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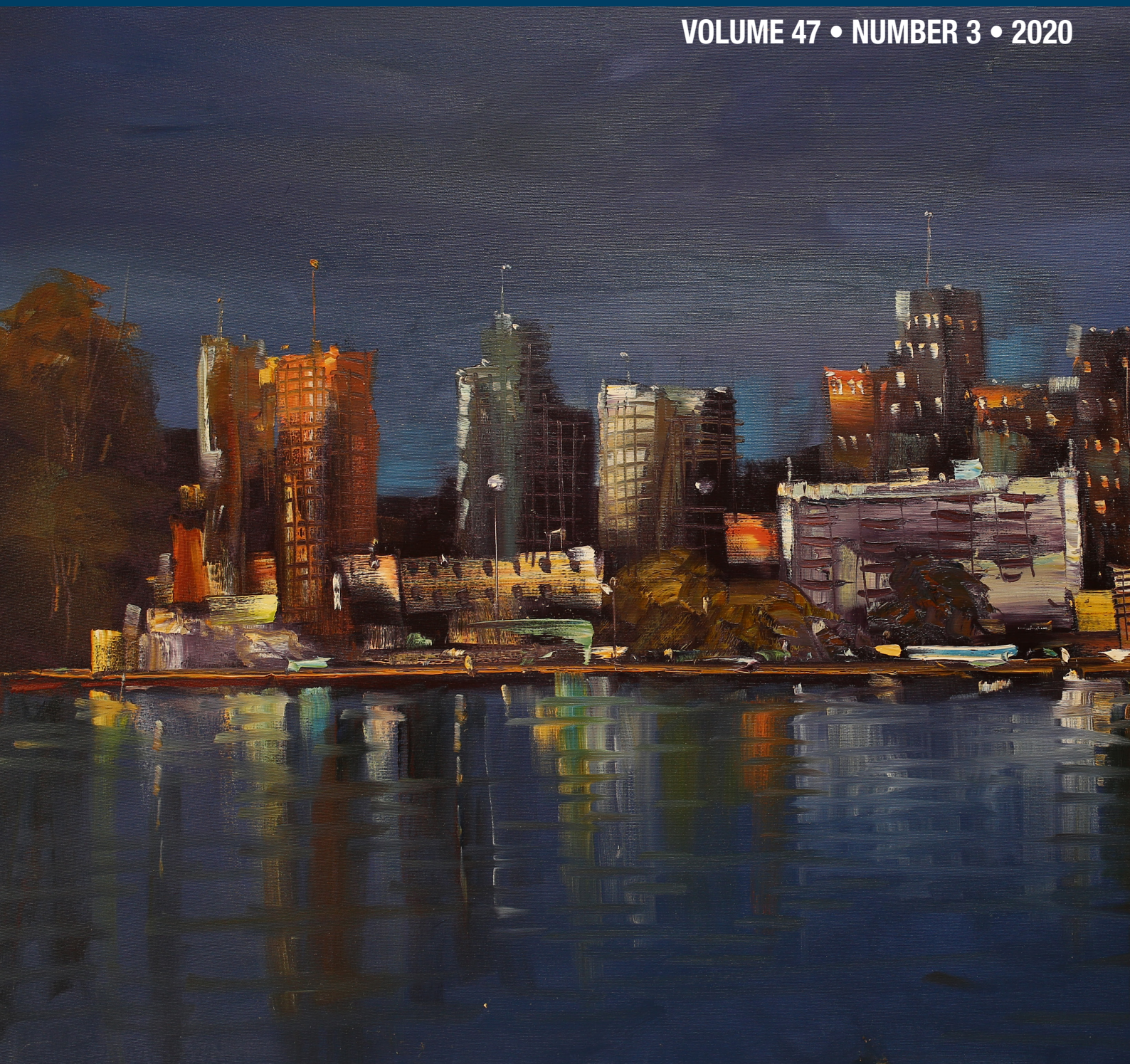

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Brief report

Letters to the editor

The role of thought suppression in conversion disorder in relation to depression, symptom interpretation and sleep hygiene: a case-control study

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Abstract

Background: Thought suppression has been associated with a number of psychiatric disorders. However, the association with conversion disorder (CD) has not been investigated yet. **Objective:** To investigate the role of thought suppression in CD. **Methods:** Eighty consecutive outpatients with a diagnosis of CD and sixty age, sex and neighborhood-similar controls were evaluated using Beck Depression Inventory-I (BDI-I), White Bear Suppression Inventory (WBSI), Symptom Interpretation Questionnaire (SIQ) and Sleep Hygiene Index (SHI). Cases and controls were compared in regard to thought suppression scores considering their status of high depression scores via a logistic regression model. The reciprocal associations of thought suppression with other clinical dimensions in CD were assessed. Finally, structural equation modelling was applied to untangle the possible connections. **Results:** CD patients had significantly higher scores of thought suppression than the control group. However, the difference was below the significance level when CD patients without comorbid high depression scores were taken into account. Thought suppression was associated with the clinical severity of CD. According to the structural equation model, older age and somatic attributions to the common bodily sensations were the significant correlates of thought suppression among CD patients. **Discussion:** Thought suppression may be considered as a non-specific marker of clinical severity in CD.

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Keywords: Conversion, thought suppression, depression, sleep hygiene, somatic attribution.

Introduction

Conversion disorder (CD) – also addressed as functional neurological symptom disorder – manifests with neurological symptoms incompatible with the recognized conditions. To date, some models on the onset and course of these symptoms have been proposed[1]. One of these models suggests that symptoms are indeed blurry observed dissociated materials which partly intrude into awareness in response to a reminder[2]. Another model conceptualizes symptoms as basic biological responses aiming to regulate arousal against acute threats or post-traumatic reactions[3]. An alternative model proposes that symptoms occur in the context of operant conditioning and/or are driven by primary or secondary gains[4]. Finally, these symptoms are considered as a part of a defensive mechanism against emotional awareness. An important proportion of these models refer to *thought suppression* which is a type of motivated forgetting process aiming to alleviate conflicting thoughts and feelings[5]. Accordingly, it may be proposed that stress-related thoughts and images are partly replaced by bodily symptoms and related thoughts at the conscious level[6]. Recent studies provided some indirect evidence for the association between CD and thought suppression. CD patients were found to have elevated rates of both severe life events history and "escape" from stressors[7]. Furthermore, a functional magnetic resonance imaging (fMRI) study demonstrated abnormal activities in brain areas related to memory and emotion during the recall of the etiologically relevant event in CD patients[8]. Surprisingly, no studies to date have directly investigated the role of thought suppression in CD.

In addition to the potential association with CD, thought suppression was associated with tendency to somatization[5]. On the other hand, many studies consistently showed higher somatization sub-scale scores in CD mainly independent of the levels of anxiety, depression or trauma-exposure. Relatedly, psychosomatic symptom "reporting" level was associated with the clinical severity of CD[9]. Taken together, these clues suggest potential interactions between thought suppression and tendency to somatization in CD.

Thought suppression was associated with poor sleep hygiene via exacerbation of intrusive thoughts at sleep onset and increased occurrence of the suppressed thoughts in dreams. At the same time, thought suppression was associated with depression via a similar mechanism[5]. Furthermore, poor sleep hygiene was shown to be common and associated with functional impairment in CD[10]. Similarly, depression is one of the most prevalent conditions co-occurring with CD. Finally, poor sleep quality is one of the core features of depression. From this point of view, evaluation of the complex interactions between thought suppression, sleep hygiene, depression and tendency to somatization in CD may provide important insights into the underlying mechanisms of the disorder. However, no studies to date have investigated these interactions in CD.

The aims of this paper were to analyze:

(i) The difference in thought suppression scores between CD patients and individuals with no current or past functional neurological symptom;
(ii) The specificity of thought suppression to CD;
(iii) The complex associations between thought suppression and other clinical entities including sleep hygiene, depression, reported number of common bodily sensations and attributions to these sensations in CD.

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It is hypothesized that CD patients will have more thought suppression scores than the control group. Furthermore, thought suppression scores will be higher in CD patients without comorbid high depression scores. Finally, thought suppression will be associated with more common bodily sensations, more severe depressive symptoms and worse sleep hygiene among CD patients.

Methods

Participants

A hundred consecutive patients who attended to the outpatient clinic and diagnosed with CD between June 2015 and May 2016 were referred to this case-control study. In order to make differential diagnosis with CD and assess the comorbid and past diagnoses of the participants, clinical psychiatric interviews were conducted using DSM-5 criteria by two separate psychiatrists (junior psychiatrist: in charge of the outpatient clinic; senior psychiatrist: performing the clinical interviews for this study). The inclusion criteria for the study were as follows: Being 18 to 50 years of age with a referral from the outpatient clinic due to a primary diagnosis of CD and volunteering to participate in the study. The exclusion criteria was having a diagnosis of a schizophrenia spectrum and other psychotic disorders, disorders with psychotic features specifier, substance-related and addictive disorders, neurodevelopmental disorders, neurocognitive disorders or progressive neurological diseases. The upper limit of the age range was set to 50, because of the increasing incidence of minor cognitive disabilities above this age. Furthermore, individuals with the above-mentioned comorbid psychiatric diagnoses were excluded because of the potential cognitive deficits associated with these disorders. Neurological examinations were performed to all cases by the consulting neurologist in order to exclude the possibility of a neurological cause. Twenty patients who had been referred to the study were excluded by the senior psychiatrist due to the DSM-5 Criterion C of CD: "The symptom or deficit is not better explained by another medical or mental disorder". In more detail, the primary diagnoses changed to panic disorder in twelve patients, to somatic symptom disorder in four patients, to post-traumatic stress disorder (PTSD) in three patients, to depersonalization/ derealization disorder in one patient in the second clinical interview. No cases were excluded due to the exclusion criteria of the comorbid diagnosis. Consequently, eighty cases were included in the study. Control group was selected via local announcements to the nearest household to the case's address in order to control for the confounders related to sub-cultural aspects. Junior psychiatrist invited eighty age (within five years) and sex-similar volunteers with no current or past symptoms of altered voluntary motor or sensory function and no self-reported disorders within the exclusion criteria. Sixty-six individuals attended to the research hospital in response to these invitations. Six individuals were excluded as a result of the clinical interview performed by the senior investigator (due to the history of the disorders within the exclusion criteria). Consequently, control group included sixty individuals.

