Current Research in Neurobiology 2 (2021) 100021

Contents lists available at ScienceDirect

Current Research in Neurobiology

journal homepage: www.sciencedirect.com/journal/current-research-in-neurobiology

Cognitive profile in Restless Legs Syndrome: A signal-to-noise ratio account

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ARTICLE INFO

Keywords:
Restless legs syndrome
Cognition
Signal-to-noise ratio
Dopamine
tRNS

ABSTRACT

Restless legs syndrome (RLS) is a common neurological disorder characterized by a sensorimotor condition, where patients feel an uncontrollable urge to move the lower limbs in the evening and/or during the night. RLS does not only have a profound impact on quality of life due to the disturbed night-time sleep, but there is growing evidence that untreated or insufficiently managed RLS might also cause cognitive changes in patients affected by this syndrome. It has been proposed that RLS is caused by alterations in the signal-to-noise ratio (SNR) and in dopamine (DA) neurotransmission in the nervous system. Based on this evidence, we propose the "SNR-DA hypothesis" as an explanation of how RLS could affect cognitive performance. According to this hypothesis, variations/reductions in the SNR underlie RLS-associated cognitive deficits, which follow an inverted U-shaped function: In unmedicated patients, low dopamine levels worsen the SNR, which eventually impairs cognition. Pharmacological treatment enhances DA levels in medicated patients, which likely improves/normalizes the SNR in case of optimal doses, thus restoring cognition to a normal level. However, overmedication might push patients past the optimal point on the inverted U-shaped curve, where an exaggerated SNR potentially impairs cognitive performance relying on cortical noise such as cognitive flexibility. Based on these assumptions of SNR alterations, we propose to directly measure neural noise via "1/*f noise*" and related metrics to use transcranial random noise stimulation (tRNS), a noninvasive brain stimulation method which manipulates the SNR, as a research tool and potential treatment option for RLS.

1. Introduction

Restless legs syndrome (RLS), also called Willis-Ekbom Disease, is a common neurological disorder characterized by a sensorimotor condition, where patients feel an uncontrollable urge to move the (lower) limbs in the evening and/or during the night (Allen et al., 2003; Klingelhoefer et al., 2016; Trenkwalder et al, 2005, 2015). RLS has a profound impact on the quality of life because disturbed night-time sleep and daytime somnolence can cause substantial economic burden at both individual and societal levels (Trenkwalder et al., 2021). A groundbreaking hypothesis proposed by Trenkwalder and Paulus (2004) suggested that this condition might be considered a sign of increased "sensorimotor noise"/a decreased signal-to-noise ratio (SNR) during sensorimotor processing. Importantly, the ability to disentangle neuronal signals and noise is also crucial for adopting effective decision-making strategies (Gureckis and Love, 2009). So if the hypothesis by Trenkwalder and Paulus holds true, this does not only means that in RLS, irrelevant motor noise (uncontrolled urge to move the lower limbs) is interpreted as relevant signal that needs to be gated/controlled (Lin et al., 2018; Rizzo et al., 2010), but it also means that decision-making likewise be impaired in RLS (Bayard et al., 2013). While unmedicated RLS patients showed disturbed sensorimotor integration (Lin et al., 2018; Rizzo et al., 2010), the intake of dopaminergic medication is thought to restore sensorimotor integration in the same patient group (Rizzo et al., 2010), thus providing evidence for a pathological alteration of dopamine (DA) neurotransmission in the nervous

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https://doi.org/10.1016/j.crneur.2021.100021
Received 1 April 2021; Received in revised form 5 July 2021; Accepted 29 July 2021
Available online 8 August 2021

system of RLS patients (Paulus and Trenkwalder, 2006). Further, an imaging study revealed increased functional connectivity between the thalamus and frontal regions in RLS patients on DA medication compared to untreated patients and controls suggesting that DA agonists can compensate for hypo-activity in brain regions crucial for cognitive processes (Tuovinen et al., 2021). As proposed by Paulus and Trenkwalder (2006), the inverted 'U'-shaped function in RLS suggests that, low dopamine levels cause/worsen the clinical symptoms of unmedicated patients. In medicated patients, pharmacological treatment enhances DA levels "back to normal", which reduces or entirely stops RLS symptoms. However, overmedication, which is likely to produce augmentation (Trenkwalder et al., 2015), might push patients past the optimal point on the inverted U-shaped curve, which might ultimately prompt a reoccurrence of RLS symptoms (and associated cognitive issues).

While previous reviews mainly focused on clinical features, diagnosis, management, and the treatment of augmentation (Guo et al., 2017; Klingelhoefer et al., 2016; Trenkwalder et al., 2015; Trenkwalder and Paulus, 2019; Wijemanne and Ondo, 2017), the focus of our article are RLS effects on general cognitive processes. The motivation behind this is that a) cognitive impairment in movement and sleep disorders reflects a major challenge (Burn et al., 2014) and that b) intact cognition is indispensable for accomplishments in working environments (Diamond, 2013) and healthy aging (Rowe and Kahn, 1997). Specifically, our aim is to review cognitive processes affected by RLS (like attention, verbal fluency and executive functions) in order to propose a model in which we combine the SNR account (Trenkwalder and Paulus, 2004) with the DA U-shaped function hypothesis of RLS (Paulus and Trenkwalder, 2006), both of which had originally developed to explain clinical RLS symptoms. By combining the two approaches, we propose a novel, combined "SNR-DA hypothesis" of RLS as an explanation of how RLS could affect cognitive performance.

