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Original Article

Further evidence for executive dysfunction in subjects with RLS from a non-clinical sample

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ABSTRACT

Objective and background: Previous studies exploring cognitive functioning in RLS have either relied on medication free subjects sampled within a clinical context or on subjects with RLS symptoms identified within population samples. However, in contrast to clinical samples, population studies so far have not excluded the use of antidepressants, hypnotics, or RLS relevant medication, and study subjects were exclusively older in age. We therefore report on cognitive functioning in predominantly middle-aged individuals with RLS symptoms sampled from the general population and free of mental disorders and of hypnotic, psychopharmacological, or RLS relevant medication.
Methods: Participants with RLS symptoms and individually matched controls were identified within the MARS control study, a non-clinical control group study of 550 participants between 18 and 75 years. Cognitive functioning was assessed with the Trail Making Test A and B and a computerized German version of the Wisconsin Card Sorting Test (WCST). Performance was compared between 41 participants with RLS and 133 controls, and between a subgroup of 10 participants with frequent RLS symptoms ($\geqslant$2/week) and 36 matched controls.
Results: There was no difference in cognitive functioning for the complete group of participants with RLS and controls. However, participants with frequent RLS symptoms showed impaired performance in the WCST.
Conclusion: The results of this study add to the evidence that executive functioning is impaired in individuals with frequent RLS.

1. Introduction

Restless legs syndrome (RLS) is a prevalent sleep-related movement disorder that is associated with impaired daytime functioning [1,2] and, in particular, decreased quality of life [3–5]. In recent years a small number of studies have examined cognitive function in individuals with RLS [6–10] (Table 1). In particular, three studies that sampled RLS patients within a clinical setting have found deficits in the area of short-term attention and verbal fluency [6,7,10]. RLS subjects in these studies were medication-free and suffered from moderate to severe RLS. Besides these clinical studies, two further studies have used population samples where RLS positive cases were identified within these samples and compared to RLS negative cases [8,9]. Participants in the two population studies were exclusively elderly (mean ages 68 [9] and 77 [8] years) and both studies allowed concomitant hypnotic or antidepressant use. In contrast, participants in clinical samples were decidedly younger (mean ages 57, 65, and 55 years) and hypnotic and psychopharmacological medications were excluded (see Table 1).

Overall, clinical studies with RLS patients in the middle age range have shown consistent deficits in cognitive functioning, while in epidemiological studies cognitive dysfunction may depend on RLS severity. Our aim was to further explore cognitive function in RLS focusing on attention/processing speed and executive function. To our knowledge, no previous published study has assessed set-shifting and cognitive flexibility in medication free de novo individuals with RLS.

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Table 1
Cognitive functioning in RLS subjects.

Study	RLS subjects vs. controls	RLS severity/medication	Main finding
Clinical samples			
Saletu et al. [6]	*n* = 12 vs. 12 57 vs. 59 years	• No RLS severity stated, PLMS/h >5 • Free of psychotropic medication	Reduced performance in fine motor activity and a reaction time task
Pearson et al. [7]	*n* = 16 vs. 15 65 vs. 59 years	• Moderately severe symptoms (JHRLSS), >20 PLMS/h • At least 2 weeks off RLS medication	Reduced performance in verbal fluency and TMT-B
Fulda et al. [10]	*n* = 23 vs. 23 55 vs. 55 years	• Average IRLS 24 ± 7 (SD) • At least 2 weeks off RLS medication and psychotropic medication	Reduced performance in verbal fluency, Stroop task, and a cancelation task
Population studies			
Driver-Dunckley et al. [8]	*n* = 26 vs. 208 77 vs. 78 years	• Average IRLS 11 ± 8 (SD) • Concomitant RLS medication, hypnotics, and antidepressants	No difference in performance
Celle et al. [9]	*n* = 77 vs. 241 69 vs. 69 years	• Average IRLS 17 ± 5 (SD) • Concomitant hypnotics, antidepressants	Reduced performance in verbal fluency and Stroop task

IRLS, international RLS study group scale; JHRLSS, John Hopkins RLS scale; PLMS, periodic limb movements during sleep; RLS, restless legs syndrome; SD, standard deviation; TMT-B, Trail Making Test, part B.