Ethical standards

This study was conducted according to tenets of the Declaration of Helsinki and approved by the Clinical Ethics and Research Committee of Yuzuncu Yil University, Faculty of Medicine. All participants signed an informed consent form declaring that they had been fully informed of the purposes and conduct of the study. Participants were not paid for their participation.

Assessments

After the clinical interview by the senior psychiatrist for the inclusion and exclusion criteria, background information concerning self-reported somatic and psychiatric disorder history was collected through an interview by the junior psychiatrist. Then, the scales were administrated to the cases and controls accompanied by the junior psychiatrist. All participants were able to complete scales. No time limit was set to complete the scales. It took about 1 hour in average to complete the scales.

Beck Depression Inventory Version I (BDI-I) was used to assess the severity of depressive symptoms. BDI-I score was evaluated in two ways: i) a total sum score obtained by adding the points for the 21 items, ranging from zero to 63 points ii) a cut-off value of 17 points was used to define the participants with *high depression scores*, accepted as the reference assessment rate in Turkish population[11]. Mean internal-consistency estimates of the total scores were obtained as 0.86 for psychiatric patients. The mean correlation between the BDI total score and clinical ratings of depression was demonstrated to be greater than 0.60[12]. The Turkish version of the instrument was used in various surveys, and showed reasonable internal consistency (Cronbach's alfa = 0.8) and concurrent validity (r = 0.63)[11].

Symptom Interpretation Questionnaire (SIQ) was used to assess different styles of causal attributions about the common bodily sensations. SIQ includes 13 common bodily sensations, evaluates the number of common bodily sensations experienced as well as somatic, psychological and normalizing attributions to these sensations. Respondents indicate how much each attribution is related to each bodily sensation. Psychological, somatic, and normalizing scales were demonstrated to have reasonable internal consistency with alphas of 0.88, 0.73, and 0.79, respectively[13]. The Turkish version of the questionnaire has two differences from the original version: The four-point Likert type was changed to five-point Likert type and a new item (14th) was added. The SIQ Turkish version in its adapted form was used in different samples and showed satisfactory criterion related validity, discriminating power for specific groups and construct validity. Furthermore, psychological, somatic, and normalizing subscales of the Turkish version in its adapted form showed good internal consistency with Cronbach's alpha values of 0.87, 0.87 and 0.86, respectively[14].

White Bear Suppression Inventory (WBSI) was used to assess the individual's tendency to suppress unwanted intrusive thoughts[15]. WBSI is a 5-point Likert type self-report inventory consisting of 15 items. The total score ranges from 15 to 75. Higher WBSI scores reflect greater suppression of unwanted thoughts. To date, the inventory has been used in samples with various disorders including obsessive compulsive disorder, anxiety disorders and depression. Previous studies indicated high internal reliability of WBSI (Cronbach alphas of 0.87-0.89 across several studies)[15]. Turkish version of the instrument was used in different samples, and showed high internal consistency (α = 0.92) and appropriate discriminating power[16].

Sleep Hygiene Index (SHI) was used to assess environmental and behavioral variables that could promote inadequate sleep[17]. SHI consists of 13-items derived from the diagnostic criteria for inadequate sleep hygiene in the International Classification of Sleep Disorders (ICSD). Individuals are requested to provide information on the frequency of these behaviors. Item scores are summed up providing a global assessment of sleep hygiene ranging from 13 to 65. Higher scores are indicative of worse sleep hygiene practices. The original version of the scale showed a superior internal consistency (α = 0.66) to previous sleep hygiene instruments and a good test-retest reliability (r = 0.71) (17). The Turkish version of the scale was used in different samples, and showed satisfactory internal consistencies both in community-based and in clinical samples with Cronbach's alpha values of 0.70 and 0.71 as well as adequate concurrent validities[18].

Statistical analysis

All analyses were conducted using the software package STATA, version 13 (StataCorp, 2013). First, the CD patients were compared with the control group in terms of demographic variables using the chi-square test and t test where appropriate. Results were presented with effect size measures (Cramer's *V* for chi-square test and Cohen's *d* for t test). Then, CD patients and the control group were compared in terms of thought suppression scores using logistic regression. To evaluate the specificity of thought suppression to CD, an independent variable combining CD and *high depression scores* was constructed

(0: *no CD, no high depression scores*; 1: *CD, no high depression scores*; 2: *no CD, high depression scores*; 3: *both CD and high depression scores*). This variable was used in a logistic regression model of the outcome variable *thought suppression score*. Subsequently, the model included age, sex and educational level considering the possible influence on thought suppression scores. Results were presented showing both the unadjusted and the adjusted odds ratios (OR) with the 95% confidence intervals (CI). Finally, in order to evaluate the complex associations between thought suppression and other clinical entities in CD, a two-step analysis were carried out. First, Pearson correlation coefficients (two-tailed) of the thought suppression, attributions to the common bodily sensations, depression and sleep hygiene scores as well as the number of bodily sensations were computed. Guided by previous literature[19], Pearson correlations (r) with absolute values < 0.3 were evaluated as weak, 0.3 to <0.5 as moderate and ≥0.5 as strong correlations. Then, regarding the multivariate relations between variables, a structural equation model (SEM) was run to investigate the associations of thought suppression score with scores of depression, sleep hygiene, number of bodily sensations and somatic attributions to the common bodily sensations as well as age and sex. The SEM was specified in such a way that complies with flexible modelling paradigm using modification indexes in each step of the analysis. Model fit was assessed using the chi-square. In all analyses, alpha was set at 0.05.

Results

Sample characteristics

The sample characteristics of the case and control group were presented in Table 1. The sex distribution, age and proportion of participants reporting general medical condition did not significantly differ between the CD patients and the control group. Participants of the control group had significantly higher educational level and were more non-married in comparison with the CD patients (Table 1).

Thought suppression in presence of conversion disorder and high depression scores

CD patients had significantly higher scores of thought suppression in comparison with the control group (WBSI score: CD patients 37.2 ± 10.9 *vs.* control group 30.1 ± 15.3, t = 3.2, p = 0.001). CD patients had 2.6-fold increase in risk of high depression scores in comparison with the control group (OR: 2.6, 95% CI: 1.7 to 4.0, p < 0.001). Furthermore, CD patients had higher SHI scores than the control group, indicative of worse sleep hygiene practices (OR: 1.17, 95% CI: 1.11 to 1.24, p < 0.001). In comparison with the reference category of *no CD, no high depression scores; CD in isolation* group was not significantly associated with thought suppression scores. However, *high depression scores in isolation* group was significantly associated with thought suppression scores. The latter association remained significant when adjusted for age, sex and educational level. Details of the associations between thought suppression scores and CD stratified by presence of comorbid high depression scores were depicted in Table 2.

Correlates of thought suppression among conversion disorder patients

Pearson correlations of the WBSI, BDI, SHI and SIQ scores among CD patients were presented in Table 3. Thought suppression score was moderately correlated with depression, psychological and somatic attributions to common bodily sensations scores. Furthermore,

Table 1. Demographic variables of the participants with conversion disorder (CD) and the control group

		CD patients (n = 80)		Controls (n = 60)				
		Mean	SD	Mean	SD	t	Cohen's *d*	p
Age (y)		27.25	9.5	24.91	6.0	1.66	0.28	0.09
Educational level (y)		8.81	4.8	15.86	0.7	-11.1	-1.9	<0.001
		N	%	N	%	χ^2	Cramer's *V*	p
Sex	Male	18	22.5%	21	35.0%	2.66	0.13	0.103
	Female	62	77.5%	39	65.0%			
Marital status	Non-married	36	45.0%	47	78.3%	15.78	0.34	<0.001
	Married	44	55.0%	13	21.7%			
General medical condition	Yes	13	16.2%	4	6.7%	2.95	0.14	0.086
	No	67	83.8%	56	93.3%			
Symptoms	Attacks or seizures	49	61.2%					
	Anaesthesia or sensory loss	25	31.2%					
	Weakness or paralysis	3	3.8%					
	Speech symptoms	3	3.8%					
Life events	Yes	38	47.5%					
	No	42	52.5%					

CD: conversion disorder.