This article aims to sum up the cognitive profile of individuals with RLS and to elucidate the contradictive findings on the effects of SNR alterations reported in the literature. In the following, we propose the SNR-DA hypothesis of RLS. This is followed by detailed information on the cognitive profile of RLS patients OFF medication vs. ON medication, and future directions of research based on the assumption of altered SNR.

2. The SNR-DA hypothesis in RLS

Over the last decades, several hypotheses have been developed to explain the pathology underlying RLS. These include brain iron deficiency (Allen et al., 2020), the downregulation of adenosine receptors (Ferré, 2019), altered hormone levels (Fulda et al., 2005), the dopamine (DA) hypothesis from the spinal cord perspective (Clemens et al., 2006; Clemens and Ghorayeb, 2019; Rye, 2004) and the deficient gain control hypothesis (Trenkwalder and Paulus, 2004). According to the last hypothesis, RLS is caused by an alteration of an overarching neural principle, i.e., the processing of neural noise and adaptation of the SNR during information processing. An increased SNR has been considered to reflect an increase in neuronal gain control (Li and Rieckmann, 2014; Servan-Schreiber et al., 1990a; Yousif et al., 2016; Ziegler et al., 2016). Similarly to the volume control on a radio, our brain needs "gain control" to adjust the relation between neuronal input, which can change dramatically depending on variations in the environment, and neuronal output, which is essentially bound to happen within a limited range of amplitudes (Priebe and Ferster, 2002). The relation between neuronal input and output can be depicted by a sigmoid function in which the x-axis demonstrates a net-input and the y-axis shows the net-output: the steeper the sigmoid function, the stronger the gain modulation processes and the SNR and the better the ability to efficiently distinguish between signal and noise. Within the SNR framework, it has been suggested that the uncontrolled urge to move the lower limbs is due to increased neuronal noise during sensorimotor processing (Trenkwalder and Paulus, 2004). This idea of increased noise in RLS during sensorimotor processing has been investigated using transcranial magnetic stimulation-motor evoked potentials (TMS-MEPs), which is the pairing of electrical peripheral nerve stimulation with a TMS pulse over the primary motor cortex. While unmedicated RLS patients showed disturbed sensorimotor integration (Lin et al., 2018; Rizzo et al., 2010), the intake of DA medication restored sensorimotor integration in the same patient group (Rizzo et al., 2010). In other words, converging evidence suggests that unmedicated RLS patients may suffer from a decreased SNR. As a result from this neurobiological problem, they should be prone to (mis)interpret sensory/motor noise as relevant signal, which then results in the typical sensorimotor complaints. The intake of DA agonists increases gain control and the related SNR so that medicated RLS patients should no longer confuse irrelevant (sensorimotor) noise with relevant signal. The idea that DA agonists can restore sensorimotor integration in RLS is further supported by convergent evidence of a solid link between increased DA levels and increased SNR/gain control (Li and Rieckmann, 2014; Servan-Schreiber et al., 1990a; Yousif et al., 2016; Ziegler et al., 2016). Aside from this general functioning principle, it has further been proposed that RLS is specifically caused by hypo-activation of dorsoposterior hypothalamic dopaminergic A11 cell group/the diencephalic dopaminergic cluster (Clemens et al., 2006; Clemens and Ghorayeb, 2019; Rye, 2004), where less DA is released in RLS patients (Paulus and Trenkwalder (2006)). This assumption is supported by converging evidence that even though the primary pharmacological treatment of RLS targets D2-like (D2, D3, and D4) receptors, cortical DA signaling seems to remain unaffected in RLS. The analysis of dopaminergic pathway gene polymorphisms in RLS did not reveal any vulnerability in different variants of proteins involved in dopamine synthesis and signaling (Desautels et al., 2001). Further, Stiasny-Kolster et al. (2004) found normal DA metabolites in the cerebrospinal fluid and blood of RLS patients. Along the same lines, neuroimaging studies employing functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET) yielded inconsistent results on RLS-associated abnormalities in the nigrostriatal DA system (for reviews on this issue, see (Provini and Chiaro, 2015; Wetter et al., 2004). Following the DA hypothesis from the spinal cord perspective (Clemens et al., 2006), based on evidence from lesioned rats (Lopes et al., 2012) and from D_3-receptor knockout (D_3KO) mice (Accili et al., 1996), the functioning of dopaminergic area A11 nucleus seems to be altered in RLS. Indeed, both A11 lesioned rats and D_3KO mice display hyperactive behavior (Accili et al., 1996; Lopes et al., 2012), which resembles the typical pattern of symptoms reported by human RLS patients. In line with the evidence derived from D_3KO mice, the A11 nucleus projects to the spinal cord and is rich in D3 receptors (Takada et al., 1988), which are responsible for spinal reflex excitability (Keeler et al., 2012) and the primary target of action of pharmacological challenges to treat both sensory and motor symptoms of RLS (Clemens and Ghorayeb, 2019). As proposed by Paulus and Trenkwalder (2006), the dopaminergic A11 cell group releases slightly less DA in RLS, when this condition is left untreated. While normal DA concentrations are restored with appropriate medication, overmedication and the resulting excessive DA concentration in the synaptic cleft should overstimulate dopamine D1 receptors (compared with D2 receptors) in the spinal cord producing the phenomenon of augmentation. This may then trigger D1-related pain and a reoccurrence of periodic limb movements. Further, as pointed out by Paulus and Trenkwalder (2006), A11 also projects to the prefrontal cortex (PFC) (Takada et al., 1988), which is densely innervated by DA projections and crucial for many cognitive processes (Diamond, 2002). Based on the assumption of altered functioning of A11 nucleus and its projection to the PFC, a suboptimal SNR should therefore be the key mechanism underlying both the uncontrolled urges to move and the cognitive profile in RLS as well. Gain control is indeed a common functional principle that has been reported in neural networks at sensory, cognitive (Adelhöfer et al., 2018; Salinas and Thier, 2000;

