Slow Waves And Sleep Spindles In Schizophrenia And Healthy First Degree Relatives: Association With Impaired Cognitive Function And Potential Intermediate Phenotype

[1]Dr. Althea S Wotsa, [2]Dr. Dasuk Lang Roy Disiar

[1]Consultant Psychiatrist, [2]Consultant Neurosurgeon, Faith Hospital & Institute of Medical Sciences, Dimapur, Nagaland, India

Corresponding Author: Dr. Dasuk Lang Roy Disiar,
Consultant Neurosurgeon, Faith Hospital & Institute of Medical Sciences, Dimapur, Nagaland, India

ABSTRACT

Introduction- Multiple investigations conducted on individuals diagnosed with schizophrenia have documented a significant decrease in sleep spindle activity. In order to examine the potential connection between the decrease in sleep patterns and the genetic susceptibility to the illness, this study was conducted to compare the sleep spindles and slow waves in individuals diagnosed with schizophrenia according to the ICD-10 DCR criteria. Additionally, the study aimed to assess the relationship between these sleep patterns and cognitive functioning, and to compare them with healthy first degree relatives and healthy controls.

Material and methods- The present hospital based cross-sectional study was conducted among 30 cases of schizophrenia, 30 first degree healthy relatives and 30 healthy controls at Indoor and out-patient department of Institute of Psychiatry, IPGME&R, Kolkata for a duration of one year from April 2019 to April 2020. All the cases and controls were selected on the basis of inclusion and exclusion criteria. Cases and controls were analyzed on the basis of various tools and parameters and results were analyzed using SPSS verison 25.0

Results – The mean age of cases and controls was between 30 to 40 years with male dominating female patients. The PANSS score in Schizophrenia patient of mean negative and positive score is 20.8 & 18.9 respectively. Statistically significant differences were found in mean values of Total Sleep Time (in min), NREM, N2, N3 and sleep density among the three groups($p<0.01$).

Conclusion- Patients with schizophrenia and healthy first-degree relatives exhibited a decrease in fast spindle density compared to healthy volunteers, which aligns with the presumed genetic predisposition for schizophrenia. The observed reduction in spindle density was predominantly observed in rapid spindles and was found to be correlated with a decline in memory performance.

Keywords-
DOI Number: 10.48047/nq.2024.22.3.NQ24014 **NeuroQuantology 2024; 22(3):130-140**

INTRODUCTION

Disrupted sleep is an often observed characteristic of schizophrenia. Microstructural alterations, such as the decrease in sleep spindles, have garnered significant interest in the field of schizophrenia research and have been successfully reproduced in multiple investigations, as documented in the review. However, the underlying pathophysiological mechanisms associated with these changes remain inadequately comprehended.[1,2]

Sleep spindles are transient episodes of rhythmic synchronous electroencephalogram (EEG) activity within the frequency range of 9–15 Hz that manifest during non-rapid eye movement (NREM) sleep. These spindles serve as a distinctive characteristic of stage 2 sleep. Sleep spindles have consistently been associated with overall cognitive and memory functions, neuroplasticity, and the consolidation of nighttime memory in several learning models [3,4]. In the thalamocortical network, spindles are formed through the projection of rhythmic inhibition from GABAergic thalamic reticular neurons to glutamatergic thalamocortical neurons. These glutamatergic neurons, in turn, receive synchronizing input from corticothalamic projections [5].

Based on their frequency (12–15 Hz fast spindles, 9–12 Hz slow spindles), topographical distribution over the scalp (centroparietal fast spindles, frontal and centroparietal slow spindles), and the activation of partially segregated cortical networks, two distinct types of sleep spindles can be identified [6]. Emerging research indicates that there is a possibility of differential generation or modulation of these entities [7]. The extent to which they serve distinct parts of brain function is uncertain.

The correlation between the sleep spindle deficit and indices of psychopathology, as well as abnormalities in sleep-dependent memory consolidation, has been described in previous studies [8,9]. However, the investigation of individuals who are chronically treated raises the question of whether the deficit in the sleep spindle is associated with the hereditary risk architecture of the illness or with other factors related to the illness, such as the use of antipsychotics or specific characteristics of the disease history.[10]

Hence the present study was done to compare the sleep spindles and slow waves in patients diagnosed with schizophrenia as per the ICD-10 DCRcriteria , its association with cognitive functioning and compare with healthy first degree relatives and healthy controls.