Table 2. Associations between thought suppression scores and conversion disorder stratified by the presence of comorbid depression

Diagnosis		WBSI Score	Model 1		Model 2*	
Category	N (%)	Mean (SD)	B (CI)	p	B* (CI)	p
CD (-) Depression (-)	43 (30.7)	26.9 (15.3)	ref	ref	ref	ref
CD (+) Depression (-)	20 (14.3)	33.5 (10.2)	0.57 (-0.33-1.49)	0.215	0.78 (-0.41-1.96)	0.201
CD (-) Depression (+)	17 (12.1)	38.2 (12.2)	1.47 (0.45 - 2.51)	0.005	1.63 (0.55-2.72)	0.003
CD (+) Depression (+)	60 (42.9)	38.5 (11.0)	1.54 (0.81-2.27)	<0.001	1.71 (0.78-2.64)	<0.001

*Adjusted for age, sex and educational level. CD: conversion disorder.

Table 3. Pearson correlations between the scales in patients with conversion disorder

	BDI	WBSI	SHI	SIQ Psychological attribution	SIQ Somatic attribution	SIQ Normalizing attribution	SIQ Number of symptoms
BDI	1						
WBSI	0.33*	1					
SHI	0.42**	0.1624	1				
SIQ Psychological Attribution	0.5987**	0.363**	0.3063**	1			
SIQ Somatic Attribution	0.2302*	0.3024**	0.1547	0.4449**	1		
SIQ Normalizing Attribution	0.2247*	0.2838**	0.2233	0.4634**	0.7329**	1	
SIQ Number of Symptoms	0.3816**	0.2562*	0.2611*	0.4499**	0.2661*	0.0692	1

BDI: Beck Depression Inventory; WBSI: White Bear Suppression Inventory; SHI: Sleep Hygiene Index; SIQ: Symptom Interpretation Questionnaire. * $p < 0.05$. ** $p < 0.001$.

thought suppression score was weakly correlated with normalizing attribution to common bodily sensations and number of bodily sensations. However, there was not a significant correlation between thought suppression and sleep hygiene scores. Sleep hygiene in CD had a significant negative correlation with severity of depressive symptoms and number of bodily sensations. Furthermore, sleep hygiene in CD had a significant negative correlation with psychological attributions to common bodily sensations but the correlations with somatic or normalizing attributions were below the significance level.

The correlations of reported number of bodily sensations with depression scores and attribution to common bodily sensations styles were assessed as a sensitivity analysis. As expected, number of bodily sensations was significantly correlated with scores of depression, psychological and somatic attributions but not with normalizing attributions to the common bodily sensations.

The multivariate associations of thought suppression score with other clinical entities in CD as well as age and sex were assessed via a SEM. Model chi-square test revealed adequate goodness of fit ($\chi^2 = 2.1$, df = 1, $p = 0.14$). In the model, as seen in Figure 1, thought suppression score was significantly associated with age and the somatic attribution score ($p < 0.01$) and was borderline associated with the depression score ($p = 0.06$). However, no large or significant association was found with the sleep hygiene score.

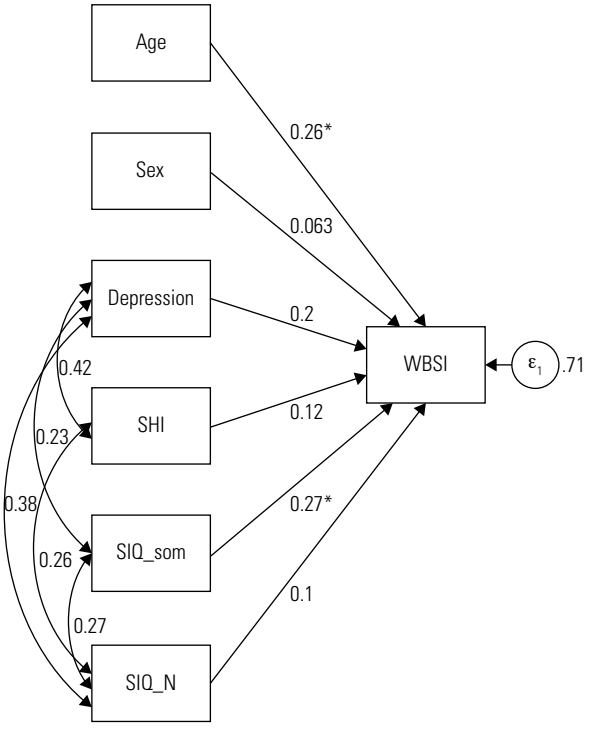

Figure 1. Structural equation model of the association of thought suppression with somatic attributions to the common bodily sensations, number of common bodily sensations, sleep hygiene, depressive symptoms, age and sex among conversion disorder patients. NOTE: Exogenously observed variables are inter-correlated in the model (15 covariance parameters exist), but only significant correlations are indicated in the diagram. Sex: 0 Male, 1 Female, Depression: Beck Depression Inventory Score, SHI: Sleep Hygiene Index Score, SIQ som: Symptom Interpretation Questionnaire Somatic Attribution subscale score, SIQ_ N: Symptom Interpretation Questionnaire number of symptoms; * p<0.01.

Discussion

Findings

In line with our hypothesis, CD patients used greater amount of thought suppression in comparison with the control group. As far as we are aware, no studies to date have directly investigated thought suppression in CD which we can directly compare our results with. However, previous reports suggested a "elective retrieval" of memories[20] which was then associated with thought suppression evaluated by WBSI[21]. Furthermore, an fMRI study demonstrated neural correlates of a similar cognitive processing in CD[8]. These results are both in line with our findings and the classical "repression" of stressful memories and "conversion" into physical symptoms model. The more recent "integrative cognitive model" of CD, having origins from the previous models, briefly proposes that symptoms of CD arise due to the preconscious "mismatching" of the stimuli with the mental representations[1]. Bridging with the classical theories, thought suppression may have a role on this mismatching process through inhibition of the retrieval of the closest match. On the other hand, objective evidence was found for increased arousal prior to the onset of the symptoms of CD, followed by a reduction after the emergence[22]. Alternatively, thought suppression may be a compensation mechanism to the activation of this "rogue" representations and the related hyper-arousal state. Further studies are needed to shed light to these open questions.

In contrast to our hypothesis, patients with CD in isolation (without high depression scores) showed no significantly higher

scores of thought suppression, suggesting the non-specificity of thought suppression to CD. In line with this finding, thought suppression has been associated with various disorders including depression, anxiety disorders, obsessive compulsive disorder, PTSD and insomnia[5,23,24]. This result, taken together with the previous literature, suggests ubiquitous nature of the thought suppression.

In line with our hypothesis, thought suppression was significantly correlated with number of common bodily sensations and severity of depressive symptoms among CD patients, suggesting an association with the clinical severity of CD. Thought suppression was previously conceptualized as a representative of avoidance coping strategy usage, and associated with greater levels of rebound and higher levels of distress, thereof[5]. Relatedly, thought suppression may be considered as a non-specific marker of severity in CD. Prospective and/or experimental studies are needed to evaluate whether thought suppression has a causal role on the severity of the disorder or is only a factor that follows passively as a function of the general severity of psychopathology.

Our results replicated previous reports demonstrating poor sleep hygiene in CD[10]. However, incompatible with our hypothesis, we did not find a significant correlation between thought suppression and sleep hygiene scores among CD patients. Previous literature linked thought suppression with reduced quality of sleep[5]. Inconsistency with the previous studies may be explained by different samples, as none of these studies were conducted in CD samples. Interestingly, our results showed that sleep hygiene in CD was associated with psychological attributions rather than somatic or normalizing attributions, replicating a previous finding[25]. Hypothetically, sleep hygiene in CD may be associated with the content of the suppressed thought than the thought suppression process itself.

According to the SEM, older age and somatic attributions to the common bodily sensations were the significant correlates of thought suppression among CD patients. As far as we are aware, no studies to date have investigated the determinants of thought suppression in CD that enables a direct comparison. However, a tendency to focus on somatic causes of distress and suppress emotional components has been classically referred to CD[1]. In addition to this view, tendency to somatization seems to moderate the association between thought suppression and CD, and potentially the vice versa. Further researches with longitudinal designs are needed to test these associations.

CD patients show poorer performance in attention[26]. Relatedly, decline of attentional control by age was previously demonstrated[27]. Furthermore, poor attentional control and related mind-wandering was linked to thought suppression[28]. Through these results, the finding showing an increase of thought suppression by age in CD suggests the interpretation that thought suppression may be a compensation mechanism to mind-wandering related to alterations in attentional control by age. This interpretation is also in agreement with a recent study reporting increased externally-oriented thinking (which is related to thought suppression[29]) in older individuals compared to younger[30]. CD itself may be inducing the decline of attentional control in years, thereof facilitating the association between age and thought suppression. Studies longitudinally assessing the neuro-cognitive functioning and thought suppression in CD are needed to confirm these interpretations based on our preliminary results.

Limitations

First, due to the cross-sectional design of the study, causal inferences cannot be made. Second, our CD group consisted of individuals that applied to hospital. Therefore, these results cannot be generalized to the general population. Third, the CD and control group were matched for age, sex and neighborhood but unfortunately, not for educational level. However, educational level was used as a covariate in logistic regression models. Fourth, the analysis of *thought suppression in comorbidity of CD and depression* was based on the *high depression score* variable obtained from the BDI. As it is not acceptable to make a diagnosis of clinical depression with a scale, the findings relying on this analysis should be considered as preliminary and needs to be confirmed in future research. Finally, the variables *thought suppression, attributions to common bodily sensations and sleep hygiene* are proxy variables and constructs, not variables per se. Therefore, a possible measurement error may occur. However, this is a limitation of all studies investigating these constructs. Furthermore, the interviews were carried out by clinicians who have remarkable experience on CD and the instruments used, minimizing the probability of measurement error.