Servan-Schreiber et al., 1990b), and motor levels (Greenhouse et al., 2015; Thura and Cisek, 2016). Based on the deficient gain control account (Trenkwalder and Paulus, 2004) and the idea of DA levels being at the lower end of the U-shaped function in RLS (Paulus and Trenkwalder, 2006), we propose the SNR-DA hypothesis of RLS. It suggests that RLS effects on cognition mirror the reductions in gain control/SNR, see Fig. 1. According to this hypothesis, variations/reductions in the SNR underlie RLS-associated cognitive deficits, which follow an inverted U-shaped function: In unmedicated patients, low dopamine levels decrease the SNR, which eventually impairs cognition. Pharmacological treatment enhances DA levels in medicated patients, which likely improves/normalizes the SNR in case of optimal doses, thus restoring cognition to a normal level. However, overmedication might push patients past the optimal point on the inverted U-shaped curve, where an exaggerated SNR potentially impairs cognitive performance relying on cortical noise such as cognitive flexibility (Armbruster-Genç et al., 2016). It is important to keep in mind that several factors that also play a relevant role for RLS, such as the co-medication with GABAergic agents, the severity of symptoms, the duration since disease onset, and circadian rhythm, are also known to alter DA levels. Regarding the co-medication with GABAergic agents, we expect drugs, such as pregabalin and gabapentin, to increase gain control and the SNR, because high GABA levels decrease cortical excitability via shaping and controlling cortical glutamatergic excitation (Petroff, 2002). That is, the GABA based co-medication can help to optimize the balance between excitatory and inhibitory modulatory effects which are relevant for gain control mechanisms (Fu et al., 2014). However, in contrast to DA, to date, it is not possible to trace online changes (i.e. during cognitive task performance) for the GABA system. Indeed, compared to DA, salivary measurements of GABA are non-validated and unreliable and magnetic resonance spectroscopy, by means of which would be possible to trace GABA in the brain does not allow to track online changes (i.e. during task performance). For these reasons, the focus of the hypothesis presented in this paper is on the DA system. More severe symptoms and/or longer disease duration are supposed to be associated with lower DA levels (Allen, 2015). This should further weaken gain control and the SNR, thus further aggravating any accompanying cognitive deficits. Lastly, the circadian rhythm is known modulate DA, with typically lower levels of DA during the evening than during the morning (Domínguez-López et al., 2014; Garcia-Borreguero, Larrosa, et al., 2004; Garcia-Borreguero, Serrano, et al., 2004). Further, Trenkwalder et al. (2003) found that high doses of DA-based pharmacological long-term treatments disrupt the circadian rhythm of the dopaminergic tone in a way to increase the tone in the early morning and to decrease it during the night. As a consequence, gain control and SNR should be more impaired during the evening, thus producing stronger cognitive deficits than during the morning.

In sum, the SNR-DA hypothesis in RLS would predict cognitive impairments in OFF medicated/drug-naïve patients (i.e., untreated patients located on the lower/left part of the inverted U-shaped function in Fig. 1), which should be further worsened by daytime (evenings), more severe symptoms, and longer disease duration (Allen, 2015). Medicated patients (i.e., optimally treated patients who are located in the central part of the inverted U-shape function in Fig. 1) should however show normal cognitive functioning as the pharmacological increase in DA levels should increase SNR/gain control back to normal levels, thus restoring the neuronal processing principles underlying cognitive performance.

3. Cognitive profile of RLS patients

In this section, we will provide an overview of findings on cognitive functioning in RLS patients who are OFF medication/drug-naïve, described in the section "3.1", those who are medicated with dopaminergic drugs, described in the section "3.2" and those are overmedicated (augmented) with dopaminergic drugs, described in the section "3.3". We performed an electronic search on the PubMed database using the search terms: "(Restless Legs Syndrome OR RLS OR Willis-Ekbom Disease) AND cognition AND cognitive functions", "(Restless Legs Syndrome OR RLS OR Willis-Ekbom Disease) AND decision making", "(Restless Legs Syndrome OR RLS OR Willis-Ekbom Disease) AND augmentation AND cognition AND cognitive functions" and "(Restless Legs Syndrome OR RLS OR Willis-Ekbom Disease) AND augmentation AND decision making). This electronic search yielded single case studies, human studies, and animal studies, even though there are no animal models for studying the cognitive effects of RLS as of yet, see Fig. 2.

We then included studies based on the titles' and abstracts' significance to cognitive functions. We also performed a forward and backward citation search for further studies. Only articles written in English were included. All the studies outlined below are summarized in Table 1.

