary in the population of patients with RBD.

For disorders such as RBD that can progress to other conditions, in this case, neurodegenerative disease, it is important to understand how symptoms and clinical presentation change over time. One way of doing this is to study the same cohort of patients throughout their disease. The particular RBD cohort we use in this thesis has been followed up with yearly for many years; though new patients are continually enrolled, some of the original patients have had as many as 15 years of follow-up.

We hypothesize that by using the data obtained from this cohort over the past 15 years, we will be able to identify key differences between RBD patients and controls in multiple areas of interest. Furthermore, we will be able to track patient progression over time; we can compare how symptoms and clinical presentation have changed from a patient's first visit to their last, with particular interest in the effect of phenoconversion to parkinsonism and dementia.

There are three specific aims to this thesis. First, we will investigate how mutations in the glucocerebrosidase (*GBA*) gene affect clinical presentation, both at baseline and at time of phenoconversion, and how *GBA* mutations influence disease progression. Next, we want to gain insight on the cognitive changes that can occur in patients with RBD. We will correlate false noise errors on the pareidolia test with results of neuropsychological tests and clinical measures.

We will also attempt to determine the association, if any, between false noise errors and phenoconversion to parkinsonism and dementia. Finally, we will try to construct a profile of a depression and anxiety in patients with RBD. We will attempt to stratify global depression and anxiety into distinct factors and determine whether these factors can be used to compare RBD patients to controls and track progression over time.

Literature Review

Overview

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that affects approximately 1% of the population over the age of 60, though it can affect younger patients [1]. It is primarily a movement disorder but features both motor and non-motor symptoms. While the exact mechanism of degeneration is unknown, research has shown that PD is associated with severe dopaminergic cell loss, primarily in the substantia nigra [2]. Furthermore, studies of have linked PD pathology to an accumulation of α-synuclein, a protein normally found in the body that can misfold and aggregate in PD [3]. As such, PD is considered a synucleinopathy. It is closely linked to Dementia with Lewy Bodies (DLB), another synucleinopathy. DLB can present similarly to PD but is distinct in that it is defined by cognitive rather than motor symptoms. Many patients with DLB can eventually develop PD, but parkinsonism is not required for diagnosis [4].

There are three cardinal motor symptoms of PD: bradykinesia (slowness of movement), rest tremor, and rigidity. In addition, patients can develop multiple other motor symptoms including postural instability, gait freezing, swallowing deficits, drooling, and speech difficulties [5].

Non-motor symptoms are common in PD and are particularly of interest when studying prodromal patients who have not yet begun to show motor symptoms in the clinic; pre-motor symptoms can predate the onset of neurodegenerative disease by many years [6]. Non-motor symptoms can include sleep disturbances (i.e. REM Sleep Behavior Disorder [RBD]), autonomic dysfunction, hyposmia, and mood disorders (such as anxiety and depression) [7]. A major risk factor for disease onset is the presence of genetic mutations. As the onset of neurodegenerative

disease progresses, cognitive changes may occur. Here we focus on three intersectional issues in RBD: genetic mutations, cognition, and mood disturbances in order to further our understanding of the disease.

REM Sleep Behavior Disorder

RBD is a parasomnia characterized by loss of muscle atonia during REM sleep, with patients often violently acting out their dreams [8]. Most patients in sleep clinics are men (although population-based studies suggest only modest sex differences) and the onset of symptoms can begin at any age, though typically falls between 40-70 years of age [9]. RBD is diagnosed clinically through polysomnography (PSG) to confirm the presence of REM sleep without atonia (RSWA) and abnormal motor behavior [10]. Furthermore, the International Classification of Sleep Disorders-II states that in order for a diagnosis of RBD to be made, one requires also an absence of epileptiform activity on EEG and an assessment that the RBD symptoms are not a result of another sleep, neurological, or mental disorder or a result of medication or substance use [11]. While the exact pathophysiology of RBD is unknown, animal studies have led to a proposed human pathophysiology in which RBD results from decreased inhibition of the spinal motor neurons and interneurons that typically provide tonicity during REM sleep; thus, these motor neurons and interneurons are not inhibited, and one is able to move during REM sleep [10].

RBD is common in patients with PD, with a prevalence between 33-46% [12]. RBD has also been demonstrated to be part of the prodromal stage of parkinsonism and dementia, that is, a stage of neurodegeneration that can precede the onset of clinical motor symptoms by many years [13]; as many as 80% of RBD patients go on to convert to neurodegenerative disease such as PD,

DLB, and Multiple System Atrophy (MSA) [14]. Given this neurodegenerative risk, it is of interest to identify potential disease predictors that could be recognized before the onset of motor symptoms or dementia. These could include risk factors such as genetic mutations or manifestations such as pre-dementia cognitive deficits and mood disorders.

Genetic Mutations

Genetic mutations have been documented in patients with PD and RBD. Common genetic mutations in PD include mutations to *SNCA*, *LRRK2*, *Parkin, PINK1, APOE,* and *GBA* [15]. Some of these have been proven to not be present in patients in RBD, for example *LRRK2* [16] and *APOE* [17]. Others, such as *SNCA* [18], have been documented in RBD, but by far the genetic mutation that has been implicated the most in RBD is *GBA* [19].

Glucocerebrosidase (*GBA*) Mutations.

Glucocerebrosidase (*GBA*) is a lysosomal enzyme that cleaves glucosylceramide [20]; deficiency in *GBA* results in an accumulation of lipids within lysosomes and can cause the symptoms of Gaucher's disease [21]. Mutations to *GBA* are linked to PD patients with and without Gaucher's disease [20]; these mutations have been reported in 3-20% of patients with PD from different populations [22] and 10-14% of patients with RBD from a European population [19]. Mutations to the *GBA* gene are common in patients of French-Canadian descent, and so are of interest to study in our cohort [23]. In the larger population, odds ratios for developing PD range from 2.2 for mild *GBA* mutations to >10 for severe mutations [22]. In PD patients, *GBA* mutations have been linked to reportedly more severe non-motor symptoms (such as autonomic dysfunction or impaired olfaction) and earlier onset of dementia [24]. Furthermore, *GBA* mutations have been found to be twice as common in early-onset PD

cases than in later-onset PD [25]. RBD itself can also be considered a manifestation of *GBA* mutations as the two are strongly associated [19,26].

Cognition

As patients phenoconvert to parkinsonism and particularly dementia, cognition can be affected. RBD itself acts as a risk factor for the onset of dementia in PD [12]. Patients with PD and RBD have been shown to be affected by mild cognitive impairment (MCI), an intermediate step between normal cognitive functioning and dementia [27]. A study of PD patients with and without RBD demonstrated that the incidence of MCI is significantly higher in PD patients with RBD than PD patients without (66% compared to 23%) [12]. Other studies estimate the risk of MCI to be 50-65% in RBD patients compared to 8% in healthy controls [28] and 30-50% in PD patients [29].

Cognitive changes can manifest as hallucinations or visual illusions, which though very common in PD and DLB [30] are relatively uncommon in patients with still-idiopathic RBD [31]. Another feature is the presence of cognitive "fluctuations" that are common in patients with DLB; fluctuating cognition is thought to be a problem with attention and alertness and has been linked to poor attention, visuospatial function, and executive function in DLB patients [32]. These cognitive domains have been found to be similarly affected in RBD [27]. A study of PD patients in Norway found that patients who experienced hallucinations before baseline were more likely to be later diagnosed with dementia [33]. This is of interest because some of these patients may have been in the prodromal stage of PD when they experienced hallucinations since reportedly 30-50% of PD patients have RBD [34]. Because we do not typically observe

hallucinations or visual illusions in our cohort in the clinic, this suggests that more sensitive measures of pre-clinical hallucinations are needed.

Depression and Anxiety

Depression and anxiety are common non-motor features of RBD and thus of parkinsonism and dementia. Furthermore, some studies have shown that PD patients with RBD have a higher prevalence of depression and anxiety than PD patients without RBD [35,36]. However, though depression and anxiety are frequently associated with RBD, neither serve as predictors of disease conversion; the prevalence of anxiety and depression in disease-free RBD patients does not differ significantly from the prevalence in RBD patients who have phenoconverted to parkinsonism or dementia [13]. It should be noted that antidepressants can trigger or enhance RBD symptoms; these patients show symptoms of prodromal synucleinopathy but may be at an earlier stage of neurodegeneration [37].

Because mood disorders can have extremely variable presentations, it is of interest to understand particular aspects of anxiety or depression that may be common amongst patients with RBD. Most studies typically use clinical measures such as the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) to look at depression and anxiety, but these measures only provide insight as to whether or not a patient is depressed or has anxiety globally, rather than any specific aspects of their condition. Furthermore, many questions on the BDI and BAI may be potentially confounded PD and RBD patients, such as “hands shaking or trembling” for PD patients or “changes in sleep pattern” or “tiredness and fatigue” in RBD patients. Therefore, it may be of interest to break these questionnaires down into similar factors in order to obtain a more detailed analysis of specific aspects of depression and anxiety in RBD patients and to attempt to avoid any potential confounds.

Chapter 1: Glucocerebrosidase Mutations and Phenoconversion of REM Sleep Behavior Disorder to Parkinsonism and Dementia.

Authors: [1]Lucy Honeycutt, [2,3]Jacques Y Montplaisir MD, PhD, [2,4]Jean-François Gagnon PhD, [7]Jennifer Ruskey, [2,5]Amélie Pelletier PhD, [6,7]Ziv Gan-Or MD, PhD*, [1,2,5]Ronald B. Postuma MD, MSc*

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada,

[2]Centre d'études avancées en médecine du sommeil, CIUSSS-NÎM-Hôpital du Sacré-Cœur de Montréal, Montreal, Canada,

[3]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada

[4]Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada.

[5]Department of Neurology, The Research Institute of the McGill University Health Centre, Montreal, Canada,

[6]Department of Human Genetics, McGill University, Montreal, Canada

[7]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Canada

*Correspondence to:

Dr. Ronald B. Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Ave, Montreal, Canada H3G1A4; ron.postuma@mcgill.ca

Ziv Gan-Or, Montreal Neurological Institute, McGill University, 1033 Pine Avenue West, Ludmer Pavilion, Room 312 Montreal, QC, H3A 1A1, Phone: +1-514-398-5845, ziv.gan-or@mcgill.ca

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Abstract

Background: Mutations in the glucocerebrosidase (*GBA*) gene are strongly associated with REM sleep behavior disorder (RBD). It is unclear whether *GBA* mutations might affect clinical phenotype or rate of phenoconversion to parkinsonism or dementia.

Methods: We sequenced *GBA* in polysomnographic-proven idiopathic RBD (iRBD) patients. The effect of *GBA* mutations on clinical neurodegenerative markers and phenoconversion rate was assessed.

Results: Of 102 patients sequenced, 13 (13%) had *GBA* mutations and 89 did not. Aside from lower self-reported age of RBD onset in subjects with *GBA* mutations, no significant differences were observed in any clinical marker between patients with and without mutations. However, *GBA* mutations were associated with 3.3-fold higher phenoconversion rate from RBD to parkinsonism and/or dementia (95% CI=1.4-7.5, p=0.005).

Conclusion: Although *GBA* mutations do not appear to affect clinical neurodegenerative markers (and thus are not differentiable as an independent subtype of iRBD), they nevertheless accelerate the conversion of RBD to defined neurodegenerative synucleinopathy.

Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by a loss of muscle atonia and dream enactment behavior [1]. It has emerged as the most powerful clinical predictor of neurodegenerative synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Recently, it has been discovered that 3-20% of patients with PD from different populations have a mutation of the glucocerebrosidase (*GBA*) gene. Odds ratios (OR) for developing PD range from 2.2 for mild mutations to >10 for severe mutations [2], and mutation carriers have an earlier age of onset. *GBA* mutations are common in patients of French-Canadian descent [3]. Moreover, they are commonly observed in patients with idiopathic/isolated RBD; studies have found that 10.2% of European RBD patients had a known pathogenic *GBA* mutation, corresponding to an OR=6.2. When the PD risk variants p.E326K and T369M are included, the proportion of *GBA* pathogenic variants in RBD rises to 14% [4].