MATERIAL AND METHODS

The present hospital based cross-sectional study was conducted among schizophrenia patients at Indoor and out-patient department of Institute of Psychiatry, IPGME&R, Kolkata for a duration of one year from 7th April 2019 to 6th April 2020. Ethical permission was taken from institutional ethical committee before commencement of study. Patients and their relatives were asked to sign an informed consent form after explaining them the complete procedure.

Through purposive sampling total 30 cases of schizophrenia, 30 first degree healthy relatives and 30 healthy controls were selected on the basis of inclusion and exclusion criteria.

INCLUSION CRITERIA FOR CASES

1. Diagnosed schizophrenia cases as per ICD 10 DCR
2. 18 -60 years
3. Stable psychopharmacological treatment for at least 2 weeks in the form of monotherapy with second generation antipsychotic
4. Off benzodiazepines for at least 48 hours
5. All patients who consent to participate in the study

INCLUSION CRITERIA FOR HEALTHY FIRST DEGREERELATIVES

1. First degree healthy relative of schizophrenia having General Health Questionnaire-12 (GHQ-12) score $\leq$2.
2. 18-60 years

INCLUSION CRITERIA FOR HEALTHY CONTROLS

1. Healthy controls having General Health Questionnaire-12 (GHQ-12) score ≤2.
2. 18-60 years

EXCLUSION CRITERIA FOR CASE

1. Not on any other psychotropic medication since 1 month other than second generation antipsychotic.
2. Drug naïve cases and patients with other comorbid physical or psychiatric disorders
3. Patients on long acting injectable.
4. Absence of sleep disorder previously known or detected by polysomnography.
5. Substance dependence except nicotine.
6. History of severe head injury, brain damage, any neurological disorder.
7. Patients who do not give consent.

EXCLUSION CRITERIA FOR CONTROL

1. Absence of sleep disorder previously known or detected by polysomnography.
2. Substance dependence except nicotine.
3. History of severe head injury, brain damage, any neurological disorder.
4. Patients who do not give consent.

Patients selected were from OPD in IOP-COE, diagnosed as having Schizophrenia as per ICD-10(DCR) criteria. Then they were asked to bring their first degree relative. Healthy controls were included in the study as well. The socio-demographic and clinical profile of patients were noted in the self designed performa. Positive and negative syndromes Of Schizophrenia (PANSS) scale [Of the 30 items included in the PANSS, 7 constitute Positive Scale, 7 Negative Scale, and remaining 16 a General Psychopathology Scale. Each item is scored from 1 to 7 in terms of increasing severity of symptoms. The scores for the scales is the summation of ratings across component items. Therefore, the ranges are 7 to 49 for the Positive and the Negative Scales, and 16 to 112 for General Psychopathology Scale] was applied on schizophrenia patients [11]. Epworth sleepiness scale [Scored how likely one would doze off or fall asleep in the different situations- 0 = would never doze off, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing] and Addenbrooke's cognitive examination [Has 5 components- Attention , Memory, fluency ,language and visuospatial with total score of 100] was applied on them. For Healthy controls, General Health Questionaire-12(GHQ-12) was used [It focuses on two major areas- the inability to carry out normal functions and the appearances of new and distressing symptoms. GHQ can be scored as a 4-point Likert scale with weights assigned to each position (0-1-2-3). Cut off point 2/3 is used for indicating a level of psychological distress of potential clinical significance] [12]. Philips Respironics (Model: ALICE 6) was used to record automated readings of various sleep parameters. Scoring was done visually from the EEG tracings as well , analysing each 30 second epoch, using the AASM 2007 criteria for scoring of the sleep stages.[13]

Sociodemographic parameters were analysed using analyses of variance (ANOVA) for age, education years and verbal IQ, and Chi-square test for gender distribution. The Statistical Package for Social Sciences version 25.0 (IBM SPSS, Inc., Chicago, Illinois) was used to analyze results.