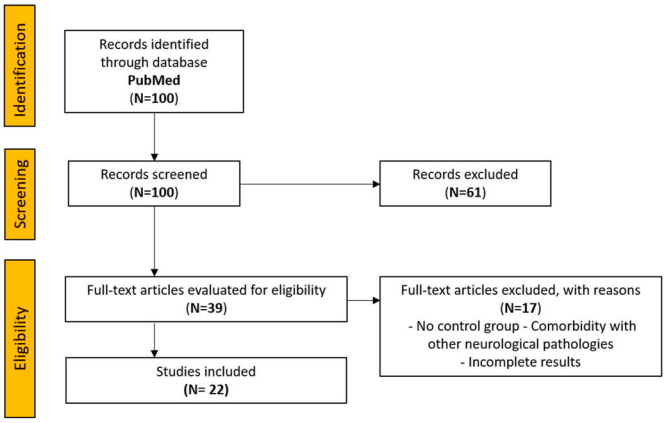

Fig. 2. Flow-chart of the literature search.

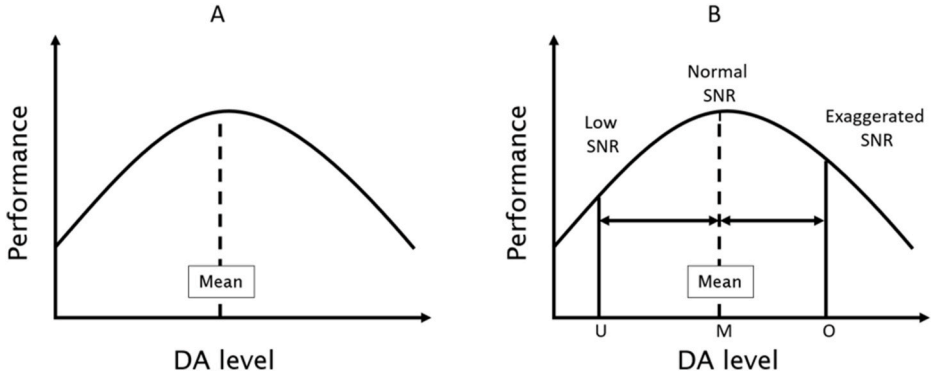

Fig. 1. Schematic illustration of the SNR-DA hypothesis of RLS, which centers around the gain control and the nonlinearity principles. (A) Cognitive performance tends to relate to DA levels in a nonlinear inverted-U-shaped fashion, where medium levels are associated with best possible performance. (B) Unmedicated RLS patients ("U") should have low DA levels, which worsen the SNR and impair cognition. Optimally medicated RLS patient ("M") should have medium DA levels, which likely normalize the SNR, thus restoring cognition to a normal level. Overmedicated (augmented) RLS patients ("O") should have high DA levels, which likely cause an exaggerated SNR to impair cognitive performance.

Table 1
Overview of studies investigating cognitive functions in RLS. For statistically significant effects, the thickness of the arrow illustrating the cognitive effects reflects the effect size: slim arrows correspond to small effect sizes, intermediately wide arrows correspond to a medium effect size and wide arrows correspond to a large effect size. When the effect size was not available, z-score, Cohen's d, the coefficients (β) or (OR) with corresponding confidence intervals (CI), interquartile range (IQR) and exact p values are reported (if available).

Study	Age (mean)	Sample size	Demographic covariates in the analysis	Effect size Cognitive effect (s) and p values	Cognitive Effect(s)
Bayard et al. (2013)	55.9 years	N = 39 drug-naïve RLS N = 50 medicated RLS N = 60 controls Groups matched for age, educational level, gender	None	p = .013 p = .39	↓ decision making (Iowa Gambling task) = decision making (Game of Dice Task)
Celle et al. (2010)	68.6 years	N = 77 drug-naïve RLS N = 241 controls Groups matched for age, educational level, alcohol intake, BMI	Medication (hypnotics or antidepressant), depression, smoking and alcohol use, hypertension, diabetes, and subjective sleep	OR, 95% CI: 0.97, 0.95–0.99; p = .02 OR, 95% CI: 0.95, 0.93–0.99; p = .01 OR, 95% CI: 0.95, 0.92–0.99; p < .05 OR, 95% CI: 0.93, 0.87–0.97; p < .003	↓ Stroop word time ↓ Stroop color time ↓ Verbal phonemic fluency ↓ Verbal semantic fluency
Choi et al. (2012)	54.1 years	N = 17 drug-naïve RLS N = 13 controls Groups matched for age, gender, educational level	None	p = .004 p < .001 p < .001 p < .001	↑ reaction times ↑ bothersomeness during visual oddball ↓ induced gamma-band activity (GBA) ↓ delay of P300 ERP
Driver-Dunckley et al. (2009)	77.5 years	N = 26 mild medicated RLS N = 208 controls Groups matched for age, educational level	None	All of the mean cognitive scores were equivalent within one standard deviation of the group without RLS.	= Stroop test, short-term memory, verbal fluency, verbal learning, Folstein mini-mental status examination (MMSE), clock drawing
Ellmerer et al. (2020a)	62.3 years	N = 27 medicated RLS N = 26 augmented (AUG) RLS N = 21 controls Groups matched for age, educational level, gender	None	p = .001, η2 = 0.160	⬇ facial emotion recognition in AUG compared to RLS medicated and controls
Ellmerer et al. (2020b)	60.9 years	N = 23 medicated RLS N = 15 augmented (AUG) RLS N = 21 controls Groups matched for age, educational level, gender	None	p = .001, η2 = 0.201	⬇ Frontal Assessment Battery in AUG than medicated RLS and controls
Fulda et al. (2010)	54.8 years	N = 23 unmedicated RLS N = 23 controls Groups matched for age, gender, educational level	None	Cohen's d = .54 Cohen's d = .48 Cohen's d = .78 Cohen's d = .49	⬇ verbal fluency (Letter fluency) ⬇ verbal fluency (Category fluency) ⬇ attention (Stroop task) ⬇ attention (D2 Cancellation test)
Fulda et al. (2011)	49.6 years	N = 41 drug-naïve RLS N = 133 controls N = 10 frequent drug-naive RLS N = 36 matched controls	None	ps < 0.025 (Bonferroni-adjusted)	↑ more errors (total and non-perseverative errors) in the WCST in frequent RLS patients
Galbiati et al. (2015)	46.6 years	N = 20 RLS untreated (baseline) and treated (follow-up) N = 15 controls Groups matched for age, gender, educational level	None	ps < 0.05 ps < 0.05	Comparison RLS untreated (baseline) and controls: ↓ performance in decision making (Iowa Gambling Task (IGT) and the Wisconsin Card Sorting Test (WCST) (at baseline when untreated) Comparison RLS untreated (baseline) and RLS treated (follow-up): ↑ performance in decision making (Iowa Gambling Task (IGT) and the Wisconsin Card Sorting Test (WCST)) (at follow-up when treated) Comparison RLS treated (follow-up) and controls (descriptive statistics): = cognitive performance
Gamaldo et al. (2008)	61.8 years	N = 16 off treatment RLS N = 13 sleep-deprived controls	None	p < .05	= Stroop test, Trail making task ↑ Letter fluency, Category fluency