In this study, we investigated the role of the *GBA* gene in determining phenoconversion of RBD to parkinsonism and dementia, and whether patients with *GBA* mutations are identifiable as an independent subtype of RBD.

Methods

Patients

Patients with polysomnographic-proven RBD were recruited from the Center for Advanced Research in Sleep Medicine of the *Hôpital du Sacré-Coeur de Montréal* (Montreal, QC, Canada) from 2004 to 2017, as previously described [5]. Ethics approval was obtained from the research ethics board of the hospital and all patients gave informed consent to participate according to the Declaration of Helsinki. All patients had idiopathic RBD as defined by the

standard International Classification of Sleep Disorders-II criteria and were free of parkinsonism or dementia at baseline.

Procedures

Patients had a comprehensive neurological/neuropsychological examination as it has been extensively described elsewhere [5]. Neurodegenerative markers included motor measures (the Unified Parkinson Disease Rating Scale 2 and 3, Purdue Peg Board, Timed Up and Go, alternate tap test, cognition (the Montreal Cognitive Assessment), autonomic manifestations (systolic blood pressure drop, symptoms of urinary, erectile, constipation, and orthostatic dysfunction from the 1-4 point MSA rating scale), olfaction (the 12-item cross-cultural version of the University of Pennsylvania Smell Identification Test), color vision (the Farnsworth-Munsell 100 Hue test), and the Beck Anxiety and Depression scales. This visit was then repeated annually. At each follow-up visit, neurological examination was conducted for parkinsonism and dementia, diagnosed according to standard criteria as previously described [5].

GBA Analysis

Genetic analysis of *GBA* was performed as previously described [6], and the full protocol is available upon request. In brief, molecular inversion probes (MIPs) were used for targeted capturing of the coding sequences of *GBA,* followed by sequencing using the Illumina HiSeq 2500 platform at the McGill University and Genome Quebec Innovation Centre. Since exons 10 and 11 were not properly aligned due to the high similarity to the pseudo-*GBA* gene, they were also sequenced using Sanger sequencing in all samples. *GBA* mutations were also confirmed using Sanger sequencing. Full protocols are available upon request.

Statistical Analysis

All statistical analyses were performed in Statistical Package for the Social Sciences version 24 statistical software (SPSS, Chicago, IL, USA). Differences in clinical markers between RBD patients with or without mutations in the *GBA* gene were determined using independent sample t-tests. The influence of the *GBA* gene on rate of conversion of RBD patients to parkinsonism or dementia was determined using Cox regression analysis, adjusting for baseline age and sex.

Results

Baseline Results

Of 102 patients who were genotyped, 13 (13%) had an identified *GBA* mutation; the specific mutations are detailed in Supplemental Table 1. Age at baseline, sex, and RBD duration were not significantly different between the RBD subjects with and without *GBA* mutations (Table 1). Similarly, no difference was observed in any motor feature, autonomic manifestation, or measure of cognition, olfaction, color vision, anxiety, or depression. The only difference between groups was the self-reported age of RBD onset, which was lower among *GBA* mutation carriers (50.2 ± 15.3) than non-carriers (57.7 ± 12.1, p=0.047).

Disease Conversion

Despite having no differences in any clinical marker, patients carrying *GBA* mutations had a higher rate of phenoconversion of RBD to defined neurodegenerative disease (Figure 1). Overall, the HR for phenoconversion with a *GBA* mutation was 3.3 (95% CI = 1.4–7.5, p=0.005, unadjusted HR=2.5 [1.2-5.3]). As of last visit, 9/13 (69%) of patients with *GBA* mutations had phenoconverted to defined neurodegenerative synucleinopathy vs. 24/89 (27%) of non-carriers

(5 non-carriers have been seen only once without prospective follow-up). Among the patients with *GBA* mutations who phenoconverted, 6/9 (67%) of *GBA* mutation carriers developed parkinsonism as the first manifestation, similar to 16/24 (64%) of mutation non-carriers.

Among phenoconvertors at the time of phenoconversion, we again saw no differences in any neurodegenerative marker between patients with and without *GBA* mutations (supplemental Table 2).

Discussion

The findings of this study suggest that RBD patients who carry mutations in the *GBA* gene, despite having a similar profile of neurodegenerative markers at baseline, have an accelerated phenoconversion from idiopathic RBD to parkinsonism and dementia.

There has been one study previously assessing *GBA* and phenoconversion in RBD. This study found no increased risk among *GBA* mutation carriers and non-carriers [7]. It is not clear why we found different results; of note, our sample size was larger (13 carriers in our study vs. 8 in Gamez-Valero, which included two novel variants of uncertain pathophysiologic significance), suggesting the possibility that simple random variation may be responsible for the difference. We also found that the reported age of RBD onset was significantly lower in patients who carry the *GBA* gene. This (along with the faster phenoconversion rate) is consistent with previous findings that PD patients with *GBA* mutations have an age of disease onset approximately 5 years earlier than controls [8].

It is notable that despite a significantly higher phenoconversion rate, there were no differences between *GBA* mutation carriers and non-carriers in any of the other clinical markers we investigated either at baseline or at phenoconversion. This suggests that within idiopathic

RBD patients, those with *GBA* mutations are not clinical differentiable from those without, and therefore do not delineate a distinct subtype. This is contrast to findings in PD overall, in which subjects with *GBA* mutations have faster motor progression and are more likely to develop dementia [9]. Notably, the presence of RBD in PD also marks a similar severe subtype of PD characterized by increased risk of dementia, more autonomic dysfunction, and worse overall prognosis [10]. This suggests that RBD and *GBA* largely mark a similar subtype of PD. If clinical subtype is similar, there may be important pathophysiologic overlaps between RBD and *GBA*. There is some evidence for this; for example, lysosomal *GBA* mutations may increase PD risk via specific bidirectional feed-forward interaction with synuclein, [11] and within autopsy studies of PD and DLB, RBD is associated with increased deposition of synuclein (i.e. marking a 'synuclein-driven' pathophysiology) [12].

The main limitation of this study is the relatively small sample size. This is particularly important for the comparison of patients at phenoconversion (n=9 vs n=24); this analysis should be considered preliminary, and it is possible that some clinical differences will emerge in larger studies. One of the positive findings of this study (lower age of RBD onset in subjects with *GBA* mutations) is limited by the age of onset being self-reported, and so uncertain in its reliability.

In conclusion, we see no difference in clinical subtype between RBD patients with and without *GBA* mutations, but a clear increase in phenoconversion rate with mutations. That may suggest *GBA* mutations function primarily as an accelerant of a similar pathophysiologic mechanism as which occurs in the RBD subtype of PD/DLB.

Figures and Tables

Supplemental Table 1. Frequencies of GBA mutation types in our cohort.

Mutation Type	Frequency (No. of Subjects)
p.E326K	4
p.H255Q	1
p.T369M	4
p.W378G	2
p.W291X	1
p.N370S	1

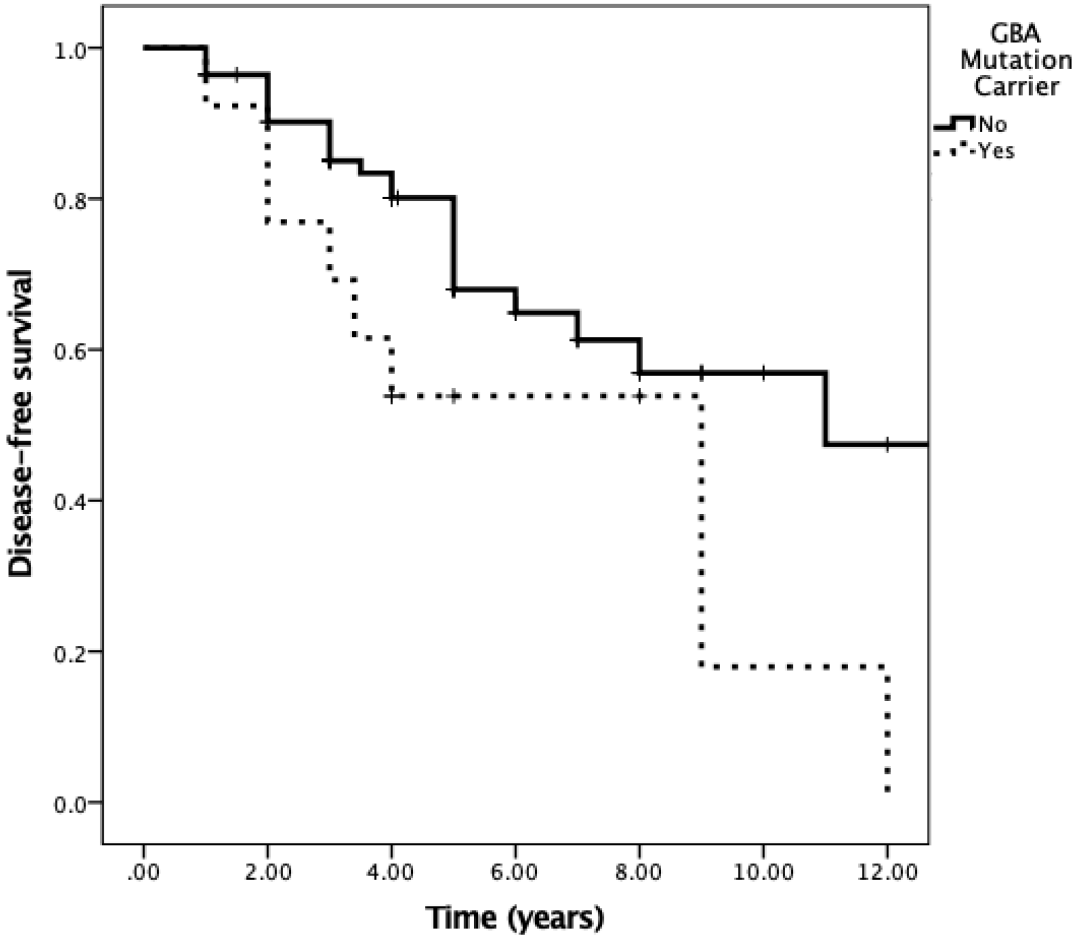

Figure 1. Phenoconversion rate in RBD patients with and without *GBA* mutations. Ticks indicate censoring events.

Table 1. Clinical characteristics of neurodegeneration in GBA mutation carriers and non-carriers at baseline.

	Non-Carriers (n = 89)	GBA Mutation Carriers (n = 13)	p value
Age at Baseline (years)	66.0 ± 8.0	63.9 ± 5.9	0.36
Sex (% Male)	66/89 (74.2)	10/13 (76.9)	0.83
Age Self-Reported RBD Onset (years)	57.7 ± 12.1	50.2 ± 15.3	0.047
PSG-Diagnosed RBD Duration (years)	8.1 ± 7.8	13.7 ± 13.6	0.17
Systolic Drop (mm Hg)	9.9 ± 13.0	16.3 ± 16.0	0.11
Urinary dysfunction	0.43 ± 0.59	0.38 ± 0.65	0.79
Erectile dysfunction N	1.7 ± 1.5 (n = 64)	1.3 ± 1.3 (n = 10)	0.44
Endorses Erectile Dysfunction (%) N	52% (n = 64)	30% (n = 10)	0.40
Constipation	0.64 ± 0.82	0.54 ± 0.78	0.68
Constipated (%)	18%	15%	0.79
Orthostatic symptoms	0.33 ± 0.56	0.15 ± 0.38	0.15
UPSIT (% Normal)	77.4 ± 27.1	65.0 ± 25.9	0.13
Farnsworth-Munsell test (% normal)	48%	42%	0.70
UPDRS 2	1.6 ± 1.8	1.9 ± 2.0	0.65
UPDRS 3	3.9 ± 3.4	4.7 ± 5.5	0.47
Purdue Peg Board (no. pegs)	11.4 ± 1.7	11.2 ± 2.5	0.64
Timed Up and Go (seconds)	6.3 ± 1.0	6.6 ± 1.2	0.42
Alternate Tap Test (HR per 10 taps)	185.7 ± 27.7	174.5 ± 32.2	0.19
MoCA N	25.3 ± 2.8 (n = 80)	26.7 ± 2.0 (n = 12)	0.12
Beck Anxiety Inventory N	8.6 ± 7.2 (n = 68)	8.5 ± 7.0 (n = 10)	0.96
Beck Depression Inventory N	10.2 ± 7.2 (n = 67)	7.7 ± 5.2 (n = 11)	0.27
UPDRS Depression N	0.50 ± 0.86 (n = 46)	0.44 ± 0.73 (n = 9)	0.86
Depression Diagnosed (% yes) N	39% (n = 46)	25% (n = 8)	0.45

Supplemental Table 2. Clinical markers in GBA mutation carriers and non-carriers at time of phenoconversion.