RESULTS

The mean age of Schizophrenia patient in this study is 32.1 years, with Standard deviation 13.14 and that of Healthy first degree relatives is 35.1 years, with standard deviation 12.20 and that of Healthy controls is 36.7 years, with standard deviation 13.85. Difference of mean age in three groups was not statistically significant (p = 0.38). Schizophrenia patient and healthy controls there were more males. Among healthy first degree relatives, there were more females and the p value was calculated as 0.732, which shows that this distribution is not statistically significant. Schizophrenia patient only 2 was illiterate and majority of schizophrenia and healthy first degree relatives were educated till primary level. Among healthy controls, majority were educated till secondary level and p value is 0.165, which was statistically not significant. Among Schizophrenia patients, healthy first

degree relatives and healthy controls maximum patients were middle class and p value was 0.99, which was statistically not significant as shown in table 1

Table 1 Demographic detail of patients, healthy first degree relatives and healthy controls.

Variable		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
ATTENTION	Schizophrenia	30	13.600	2.2221	12.770	14.430	10.0	17.0	p<0.001*
	Healthy first degree relatives	30	15.000	2.1656	14.191	15.809	11.0	18.0	
	Healthy controls	30	16.667	1.3979	16.145	17.189	14.0	18.0	
	Total	90	15.089	2.3158	14.604	15.574	10.0	18.0	
MEMORY	Schizophrenia	30	18.233	2.4023	17.336	19.130	12.0	21.0	p<0.001*
	Healthy first degree relatives	30	22.433	2.0117	21.682	23.185	19.0	26.0	
	Healthy controls	30	24.300	1.5347	23.727	24.873	21.0	26.0	
	Total	90	21.656	3.2366	20.978	22.333	12.0	26.0	
FLUENCY	Schizophrenia	30	11.033	.8503	10.716	11.351	10.0	12.0	p<0.001*
	Healthy first degree relatives	30	12.833	1.1167	12.416	13.250	11.0	15.0	
	Healthy controls	30	13.033	1.0662	12.635	13.431	11.0	14.0	
	Total	90	12.300	1.3529	12.017	12.583	10.0	15.0	
LANGUAGE	Schizophrenia	30	19.567	1.7157	18.926	20.207	17.0	22.0	p<0.001*
	Healthy first degree relatives	30	23.200	1.5625	22.617	23.783	21.0	26.0	
	Healthy controls	30	24.200	1.9010	23.490	24.910	20.0	26.0	
	Total	90	22.322	2.6344	21.770	22.874	17.0	26.0	
VISUOSPATIAL	Schizophrenia	30	8.833	1.3667	8.323	9.344	7.0	11.0	p<0.001*
	Healthy first degree relatives	30	12.033	1.6709	11.409	12.657	10.0	16.0	
	Healthy controls	30	14.500	1.3582	13.993	15.007	12.0	16.0	
	Total	90	11.789	2.7498	11.213	12.365	7.0	16.0	

The PANSS score in Schizophrenia patient of mean negative and positive score is 20.8 & 18.9 respectively with SD 1.186 & 1.398 respectively. P value was calculated as < 0.001, which is statistically significant. Thus the PANSS score for two groups positive & negative score in schizophrenia patients is statistically significant as shown in table 2.

Table 2 Distribution of PANSS score in schizophrenia patient

PANSS score	Number	Mean	SD	p-value
NEGATIVE SCORE	30	20.8	1.186	P<0.001*
POSITIVE SCORE	30	18.9	1.398	

Table 3 shows that there is statistically significant differences in mean values of ACE III parameters among the three groups Schizophrenia, , Healthy first degree relatives and Healthy controls as the p-value is < 0.01 (at 1 % level of significance).

Table 3 Significance of ACE III score in schizophrenia patients, healthy first degree relatives and healthy controls