(*continued on next page*)

Table 1 (*continued*)

Study	Age (mean)	Sample size	Demographic covariates in the analysis	Effect size Cognitive effect (s) and p values	Cognitive Effect(s)
		Groups matched for age, gender			
Heim et al. (2017)	60.8 years	N = 24 medicated RLS N = 40 augmented (AUG) RLS N = 21 controls Groups matched for age, educational level, gender	None	p = .037 p < .001	↑ irrational decisions in AUG compared to medicated RLS ↑ irrational decisions in AUG compared to controls
Heim et al. (2021)	62.5 years	N = 19 augmented (AUG) + ICD RLS N = 21 augmented (AUG) RLS N = 21 controls Groups matched for age, educational level, gender	None	p = .008	↑ irrational decision making in AUG + ICD and AUG compared to controls
Kim et al. (2014)	52.0 years	N = 13 drug-naïve RLS N = 13 controls Groups matched for age, gender, educational level, sleep duration	None	p = .005 ps < .033	↓ prolonged RT in all memory load size ↓ P300 amplitude in parietal regions
Lee et al. (2014)	67.3 years	N = 23 untreated RLS N = 31 medicated RLS N = 35 controls Groups matched for age	Education and age	p = .01	= cognitive performance (executive functions, verbal fluency, attention) ↑ Clock drawing test in treated RLS
Li et al. (2018)	57.7 years	N = 40 drug-naïve RLS N = 40 controls	Depression, anxiety, concomitant sleep disturbances	p < .0001 ps < .002 p = .008	↓ Stroop test ↓ Clock drawing test ↓ Rey-Osterrieth Complex Figure Test
Moon et al. (2014)	18–70 years	N = 15 drug-naïve RLS N = 17 controls Groups matched for age	None	IQR = 13.62–14.73, p = .033 IQR = 14.64–18.77, p = .033	↓ verbal memory ↓ category word fluency
Pearson et al. (2006)	62.3 years	N = 16 off treatment RLS N = 15 controls Groups matched for age, gender, educational level	Age	p = .01 p = .05	↓ verbal fluency (sum- category number of words) ↓ Trail Making Test B
Rist et al. (2015)	82.2 years	N = 417 RLS (possible misclassification) N = 1653 controls	Age, sex, smoking status, alcohol consumption, physical activity, BMI categories, history of high blood pressure, history of high cholesterol, history of diabetes, history of cardiovascular disease, and education	z-score - 0.003 (SE 0.173) for RLS patients z-score - 0.007 (SE 0. 129) for controls	= cognitive z-score (Isaacs'test of verbal/categoryfluency, the Benton VisualRetention Test, the Trail Making Test B, and the Mini-Mental State Examination)
Tak et al. (2019)	36.6 years	N = 30 RLS N = 30 controls Groups matched for age, gender, level of education	None	p = .000	↓ Montreal Cognitive Assessment
Zhang et al. (2017)	64.8 years	N = 33 medicated RLS but drug-free during testing N = 29 controls Groups matched for age and gender	None	η2 = 0.151, p = .023 η2 = 0.070, p = .039	⬆ Flanker interference effects in the evening than in the morning ⬇ N1 amplitudes in the interfering task condition in the evening, but not in the morning (electrode P9).
Zhang et al. (2018)	64.1 years	N = 33 medicated RLS but drug-free during testing N = 27 controls Groups matched for age and gender	None	η2 = 0.115, p = .018 η2 = 0.106, p = .026	⬆ task performance due to reduced visuo-motor priming in the evening ⬇ less positive LRP-S in the evening than in the morning in the incompatible condition
Zhang et al. (2019)	60.2 years	N = 25 medicated RLS but drug-free during testing N = 31 controls Groups matched for age, gender and educational level	None	η2 = 0.183, p = .001 η2 = 0.116, p = .010	⬇ behavioral performance (lower response accuracy) ⬆ accuracy differences between the low and high demand tasks

3.1. Cognitive profile in OFF medication/drug-naïve RLS patients

Several studies have looked at the cognitive profile of RLS patients who were OFF medication or drug-naïve. In the following, we will describe cognitive processes affected by (untreated) RLS, including DA-driven functions such as verbal fluency, attention, and executive functions (interference control, working memory, cognitive flexibility) (Cools, 2006, 2016, 2006; Nieoullon, 2002).