Conclusion

The primary importance of this study is to be the first to explore thought suppression, symptom interpretation and sleep hygiene in CD. Briefly, the results revealed a non-specific association of thought suppression with CD. Furthermore, thought suppression was potentially associated with the clinical severity of CD. Finally, older age and somatic attributions to the common bodily sensations were the significant correlates of thought suppression among CD patients. Further research is needed to assess if thought suppression has a causal role on CD. These results take attention to psychosocial interventions that target thought suppression in CD.

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Using data from schizophrenia outcome study to estimate the time to treatment outcome and the early-response cut-off score that predicts outcome at week 16

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Abstract

Background: Being able to make an estimation of the time to clinical outcome, and making predictions early during treatment about the possibility of later response/non-response to treatment, is an important asset that can help to guide treatment strategies and counsel patients and caregivers about treatment expectations. **Objectives:** The study aimed to determine the time course to treatment outcome and the psychopathological cut-off score at week 4 that predicts outcome at week 16. **Methods:** This was a naturalistic follow-up study of 160 incident cases of schizophrenia over 16 weeks. Four intervals of follow-up clinical assessments were done. Standard criteria for response and remission were applied. **Results:** The mean (median) times, in weeks, to response and remission using Brief Psychiatric Rating Scale (BPRS) data were 8.1(8.0); 8.4(8.0); and 10.9 (12.0), respectively. The Areas Under the Curves were high, for response (0.909; 95% C.I., 0.85-0.97) and remission (0.86; 95% C.I., 0.81 -0.94) at week 16. A cut-off score of 20.7% reduction in the total BPRS score at week 4, predicted response status (79.5% sensitivity, 84.2% specificity) and remission status (77.6% sensitivity, 73.3% specificity) at week 16. In addition, a cut-off of 10.21% reduction in the total Scale for Assessment of Negative Symptoms (SANS) score at week 4, predicted response (70.8% sensitivity, 95.5% specificity) at week 16. **Discussion:** The results are in line with the general clinical impression that, by 2 months, most acutely ill inpatients are fit for discharge; and introduced for further investigation 10.21% reduction in SANS Score as a marker of treatment resistance in schizophrenia.

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Keywords: Time-to-outcome, early-response, cut-off, prediction, schizophrenia.

Introduction

Schizophrenia is a disorder with varied pathophysiology and heterogeneous treatment outcome across cultures[1]. Being able to make an informed estimation about the time to clinical outcome events (i.e., response, remission and recovery), and making predictions early during treatment about the possibility of later response/non-response to treatment among patients with schizophrenia, is an important asset that can help to guide treatment strategies and counsel patients and caregivers about treatment expectations[2]. The best guide for such estimates is one derived from follow-up studies of first- episode patients.

Many factors are considered when making decisions on the optimum duration of therapeutic trial either in clinical or research situations among schizophrenia patients. An important consideration is balancing the negative consequences of prematurely terminating a therapeutic trial, with the negative consequences of prolonging an ineffective treatment[3]. In Africa, there is dearth of data that suggest how long a therapeutic trial should last, or what volume or percentage of symptom reduction early in treatment predicts response/non-response later on in treatment. Emsley *et al.*[4] and Lieberman *et al.*[5] found that the median time to response and remission among schizophrenia patients on treatment was 3 and 11 weeks, respectively. Correll *et al.*[2] found that failure to achieve 20% improvement in symptoms after 1 week predicted non-response after 4 weeks. In addition, Kane *et al.*[6,7] in their widely accepted definition of drug-refractoriness pegged treatment non-response as failure to achieve at least 20% reduction in the total Brief Psychiatry Rating Scale (BPRS) score by 6 weeks of optimal treatment. However, Gallego *et al.*[8] using receiver operating characteristics analyses did not find any level of percent symptom reduction that was clinically useful as a predictor of response by week 16.

The validity of these observations has not been tested in African populations, where the clinical manifestations and treatment outcome have been postulated to be different from Caucasian populations[9-11]. Using standard operational definitions[6,12,13], this study aimed to estimate the mean and median times to treatment response, remission and recovery, as well as the early response cut-off in percentage reduction of symptoms that would predict response/remission/recovery at 16 weeks of naturalistic follow-up of a cohort of Nigerian patients with first-episode schizophrenia.

Subjects and methods

Details about the recruitment of patients, operational definitions, assessment for family history of illness, follow-up and clinical outcome (response/ remission/ social recovery) are being presented elsewhere (Onu & Ohaeri, In Press). This was a naturalistic longitudinal follow-up outcome study which took place at the Federal Neuropsychiatric Hospital (FNH), Enugu, Nigeria. Participants were recruited from April to July 2016. Consecutive incident cases of schizophrenia, who presented at the hospital, aged 18-49 years, and resident within Enugu metropolis (to facilitate follow-up) were invited, with their available family members, to participate in the study. Patients with schizophrenia of suspected organic aetiology, including substance use disorders, medical or psychiatric co-morbidities, or both, were excluded. Diagnosis of schizophrenia was confirmed using Mini International Neuropsychiatric Interview (MINI)[14]. Patients were assessed at baseline and followed up at intervals of 4 weeks for 16 weeks. Symptom changes and functional status were assessed at baseline and at each interval of treatment follow-up, using the Brief Psychiatry Rating Scale (BPRS)[15], Scale for Assessment of Negative Symptoms (SANS)[16], as well as Global Assessment of Functioning (GAF)[17], and the World Health Organization Disability Assessment Scale (WHODAS)[18], respectively.

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Treatment response, remission and recovery: Response was defined as symptom reduction greater than 50% of the baseline scores in BPRS and SANS scores during each period of follow-up[13]. Symptomatic remission was defined as a rating of 'mild' or less, concurrently on the following seven BPRS items (BPRS only criteria): grandiosity, suspiciousness, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerism/posturing, and blunted affect[13]. In addition, as suggested by Andreasen[13] when using SANS, a score of 2 or less on the following 4 SANS items: affective flattening, avolition-apathy, anhedonia-asociality, and alogia (SANS criteria). Functional or social recovery (also termed functional remission) was based on both clinical and psychosocial functional dimensions as proposed by Jaaskelainen *et al.*[12]. Hence, social recovery in this study was defined as: (a) maintaining symptomatic remission as described above through the particular follow-up period; and (b) having a GAF score greater than or equal to 61. This GAF score indicates that the subject is judged to be capable of returning to the premorbid level of psychosocial functioning[17].

Mode of onset of illness was dichotomized as: acute vs. chronic (insidious). Acute onset means that the positive symptoms of schizophrenia dramatically rose to a crescendo within one month, with a sudden deterioration from the premorbid level of functioning in that period. Insidious onset means that there was a gradual deterioration in premorbid level of functioning that spread over several months, along with the appearance of negative symptoms, while the onset of positive symptoms was slow and occurred after a period of noticeable change in premorbid functioning[19].

Family history of mental illness was assessed with the Family Interview for Genetic Studies[20]. The FIGS was developed by principal investigators in the National Institute of Mental Health (NIMH) Schizophrenia and Bipolar Disorder Genetics Initiatives and NIMH extramural program staff in 1992, as a guide for systematically collecting information about relatives in family genetic studies of these disorders.

Ethical considerations

Ethical approval was obtained from the Ethical Committee of the Federal Neuropsychiatric Hospital Enugu, Enugu State, Nigeria. International ethical norms and standards were strictly adhered to. After explaining the objectives and procedures, consenting patients were required to sign the written informed consent, with the understanding that they could withdraw from the study at any stage without any adverse impact on their right to treatment.

Data analysis

Mean and median times to response, remission and recovery were estimated using Kaplan-Meier survival analysis, which also estimated significant differences in time to event for variables, such as: gender, family history of illness, mode of onset of illness, and adequacy of social support in the cohort. Significant differences in time to outcome event between categories of subjects (e.g., male/female, satisfactory/non-satisfactory social support, family history of illness, and age at onset of illness) were assessed by the log rank (Mantel-Cox), Breslow (generalized Wilcoxon) and Tarone-Ware. However, we present the Breslow results because they were similar to the others. For the ROC analyses (i.e., the early percentage reduction in total BPRS cut-off score that would predict outcome at week 16), we used the response at week 4, versus, the outcome at week 16. This was because the first follow-up assessment was at week 4, in line with the recommendation of Trivedi *et al.*[21].

Results

The socio-demographic and some clinical characteristics of the 160 participants shows that they were mostly young (mean age 31.13 ± 12.50), and the mean age at onset of schizophrenia and duration of illness were 26.33 ± 12.15 years and 63.18 ± 74.15 months, respectively. Majority (51.2%) were females, never married (66.3%), with at least high school education (74.4%), and unemployed (63.8%). The attrition rate at week 16 was 29.4%; hence 113 subjects (out of 160) were available for assessment of response, remission and recovery at that time. Table 1 shows that, for the BPRS data, the mean (median) times, in weeks, to response, remission and recovery, were, respectively: 8.1 (8.0); 8.4 (8.0); and 10.9 (12.0). The equivalent results using SANS criteria were as follows: 9.1 (8.0); 9.4 (8.0); and 11.1 (12.0), respectively. The tendency for longer mean time to response, remission and recovery for SANS, *vs.* BPRS, did not reach significance (Standardized Effect Size for response: 0.19, 95% CI: 0.06-0.44). There were no significant differences in gender (Tables 2-4; Figure 1), marital status and employment status (Tables 2-4) in times to response, remission and social recovery. However, there was a tendency for those who were married and employed to have shorter time to these outcome events (For the BPRS data only, employment status was associated with earlier time to recovery – $P < 0.05$: Table 4). These indices of social advantage were manifest as significantly shorter time to response ($p < 0.001$) (Table 2) and recovery ($p < 0.04$) (Table 4) for subjects with perception of satisfactory social support.