	Non-Carriers (n = 24)	**GBA Mutation Carriers (n = 9)**	**p value**
Age at Conversion (years)	70.4 ± 8.0	69.4 ± 5.9	0.73
Age of Self-Reported RBD Onset	62.0 ± 9.2	54.8 ± 13.0	0.08
Avg Years Between RBD Onset and Conversion	8.6 ± 5.8	14.7 ± 12.0	0.06
Sex (% Male)	16/24 (66.7)	7/9 (77.8)	0.55
Systolic Drop (mm Hg)	19.5 ± 13.7	27.6 ± 14.6	0.17
Urinary dysfunction	0.93 ± 0.73	0.56 ± 0.73	0.20
Erectile dysfunction N	2.5 ± 1.6 (n = 10)	3.0 ± 1.2 (n = 7)	0.50
Endorses Erectile Dysfunction (%) N	70% (n = 10)	86% (n = 7)	0.80
Constipation	1.3 ± 0.87	1.8 ± 1.1	0.23
Constipated (%)	48%	67%	0.55
Orthostatic symptoms	0.54 ± 0.69	0.56 ± 0.73	0.97
UPSIT (% Normal)	59.7 ± 27.9	47.4 ± 27.4	0.30
Farnsworth-Munsell test (% normal)	27% (n = 11)	0% (n = 3)	0.29
UPDRS 2	8.1 ± 4.8	5.9 ± 3.9	0.25
UPDRS 3	20.7 ± 8.4	18.9 ± 4.2	0.42
Purdue Peg Board (no. pegs)	18.4 ± 4.3	19.8 ± 4.8	0.47
Timed Up and Go (seconds)	8.0 ± 2.0	7.4 ± 1.3	0.38
Alternate Tap Test (HR per 10 taps) N	144.4 ± 33.0 (n = 17)	151.1 ± 29.6 (n = 8)	0.76
MoCA	23.0 ± 5.2	24.1 ± 5.1	0.59
UPDRS Depression	0.76 ± 0.94	0.50 ± 0.76	0.49

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Chapter 2. Pareidolias and Cognition in Isolated REM Sleep Behavior Disorder.

Authors: [1]Lucy Honeycutt, [2,3]Jean-François Gagnon PhD, [2,4]Amélie Pelletier PhD, [2,3]Jessie De Roy, [2,5]Jacques Y Montplaisir MD, PhD, [1,2,4]Ronald B. Postuma MD, MSc*

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada,

[2]Centre d'Études Avancées en Médecine du Sommeil, CIUSSS-NÎM-Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada,

[3]Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada.

[4]Department of Neurology, The Research Institute of the McGill University Health Centre, Montreal, Canada,

[5]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada

*Correspondence to:

Dr. Ronald B. Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Ave, Montreal, Canada H3G1A4; ron.postuma@mcgill.ca

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Abstract

Background: Though visual illusions and hallucinations are common in dementia with Lewy bodies (DLB) and Parkinson's disease (PD), they are not typically observed clinically in prodromal stages, including isolated REM sleep behavior disorder (iRBD). False-noise errors on the pareidolia test (seeing faces when none are present) may be an effective measure of susceptibility to future hallucinations in iRBD.

Methods: One hundred patients with iRBD underwent the 20-image pareidolia test. Clinical markers were assessed and a neuropsychological battery was administered. An exploratory analysis on the impact of pareidolic errors on phenoconversion was also performed.

Results: In our cohort, 17 patients (17%) made false-noise pareidolic errors. These patients had significantly lower total Montreal Cognitive Assesment (MoCA) scores (26.7 ± 2.3 vs. 24.4 ± 2.6, B = -1.88, 95% CI: [-3.17, -0.59]), with lower subcomponent MoCA scores on memory and visuospatial-executive sections. Pareidolic errors were also associated with lower visuospatial, attention/executive, and memory scores on the neuropsychological tests. Furthermore, after 1.6 years follow-up, 3/16 (19%) patients making pareidolic errors had phenoconverted at time of publication compared to 6/71 (8%) patients who did not make errors.

Conclusion: Pareidolic errors in patients with iRBD are associated with poorer overall cognition and may indicate higher risk of DLB.

Introduction

Isolated Rapid Eye Movement (REM) Sleep Behavior Disorder (iRBD) is a parasomnia that marks the prodromal stage of neurodegenerative diseases such as Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB) [1]. DLB and PD dementia are strongly associated with visual illusions and hallucinations [2]; we have previously observed that clinical hallucinations are uncommon in iRBD, even at the time of phenoconversion to DLB [3]. Therefore, more sensitive measures of potential precursors to hallucinations are needed.

Pareidolias are illusions in which one sees figures (e.g. a face) in abstract stimuli. Pareidolic illusions have been documented in patients with neurodegenerative diseases, such as PD [2], DLB [4], Alzheimer's Disease (AD) [4], as well as in healthy controls [2]. Patients with DLB and PD are more likely than AD patients or healthy controls to make pareidolic errors [4]. A clinical measure has been designed in order to test for pareidolic visual illusions [4,5] which uses abstract images made of visual 'blobs'; some have pictures of faces inserted and others do not. Visual illusions are detected using this test when a patient reports seeing a face when none is present – i.e. a "false noise" error.

In this study, we investigated the frequency of false noise pareidolia errors in iRBD and the correlations between pareidolic errors on neuropsychological tests and clinical assessments.

Methods

Patients

Patients were enrolled from the Center for Advanced Research in Sleep Medicine of the *Centre Intégré de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal – Hôpital du Sacré-Coeur de Montréal* (Montreal, QC, Canada) from 2004 to 2019, as previously described

[1]. All patients had polysomnographic-proven iRBD according to the criteria for the International Classification of Sleep-Disorders II and were free of parkinsonism or dementia at baseline. All patients gave informed consent per the Declaration of Helsinki and ethics approval was obtained from the research ethics board of the hospital.

Procedures

The primary outcome measure in this study was the pareidolia test [5]. In this test, patients are presented with a series of 20 images; 7 images contain a clearly identifiable face mixed in with abstract ink spots and the remaining 13 images contain only abstract ink spots (see supplementary figures for examples). Patients are assessed on their ability to correctly identify which pictures contain faces and which pictures do not.

In addition to the pareidolia test, patients were assessed with a comprehensive neurological examination and administered a battery of neuropsychological tests (as described in detail previously [1]). The neurological examination included measures of autonomic dysfunction (systolic blood pressure drop, symptoms of urinary, erectile, constipation, and orthostatic dysfunction from the 1-4 point Multiple System Atrophy [MSA] rating scale), motor functions, (the Unified Parkinson Disease Rating Scale [UPDRS] 2 and 3, Purdue Peg Board, Timed Up and Go, alternate tap test) global cognition (the Montreal Cognitive Assessment), sleep (Epworth sleepiness scale [ESS] and Insomnia Severity Index [ISI]), the Beck Anxiety and Depression scales, the University of Pennsylvania Smell Identification Test (UPSIT) and the Farnsworth-Munsell 100 Hue test of color vision (FM-100). The neuropsychological battery included measures of attention/executive functions (Digit Span, Trail Making Test A and B, Stroop Color Word test, and semantic and phonemic verbal fluency), episodic memory (Rey

Auditory Verbal Learning Test [RAVLT] total 1 to 5, list B, immediate and delayed recalls, and recognition), visuospatial abilities (Rey-O Complex Figure copy) and language (Boston Naming Test 30 items [BNT-30]).

Statistical Analysis

All statistical analyses were performed in Statistical Package for the Social Sciences version 26 statistical software (SPSS, Chicago, IL). For the neuropsychological tests, an age-education and sex-adjusted Z score for each measure was generated for each patient. Between-group differences were determined using independent sample t-tests. For clinical variables, values were adjusted for age and sex using linear regression (with the exception of UPSIT scores, which are already adjusted for age and sex). A p-value of 0.05 was considered to be significant.

Results

Clinical Measures

Of 100 iRBD patients, 17 (17%) made at least one false noise error (i.e. seeing a face when none was present). Patients making "false noise" errors were significantly older than those who did not make errors (73.2 ± 7.3 vs 66.6 ± 7.3 years), with no difference in sex (Table 1). Most motor, sleep, autonomic, and special sensory variables were similar between groups, except that patients making pareidolic errors reported more erectile dysfunction and self-reported less daytime somnolence on the ESS. However, on global cognitive testing, differences were clearer. Patients making pareidolic errors had lower MoCA total scores (26.7 ± 2.3 vs. 24.4 ± 2.6, age/sex adjusted B = -1.88, 95% CI: [-3.17, -0.59]). On subcomponent analysis those making errors had lower scores on the visuospatial-executive and memory sections.

Neuropsychological Testing

On numerous measures, patients making pareidolic errors demonstrated worse cognition. These were significantly different in tests measuring attention/executive functions (Stroop D1 time, Stroop D2 time, Stroop D4 error, and semantic verbal fluency), verbal memory (RAVLT immediate recall and RAVLT delayed recall), visuospatial abilities (Rey-O Complex Figure copy), and language (BNT-30). Forty-seven percent of patients making errors had at least two tests impaired in one cognitive domain vs. 27% of patients without ($p=0.04$).

Phenoconversion

An exploratory analysis was performed to assess the impact of false noise errors on the pareidolia test on phenoconversion to parkinsonism and dementia. As of time of publication, 87 patients had at least one year of follow-up, with an average 1.61 ± 0.62-years follow-up. Of the 71 patients who did not make an error, 6 (8%) had phenoconverted; 4/6 (67%) to parkinsonism first (without dementia at diagnosis) and 2/6 (33%) had converted to primary DLB (both with parkinsonism). Of the 16 patients who made false noise errors, 3 (19%) had phenoconverted (Cox proportional hazard ratio = 1.81 [95% CI=0.40-8.1]), 1/3 (33%) to parkinsonism-first and 2/3 (67%) to primary dementia (both with parkinsonism at diagnosis). Of the 4 patients with DLB, 2 had an abnormal pareidolia response for the first time only in the year of phenoconversion, whereas the other 2 made an error first in the prior year.

Discussion

The results presented here demonstrate that overall, 17% of iRBD patients made false-noise errors on the pareidolia test. Those who made false noise errors scored lower on the

MoCA, and performed more poorly in selected visuospatial, attention/executive, and memory measures. Otherwise, clinical differences were modest, with only a slightly higher prevalence of erectile dysfunction and less self-reported sleepiness. Over time, patients making false noise errors had equivocally higher rates of phenoconversion than those who did not, particularly with regards to dementia (although conclusions on outcome are preliminary, related to inadequate power).

Though limited research has been conducted on this topic, our results do align with some previous investigations. In a study by Uchiyama et. al. of the pareidolia test in PD patients and healthy controls, the median number of illusory responses in PD patients was 5, compared to only 1 in controls [2]. Furthermore, when comparing PD patients with and without hallucinations, 57% of PD patients without hallucinations produced at least one error, whereas 100% of patients experiencing hallucinations produced two or more errors [2]. It is notable that only a minority of our patients had abnormal pareidolic responses, including only 47% of those with at least two cognitive tests impaired, and 50% of those only one year before DLB diagnosis. This is a lower proportion than that described by Uchiyama, which may be due to differences in visual stimulus. The stimulus in our assessment is quite ambiguous and relatively ‘easy’; the median time for an RBD patient to complete 20 panels is 65 seconds, implying that it may be less sensitive to subtle changes.