In this study, we compare cognitive functioning in middle-aged individuals with RLS without mental disorders and medication with carefully matched controls according to age, sex, and education level.

2. Methods

2.1. Subjects

Participants were recruited at the Max Planck Institute of Psychiatry in Munich as a healthy control group for depressed patients from the Munich Antidepressant Response Signature (MARS) project [11]. A total of 550 community-dwelling individuals (300 females, 250 males) with a mean age of 47 years participated in the study. They were randomly drawn from the registration office of Munich, comprising residents aged between 18 and 75 years. After a provisional screening of basal inclusion (being Caucasian of European decent) and exclusion criteria (having sought professional psychological or psychiatric help at any time in their life and suffering from severe somatic disorders) by telephone, participants were invited to participate in the study. All participants underwent a vis-à-vis psychiatric interview with a modified version of the Munich-Composite-International-Diagnostic Interview (DIA-X/M-CID I [12]) conducted by trained psychologists. Subjects with a history of alcohol dependence, drug abuse or dependence, psychotic disorders, mood disorders, anxiety disorders including obsessive–compulsive disorder and post-traumatic stress disorder, somatoform disorders, dissociative disorders, and eating disorders were excluded. Subjects older than 65 years were additionally tested with the Mini Mental State Examination (MMSE [13]) and were excluded if they had an MMSE score lower than 26. The study was approved by the ethics committee of the Ludwig Maximilian University in Munich, and all subjects gave written informed consent prior to study inclusion.

RLS status was assessed with three questions according to the International Restless Legs Study group criteria [14] that were previously employed in German epidemiological studies [15] and have been validated against physician diagnosis [16,17]. Participants answering yes to all three questions were classified as being RLS positive. Additional questions asked for current frequency of RLS symptoms, age at onset of first RLS symptoms, and whether other family members were affected. All participants had to be free of any RLS relevant medication, hypnotics, or psychopharmacological medication (including any dopaminergic medications, iron, iron supplements, gabapentin, pre-gabalin, melatonin, hypnotic medication, psychiatric medication, anti-epileptic medication, and multivitamins containing iron or folic acid).

In the complete sample, 43 participants were RLS positive and 41 of them were included in the present analysis. Two RLS positive participants were excluded, one because of antidepressant use and one because we were unable to find matching control subjects. RLS negative controls were matched individually (up to 1:4) to RLS participants according to sex, age, and educational level. For 34 participants with RLS the age of the controls was within a ±1 year range. The age difference was ±2 years between 5 participants with RLS and their controls and ±3 years between 2 participants with RLS and their controls. The number of matched controls was 4 for 22 participants with RLS, 3 for 8, 2 for 10, and 1 for 1 participant with RLS.

2.2. Procedure

All participants completed the Beck Depression Inventory (BDI [18]), the symptom check list SCL-90-R [19,20], and the state-trait anxiety inventory [21]. We extracted a measure of sleep disturbances from three item of the SCL-90-R, which asked for the presence of sleep onset difficulties, early awakenings, and disturbed or restless sleep during the last seven days on a five-point scale (0–4), each. Sleep disturbances were defined as the sum of all three items.

2.2.1. Neuropsychological testing

Two neuropsychological tests were administered by trained examiners. The tests were administered in the morning for the vast majority of participants. The Trail Making Test (TMT [22]) was used to assess attention/processing speed (TMT-A) and executive functioning/mental flexibility (TMT-B). For TMT-A participants were presented with circles numbered from 1 to 25 and asked to draw lines to connect the 25 circles in correct order as fast as possible. TMT-B requires connecting numbers and letters in an alternating sequence as quickly as possible. The time to complete parts A and B, and the difference score B–A, were used as outcome measures.

The 'Computergestütztes Kartensortierverfahren' (CKV) [23] is a computerized adaption of the Wisconsin Card Sorting Test (WCST) used to assess cognitive flexibility, set-shifting, and the development and maintenance of problem-solving strategies.

The CKV consists of four stimulus cards and 96 response cards. Participants were instructed to match each response card to one of the stimulus cards. After each selection feedback was given whether or not their trial was correct. The concept-change occurred after ten consecutive correct trials (referred to as completing a concept) and was not announced by the examiner. The test continued until six concepts were completed or until all 96 response cards had been presented.