Subjects with acute onset of illness had significantly shorter time to response ($p < 0.05$) (Table 2) and remission ($p < 0.005$) (Table 3), than those with insidious onset. The tendency for those with no family history of mental illness to have shorter time to response and remission, did not reach significance ($p > 0.05$).

For the ROC analyses (Figures 1a and 1b), using BPRS data for response at week 4 to predict outcome at week 16, the Areas Under the Curves (AUC) met the recommended cut-off for significance, for response (0.901, 95% CI: 0.85-0.963), remission (0.875; 95% CI: 0.811-0.938) and recovery (0.874; 95% CI: 0.84-0.944) at week 16. In addition, the cut-off score of 20.7% reduction in BPRS score at week 4, predicted response (79.5% sensitivity, 84.2% specificity), remission (77.6% sensitivity, 73.3% specificity) and recovery (88% sensitivity, 67.7% specificity) at week 16. The equivalent AUC values (95% CI) for the SANS data were: 0.897 (0.84-0.935), 0.84 (0.775-0.919), 0.874 and (0.804-0.944), respectively, for response, remission and recovery. Also, a cut-off of 10.21% reduction in SANS total score at week 4, predicted response (70.8% sensitivity, 95.5% specificity), remission (70.8% sensitivity, 91.9% specificity) and recovery (78.0% sensitivity, 82.7% specificity) at week 16.

Discussion

The highlights of the findings of this 16-week naturalistic follow-up study of a Nigerian schizophrenia cohort are: (1) the mean (median)

Table 1. The mean and median time to response, remission and recovery among schizophrenia patients: survival analyses

Outcome	Using BPRS Criteria		Using SANS Criteria	
	Mean in weeks (95% CI)	Median in weeks (95% CI)	Mean in weeks (95% CI)	Median in weeks (95% CI)
Response	8.1(7.2-9.0)	8.0 (6.7-9.3)	9.1(8.2-10.1)	8.0 (6.5-9.5)
Remission	8.4 (7.5-9.2)	8.0 (7.0-9.0)	9.4 (9.0-9.5)	8.0 (6.9-9.5)
Recovery	10.9 (9.9-11.7)	12.0 (10.6-13.4)	11.1 (10.3-11.7)	12.0 (10.5-13.3)

NB: Response is defined as ≥50% reduction in total BPRS & SANS scores, Remission using BPRS = Scores ≤ 2 in psychosis BPRS items (grandiosity, suspiciousness, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerism/posturing, and blunted affect). Using SANS, a score of 2 or less on the following 4 SANS items: affective flattening, avolition-apathy, anhedonia-asociality, and alogia. Recovery = maintenance of remission + GAF-score ≥ 61.

times, in weeks, to response, remission and social recovery were 8.1(8.0); 8.4(8.0); and 10.9 (12.0), respectively, for the BPRS data, *vs.* 9.1(8.0), 9.4 (8.0) and 11,1 (12.0), for the SANS data; (2) the time to response, remission and recovery differed with regards to baseline variables such as social support and mode of onset of illness; (3) the tendency for longer mean time to response, remission and recovery for negative symptoms, did not reach significance (Standardized Effect Size for response: 0.19, 95% CI: 0.06-0.44); (4) early response at week 4 significantly predicted 16-week response, remission and recovery; and (5) a threshold for early response of ≥20.7% BPRS-score reduction and ≥10.21% for the SANS at week 4 had significant predictive validity for later response, remission and recovery

For the survival analyses, our choice of 4 weeks as the first outcome assessment is in line with the American Psychiatric Association's practice guideline recommendation that an initial trial of 4-6 weeks generally is needed to determine if the patient will have any symptomatic response, although symptoms can continue to improve over longer periods of time[22,23]. Understandably, our mean/median time to response, based on >50% reduction in psychopathology, is higher than the results for studies where response was defined as >20% reduction, and median time to response was 3 weeks[2]. Furthermore, although our patients were incident cases, the mean duration of untreated psychosis was long (about 5 years), a factor that has been consistently associated with poor treatment response[24,25]. Perkins *et al.* found that shorter duration of untreated psychosis was associated with greater response to antipsychotic treatment, as measured by severity of global psychopathology, positive symptoms, negative symptoms and functional outcome[26]. However, our findings on time to response and remission support a recent recommendation by Kane *et al.* on guidelines for defining

Table 2. Time to Response: by baseline independent variables among schizophrenia patients

Variables	Time to Response Using BPRS Criteria			Time to Response Using SANS Criteria		
	Mean (SE)	Median (SE)	Stat. (p-value)	Mean (SE)	Median (SE)	Stat. (p-value)
Gender						
Male	8.4 (0.7)	8.0 (0.0)	0.59 (0.44)	9.5 (0.7)	8.0 (1.7)	0.0 (1.99)
Female	7.8 (0.5)	8.0 (0.7)		8.7 (0.6)	8.0 (0.7)	
Marital Status						
Single	8.2 (0.6)	8 (0.8)	0.12 (0.73)	9.5 (0.6)	8.0 (1.0)	2.0 (0.15)
Married	8.1 (0.8)	8.0 (1.2)		8.0 (0.9)	8.0 (1.1)	
Employment Status						
Unemployed	8.7 (0.6)	8.0 (0.8)	2.70 (0.11)	9.7 (0.6)	8.0 (1.0)	1.6 (0.21)
Employed	6.9 (0.5)	4.0 (0.0)		8.3 (0.7)	8.0 (1.2)	
Social Support						
Satisfactory	4.9 (0.3)	4.0 (0.0)	6.60 (0.01)	6.2 (0.6)	4.0 (0.0)	4.0 (0.04)
Unsatisfactory	7.5 (0.5)	4.0 (0.0)		8.7 (0.6)	8.0 (1.1)	
Mode of Onset						
Insidious	8.9 (0.7)	8.0 (0.9)	3.90 (0.05)	8.0 (0.7)	8.0 (0.0)	7.8 (0.005)
Acute	7.3 (0.6)	4.0 (0.0)		10.3 (0.7)	8.0 (1.2)	
Family History						
Positive	8.4 (0.6)	8.0 (0.7)	1.70 (0.19)	9.0 (0.6)	8.0 (0.8)	0.07 (0.79)
Negative	7.1 (0.6)	4.0 (0.0)		9.4 (0.8)	8.0 (1.6)	

NB: response is defined as ≥50% reduction in total BPRS and SANS score; SE: standard error.
Statistical significance was based on Breslow (generalized Wilcoxon).

Table 3. Time to Remission: by baseline independent variables among schizophrenia patients

Variables	Time to Remission Using BPRS Criteria			Time to Remission Using SANS Criteria		
	Mean (SE)	Median (SE)	Stat. (p-value)	Mean (SE)	Median (SE)	Stat. (p-value)
Gender						
Male	8.2 (0.7)	8.0 (0.8)	1.14 (0.29)	7.9 (0.5)	8.0 (1.0)	0.3 (0.62)
Female	8.6 (0.6)	8.0 (0.6)		8.6 (0.6)	8.0 (0.7)	
Marital Status						
Single	8.6 (0.5)	8.0 (0.5)	0.22 (0.64)	8.9 (0.5)	8.0 (0.8)	3.2 (0.08)
Married	7.9 (0.8)	8.0 (0.0)		7.2 (0.7)	8.0 (0.6)	
Employment Status						
Unemployed	8.7 (0.6)	8.0 (0.7)	0.27 (0.60)	8.8 (0.6)	8.0 (0.8)	0.8 (0.39)
Employed	7.9 (0.6)	8.0 (0.7)		8.0 (0.6)	8.0 (0.8)	
Social Support						
Satisfactory	6.1 (0.5)	4.0 (0.0)	2.63 (0.11)	5.6 (0.4)	4.0 (0.0)	6.7 (0.01)
Unsatisfactory	7.9 (0.6)	8.0 (0.7)		8.0 (0.6)	8.0 (0.7)	
Mode of Onset						
Insidious	9.5 (0.7)	8.0 (0.6)	8.10 (0.005)	7.2 (0.6)	8.0 (0.0)	13.6 (<0.001)
Acute	7.4 (0.6)	8.0 (0.0)		9.7 (0.6)	8.0 (0.7)	
Family History						
Positive	8.7 (0.5)	8.0 (0.6)	2.60 (0.11)	8.1 (0.5)	8.0 (0.7)	0.2 (0.65)
Negative	7.9 (0.7)	8.0 (0.9)		8.8 (0.7)	8.0 (0.9)	

NB: remission using BPRS = Scores ≤ 2 in the following BPRS items (Grandiosity, Suspiciousness, unusual thought content, Hallucinatory behavior, conceptual disorganization, mannerism/posturing, and blunted affect). Remission in SANS = Scores ≤ 2 in the following SANS items (Affective flattening, Avolition-apathy, Anhedonia-asociality, and Alogia). SE: standard error. Statistical significance was based on Breslow (generalized Wilcoxon).