We generally found that pareidolic errors were associated with cognitive decline, but not with most non-cognitive variables. Associations between pareidolic errors in iRBD and older age, decreased visuospatial function, and impaired memory were also observed in the other cohort study of pareidolias in iRBD [6]. Our findings also echo a previous study in which DLB patients exhibited pareidolias more frequently than patients without dementia [2]. Of note, there

was no specific association between pareidolias and ‘posterior’ visuospatial tests; rather, we saw associations with three different cognitive domains (visuospatial, attention/executive, and memory), all of which are common in DLB.

Pareidolias, as visual illusions, may be considered ‘minor hallucinations’; this is of note because minor hallucinations are closely associated with more complex visual hallucinations in PD [7]. Future studies should further explore the relationship between minor hallucinations and PD as well as other synucleinopathies.

The primary limitations of this study are relatively small sample size and short follow-up duration in regards to the exploratory analysis on phenoconversion. Hallucinations and visual illusions are not typically a very early symptom of neurodegeneration, and so a 1-year average follow up may not be sufficient. Visual acuity was not directly measured (although all patients wore their usual corrective lenses); although the figures are relatively large and easily seen, severe unrecognized acuity deficits could potentially explain some of the differences between groups. On the other hand, the strengths of our study are a large sample size for the primary analysis, combined with an extensive profile of clinical and neuropsychological markers, which allowed comprehensive correlation between pareidolic errors and other variables.

In conclusion, pareidolic errors can be observed in iRBD, and are linked to poorer cognitive functions. Future studies may help to confirm whether false-noise pareidolic errors indicate a high risk of phenoconversion to DLB.

Acknowledgements

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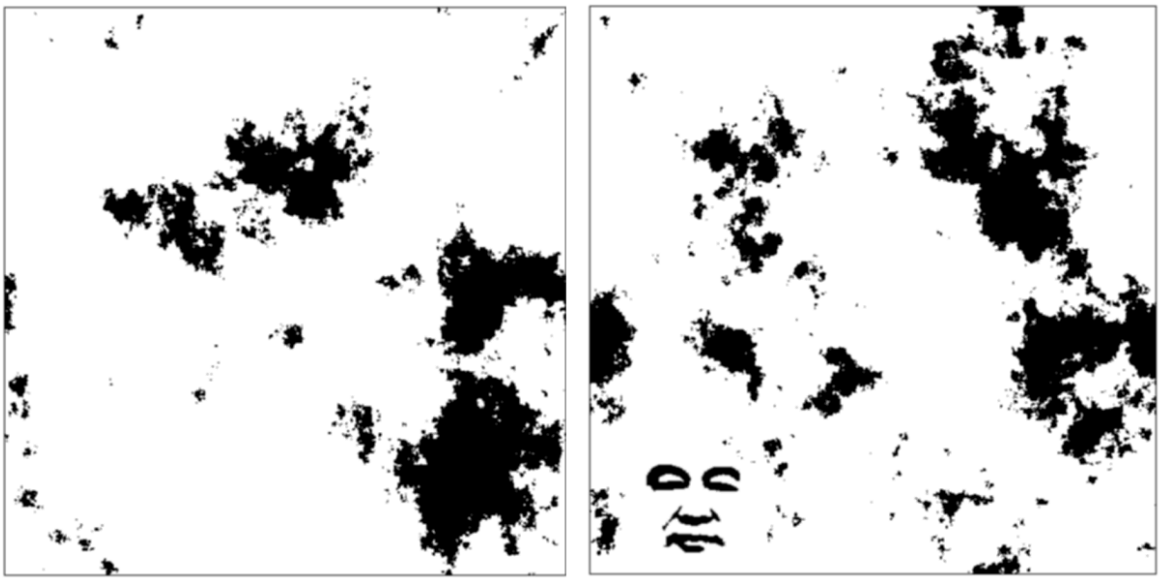
Figures and Tables



Supplemental Figure 1. Example of pareidolia test images with and without a face present. Unpublished images (copyright free), used with permission.

Table 1. Clinical measures in patients who made false noise errors (i.e. seeing a face when there was none) on the pareidolia test vs. those who did not make false noise errors.

	No Pareidolia n = 83	Pareidolia (False Noise) n = 17	Age/Sex Adjusted Difference (95% CI)
Age (years)	66.6 ± 7.3	73.2 ± 7.3	-
Gender (% Male)	68/83 (81.9)	14/17 (82.4)	-
RBD Duration (years)	10.1 ± 8.2	14.3 ± 11.1	3.04 (-1.8, 7.9)
Orthostatic Symptoms	0.45 ± 0.74	0.82 ± 0.81	0.31 (-0.1, 0.7)
Urinary Dysfunction	0.55 ± 0.73	0.50 ± 0.73	-0.81 (-0.5, 0.3)
Erectile Dysfunction	1.7 ± 1.6	3.4 ± 1.1	**1.04 (0.2, 1.9)**
Constipation Symptoms	0.84 ± 0.87	0.82 ± 0.88	-0.89 (-0.6, 0.4)
Systolic Drop (mm Hg)	9.5 ± 15.4	19.9 ± 22.4	8.94 (0.4, 18.3)
Timed Up and Go (average)	6.8 ± 2.0	6.8 ± 0.67	-0.23 (-1.3, 0.8)
UPDRS I Total	1.5 ± 1.9	2.3 ±1.7	0.45 (-0.6, 1.5)
UPDRS II Total	2.1 ± 2.4	3.2 ± 2.5	0.89 (-0.5, 2.2)
UPDRS III Total	5.6 ± 4.9	8.6 ± 5.5	1.98 (-0.8, 4.8)
UPSIT (% Normal)	75.5 ± 29.9	71.2 ± 21.9	-0.04* (-0.2, 0.1)
FM-100	107.5 ± 55.0	141.5 ± 81.2	24.25 (-10.4, 58.9)
Alternate Tap Average Both Hands	179.9 ± 32.1	163.8 ± 24.2	-10.44 (-26.6, 5.7)
MoCA Total Scores	26.7 ± 2.3	24.4 ± 2.6	**-1.88 (-3.2, -0.6)**
Visuospatial/Executive	4.5 ± 0.67	3.6 ± 1.2	**-0.66 (-1.1, -0.2)**
Naming	2.9 ± 0.31	2.8 ± 0.44	-0.69 (-0.3, 0.1)
Attention	1.8 ± 0.54	1.6 ± 0.70	-0.14 (-0.5, 0.2)
A Test	0.99 ± 0.11	0.94 ± 0.24	-0.04 (-0.1, 0.04)
Serial 7s	2.7 ± 0.51	2.6 ± 0.49	-0.11 (-0.4, 0.2)
Repetition	1.9 ± 0.35	1.8 ± 0.39	-0.03 (-0.2, 0.2)
Verbal Fluency Number	13.6 ± 4.4	11.6 ± 5.6	-1.48 (-4.1, 1.1)
Verbal Fluency Points	0.76 ± 0.46	0.59 ± 0.51	-1.05 (-0.4, 0.2)
Abstraction	1.9 ± 0.33	1.9 ± 0.33	0.01 (-0.2, 0.2)
Memory	3.3 ± 1.3	2.2 ± 1.4	**-1.02 (-1.8, -0.3)**
Orientation	5.7 ± 0.87	5.9 ± 0.33	0.20 (-0.3, 0.7)
BDI Total	9.7 ± 7.5	10.7 ± 6.8	0.93 (-3.5, 5.4)
BAI Total	6.3 ± 7.3	9.9 ± 9.1	4.01 (-0.4, 8.4)
ESS Total	7.8 ± 4.4	4.7 ± 2.4	**-2.81 (-5.3, -0.4)**
ISI Total	9.1 ± 5.8	8.1 ± 4.9	-0.17 (-3.5, 3.2)

Linear regression was used to determine age-and-sex adjusted beta and 95% CI except where indicated.
Values highlighted in bold denote statistical significance at threshold <0.05
* = Results are based upon expected values for age and sex, so duplicate age/sex adjustment with regression was not performed

Abbreviations: BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, FM-100 = Farnsworth-Munsell 100 Hue color vision test, ISI = Insomnia Severity Index, MoCA = Montreal Cognitive Assessment, RBD = REM sleep behavior disorder, UPDRS = Unified Parkinson's Disease Rating Scale, UPSIT = University of Pennsylvania Smell Identification Test

Table 2. Neuropsychological test measures of cognition between patients who made false noise errors (i.e. seeing a face when there was none) on the pareidolia test and those who did not make false noise errors.

	No Pareidolia n = 83	Pareidolia (False Noise) n = 17	Difference (95% CI)
Attention/Executive			
Digit Span Total	-0.04 ± 0.90	-0.04 ± 0.73	-0.003 (-0.5, 0.5)
Trail A Time	0.21 ± 1.5	-0.56 ± 1.5	-0.77 (-1.6, 0.03)
Trail B Time	-0.73 ± 2.8	-0.97 ± 2.1	-0.25 (-1.7, 1.2)
Stroop D1 Time (Color)	-0.03 ± 0.80	-0.49 ± 0.68	**-0.46 (-0.9, -0.1)**
Stroop D2 Time (Word)	0.07 ± 0.68	-0.31 ± 0.76	**-0.39 (-0.8, -0.2)**
Stroop D3 Time (Inhibition)	0.24 ± 0.75	-0.14 ± 0.88	-0.38 (-0.8, 0.04)
Stroop D4 Time (Inhibition/Switch)	0.20 ± 1.0	-0.36 + 1.0	-0.56 (-1.1, 0.01)
Stroop D3 Error Total	0.30 ± 0.65	-0.02 ± 0.97	-0.32 (-0.7, 0.1)
Stroop D4 Error Total	0.24 ± 0.76	-0.33 ± 0.88	**-0.57 (-1.0, -0.1)**
Semantic Verbal Fluency Total	-0.81 ± 0.79	-1.3 ± 0.70	**-0.48 (-0.9, -0.1)**
Phonemic Verbal Fluency Total	-0.21 ± 0.97	-0.44 ± 0.82	-0.22 (-0.7, 0.3)
Memory			
RAVLT Total 1 to 5	0.28 ± 1.3	-0.21 ± 0.95	-0.49 (-1.2, 0.2)
RAVLT List B	-0.36 + 0.96	-0.76 ± 0.96	-0.40 (0.9, 0.1)
RAVLT Immediate Recall	-0.03 ± 1.0	-0.71 ± 0.72	**-0.68 (-1.2, -0.2)**
RAVLT Delayed Recall	0.15 ± 1.1	-0.64 ± 1.1	**-0.79 (-1.4, -0.2)**
RAVLT Recognition Correct	0.25 ± 1.4	-0.32 ± 0.93	-0.58 (-1.3, 0.2)
Visuospatial			
Rey-O Complex Figure copy	0.41 ± 0.86	-0.53 ± 1.5	**-0.94 (-1.5, -0.4)**
Language			
BNT-30 Spontaneous Response	0.13 ± 1.2	-0.57 ± 0.91	**-0.70 (-1.3, -0.1)**
At least two cognitive tests impaired	22/82	7/15	**p = 0.042**

Values are given as mean age, sex, and education-adjusted z-scores. Negative z-scores indicate worse function. Linear regression was used to determine beta and 95% CI.
Values highlighted in bold denote statistical significance at threshold <0.05

Abbreviations: BNT-30 = Boston Naming Test 30 items, RAVLT = Rey Auditory Verbal Learning Test

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Chapter 3. Characterization of Depression and Anxiety in Patients with Isolated REM Sleep Behavior Disorder.

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Authors: [1]Lucy Honeycutt, [2,3]Jean-François Gagnon PhD, [2,4]Amélie Pelletier PhD, [2,5]Jacques Y Montplaisir MD, PhD, [1,2,4]Ronald B. Postuma MD, MSc*

[1]Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada,

[2]Centre d'Études Avancées en Médecine du Sommeil, CIUSSS-NÎM-Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada,

[3]Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada.