In a community based study, Celle et al. (2010) compared elderly individuals with RLS who were not pharmacologically treated for this condition to individuals without RLS. They found that the unmedicated RLS patients had a lower performance in verbal fluency and in the Stroop task, which indexes the ability to inhibit interference from irrelevant information (Stroop, 1935). A recent study has even replicated these results of impaired Stroop task performance in a sample of younger RLS patients (Liu et al., 2018). Likewise, comparable impairments in verbal fluency or verbal memory have been reported in three other studies (Fulda et al., 2010; Moon et al., 2014; Pearson et al., 2006).

Potts et al. (2004) and Choi et al. (2012) found RLS patients to react more slowly than matched controls in a visual oddball task, in which a series of repetitive stimuli are unpredictably interrupted by a deviant stimulus (i.e., visual oddball) to measure attentional processes. Furthermore, patients showed increased bothersomeness during the visual oddball task, which was accompanied by a delay of P300 event-related potential (ERP) and a decrease in induced gamma-band activity (GBA) and gamma-band phase synchrony (GBPS), indicating an alteration of allocation of visual attention. Along the same lines, Fulda (2010) reported impairments in short-term attention in unmedicated RLS patients, as compared to matched controls. In a follow-up study on middle-aged individuals, the same research group (Fulda et al., 2011) showed that participants with frequent RLS symptoms ($\geq$2/week) performed worse in the Wisconsin Card Sorting Test (WCST), which measures the ability to exhibit flexibility in the face of changing implicit rules. Importantly, this study suggests that a certain degree of symptom severity must be reached before cognitive deficits surface can be reliably detected. Yet, it should also be mentioned that Rist et al. (2015) failed to replicate this assumption in a population-based cross-sectional study. Still, Rist et al. (2015) acknowledged that their study design did not allow investigating whether rates of cognitive change (over time) were different amongst those with RLS compared to those without RLS. Instead and in line with the findings by Fulda et al. (2011), cognitive flexibility measured with the Trail Making Test B has been reported to be impaired in a sample of older participants with moderately severe symptoms (Pearson et al., 2006). Besides the degree of symptom of severity, disease duration also plays a pivotal role. In line with findings of impaired visual memory (as indexed by Rey-Osterrieth Complex Figure Test) (Li et al., 2018), Kim et al. (2014) found reduced working memory performance, as indexed by a Sternberg task, and a lower P300 ERP amplitude regardless of memory load sizes. Interestingly, the P300 amplitude was negatively correlated with disease duration, which seems to worsen cerebral cortical dysfunction (Kim et al., 2014). While the studies by Fulda et al. (2011) and Kim et al. (2014) highlighted the importance accounting for symptom severity and disease duration, circadian variations also seem to affect cognitive performance in RLS (Zhang et al, 2017, 2018). As DA plays an important functional role the circadian timing system, with peak values in the morning and a nadir at night (Domínguez-López et al., 2014; Garcia-Borreguero et al., 2004a, 2004b), it has been hypothesized that the cognitive profile of RLS may also vary with the time of the day (Zhang et al, 2017, 2018). In line with the assumption that RLS patients experience a stronger nighttime decrease in DA signaling than healthy individuals (Allen, 2015), Zhang and colleagues found RLS patients (but not healthy controls) to show an increased flanker interference effects in the evening as compared to the morning. This was reflected by decreased ERP N1 amplitudes (Zhang et al., 2017). Along the same lines, deficits in visuo-motor priming (which were however paradoxically associated with enhanced task performance and linked to smaller early lateralized readiness potential (e-LRP) amplitudes), have been reported to be stronger in the evening than in the morning (Zhang et al., 2018). This further indicates that cognitive changes in RLS patients are mainly present and/or enhanced in the evening (Zhang et al, 2017, 2018).

Adding to Zhang et al. (2019), who found RLS to be associated with decreased behavioral performance (i.e., lower response accuracy) in a high cognitive demand task, two more studies have reported RLS-associated increases in mild cognitive impairment, as measured with the Montreal Cognitive Assessment (Tak et al., 2019) and Clock drawing test (Li et al., 2018).

In sum, RLS patients tested OFF medication or while still drug-naïve (i.e., untreated patients located on the lower/left part of the inverted U-shaped function in Fig. 1) displayed deficits in DA-associated cognitive functions such as interference control, memory, verbal fluency, attention and executive functions. Importantly, these findings indicate a suboptimal SNR and are thus well in line with the assumptions and predictions and the SNR-DA hypothesis. Furthermore, the observed deficits seem to be more pronounced in the evening, in case of more severe symptoms and longer disease duration, all of which are known to reduce DA levels (Allen, 2015).

3.2. Cognitive profile in medicated RLS patients

Only four studies have looked at the cognitive profile of RLS patients ON medication, where the SNR-DA hypothesis of RLS predicts no impairments, as dopaminergic treatment should have normalized the SNR, thus restoring cognitive performance.