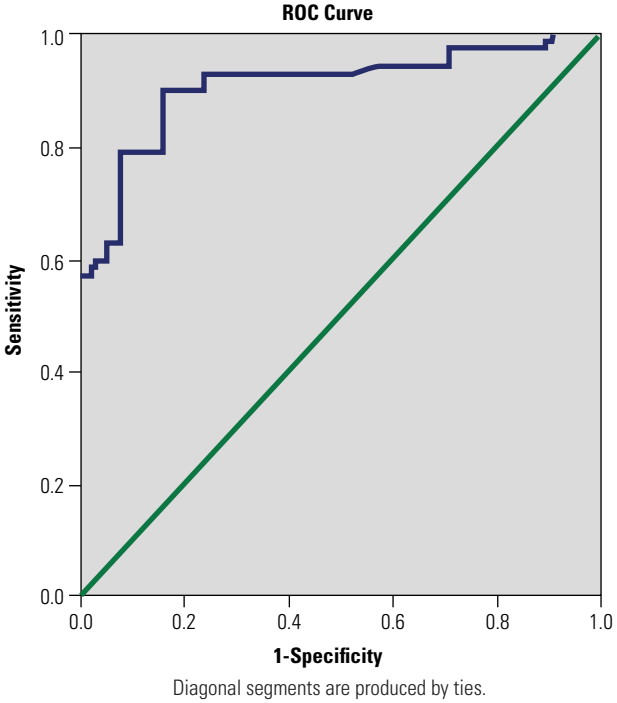
treatment resistance among schizophrenia patients that suggest a treatment duration of ≥6 weeks and ≤12 weeks to re-evaluate for non-response to treatment[7]. This is in line with recent evidence indicating that with prolonged treatment, most patients with acute schizophrenia would respond to treatment[8]. Consistent with the literature, the negative symptoms in SANS tended to confer longer time to treatment outcome, although the effect size was not significant; and the early achievement of response in SANS score was associated with good clinical outcome at week 16[27-30].

Our findings on social support and acute onset of illness are consistent with other studies that have found that adequate social support and acute onset are promotive of early response to treatment[31,32]. Other factors reported in the literature include: employment, a shorter duration of illness, female sex, being married, younger age, tertiary education, and shorter duration of untreated psychosis[24]. Our results did not support the later findings, although there were trends in that direction for being married and being employed, factors which could be viewed as contributing to social

Table 4. Time to Social Recovery: by baseline independent variables among schizophrenia patients

Variables	Time to Recovery Using BPRS Criteria			Time to Recovery Using SANS Criteria		
	Mean (S.E)	Median (SE)	Stat. (p-value)	Mean (SE)	Median (SE)	Stat. (p-value)
Gender						
Male	11.4 (0.6)	12.0 (1.0)	1.60 (0.21)	11.0 (0.4)	12.0 (0.9)	1.5 (0.20)
Female	10.4 (0.7)	8.0 (0.7)		10.6 (0.7)	8.0 (0.7)	
Marital Status						
Single	11.2 (0.5)	12.0 (0.0)	2.10 (0.15)	11.6 (0.6)	12.0 (0.1)	2.0 (0.14)
Married	10.0 (0.8)	8.0(0.7)		10.3 (0.7)	8.0 (0.7)	
Employment Status						
Unemployed	11.7 (0.6)	12 (1.0)	3.82 (0.05)	11.8 (0.6)	12 (1.0)	3.7 (0.06)
Employed	9.7 (0.6)	8.0 (0.6)		9.6 (0.5)	8.0 (0.6)	
Social Support						
Satisfactory	8.7 (0.6)	8.0 (0.7)	4.12 (0.04)	8.0 (0.3)	8.0 (0.5)	4.9 (0.03)
Unsatisfactory	11.2 (0.6)	12.0 (1.2)		11.0 (0.6)	12.0 (1.2)	
Mode of Onset						
Insidious	11.6 (0.7)	12.0 (1.1)	2.80 (0.09)	11.8 (0.7)	12.0 (1.1)	2.9 (0.08)
Acute	10.3 (0.6)	8.0 (0.7)		10.7 (0.6)	8.0 (0.7)	
Family History						
Positive	10.4 (0.6)	12 (0.8)	1.41 (0.24)	10.5 (0.6)	12 (0.8)	1.5 (0.26)
Negative	11.5 (0.7)	12.0 (1.3)		11.5 (0.7)	12.0 (1.3)	

NB: recovery = maintenance of remission + GAF-score ≥61, SE: standard error. Statistical significance was based on Breslow (generalized Wilcoxon).



Diagonal segments are produced by ties.

Figure 1a. Receiver Operating Characteristics curve showing plot of % reduction in total BPRS score at week 4 *vs.* response status (responded/not responded) at week 16. Note: Area under the curve (AUC) (95% C.I.): 0.909 (0.85-0.963). With 20.72% BPRS reduction at week 4, prediction of response status at week 16 had 79.5% sensitivity, 84.2% specificity.

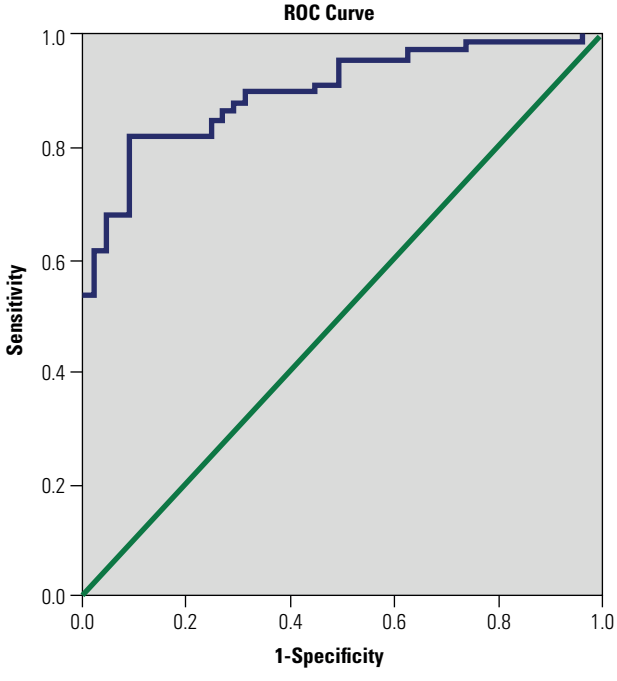


Figure 1b. Receiver Operating Characteristics curve showing plot of % reduction in total SANS score at week 4 *vs.* response status (responded/not responded) at week 16. Note: Area under the curve (AUC) (95% C.I.): 0.897 (0.84-0.955). With 10.21% SANS reduction at week 4, prediction of response status at week 16 had 70.8% sensitivity, 95.5% specificity.

support. The long held impression is that the traditional social support in the African extended family system constitutes a huge social capital for patients with schizophrenia, and could positively modify the clinical course of the disease[33,34].

For the ROC analyses, we found that early response to treatment at week 4 predicted good response at week 16. This is consistent with Agid *et al.*[35] early-onset of response hypothesis of antipsychotic drug action, which suggests that early response to medication is a stable predictor of subsequent response. Studies have evaluated the predictive value of early response to treatment among schizophrenia patients[36-38]. The results largely agree that, early response is a significant predictor of later response[4,5,38]. However, variations exist on which week of treatment has the best predictive validity for response at later stages of treatment[36]. Studies have evaluated response at weeks 1, 2, 3, 4, and 8. Although there is much support for the predictive value of response at 2 weeks[4,5,36], it has been suggested that the first critical decision point for assessing treatment outcome is 4 weeks[23], and this has been incorporated in treatment guidelines[22,23]. In line with our findings, Gallegos *et al.*[8] reported that early response at week 4 (not 2 or 8) was associated with responder status at week 16. Taken together, our data support the impression that re-evaluation of treatment in schizophrenia patients for response should occur within the first 4 weeks of commencing treatment, to identify potential candidates for treatment resistance early on in the treatment trajectory. In addition, our finding of ≥20.7% BPRS-score reduction at week 4 as having significant predictive validity for outcome events is consistent with the literature[38]. This finding validates the recommendation of Kane *et al.*[6], that treatment resistance be defined as <20% reduction in BPRS total score after adequate psychopharmacological treatment. An important addition to the literature is the finding that ≥10.21% SANS-score reduction at week 4 was predictive of response, remission and recovery at week 16.

Negative symptoms have been identified as important determinants of psychosocial functioning in schizophrenia[27-29]. In the prediction of global psychosocial functioning, negative symptom severity was the most important factor[30].

Limitations and strengths

First, being a naturalistic study (as distinct from a drug trial), we could not control treatment decisions, such as dosage/type of medications, and whether to augment or change medication when there was inadequacy of response. However, this design is in line with the international follow-up studies in the literature, and makes our results comparable with those studies. Second, treatment adherence was judged only by the verbal testimony of patients and family caregivers. Although this is less rigorous than assaying blood levels of drugs, our experience is that the accompanying family caregivers could be trusted to determine treatment adherence, Third, the relatively high attrition rate meant that we could not account for the outcome in over a quarter of the original cohort. We note that attrition is a well-known problem in follow-up studies, and we tried to avoid this problem by including only patients living within the metropolis of our study area. The major strengths of the study are that: first, we have used rigorous statistical methods and stringent operational definitions of clinical outcome, for incident cases, who were predominantly neuroleptic naïve at baseline, to estimate the time to outcome events. Second, we have validated the psychopathological cut-off points that define treatment resistance in schizophrenia. In particular, in addition to the well- known 20% cut-off for the BPRS, we have indicated that 10.21% be considered for the SANS

Conclusions

The results are in line with the general clinical impression that, by 2 months, most acutely ill inpatients are fit for discharge in our practice setting; and support the popular use of <20% reduction in BPRS psychopathological score, as a marker of treatment resistance in schizophrenia. We suggest that future studies could try to validate our finding of <10.21% reduction in SANS score as a marker of treatment resistance. In the first such rigorously designed study from Africa, this cohort of Nigerians with first – episode schizophrenia, had similar treatment response patterns, in the short-term, with such patients in the international literature.