[4]Department of Neurology, The Research Institute of the McGill University Health Centre, Montreal, Canada,

[5]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada

*Correspondence to:

Dr. Ronald B. Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Ave, Montreal, Canada H3G1A4; ron.postuma@mcgill.ca

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Abstract

Background: Depression and anxiety are common features of RBD. However, the specific profiles of these mood disorders in RBD, as well as their predictive values are unclear. Factor solutions can help to better understand the results of global questionnaires such as the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), especially in situations for which there exists potential confounding by primary symptoms of neurodegeneration.

Methods: Patients with polysomnography-confirmed idiopathic RBD and healthy controls were identified from a large database. Those with potential antidepressant-triggered RBD were excluded from analysis. Patients were administered the BDI and BAI at baseline and prospectively over follow-up. Total scores were assessed at baseline, over time, and at time of phenoconversion. A factor solution was generated for each questionnaire using SPSS and these factors were also assessed at the same time points.

Results: At baseline, differences were seen between RBD patients and healthy controls in total BDI and BAI scores, as well as many individual scale questions, and most of the scales' factors. Over time, total scores did not change significantly or predict phenoconversion. Similarly, when divided according to factors, we found no predictive value of any factor, with only equivocal change in some factors over time.

Conclusion: Symptoms of depression and anxiety are common in iRBD, even in those not taking antidepressants. However, neither total scores nor individual factors predict

phenoconversion nor change significantly with time. These exploratory factor analyses should be repeated in future studies with a larger sample size.

Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of muscle atonia during REM sleep [1]. It is part of the prodromal stage of neurodegenerative diseases such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), and as many as 80% of patients may phenoconvert to these diseases [2]. The prodromal stage of PD and DLB precedes motor symptoms by many years, and so it is of interest to study nonmotor manifestations during this time. Nonmotor symptoms can include autonomic dysfunction, cognitive changes, and mood disturbances such as depression and anxiety [3].

Depression and anxiety are common non-motor features of PD and RBD, reported in about 30% of PD patients [3] and 20-30% percent of RBD patients [4]. Of note, RBD itself can be triggered or augmented by antidepressant medications; prior studies have suggested that patients with antidepressant-triggered RBD have signs of prodromal synucleinopathy but may be at an earlier stage of neurodegeneration [5]. It has remained unclear whether depression and anxiety in iRBD predict speed of phenoconversion to dementia or parkinsonism; most studies have found no clear predictive value [6-9].

Mood disorders are typically evaluated clinically through the use of global tests, such as the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). However, mood disorders can have variable presentations; therefore, it is of interest to go beyond a total questionnaire score when studying depression and anxiety. Moreover, many global mood disorder scales include questions that may be confounded by the primary process of neurodegeneration; for example, these scales contain questions on fatigue, sleep disturbances, sexual changes, tremor, cognition, and appetite. Analyzing these scales as a whole may therefore mix true mood disturbances with non-mood symptoms of neurodegenerative synucleinopathy.

One way to obtain a more detailed picture of depression and anxiety profiles is to use factor solutions. For example, in non-RBD samples, the 21 questions of the BAI have been split into two factors (cognitive and somatic), four factors (cognitive, autonomic, neuromotor, and panic), or six factors (panic, autonomic hyperactivity, somatic, nervousness, motor tension, and fear) [10]; similarly, the BDI has been split into multiple two-factor solutions (cognitive and somatic-affective; cognitive affective and somatic; somatic-affective and cognitive), a three factor solution (cognitive, affective, and somatic), and a four factor solution (somatic, cognitive, self-criticalness, and anhedonia) [11]. These factor solutions may not apply well to patients with neurodegenerative synucleinopathy, given the high prevalence of direct confounds in our patients.

In this study, we compared total BDI and BAI scores as well as individual BDI and BAI question scores between RBD patients and controls at baseline, prospectively over time, and at time of phenoconversion. We then developed factor solutions for the BDI and BAI using SPSS in order to compare the profiles of depression and anxiety in RBD patients and controls. We also investigated how the factors changed over time and whether phenoconversion to PD or DLB resulted in any changes to the factors.

Methods

Patients

Patients were recruited from the Center for Advanced Research in Sleep Medicine of the *Hôpital du Sacré-Coeur de Montréal* (Montreal, QC, Canada) from 2004 to 2019 as previously described [12]. All patients had polysomnographic-proven RBD and met criteria for idiopathic RBD as defined by the standard International Classification of Sleep Disorders-II criteria [13]. Patients currently taking antidepressants were excluded from analysis because of potential

confounding by antidepressant-triggered RBD. Controls were selected from the general population and underwent polysomnographic testing to prove the absence of RBD.

Procedures

All patients received an extensive neurological examination, as has been described in detail elsewhere [9,12]. This study primarily used two questionnaires to quantify anxiety and depression: the Beck Anxiety Inventory (BAI) [14] and the Beck Depression Inventory (BDI) [15]. These questionnaires were administered at the baseline visit and were repeated annually since 2013. Because annual administration of these questionnaires only began in 2013, most patients only have 3 or 4 years of follow-up visits. While data exists past year 4 for some patients, the number of patients was too low to allow for reliable assessment.

Statistical Analysis

All statistical analyses were performed in Statistical Package for the Social Sciences version 24 statistical software (SPSS, Chicago, IL, USA). Baseline comparisons between RBD patients and controls on individual questions of the BDI and BAI were performed using independent sample t-tests. The progression of individual questions over time as well as factors was also assessed using linear regression in which baseline responses were compared to responses in subsequent years. An additional exploratory analysis used independent sample t-tests to compare responses of patients who converted to parkinsonism or dementia in the year they converted to their own baseline responses as well as the responses of the entire cohort. For all t-tests, a p-value of 0.05 was considered significant.

Factoring of each questionnaire was performed using the dimension reduction factor analysis feature of SPSS. An unrotated principle component analysis (PCA) was run first to establish a baseline for comparison. Combinations of other factoring techniques (principle axis factoring [PAF], maximum likelihood, unweighted least squares, and generalized least squares) and rotations (quartimax, equamax, direct oblimin, varimax, and promax) were then executed. The factoring techniques used aim to explain the variance in the questions in order to correlate like questions and reduce the total number of variables. Rotations further correlate variables to make for a simpler factor solution; an unrotated factor solution may have some heavily-loaded factors, but by rotating the solution we are able to explore more correlations so that each factor may be loaded less heavily. A factoring solution was chosen when each individual component had a higher correlation coefficient than the unrotated PCA solution. Components were then sorted into factors based on highest correlation coefficient.

For the BDI, a promax rotation PCA proved to be the most successful and resulted in 7 factors. Factor 1 consisted of loss of pleasure, guilty feelings, self-dislike, self-criticalness, loss of interest, and indecisiveness. Factor 2 consisted of past failure, agitation, and worthlessness. Factor 3 consisted of sadness, pessimism, punishment feelings, and suicidal thoughts. Factor 4 consisted of tiredness and fatigue, and loss of interest in sex. Factor 5 included loss of energy, changes in sleep pattern, and irritability. Factor 6 included changes in appetite and concentration difficulty, and factor 7 consisted of crying.

For the BAI, a promax rotation PAF proved to be the most successful. However, unlike the BDI factor solution, this rotation did not result in higher correlation coefficients for all variables, although it was the best of all of the generated solutions. From this solution, 5 factors were produced: Factor 1 consisted of fear of worst happening, terrified/afraid, nervous, fear of

losing control, difficulty in breathing, fear of dying, scared, and faint/lightheaded; Factor 2 included feeling hot, feeling of choking, indigestion, face flushed, and hot/cold sweats; Factor 3 was composed of dizzy/lightheaded, heart pounding/racing, and unsteady; Factor 4 included numbness/tingling, feeling hot, and wobbliness in legs; Factor 5 was composed of hands trembling and shaky/unsteady.

Results

A total of 114 patients and 44 controls were recruited. The average age was 69.0 ± 9.1 years for RBD patients and 66.3 ± 9.8 for controls and 88 RBD patients (77%) and 31 controls (70%) were male. 113 patients had baseline BDI and 111 had BAI, of this, 73 had at least one follow-up for BDI and 70 had at least one follow-up for BAI.

Baseline Results

Total BDI and BAI Scores. First, we compared baseline total scores for the BDI and BAI between RBD patients and controls (Table 1). These results indicate that RBD patients have significantly more pronounced depression and anxiety than controls at baseline, even when those taking antidepressants were excluded (BDI total scores: 9.1 ± 6.7 vs 5.8 ± 4.8, $p < 0.001$, BAI total scores: 7.8 ± 8.9 vs 4.5 ± 6.0, $p < 0.01$).

Subscales and Factors – Baseline Depression. A baseline comparison of average individual question scores of RBD patients and controls was then performed to obtain a more detailed view of depression presentation in RBD patients (Table 2). Effect sizes were calculated to compare the difference between scores of RBD patients and controls. These data highlighted differences in some, but not all, questions, indicating that differences in certain aspects of

depression and anxiety were more pronounced in RBD patients. Of note, the two features with the highest effect sizes (Cohen's d = 0.67), fatigue and loss of interest in sex, are also potential symptoms of neurodegenerative synucleinopathy. Agitation and crying, features that could possibly be related to RBD itself (i.e. agitation and crying out at night) had the next highest effect sizes (Cohen's d = 0.53). Smaller statistically-significant differences were noted for self-dislike, self-criticalness, indecisiveness, and irritability.

Next, we compared the various factors generated by the SPSS factor solution between RBD patients and controls at baseline (Table 3). In this analysis, all factors were found to be significantly different between RBD patients and controls with the exception of two: Factor 3, which consists of sadness, pessimism, punishment feelings, and suicidal thoughts, and Factor 5, which consists of loss of energy, changes in sleep pattern, and irritability.

Baseline Anxiety. A similar comparison of baseline RBD and control BAI scores on individual questions was also performed (Table 4). Many single items demonstrated differences between patients and controls, with no clear pattern of confounding by prodromal physical/autonomic symptoms. Both core psychiatric anxiety symptoms (fear of worst happening, unable to relax, nervousness) and potentially-confounded symptoms (wobbliness in legs, trembling in hands, shakiness/unsteadiness) showed significant differences and had similar effect sizes. On analysis of factors, all factors were significantly different between patients and controls except for Factor 2 (which included many items related to autonomic hyperactivation) (Table 5). Factor 1, which includes many core cognitive features of anxiety, was found to be just insignificantly different between patients and controls at our threshold (p = 0.05).

Progression of Depression and Anxiety. We then examined depression and anxiety symptoms progressed over time in iRBD (Figure 1). Over a four-year period, BDI total scores showed little change, progressing from 8.97 to 8.76. BAI total scores showed significant progression, changing from 7.05 to 9.32 over a four-year period (slope = 0.58, $p < 0.05$). Because confounding by non-mood symptoms could affect measures of progression, we then examined whether different patterns of progression could be seen in the individual scale factors. For depression, with the exception of Factor 6 (slope = 0.16, $p < 0.05$), no real progression was seen in the data over time (Figure 2). This analysis was repeated for anxiety (Figure 3) and significant progression was seen in Factor 3 (slope = 0.16, $p < 0.05$), Factor 4 (slope = 0.25, $p < 0.05$), and Factor 5 (slope = 0.10, $p < 0.05$).

Depression and Anxiety and Phenoconversion

Over an average 2.4 ± 3.1 years of follow-up, 37 (29%) converted to defined neurodegenerative disease. 17 developed parkinsonism first (13 PD, 4 MSA) and 20 developed dementia first (all of whom, by definition, met criteria for probable DLB). Neither baseline BDI nor BAI were different in those who phenoconverted vs. those who did not (baseline score = 9.8 ± 7.2 vs 8.4 ± 6.4 for BDI and 7.2 ± 7.9 vs 7.1 ± 8.1 for BAI).

We hypothesized that phenoconversion may influence total BDI and BAI scores, and so we compared baseline scores of non-convertors, baseline scores of convertors, and scores of convertors in the year they converted (mean interval: 3.5 ± 2.6 years) (Table 1). We saw no significant differences between groups (9.8 ± 7.2 vs 8.4 ± 6.4 vs 10.2 ± 7.2 for BDI and 7.2 ± 7.9 vs 7.1 ± 8.1 vs 6.7 ± 5.4 for BAI). Upon examination of individual factors, only Factor 6 of the BDI (change in appetite, concentration difficulty) was higher in phenoconvertors than those who

did not phenoconvert (1.4 ± 1.3 vs 0.88 ± 1.0, p=0.04). We then explored potential progression of symptoms in phenoconvertors specifically by comparing baseline scores of phenoconvertors to the scores at the year of phenoconversion. There was no significant progression in either total scores or scores on factors among phenoconvertors (Tables 6 and 7).