In a seminal study, Galbiati et al. (2015) compared healthy controls to RLS patients both OFF medication (baseline testing) and ON medication (follow-up). Interestingly, RLS patients displayed impaired performance in decision making (as indexed by the Iowa Gambling Task) and in cognitive flexibility (as measured by the WCST) only at the "OFF" baseline testing. Notably, the impairments disappeared at the follow-up "ON" testing, demonstrating that dopaminergic medication can indeed compensate the cognitive decline caused by RLS. In line with this study, Driver-Dunckley et al. (2009) found no evidence of cognitive impairments using a large battery of tests in medicated patients with mild RLS. Further, Lee et al. (2014) found no differences in cognitive performance when comparing healthy controls with medicated and untreated RLS patients. However, the authors acknowledged that their untreated RLS group showed less severe symptoms than the medicated RLS patients. This might further underline the assumption that, as pointed out by Fulda et al. (2011), a certain degree of symptom severity might be necessary for cognitive impairments to become evident. Finally, Bayard et al. (2013) showed impaired decision making, as measured by the Iowa Gambling task but not by the Game of Dice Task, in medicated and untreated RLS patients compared to healthy controls. As mentioned by the authors, reasons for finding no differences in performance between medicated and untreated RLS patients may be due to the limited duration of medication exposure and the low dose DA agonists intake in medicated patients.

In sum, RLS patients tested ON medication displayed unimpaired cognitive performance in DA-associated driven cognitive functions such as interference control, verbal fluency, attention and executive functions. In line with the SNR-DA hypothesis, this indicates that optimal dopaminergic treatment normalizes the SNR. Considering that the patients included in these studies did not report an exacerbation of RLS clinical symptoms, it is safe to assume that their DA based pharmacological treatment was sufficiently optimized (i.e., that they were located in the central part of the inverted U-shaped function in Fig. 1).

3.3. Cognitive profile in overmedicated (augmented) RLS patients

In this section the few studies investigating cognitive performance in overmedicated (augmented) patients (i.e., located in the lower right part

of the inverted U-shaped function in Fig. 1) are described.

Ellmerer et al. (2020a) found RLS patients with augmentation to display worse performance on the facial emotion recognition task compared to RLS medicated controls (without augmentation) and healthy matched controls. In line with these results, while performing a decision making task, RLS patients with augmentation committed more irrational decision compared to RLS medicated controls (without augmentation) and healthy matched controls (Heim et al., 2017), irrespective of suffering or not from an additional impulse control disorder (Heim et al., 2021). Related to the evidence of impairments in decision-making, a new study investigated the effect of augmentation on frontal lobe functions as measured by the Frontal Assessment Battery (FAB) which assesses abstract reasoning, cognitive flexibility, executive functions, resistance to interference, self-regulation and inhibitory control. RLS patients with augmentation performed poorly in the FAB compared to RLS medicated controls (without augmentation) and healthy matched controls (Ellmerer et al., 2020b).

In sum, RLS patients with augmentation showed impairments in cognitive performance in DA-associated driven cognitive functions such as emotional recognition, decision making and frontal lobe functions. As expected by the SNR-DA hypothesis, this indicates that dopaminergic overmedication causes an exaggerated SNR impairing cognitive performance, see Fig. 1.

4. Future directions of RLS research

4.1. Direct of measurements of SNR in RLS

In order to verify the SNR-DA hypothesis in RLS, future studies should directly investigate neural noise via electroencephalography (EEG) by measuring "1/*f noise*" as an index for the so-called 'pink noise' or scale-free neural activity (He, 2014). Hence, via the assessment of 1/*f noise* in neurophysiological signals, the hypothesis of low SNR in unmedicated RLS can be tested directly. Compared to 'white noise' and 'brown/red noise', 'pink noise' does not reflect meaningless unstructured noise (He, 2014), but it contains relevant signals for information processing and brain functioning (He, 2014). In brief, the idea is that the distribution of neural activation (i.e., the power spectral density [PSD]) across the entire (EEG) frequency spectrum mirrors neural noise (Dave et al., 2018). 1/*f noise* can be illustrated by a slope, a linear regression line occurring from the calculation of the logarithm of PSD across the frequency spectrum (Dave et al., 2018; He, 2014). A flatter slope indicates more neural noise, whereas a steeper slope reflects less neural noise (Dave et al., 2018; He, 2014). Notably, 1/*f noise* can be measured during task processing (Ouyang et al., 2020; Pertermann et al., 2019a, 2019b, 2019b; Podvalny et al., 2015) making of this metric the most valuable tool to investigate the SNR-DA hypothesis in RLS. However, in event-related data the problem may arise that the 1/f method can conflate narrow-band power with the broader-band 1/f component. As consequence, by calculating 1/f, it cannot be ruled that possible differences in 1/f do in fact reflect changes in oscillatory power (Donoghue et al., 2020). Yet, this can be controlled for using recent advances in signal processing and by calculating so-called aperiodic activity, which is conceptually related to 1/f noise (Donoghue et al., 2020).

In line with this hypothesis, we expect unmedicated RLS patients to display a flatter slope compared to healthy controls which will translate into impaired cognitive performance. Instead, after receiving DA agonists, the slope of RLS patients becomes steeper as indication of reduced neural noise obtained via medication use which will result in restored cognitive functions. Finally, following an inverted u-shaped function, in augmented RLS patients, we expect overmedication to cause a flatter slope boosting neural noise and impairing cognitive performance. In sum, the SNR-DA hypothesis in RLS can be verified measuring 1/*f noise* and related metrics of aperiodic activity as valuable tools to quantify neural noise which can be measured during experimental cognitive tasks. However, for that, future research still has to be determined whether the concept of "noise", as measured in the above mentioned metric, is conceptually identical to the concept of noise discussed in section 2 (Münchau et al., 2021). The reason is that in section 2, the definition of „noise" relates to a 'signal vs noise' or 'foreground vs background' framing and hence unwanted/interfering/uninteresting signal (Servan-Schreiber et al., 1990b). This definition of "noise" is different from conceptual frameworks related to "1/noise", and "aperiodic activity". In the latter, noise is conceptualized as a signal of interest and not merely 'noise' or 'background' activity (Donoghue et al., 2020).