Conflict of interest

There is no conflict of interest.

Contributors

Justus Uchenna Onu was the principal investigator. However, the first and second authors contributed to the study design, analysis and interpretation of data, and drafting the manuscript. All the authors approved the final draft for submission.

Role of funding sources

Self-financed.

Statement of ethics

Ethical approval was obtained from the Ethical Committee of the Federal Neuropsychiatric Hospital Enugu, Enugu State, Nigeria. International ethical norms and standards were strictly adhered to. After explaining the objectives and procedures, consenting patients were required to sign the written informed consent, with the understanding that they could withdraw from the study at any stage without any adverse impact on their right to treatment.

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PER3 VNTR variant and susceptibility to smoking status/substance use disorder in a Turkish population

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Abstract

Background: Substance use and smoking exert devastating impact on sleep, especially hindering the ease of falling asleep, compromising the sleep maintenance, and distorting the sleep cycles. PERIOD genes are believed to play a role in individual differences in sleep timing by influencing circadian. **Objective:** The aim of this study was to ascertain whether Per3 VNTR variant affects suspectibility of individuals to substance use disorder (SUD) and smoking status in a Turkish population. **Methods:** A total of 549 subjects, including 212 SUD patients, 160 smoker, and 177 healthy controls, matched by ethnicity, age, and gender, were recruited in a case-control study. Genotyping of *Per3* variant was performed using PCR method. **Results:** When the SUD, smoker groups and controls were compared in terms of 5R/5R, 5R/4R, 4R/4R genotypes, no significant difference was observed. Besides, allele frequencies of Per3 VNTR were similar among the groups. **Discussion:** Our data indicate that *Per3* VNTR variant is not associated with the risk of SUD and smoking status in our population.

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Keywords: Substance use disorder, smoking status, *Per3*, VNTR, PCR.

Introduction

The term substance use disorders (SUDs) refers numerous disorders, such as alcohol abuse, alcoholism, drug abuse and drug addiction. These disorders affect myriad of adults and families, cost medical, economic, criminal, and social sectors of society more than 500 billion dollars, and result in more than 75,000 deaths in the U.S.[1]. SUDs can occur in any individual, but the risk can be higher depending on an individual's biological predisposition (e.g., genetic vulnerability), environment, and developmental stage (e.g., adolescence). Tobacco use increases the risk of major health problems and is the main cause of morbidity and mortality. The relation between cigarette smoking and many health issues, such as cardiovascular disease, pulmonary disorders, and cancer, is well known. Studies have demonstrated a clear association between poor sleep pattern and a number of adverse health behaviors, such as tobacco use, alcohol consumption, illicit drug use, suicide attempts, and unintentional injury[2].

Human diurnal preference is a well-established circadian phenotype with regard to the preferred timing of daily activities[3]. Circadian rhythms are modulated by various canonical clock genes that are extremely conserved in all species, with allelic variants affecting individual rhythms at different levels[4]. The circadian rhythm is controlled by these clock genes. Period homolog 3 (Per3) or Clock homologue (CLOCK), have been investigated as potential genetic correlates of chronotypes and other circadian phenotypes in humans[5]. A variable-number tandem repeat (VNTR) polymorphism (rs57875989) in the *Per3* gene (located on chromosome 1p36.23), containing two alleles of 4 or 5 tandem 54 bp repeats (coding for a region of 18 amino acids in exon 18), has been assessed as a possible genetic factor for chronotypes and other circadian phenotypes[6]. Some research show that circadian gene variants might modify the function of these genes, hence modifying diurnal preference and sleep-wake patterns[7].

Because sleeping impairments are seen more frequently in this disorders, we aimed to ascertain whether *Per3* VNTR variant affects susceptibility of individuals to substance use disorder (SUD) and smoking status in a Turkish population

Methods

Study population

This case-control association study included 212 patients with SUD, 160 smokers, and 177 healthy controls. The subjects with SUD were selected from among the individuals with positive urine test in the Department of Psychiatry, Bakirkoy Research and Training Hospital for Psychiatry Hospital, Istanbul Turkey. All SUD patients in the study met DSM-IV (American Psychiatry Association) criteria[8]. Smoker group was selected from the Department of Chest Diseases, Yedikule Hospital for Chest Diseases and Thoracic Surgery Training and

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Research Hospital, Istanbul, Turkey. Smoker group consisted of active smokers. These subjects were defined as those who had previously smoked more than one cigarette per day but had quit smoking for more than one year. The degree of smoking was evaluated by the scores on the Fagerström Test for Nicotine Dependence (FTND)[9]. Control group was recruited from "non-smokers" were defined as those who had smoked less than one cigarette per day for no more than 1 year during their lifetime and subjects who did not have a personal history of any psychiatric disorder and chronic use of any drugs. All subjects were of Turkish origin. Before enrollment, signed informed consent was obtained from each participant. The study protocols were performed according to the principles of the Declaration of Helsinki. This study was approved by the Ethics Committees of the Istanbul University, Istanbul Medical Faculty.

Genotyping

Peripheral blood was taken from subjects, and DNA was isolated using a standard salting out method[10]. Polymerase chain reaction (PCR) was performed to amplify the exon 18 using the primers: upstream, 5'-CCTTGGTTGACCACAGGTAA-3' and downstream, 5'-CCACTACCTGATGCTGCTGA-3' (amplification conditions: 95 °C for 30 seconds, 60 °C for 30 seconds, 72 °C for 45 seconds, recycle for 28 cycles, 72 °C for 10 min, 48C forever), and in 40 ml mixture containing 3.2 mL (2.5 mM) deoxyribonucleotide triphosphate, 3.2 mL (25 mM) Mg^{+2}, 0.4 mL (5 U/mL) Taq polymerase, 4 mL 10_ buffer; 25.4 mL H2O, 1 mL of each primer (10 mM) and 1.8 mL (50 ng/mL) DNA template. Three percent agarose gel electrophoresis was used to identify whether individuals were heterozygous or homozygous for either of the *Per3* repeat alleles.

Statistical analysis

The genotype distribution and allele frequency of the *Per3* VNTR variant in the control and patient groups were compared using Chi-square test. The Hardy-Weinberg equilibrium (HWE) was calculated using the de Finetti program (Online HWE and Association Testing-Institut für Humangenetik, Munich, Germany). Odds ratio (OR) and 95% confidence intervals (CIs) were estimated using the binary logistic regression method. p values less than $p < 0.05$ were considered statistically significant.

Results

Allelic and genotypic distributions of the *Per3 VNTR* variant in subjects and controls are shown in Table 1. Among the 212 SUD patients, 16.6% were identified with the 5R/5R genotype, 45.7% with the 5R/4R genotype and 37.7% with the 4R/4R genotype; among the 160 smoker subjects, 20% were identified with the 5R/5R genotype, 38.2% with the 5R/4R genotype and 41.8% with the 4R/4R genotype; among the 177 control subjects, 15.8% were identified with the 5R/5R genotype, 43.6% with the 5R/4R genotype and 40.6% with the 4R/4R genotype. The genotype distribution of *Per3* VNTR variant did not show any statistically significant differences between subjects with SUD, smokers and controls ($p > 0.05$). Also, allele frequencies of *Per3* VNTR were similar between the groups. The observed genotype counts deviated significantly from those expected in smoker group according to the HWE for *Per3* VNTR variant.

Discussion

Circadian rhythms are universal in all living organisms and almost all physiological functions, most remarkably sleep and wake cycles, show circadian rhythmicity. Circadian rhythms occur intrinsically and remain in the lack of environmental time cues. The suprachiasmatic nucleus (SCN), a structure located in the anterior hypothalamus is the region of a master circadian clock[11]. Essentially every physiological and behavioral parameter follows the nearly 24-hour (circadian) rhythms, the sleep/wake cycle being the most evident. Sleep is a dynamic and complex set of physiological conditions that plays a fundamental role in life. Sleep is characterized by a alignment of central nervous system characteristics, such as an unequalled profile of brain-wave activity, eye movements, and muscle activity[12].

The chronic abuse of substances may arise due to a desire to relieve negative affect, including anxiety or depressed mood, to palliate physical pain, to improve sleep, or to increase experience of pleasure. After dependence has developed, withdrawal from the substance can result in many unpleasant consequences. One of the most common results of the use of and withdrawal from substances of abuse is sleep disturbance. It has been reported that sleep disturbances occur in up to 90% of alcoholic individuals[13]. The correlation between substance use and sleep problems seems to be bidirectional[14] with sleep problems enhancing risk for SUDs[15], and acute and chronic substance use causing acute and chronic sleep problems[16]. Most studies in this area are based on surveys and demonstrate that smokers subjectively report sleep problems[17]. Investigating large populations of smokers, a subjectively decreased quality of sleep and more insomnia-like symptoms (decreased sleep quality, longer time for sleep onset, less restorative sleep; compared with non-smokers have been found[18,19]. These impairments are ascribed the stimulating effect of nicotine[20,21].