Discussion

This study explored depression and anxiety as potential prodromal markers in patients with idiopathic RBD who were not currently taking antidepressants, using the Beck Depression Inventory and Beck Anxiety Inventory. We found clear differences in both total scores on the inventories and in individual questions between RBD patients and controls. These included questions that targeted mood directly as well as questions potentially confounded by other neurodegenerative symptoms. Furthermore, when factored using an SPSS-generated solution, baseline differences exist between RBD patients and controls in most depression and anxiety factors. Scores progressed only modestly over time, and analysis of factors that progressed suggested that this may have been driven by motor or autonomic symptoms. For example, Factor 3, Factor 4, and Factor 5 of the BAI showed significant progression over time; however, some of these questions refer to symptoms that may be experienced as a result of degeneration (wobbliness in legs, hands trembling). Moreover, neither total scores nor individual factors were higher among those who eventually phenoconverted to degenerative disease.

While studies have previously compared BDI and BAI total scores between RBD patients and controls and looked at the predictive value of these questionnaires, no studies have yet been conducted using factor solutions to examine the profiles of depression and anxiety in RBD patients as compared to controls or over time. Using a factor solution rather than relying on total

questionnaire scores serves two useful purposes. First, factor solutions group similar questions together and allow the changes and differences between factors to be viewed separately. Second, factoring can help draw out questions that are potentially confounded by other neurodegenerative symptoms. Patients with iRBD commonly have autonomic dysfunction, subtle cognitive loss, mild motor slowing, and primary sleep disturbances; these manifestations may have confounded previous attempts to document predictive value of depression or anxiety for phenoconversion or could have masked changes in depression and anxiety over time. In the end, however, analysis of factors showed few differences compared to analysis of scales overall. This may indicate that these factors are highly correlated (i.e. depression/anxiety, cognition, autonomic dysfunction all change similarly over time). Alternatively, patient insight may have played a role; patients may have understood the individual items as applying to the context of a depression/anxiety questionnaire, themselves discarding confounding factors (e.g. patients may answer "hands trembling" or "shakiness/unsteadiness" questions as anxiety symptoms per se, rather than reporting primary tremor or balance symptoms that are unrelated to anxiety.

The primary limitation of this study is the relatively limited number of questionnaires for the progression analysis. This is primarily because we began systematically tracking follow-up questionnaires starting in 2013 (9 years after the initiation of the cohort) Moreover, some patients were not followed up with every single year, were lost to follow up, or are newly-recruited patients with relatively few follow-up visits. This also affects the phenoconversion analysis as limited data is available at this time. However, our study is strengthened by our relatively large sample size at baseline.

In conclusion, baseline differences exist in the BDI and BAI between RBD patients and controls when assessed as total scores, individual question differences, and differences in SPSS-

derived factors. Total BAI but not BDI scores change modestly over time but do not predict phenoconversion. Few changes are seen in the SPSS-factors over time and as a result of phenoconversion, but these analyses should be repeated with larger sample sizes.

Figures and Tables

Table 1. Comparison of baseline total BDI and BAI scores between RBD patients and controls as well as a comparison between baseline total BDI and BAI scores between RBD patients who phenoconverted and those who did not.

	RBD	***Control***	***Effect Size***	***p-value***
BDI Total	9.1 ± 6.7	5.8 ± 4.8	0.62	0.001*
BDI Total (Non-convertors)	8.4 ± 6.4	-	-	0.33[a]
BDI Total (Convertors)	9.8 ± 7.2	-	-	0.33[a]
BAI Total	7.8 ± 8.9	4.5 ± 6.0	0.50	0.008*
BAI Total (Non-convertors)	7.1 ± 8.1	-	-	0.97[b]
BAI Total (Convertors)	7.2 ± 7.9	-	-	0.97[b]

* = denotes statistical significance at threshold <0.05
a = represents a comparison of nonconvertors' baseline BDI score to convertors' baseline BDI score
b = represents a comparison of nonconvertors' baseline BAI score to convertors' baseline BAI score

Abbreviations: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI)

Table 2. Question-by-question comparison of average baseline scores of RBD patients and controls on the Beck Depression Inventory.

Question #	Description	Mean ± Std. Dev. (RBD)	Mean ± Std. Dev. (Control)	Significant? (p-value)	Effect Size
1	Sadness	0.21 ± 0.41	0.13 ± 0.34	ns	0.21
2	Pessimism	0.30 ± 0.54	0.16 ± 0.43	ns	0.29
3	Past Failure	0.29 ± 0.67	0.24 ± 0.65	ns	0.08
4	Loss of Pleasure	0.44 ± 0.61	0.38 ± 0.53	ns	0.11
5	Guilty Feelings	0.30 ± 0.53	0.27 ± 0.45	ns	0.06
6	Punishment Feelings	0.19 ± 0.63	0.18 ± 0.54	ns	0.02
7	Self-Dislike	0.29 ± 062	0.11 ± 0.44	0.04	0.33
8	Self-Criticalness	0.37 ± 0.58	0.20 ± 0.40	0.03	0.34
9	Suicidal Thoughts/Wishes	0.12 ± 0.33	0.09 ± 0.29	ns	0.10
10	Crying	0.41 ± 0.78	0.09 ± 0.46	0.0004	0.53
11	Agitation	0.46 ± 0.64	0.18 ± 0.39	0.001	0.53
12	Loss of Interest	0.42 ± 0.59	0.24 ± 0.57	ns	0.31
13	Indecisiveness	0.53 ± 0.74	0.22 ± 0.56	0.005	0.47
14	Worthlessness	0.28 ± 0.54	0.16 ± 0.37	ns	0.26
15	Loss of Energy	0.78 ± 0.50	0.64 ± 0.53	ns	0.27
16	Changes in Sleeping Pattern	0.78 ± 0.88	0.60 ± 0.72	ns	0.22
17	Irritability	0.44 ± 0.58	0.22 ± 0.47	0.01	0.42
18	Changes in Appetite	0.44 ± 0.69	0.27 ± 0.58	ns	0.27
19	Concentration Difficulty	0.68 ± 0.69	0.44 ± 0.55	0.04	0.38
20	Tiredness/Fatigue	0.85 ± 0.67	0.44	ns	0.67
21	Loss of Interest in Sex	0.86 ± 0.89	0.36	0.00007	0.67

Table 3. Differences in SPSS-generated factors of the BDI between RBD patients and controls at baseline.

	Factor 1	***Factor 2***	***Factor 3***	***Factor 4***	***Factor 5***	***Factor 6***	***Factor 7***
RBD (n = 113)	2.3 ± 2.5	1.0 ± 1.4	0.76 ± 1.3	1.7 ± 1.3	1.9 ± 1.4	1.1 ± 1.1	0.37 ± 0.73
Control (n = 44)	1.4 ± 1.7	0.58 ± 0.99	0.56 ± 1.0	0.98 ± 0.78	1.5 ± 1.3	0.71 ± 0.57	0.09 ± 0.46
p-value	0.01*	0.02*	0.29	<0.001*	0.07	0.02	0.002*

* = denotes significance at threshold $p < 0.05$

Abbreviations: Beck Depression Inventory (BDI)

Factor 1: Loss of Pleasure, Guilty Feelings, Self-Dislike, Self-Criticalness, Loss of Interest, Indecisiveness
Factor 2: Past Failure, Agitation, Worthlessness
Factor 3: Sadness, Pessimism, Punishment Feelings, Suicidal Thoughts
Factor 4: Tiredness and Fatigue, Loss of Interest in Sex
Factor 5: Loss of Energy, Changes in Sleep Pattern, Irritability
Factor 6: Changes in Appetite, Concentration Difficulty
Factor 7: Crying

Table 4. Question-by-question comparison of average baseline scores of RBD patients and controls on the Beck Anxiety Inventory.

Question #	Description	Mean ± Std. Dev. (RBD)	Mean ± Std. Dev. (Control)	Significant? (p-value)	Effect Size
1	Numbness/Tingling	0.40 ± 0.70	0.31 ± 0.64	ns	0.13
2	Feeling Hot	0.39 ± 0.75	0.38 ± 0.62	ns	0.01
3	Wobbliness in Legs	0.40 ± 0.70	0.07 ± 0.26	0.00002	0.62
4	Unable to Relax	0.63 ± 0.83	0.27 ± 0.45	0.001	0.54
5	Fear of Worst Happening	0.58 ± 0.88	0.21 ± 0.52	0.002	0.51
6	Dizzy/Lightheaded	0.43 ± 0.70	0.31 ± 0.52	ns	0.19
7	Heart Pounding/Racing	0.43 ± 0.69	0.17 ± 0.44	0.004	0.45
8	Unsteady	0.46 ± 0.66	0.24 ± 0.43	0.015	0.39
9	Terrified/Afraid	0.21 ± 0.56	0.07 ± 0.34	0.06	0.30
10	Nervous	0.79 ± 0.87	0.40 ± 0.59	0.002	0.52
11	Feeling of Choking	0.27 ± 0.67	0.15 ± 0.48	ns	0.21
12	Hands Trembling	0.41 ± 0.66	0.19 ± 0.40	0.01	0.40
13	Shaky/Unsteady	0.29 ± 0.61	0.10 ± 0.30	0.008	0.40
14	Fear of Losing Control	0.26 ± 0.58	0.24 ± 0.53	ns	0.04
15	Difficulty in Breathing	0.27 ± 0.63	0.10 ± 0.37	0.03	0.33
16	Fear of Dying	0.25 ± 0.65	0.14 ± 0.42	ns	0.20
17	Scared	0.33 ± 0.72	0.14 ± 0.42	0.05	0.32
18	Indigestion	0.51 ± 0.80	0.33 ± 0.69	ns	0.24
19	Faint/Lightheaded	0.18 ± 0.54	0.07 ± 0.34	ns	0.24
20	Face Flushed	0.33 ± 0.65	0.26 ± 0.54	ns	0.12
21	Hot/Cold Sweats	0.43 ± 0.71	0.31 ± 0.56	ns	0.19

Table 5. Differences in SPSS-generated BAI factors between RBD patients and controls at baseline.