4.2. Modulating the SNR in RLS – novel treatment strategy

In addition to currently standard dopaminergic treatments, the SNR may also be modulated by noradrenergic drugs as well as by noninvasive brain stimulation techniques like transcranial electrical stimulation (tES), where electrical currents with low intensities (typically 1–2 mA) are administered via electrodes positioned on the intact skull (Paulus, 2011). tES might be especially interesting for severe cases of RLS, i.e., when pharmacological treatment becomes insufficient due to augmentation, the development of tolerance or contraindication for dopaminergic treatment. In cognitive neuroscience, this method is renowned to not only examine the relationship between brain and cognitive processes but to also act as a cognitive enhancer (Filmer et al., 2014; Schuijer et al., 2017). Specifically, tES modulates spontaneous firing rates of cortical neurons and produces alterations in cortical excitability, which can last for up to 1 h after the termination of the stimulation (Nitsche and Paulus, 2000; Paulus et al., 2016). A relatively novel tES method to modulate the SNR is transcranial random noise stimulation (tRNS), which is a specific type of transcranial alternating current stimulation (tACS). In tRNS, a low-intensity alternating current is applied so that the intensity and the frequency of the current vary in a randomized manner (Paulus et al., 2016). It has been proposed that the effects obtained by tRNS can be explained within the framework of stochastic resonance (Gammaitoni et al., 1998), which boosts undetectable signals by resonating them with supplemented white noise. That is, a signal that would usually be too low to be detected by a sensor can be boosted by supplementing white noise to it. White noise comprises a wide spectrum of frequencies so that the frequencies in the white noise matching the original signal's frequencies will resonate with one another. In so doing, the original signal, but not the rest of the white noise, is amplified. This, in turn, increases the SNR and makes the original signal easier to detect. Given that neuroimaging evidence suggests the pre-Supplementary Motor Area (SMA) to be crucial in the network of executive functions (Aron and Poldrack, 2006; Sjöberg et al., 2019) and of the starting signal for the execution of the motor act (Keller and Heckhausen, 1990), it makes sense to assume that tRNS over the SMA might ameliorate RLS symptomatology and cognitive performance related to executive functions. In general, another advantage of applying tRNS over the cortex is that its effects can be easily measured by assessing the amplitude and time course of TMS-MEPs (Nitsche and Paulus, 2000). Aside from potentially improving executive functions deficits in unmedicated RLS patients, tRNS might be a valuable method to also restore other cognitive functions affected by RLS when targeting the brain areas most strongly related to the respective functions. The stimulation of the left medial temporal lobe, which is linked to verbal fluency (Pihlajamäki et al., 2000), might compensate deficits word production. Deficits in attentional processes might instead be improved after the stimulation of the frontal eye fields, which are crucially involved in the attentional network (Shipp, 2004). Lastly, tRNS over the dorsolateral frontal cortex, which is related to memory processes (Petrides et al., 1993), should improve the encoding, storage, and retrieval of task relevant information.

In sum, tRNS over the SMA is likely to increase the SNR via stochastic resonance, a factor known to fine-tune the SNR (Chapeau-Blondeau, 1997). Given that tES is known to modulate neural plasticity for minutes or hours following stimulation (Nitsche and Paulus, 2000), we consider

tRNS a promising candidate to restore the SNR and the related cognitive profile to an optimal level in RLS who report cognitive complaints.

5. Conclusion

The current article provides a comprehensive framework of how RLS affects the cognitive profile of patients. The SNR-DA hypothesis suggests that variations/reductions in the SNR underlie RLS-associated cognitive deficits, which follow an inverted U-shaped function. In unmedicated RLS patients, their low levels of DA will weaken the SNR/gain control, ultimately impairing cognition. On the other hand, the pharmacologically enhanced DA levels of optimally medicated patients should re-adjust the SNR/gain control and thus restore cognition to a normal level. Future studies should test our hypothesis that overmedication might push patients past the optimal point on the inverted U-shaped curve, where an exaggerated SNR might potentially impair cognitive performance relying on cortical noise, such as cognitive flexibility. Even though more systematic investigation is required, we advise considering different modulators of DA levels, like the degree of symptom severity, disease duration, and circadian rhythm. We recommend that future studies examine the role of the SNR/gain control in RLS via measuring 1/*f noise* and related metrics. Further, we encourage the use of well-defined tRNS studies to clarify whether tRNS is a valuable treatment in RLS patients who report cognitive complaints.

CRediT authorship contribution statement

Lorenza S. Colzato: Conceptualization, Funding acquisition, Visualization, Roles/. **Wenxin Zhang:** Funding acquisition, Roles/. **Moritz D. Brandt:** Conceptualization, Writing – review & editing. **Ann-Kathrin Stock:** Conceptualization, Roles/. **Christian Beste:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Roles/.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by a research grant from 100 Talent Grant of the Province of Shandong, China, to LSC, WZ and CB.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crneur.2021.100021.

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