VARIABLE		SCHIZOPHRENIA PATIENT	HEALTHY FIRST DEGREE RELATIVES	HEALTHY CONTROLS	p-value
MEAN AGE		32.1±13.14	35.1±12.20	36.7±13.85	0.38
GENDER N (%)	FEMALE	13 (30.2)3	16 (37.2)	14 (32.5)	0.73
	MALE	17 (36.2)	14 (29.8)	16 (34.0)	
EDUCATION N (%)	ILLITERATE	2 (100)	0	0	0.16
	PRIMARY	16 (36.2)	14 (29.8)	8 (34)	
	SECONDARY	8 (27.6)	11 (37.9)	13 (34.5)	
	GRADUATE	4 (21.1)	5 (26.3)	9 (52.6)	
SOCIOECONOMIC STATUS N (%)	LOWER CLASS	2 (28.6)	2 (28.6)	3 (42.8)	0.99
	LOWER MIDDLE CLASS	6 (31.6)	7 (29.8)	6 (31.6)	
	MIDDLE CLASS	15 (35.7)	13 (30.9)	14 (33.4)	
	UPPER MIDDLE CLASS	4 (36.2)	5 (36.2)	5 (36.2)	
	UPPER CLASS	3 (37.5)	3 (37.5)	2 (25)	

Table 4 shows that there is statistically significant differences in mean values of Total Sleep Time (in min) among the three groups Schizophrenia, , Healthy first degree relatives and Healthy controls as the p-value is < 0.01 (at 1 % level of significance).

Table 4 Significance of total sleep time (in min) in schizophrenia patients, first degree healthy relatives and healthy controls

Descriptive									
TOTALSLEEPTIME(in min)									
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
Schizophrenia	30	273.200	7.4713	1.3641	270.410	275.990	260.0	284.0	p<0.001*
Healthy first degree relatives	30	339.600	10.7946	1.9708	335.569	343.631	320.0	354.0	
Healthy controls	30	415.600	5.5746	1.0178	413.518	417.682	408.0	426.0	
Total	90	342.800	59.0683	6.2263	330.428	355.172	260.0	426.0	

Table 5 shows that there is statistically significant differences in mean values of Duration of Total NREM Sleep (in min) among the three groups Schizophrenia, Healthy first degree relatives and Healthy controls as the p-value is < 0.01 (at 1 % level of significance).

Table 5 Significance of duration of total NREM sleep (in min) in schizophrenia patients , healthy first degree relatives and healthy controls.

Descriptive									
DURATIONOFTOTALNREMSLEEP									
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
Schizophrenia	30	202.100	7.3407	1.3402	199.359	204.841	188.0	214.0	p<0.001*
Healthy first degree relatives	30	246.500	6.3558	1.1604	244.127	248.873	236.0	255.0	
Healthy controls	30	308.100	14.7423	2.6916	302.595	313.605	288.0	333.0	
Total	90	252.233	44.8538	4.7280	242.839	261.628	188.0	333.0	

Table 6 shows that there is statistically significant differences in mean values of Duration of N2 Sleep (in minutes) among the three groups Schizophrenia, Healthy first degree relatives and Healthy controls as the p-value is < 0.01 (at 1 % level of significance).

Table 6 Significance of duration of N2 sleep (in minutes)in schizophrenia patients , healthy first degree relatives and healthy controls.

Descriptive									
DURATIONOFN2SLEEP (inmin)									
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
Schizophrenia	30	159.700	8.6309	1.5758	156.477	162.923	143.0	171.0	p<0.001*
Healthy first degree relatives	30	171.600	4.4381	.8103	169.943	173.257	165.0	178.0	
Healthy controls	30	180.300	5.5532	1.0139	178.226	182.374	169.0	189.0	
Total	90	170.533	10.6224	1.1197	168.309	172.758	143.0	189.0	

Table 7 shows that there is statistically significant differences in mean values of Duration of N3 Sleep (in minutes) among the three groups Schizophrenia, Healthy first degree relatives and Healthy controls as the p-value is < 0.01 (at 1 % level of significance).

Table 7 Significance of duration of N3 sleep (in minutes) in schizophrenia patients , healthy first degree relatives and healthy controls.

Descriptive									
DURATIONOFN3SLEEP (in minutes)									
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
Schizophrenia	30	26.300	4.4112	.8054	24.653	27.947	20.0	34.0	p<0.001*
Healthy first degree relatives	30	43.200	4.8736	.8898	41.380	45.020	37.0	54.0	
Healthy controls	30	96.800	4.9158	.8975	94.964	98.636	87.0	102.0	
Total	90	55.433	30.5827	3.2237	49.028	61.839	20.0	102.0	

Table 8 shows that there is statistically significant differences in mean values of Sleep Spindle Density among the three groups Schizophrenia , Healthy first degree relatives and Healthy controls as the p-value is < 0.01 (at 1 % level of significance).