	Factor 1	***Factor 2***	***Factor 3***	***Factor 4***	***Factor 5***
RBD (n = 111)	2.4 ± 3.5	1.5 ± 2.3	1.3 ± 1.7	1.2 ± 1.5	0.56 ± 0.95
Control (n = 42)	1.4 ± 2.7	1.4 ± 1.6	0.71 ± 1.2	0.64 ± 0.96	0.29 ± 0.60
p-value	0.05	0.72	0.02*	0.005*	0.04*

* = denotes significance at threshold $p < 0.05$

Abbreviations: Beck Anxiety Inventory (BAI)

Factor 1: Fear of Worst Happening, Terrified/Afraid, Nervous, Fear of Losing Control, Difficulty Breathing, Fear of Dying, Scared, Faint/Lightheaded
Factor 2: Feeling Hot, Feeling of Choking, Indigestion, Face Flushed, Hot/Cold Sweats
Factor 3: Dizzy/Lightheaded, Heart Pounding/Racing, Unsteady
Factor 4: Numbness/Tingling, Wobbliness in Legs, Unable to Relax
Factor 5: Hands Trembling, Shaky/Unsteady

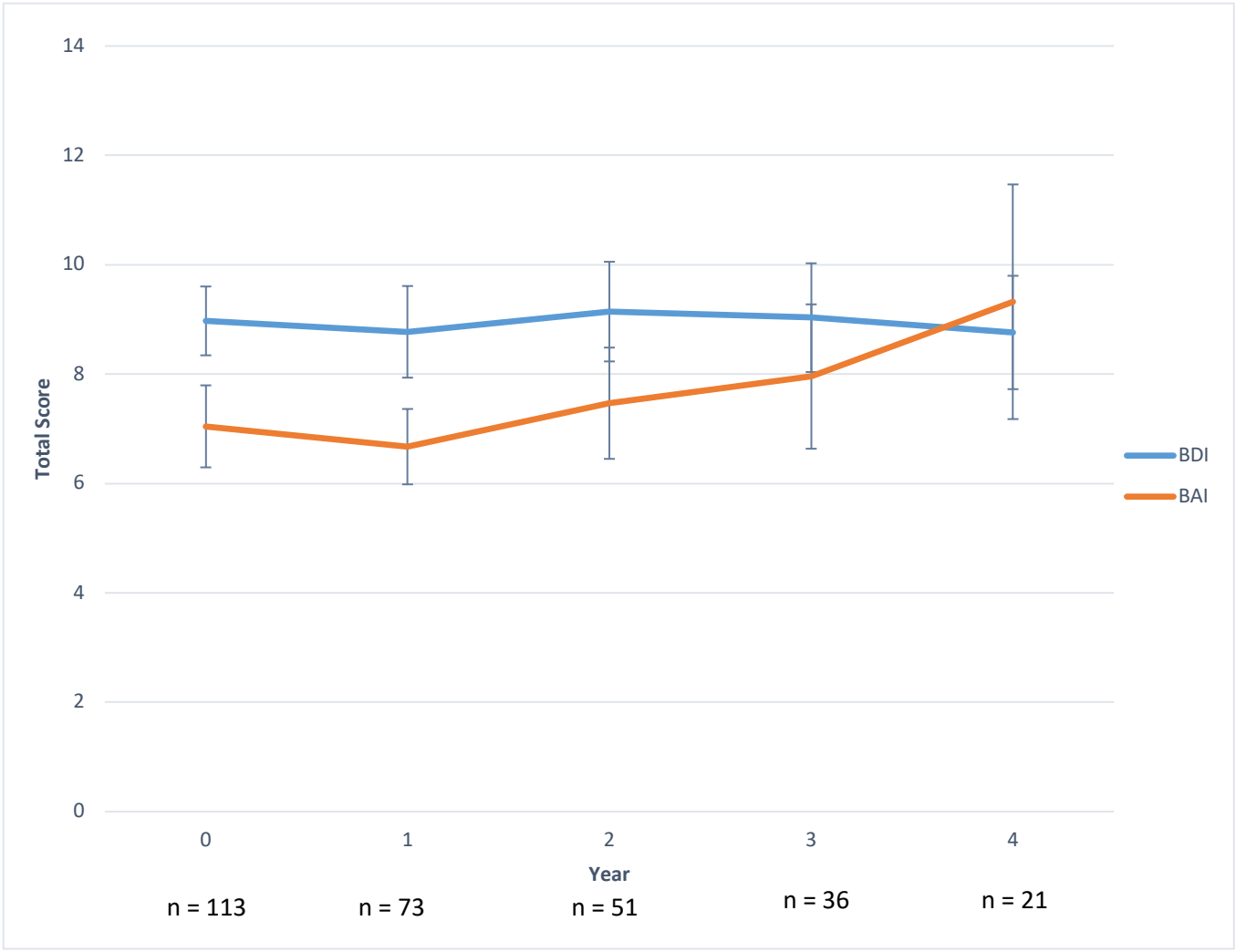

Figure 1. Comparison of total BDI and BAI scores over time in RBD patients.

Abbreviations: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI)

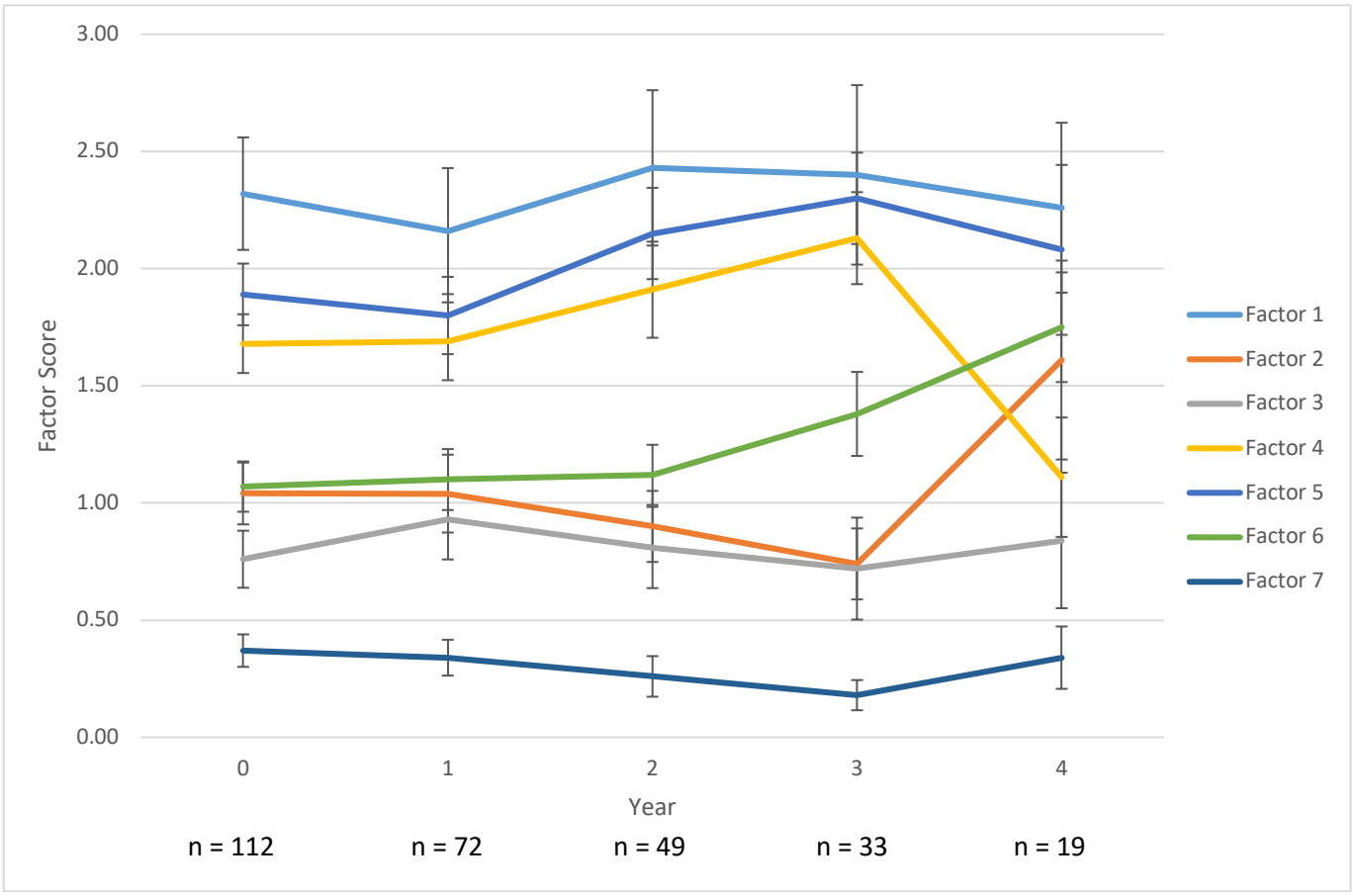

Figure 2. Progression of SPSS-derived BDI factors for RBD patients.

Abbreviations: Beck Depression Inventory (BDI)

Factor 1: Loss of Pleasure, Guilty Feelings, Self-Dislike, Self-Criticalness, Loss of Interest, Indecisiveness
Factor 2: Past Failure, Agitation, Worthlessness
Factor 3: Sadness, Pessimism, Punishment Feelings, Suicidal Thoughts
Factor 4: Tiredness and Fatigue, Loss of Interest in Sex
Factor 5: Loss of Energy, Changes in Sleep Pattern, Irritability
Factor 6: Changes in Appetite, Concentration Difficulty
Factor 7: Crying

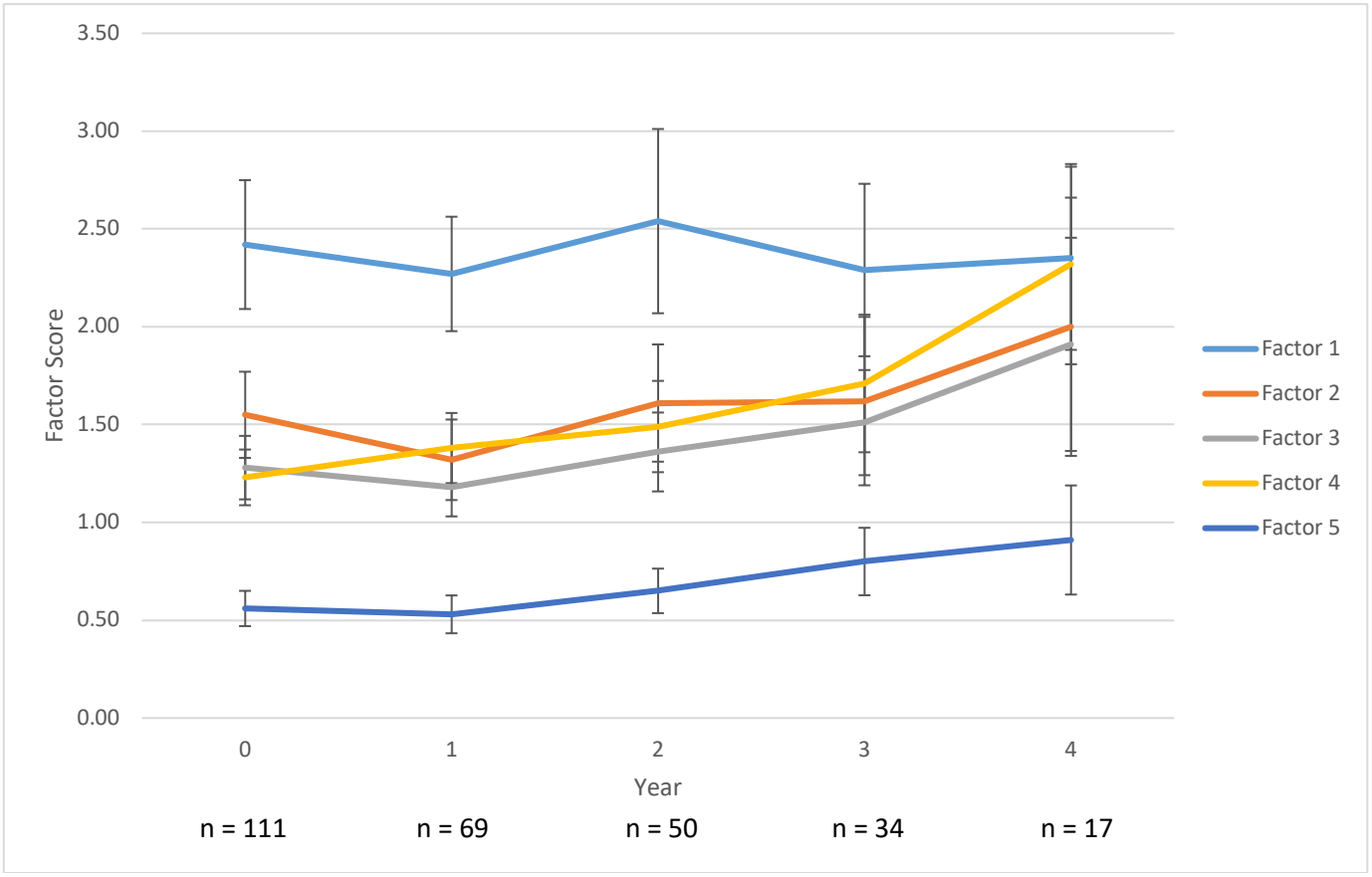

Figure 3. Progression of SPSS-derived BAI factors for RBD patients.

Abbreviations: Beck Anxiety Inventory (BAI)

Factor 1: Fear of Worst Happening, Terrified/Afraid, Nervous, Fear of Losing Control, Difficulty Breathing, Fear of Dying, Scared, Faint/Lightheaded
Factor 2: Feeling Hot, Feeling of Choking, Indigestion, Face Flushed, Hot/Cold Sweats
Factor 3: Dizzy/Lightheaded, Heart Pounding/Racing, Unsteady
Factor 4: Numbness/Tingling, Wobbliness in Legs, Unable to Relax
Factor 5: Hands Trembling, Shaky/Unsteady

Table 6. Exploratory analysis of phenoconvertors for BDI.