Table 8 Significance of sleep spindle density in schizophrenia patients , healthy first degree relatives and healthy controls

Descriptive									
SLEEPSPINDLEDENSITY									
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
Schizophrenia	30	2.467	1.0080	.1840	2.090	2.843	1.0	4.0	p<0.001*
Healthy first degree relatives	30	4.367	.6149	.1123	4.137	4.596	4.0	6.0	
Healthy controls	30	5.567	.6789	.1240	5.313	5.820	4.0	6.0	
Total	90	4.133	1.5006	.1582	3.819	4.448	1.0	6.0	

Table 9 shows there is statistically significant relation between schizophrenia patients, healthy first degree relatives & healthy controls as the p-value is <0.001 .
this concludes that sleep spindle density between schizophrenia patients and healthy first degree relatives is statistically significant differences in mean values . similarly, sleep spindle density between schizophrenia patients and healthy controls also statistically significant differences in mean values .

Table 9 Aanalysis of the relation of spindles and slow waves to the cognitive performance.

Correlations								
		ATTENTION	**MEMORY**	**FLUENCY**	**LANGUAGE**	**Visuospatial**	**SLOW WAVES**	**SLEEPSPINDLEDENSITY**
ACEIIISCORE ATTENTION	Pearson Correlation	1						
	p-value							
MEMORY	Pearson Correlation	.413**	1					
	p-value	.000						
FLUENCY	Pearson Correlation	.429**	.529**	1				
	p-value	.000	.000					
LANGUAGE	Pearson Correlation	.476**	.622**	.770**	1			
	p-value	.000	.000	.000				
Visuospatial	Pearson Correlation	.492**	.668**	.609**	.686**	1		
	p-value	.000	.000	.000	.000			
SLOW WAVES	Pearson Correlation	.535**	.683**	.497**	.617**	.782**	1	
	p-value	.000	.000	.000	.000	.000		
SLEEPSPINDLEDENSITY	Pearson Correlation	.443**	.657**	.639**	.620**	.802**	.769**	1
	p-value)	.000	.000	.000	.000	.000	.000	
**. Correlation is significant at the 0.01 level (2-tailed).								

DISCUSSION

Schizophrenia, a disorder with variable phenotypic expression is poorly understood and has complex etiology- genetic contribution and environmental factors interacting with the genetic susceptibility [14].

Although the onset of the disease is most common at the end of adolescence or the beginning of adulthood, the enteropathogenesis indicates that genetic predispositions and developmentally early hits like social stress enhances the probability of developing schizophrenia [15]. It is characterized by a generalized cognitive impairment, with varying degrees of deficit in all domains, deficits are especially pronounced in the domains of verbal memory, executive functioning and attention and less attenuated in the domains of perceptual- and basic language processes [16].

Healthy first-degree relatives of schizophrenia patients may have impairments in cognition, indicating genetic predisposition to the illness . It has been suggested that cognitive dysfunction is a trait-marker of schizophrenia. It is observed in chronic, first episode and remitted patients with schizophrenia [17]. Also, deficits in cognitive functioning are observed before the onset of illness in subjects who are at genetic or clinical high risk for psychosis (ultra-high-risk for psychosis; UHR).[18]

Sleep disturbance is a prevalent feature in schizophrenia. Specifically, microstructural changes like reduced sleep spindles have gained attention in schizophrenia research and these were replicated in various studies, but their pathophysiological underpinnings still remain poorly understood.[19]

Patients with schizophrenia perform one to two standard deviation below healthy controls on various neurocognitive tests. It has been seen that deficits appear to be present early in the course of illness. Cognitive impairment across various domains is seen in schizophrenia. Unaffected first degree relatives share similar genetic background with schizophrenic patients. As such, first-degree relatives of schizophrenia are a population of exceptional interest for many reasons, among which (1) the shared genetic background with affected relatives; (2) the partially overlapping neurophysiological, structural, neurofunctional and neurocognitive abnormalities; (3) the absence of medication-related biases. Furthermore, microstructural sleep data obtained with new generation, densearray EEG technology in this population are lacking.[20]

Hence this proposed cross sectional study was designed to compare the sleep spindles and slow waves in patients diagnosed with schizophrenia as per the ICD-10 DCR criteria and its association with healthy first degree relatives and healthy controls.

The mean age of Schizophrenia patient , Healthy first degree relatives is and that of Healthy controls was between 30 to 40 years. Difference of mean age in three groups was not statistically significant (p = 0.38). Among schizophrenia and healthy controls there were more males as compared to females, while in healthy first degree relatives, there were more females. Schizophrenia patient only 2 were illiterate and majority of schizophrenia and healthy first degree relatives were educated till primary level.. Among healthy controls, majority were educated till secondary level. Out of 30 Schizophrenia patient and healthy first degree relatives majority were from middle class and least from lower class. Among Healthy controls, majority were from middle class, least from upper class and p value is 0.99, which is statistically not significant. Claudia Schilling et al [21] in their study reported similar gender distribution and socioeconomic levels among the study groups. Vikas Kumar et al [19] in their study revealed that in FDR of schizophrenia group, the mean age was 38.40 years (SD = 3.54) and mania with psychotic symptoms group the mean age was 36.13 years (SD = 7.80).

In our study, Total sleep time was maximum in control subjects while least among Schizophrenia subjects followed by FDR with significant results. For Duration of Total NREM Sleep , that there is statistically significant differences in mean values among the three groups Schizophrenia, Healthy first degree relatives and Healthy controls as the p-value is < 0.01. Also , there is statistically significant differences in mean values of Duration of N2 Sleep (in minutes) among the three groups. This decrease can be due to lack of regular daytime activity. It can also be because of the

psychotic symptoms that causes fear or anxiety which results in disturbed sleep. The above findings are consistent with the findings of other studies like Monti and Monti (2004)[22], Yetkin et al (2011)[23], Chan et al(2016)[24] and Ilankovic et al(2014)[25] who observed that there is a decrease in total sleep time, decreased sleep efficiency, increased sleep onset latency and increased number of awakenings in schizophrenia as compared to controls. Keshavan et al (1990)[26], Keshavan et al(1998)[27], Monti and Monti (2004)[22], Ilankovic et al(2014)[25], Chan et al(2016)[24], Tandon et al (1989)[28], Roschke et al (1998)[29] and Yang and Winkelman (2006)[30] reported slow wave sleep deficits in schizophrenia.

There was statistically significant differences in mean values of Sleep Spindle Density among the three groups Schizophrenia , Healthy first degree relatives and Healthy controls as the p-value is < 0.01. Duration of slow wave sleep also statistically significant differences in mean values among the three groups. ACE-III score was lowest among schizophrenia followed by FDR and control subjects. Statistically significant difference was revealed among the three groups in relation to attention, memory, fluency, langage ,visuospatial and total ACE-III score as $p<0.05$ in the present study.There are statistically significant correlation among spindles and slow waves to the cognitive performance as all the p-values are < 0.001. Our finding is partially in line with Manoach et al., who found a trend towards a reduction of sleep spindle density that didn't reach statistical significance. The influence of several major psychiatric disorders in their FDR sample might account for the observed trend. On the other hand, another study recently found a deficit restricted to fast spindle density in 13 adult, unaffected FDRs.[31]

Healthy relatives, who share half of the genetic risk background of schizophrenia patients, display a reduction in spindle activity that maps in between the schizophrenia patients and healthy controls. Findings for slow waves were the same. This indicates heritability of these phenotype. Spindle density and slow wave correlate with less efficient memory performance, extending previous findings of a correlation between cognitive performance and spindle activity from healthy volunteers to a sample of subjects at genetic risk of schizophrenia. Regarding the functional implications of the spindle and slow wave deficit in schizophrenia, our findings thus add to the growing body of evidence for a possible contribution to cognitive dysfunction.

CONCLUSION

Present demonstration of a spindle deficit and slow waves in non-affected family members as compared to healthy controls make the spindle deficit and slow waves a promising intermediate phenotype for schizophrenia. Spindle density and slow wave should be considered a valuable endophenotype for Schizophrenia, although current sample size limitations and differences in spindle detection algorithms employed across groups warrant further larger investigations to confirm this finding. To clarify the discrepancy with the existing literature, future studies will need to explore the relationship between sleep endophenotypes and subtle neurocognitive deficits in larger samples of schizophrenia first degree relatives.

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