	Baseline (Non-convertors) N = 72	***Baseline (Convertors) N = 37***	***Year of Conversion N = 26***	***p-value***
Factor 1	2.2 ± 2.4	2.4 ± 2.8	2.5 ± 2.5	a: 0.92 b: 0.59 c: 0.83
Factor 2	0.92 ± 1.4	1.1 ± 1.3	1.1 ± 1.0	a: 0.48 b: 0.60 c: 0.86
Factor 3	0.63 ± 1.0	1.0 ± 1.6	0.77 ± 1.2	a: 0.22 b: 0.60 c: 0.52
Factor 4	1.6 ± 1.4	1.6 ± 1.2	2.0 ± 1.6	a: 0.99 b: 0.26 c: 0.29
Factor 5	1.9 ± 1.4	1.8 ± 1.5	2.1 ± 1.2	a: 0.86 b: 0.37 c: 0.36
Factor 6	0.88 ± 1.0	1.4 ± 1.3	1.5 ± 1.2	a: 0.04* b: 0.01* c: 0.71
Factor 7	0.31 ± 0.66	0.49 ± 0.84	0.15 ± 0.46	a: 0.22 b: 0.29 c: 0.07

* = denotes significance at threshold $p < 0.05$
a: comparison of both baselines
b: comparison of nonconvertors' baseline to convertors' conversion year
c: comparison of convertors' baseline to convertors' conversion year

Factor 1: Loss of Pleasure, Guilty Feelings, Self-Dislike, Self-Criticalness, Loss of Interest, Indecisiveness
Factor 2: Past Failure, Agitation, Worthlessness
Factor 3: Sadness, Pessimism, Punishment Feelings, Suicidal Thoughts
Factor 4: Tiredness and Fatigue, Loss of Interest in Sex
Factor 5: Loss of Energy, Changes in Sleep Pattern, Irritability
Factor 6: Changes in Appetite, Concentration Difficulty
Factor 7: Crying

Table 7. Exploratory analysis of phenoconvertors for BAI.

	Baseline (Non-convertors) N = 71	***Baseline (Convertors) N = 36***	***Year of Conversion N = 25***	***p-value***
Factor 1	2.5 ± 3.6	2.4 ± 3.5	1.1 ± 2.1	a: 0.89 b: 0.02* c: 0.08
Factor 2	1.6 ± 2.4	1.4 ± 2.3	1.5 ± 1.6	a: 0.79 b: 0.91 c: 0.88
Factor 3	1.2 ± 1.5	1.4 ± 2.1	1.4 ± 1.3	a: 0.58 b: 0.65 c: 0.89
Factor 4	1.3 ± 1.5	1.3 ± 1.5	1.7 ± 2.1	a: 0.87 b: 0.37 c: 0.46
Factor 5	0.54 ± 0.97	0.58 ± 0.97	0.96 ± 1.1	a: 0.81 b: 0.07 c: 0.16

* = denotes significance at threshold $p < 0.05$
a: comparison of both baselines
b: comparison of nonconvertors' baseline to convertors' conversion year
c: comparison of convertors' baseline to convertors' conversion year

Factor 1: Fear of Worst Happening, Terrified/Afraid, Nervous, Fear of Losing Control, Difficulty Breathing, Fear of Dying, Scared, Faint/Lightheaded
Factor 2: Feeling Hot, Feeling of Choking, Indigestion, Face Flushed, Hot/Cold Sweats
Factor 3: Dizzy/Lightheaded, Heart Pounding/Racing, Unsteady
Factor 4: Numbness/Tingling, Wobbliness in Legs, Unable to Relax
Factor 5: Hands Trembling, Shaky/Unsteady

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General Discussion

Results

Taken together, the results of the three chapters of this thesis provide insight on genetic, cognitive, and psychiatric features of RBD. Because longitudinal data was available, we were not only able to assess features at baseline but also able to assess how each feature changed over time and how phenoconversion was affected.

Chapter 1.

Here we investigated GBA mutations in our RBD cohort. We compared GBA mutation carriers to non-carriers at baseline and at time of phenoconversion and examined the effect of GBA mutations on rate of phenoconversion. Clinically, we found no difference in presentation between GBA mutation carriers and non-carriers at baseline, aside from lower self-reported age of RBD onset. No significant differences were seen at time of phenoconversion, though this could be related to low sample size for this analysis. We found that GBA mutations were associated with 3.3-fold higher phenoconversion rate from RBD to parkinsonism and dementia. Taken together, these results indicate that while the presence of a GBA mutation does accelerate phenoconversion to neurodegenerative disease, patients with GBA mutations do not represent a clinically differentiable subtype of RBD.

Chapter 2.

Next, we focused on cognitive changes associated with RBD and phenoconversion of RBD to parkinsonism and dementia. Using the pareidolia test [40], we compared the clinical and neuropsychological profiles of patients who made false noise errors (i.e. seeing a face when none was present) to patients who did not make errors. We also performed a preliminary analysis in which we determined the respective phenoconversion rates to parkinsonism and dementia of

those who made errors to those who did not. We found that patients who made false noise errors performed more poorly on the MoCA overall and in visuospatial-executive and memory sections. Clinically, these patients also reported less daytime sleepiness on the Epworth Sleepiness Scale (ESS) and more erectile dysfunction. Neuropsychological analysis also demonstrated decreased performance in measures of attention/executive functions, memory, and visuospatial function. Our preliminary analysis demonstrated that 6/71 patients who did not make an error (8%) had phenoconverted after an average 1.61 ± 0.62-years follow-up: 4/6 (66%) to parkinsonism-first and 2/6 (33%) to primary DLB. This is a lower proportion than was observed in patients who made false-noise errors, where 3/16 (19%) phenoconverted after an average 1.61 ± 0.62-years follow-up: 1/3 (33%) to parkinsonism-first and 2/3 (66%) to primary DLB.

Chapter 3.

Finally, we examined the profiles of mood disorders in patients with RBD. Using the BDI and BAI, we compared baseline total scores and individual question scores to controls. We also assessed how total scores changed over time and how they were influenced by phenoconversion. A factor solution was generated for each questionnaire and differences were assessed between RBD patients and controls at baseline and between baseline RBD factor scores and scores over time and at phenoconversion. We found that baseline differences exist between RBD patients and controls in terms of total questionnaire scores, individual question scores, and most SPSS-derived factors. Significant changes were seen over time in BAI, but not BDI, scores; however, comparing baseline scores to scores at time of phenoconversion showed no predictive values. One factor of depression (Factor 6: changes in appetite and concentration difficulty) and three factors of anxiety (Factor 3: dizzy/lightheaded, heart pounding/racing, unsteady; Factor 4:

numbness/tingling, wobbliness in legs, unable to relax, and Factor 5: hands trembling, shaky/unsteady) showed significant progression over a four-year period.

Overall Impressions

As research on RBD has increased in the past few decades, we have come to understand that RBD is closely linked to parkinsonism and dementia, with as many as 80% of RBD patients developing these diseases later in life [41]. What we have less of an understanding of is how various aspects of RBD contribute to or are affected by phenoconversion. Because RBD is part of the prodromal stage of neurodegeneration [39], it is of interest to identify non-motor disease predictors that could assist in the diagnosis and treatment of neurodegenerative disorders before the onset of motor symptoms.

Here we focused on three aspects of RBD that we hoped would provide insight into disease progression and potentially serve as disease predictors. Based on the results seen, the most promising feature of RBD that may act as a disease predictor is the presence of a *GBA* mutation. While patients with *GBA* mutations do not represent a sub-type of RBD, they are associated with a higher phenoconversion rate to parkinsonism and dementia in our cohort. These findings are supported by other studies in larger cohorts which showed that not only are *GBA* mutations associated with phenoconversion to PD but also that more severe *GBA* mutation variants are associated with higher risk of PD [22,42]. Our results may indicate that mutations to *GBA* do not act as disease modifiers, but rather act as accelerators of natural disease progression. Future studies should investigate other mutations in RBD, such as *SNCA*, to see if these mutations have effects on RBD clinical presentation and phenoconversion rate that are similar to effects seen in *GBA* mutations.

Changes in cognition may also be promising early measures of disease, but the results seen in our cohort were not overwhelmingly conclusive. However, this may simply be a result of short average follow-up time (in this case, only 1.6 years). Cognition has been demonstrated to be affected in disease progression, with those who phenoconvert demonstrating more severe cognitive impairment than patients who remain free from neurodegenerative disease [13]. Therefore, our analysis of the effect of false noise pareidolic errors on phenoconversion may have been premature in our cohort and should be repeated when we have sufficient follow-up data from a larger portion of patients. On the other hand, loss of cognition defines dementia, and so an extremely sensitive measure would be required in order to detect subtle changes in cognition prior to full disease onset. The pareidolia test may be effective in this regard, as a higher percentage of patients who made false noise errors phenoconverted than those who did not make errors, but our sample size is too small to make conclusions at this time.

Our third area of interest, depression and anxiety, showed clear differences between RBD patients and controls in terms of total questionnaire scores, individual scale questions, and scale factors. As expected, many of the questions we had flagged as being potentially confounding showed clear differences between RBD patients and controls in both individual question scores and factor scores. However, it is unclear whether these results are a true confound or a result of patient insight; patients may have interpreted the questions to be referring solely to symptoms of their anxiety or depression, and not as a result of an underlying neurodegenerative disease or RBD. Unfortunately, there is no way to know for sure how patients are interpreting questions. One potential solution to this problem would be to develop RBD specific questionnaires for depression and anxiety that attempt to phrase questions in a way that cannot possibly be confounded by RBD symptoms. Disease-specific questionnaires are not unusual; for example,

the Parkinson's Disease Sleep Scale (PDSS-2) was created to identify characteristics of sleep disturbances that may be specific to PD [43]. Also of interest is that many questions regarding symptoms of autonomic hyperactivation did not show significant differences between RBD patients and controls; this may be because patients with RBD suffer from autonomic dysfunction and as a result do not experience these symptoms of depression and anxiety. We were unable to see any predictive value of depression and anxiety in our cohort; BAI total scores and some BDI and BAI factor scores progressed significantly over time, but neither total scores nor factor scores changed as a result of phenoconversion. However, this may be a result of insufficient power in our cohort and so this analysis should be repeated in the future.

Future studies should continue to look at these and other potential predictors of phenoconversion from RBD to parkinsonism and dementia using longitudinal data. Furthermore, some of the preliminary analyses conducted here – such as the comparison of the clinical profiles of *GBA* mutation carriers to non-carriers at time of phenoconversion, effect of pareidolic false noise errors on phenoconversion, and change in SPSS factors for the BDI and BAI over time and at phenoconversion – should be repeated when sufficient follow-up data has been gathered to obtain statistical power.

Concluding Remarks

Here we have demonstrated the success in using a longitudinal cohort to study various genetic, psychiatric, and cognitive correlations to clinical features of RBD. In chapter 1, we showed that *GBA* mutations accelerate phenoconversion of RBD to neurodegenerative disease but do not represent a distinct clinical subtype of RBD. Chapter 2 focused on cognitive changes in RBD supplied three main findings: patients with RBD do experience pareidolias, patients who experience pareidolias have impaired cognitive functions in the domains of memory, visuospatial, and attention/executive function, and those who make pareidolic errors may be more likely to phenoconvert to DLB. In chapter 3, we looked at depression and anxiety in RBD patients and showed that total BDI and BAI scores are different at baseline but do not change over time and that SPSS-derived factors are different at baseline and may change over time in larger sample sizes.

Together, these findings help shed light on the genetic, psychiatric, and cognitive features of RBD, how they influence phenoconversion, and how they change over time. Understanding these various aspects of the disease may allow us to apply targeted interventions early in disease progression. Future studies should continue to use a longitudinal approach to attempt to understand correlations of clinical features and disease progression in RBD.

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