The circadian rhythm is subject to coordinated modulation of clock genes including *Arntl*, *Dbp* and *Csnk1d*, and the period homologs *Per1*, *Per2* and *Per3*[22]. One of the main parts of the endogenous clock system is gene *Per3* that is periodically transcribed contributing to generate 24-h cycles of physiological and metabolic processes in certain cells. The *Per3* gene from the protein PERIOD family has a pleiotropic effect on the cell clock mechanism, particularly in the modulation of sleep homeostasis and chronotype preferences[6]. The principal role of *Per3* involves regulating sleep/wake timing and sleep homeostasis[23].

Table 1. Genotypes and alleles distribution of *Per3* VNTR variant in cases and controls

Per3 VNTR	SUD group	Smoker group	Control group	OR*	%95 CI*	P
Genotypes	n: 212 (%)	n: 160 (%)	n: 177 (%)			
5R/5R	35 (16.6)	32 (20)	28 (15.8)	0.950[a] 0.752[b]	0.552-1.635[a] 0,430-1.315[b]	0.854[a] 0.316[b]
5R/4R	97 (45.7)	61 (38.2)	77 (43.6)	0.913[a] 1.250[b]	0.611-1.364[a] 0.808-1.933[b]	0.656[a] 0.316[b]
4R/4R	80 (37.7)	67 (41.8)	72 (40.6)	1.131[a] 0.952[b]	0.752-1.703[a] 0.616-1.469[b]	0.554[a] 0.824[b]
Alleles						
5R 4R	167 (39.3) 257 (60.7)	125 (39.1) 195 (60.9)	133 (37.5) 221 (62.5)	0.926[a] 0.939[b]	0.693-1.238[a] 0.688-1.281[b]	0.604[a] 0.691[b]
HWEp	0.543	**0.011**	0.333			

*Pearson chi-square test; a: SUD group versus control group; b: Smoker group versus control; HWE: Hardy-Weinberg equilibrium. The results that are statistically significant are shown in boldface.

The most investigated variant in *Per3* gene is a biallelic VNTR polymorphism in a region encoding an assumed phosphorylation site[24]. In humans, this primate-specific polymorphism consists of a 54-nucleotide unit that is repeated 4 (*Per* 4 allele) or 5 (*Per* 5 allele) times[25]. The longer, 5-repeat allele has been related with enhanced morning preference, higher sleep propensity and poorer cognitive performance in response to sleep deprivation, while the 4-repeat allele is related with eveningness. Individuals with the *Per3* 5/5 genotype displayed an extreme diurnal preference-earlier wake-up and sleep-times[26]. *Per3* VNTR has been associated with multiple phenotypic parameters, such as diurnal preference, myocardial infarction, sleep disturbances in multiple sclerosis, mood disorders, and also with an increased breast cancer risk[6,25,27-29].

While the PERIOD family could be considered as possible modulators of sleep function, we focused on the gene for Per3 VNTR variant and SUD/smoking status and we aimed to clarify the impact of the *Per3 VNTR* variant on susceptibility SUD and smoking status in a Turkish population. This is the first study carried out in the Turkish population regarding the association *Per3* VNTR variant and SUD/smoking status. Some studies have proposed the role of *Per2* in alcohol consumption behavior in humans and animal models. Spanagel *et al.* showed that a SNP in Per2 (rs56013859) was associated with high levels of alcohol use in alcohol dependent patients[30]. Gamsby *et al.* reported that mutation of either Per1 or Per2, as well as mutations of both genes, increases ethanol intake and reinforcement in an ethanol-preferring mouse model[31]. Malison *et al.* found that there was no link between *CLOCK*, *Per1* or *Per2* variants and susceptibility to cocaine addiction[32]. In another study, it was reported that *Per2* VNTR variant was significantly associated with vulnerability to cocaine addiction[33]. Brower *et al.* evaluated that the association *Per3* genotype and insomnia severity in subjects with alcohol dependence[34]. They found that the subjects with the *Per3* (4/4) genotype had the greatest severity of insomnia symptoms. In this study, we did not reveal any association between the *Per3* VNTR and both SUD and smoking status. Also, allele frequencies were similar in groups.

As far as we know, this is the first study reporting the association of *Per3* VNTR variant, located in the intron, with the SUD and smoking status. Our results suggest the *Per3* VNTR variant was not associated with SUD and smoking status in a sample from the Turkish population. But distribution of variants varies significantly among different ethnic groups, this may contribute to the observed differences in ethnicity-dependent prevalence. Therefore additional studies on larger population will be necessary to confirm our results and to provide further insights into cellular clock gene circadian mechanism underlying addiction and/or smoking status.

Conflict of interest

The authors confirm that this article's content has no conflicts of interest.

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Informed consent

Written informed consent was obtained from subjects and patients who participated in this study.

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Correlates of neuropsychiatric and motor tests with language assessment in patients with Lewy body dementia

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Abstract

Background: Lewy body dementia (LBD) impairs performance in daily activities and affects motor, language and visuospatial tasks. **Objective:** We aimed to correlate neuropsychiatric and motor assessments with language and visual organization tests in LBD. **Methods:** Twenty-two patients with dementia with Lewy bodies and ten patients with Parkinson's disease dementia participated on a cross-sectional study that assessed cognition, functionality, caregiver burden, verbal fluency, the primer-level dictation section of the Boston Diagnostic Aphasia Examination (PLD-BDAE), the Hooper Visual Organization Test, the Neuropsychiatric Inventory and the Movement Disorder Society – Unified Parkinson's Disease Rating Scale. **Results:** Language and visuospatial test results followed motor impairment and general cognitive performance. Whereas visual organization did not predict performance in the PLD-BDAE, visuospatial abilities and verbal fluency were concurrently associated, suggesting that linguistic impairment in LBD may be attributed to neuropsychological components of cognition and language. Only visual organization was associated with behaviour, suggesting that neuropsychiatric symptoms associate with differential impairment of visual organization in comparison with language in LBD. Schooling did not affect visual organization or language test performance, while the length of dementia was negatively associated with visual organization and verbal fluency. **Discussion:** Though visual organization tests follow behaviour and motor performance in LBD, there is differential impairment regarding language skills.

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Keywords: Lewy body dementia, language, spatial processing, neuropsychiatry, neuropsychological tests.

Introduction

Deficits in visuospatial abilities, memory, executive functions and language are the most evident neuropsychological symptoms in patients with Lewy body dementia (LBD) syndromes, corresponding to frontal-striatal dopaminergic dysmodulation associated with diffuse cholinergic cortical dysfunction[1]. Essentially, the spectrum of these syndromes consists of dementia with Lewy bodies and Parkinson's disease dementia[2], comprising the second leading cause of degenerative dementia in older people after Alzheimer's dementia (AD)[3,4]. Nevertheless, sensitivity of clinical diagnosis of LBD is not always good, particularly in severe dementia, although specificity tends to be high[5].

The main etiological hypothesis for LBD entails the histopathological presence of Lewy bodies in the brainstem, subcortical nuclei, limbic cortex (cingulate cortex and amygdala), and in the neocortex[6,7]. In Parkinson's disease dementia, Lewy body formation and neuron loss usually start in brainstem nuclei and in the substantia nigra, whereas in dementia with Lewy bodies they occur in paralimbic and neocortical structures from disease onset[8]. In addition, amyloid pathology helps predict the onset of dementia in parkinsonian syndromes[9]. Nevertheless, cholinergic denervation is the main source of linguistic impairments in patients with LBD, particularly when involving cortical or subcortical language networks[10].

Approximately 80% of all patients with Parkinson's disease develop dementia, more frequently when they are male and have more severe motor signs at examination[11]. The burden of motor and neuropsychiatric manifestations of LBD considerably affects functional independence and social activities, impacting quality of life[2,8]. Visuospatial skills and behavioural symptoms are helpful for differential diagnosis between LBD and AD, whereas cerebrovascular risk might be more important for pathogenesis of AD[8,12], but cholinesterase inhibitors are usually valuable for treatment of neuropsychiatric symptoms of both AD and LBD[13,14].

Despite the fact that some associations are well established for dementia syndromes, such as functional decline following cognitive decline in severe dementia[15], impairment of language has not been deeply studied in LBD. We hypothesized that language domains could be primarily affected in LBD, whereas motor signs, behavioural symptoms, linguistic and cognitive features would be concurrently impaired; therefore, we aimed to analyse associations of neuropsychiatric and motor assessments with language and visual organization test results in patients with LBD.

Methods

Participants

In this cross-sectional study, consecutive outpatients with LBD in different levels of clinical evolution were recruited from the Department of Neurology and Neurosurgery at *Hospital São Paulo*, Federal University of São Paulo (Unifesp). All patients with LBD who were followed at the outpatient clinic were assessed from January 2014 to April 2015. Diagnosis of Parkinson's disease followed traditional

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clinical criteria[16]. Patients had to be diagnosed with either probable or possible Parkinson's disease dementia according to Movement Disorder Society Task Force clinical diagnostic criteria[17], or either probable or possible dementia with Lewy bodies[18]. Basically, Parkinson's disease dementia developed within the context of established Parkinson's disease, requiring a combination of typical cognitive and behavioural features for diagnosis, while dementia with Lewy bodies preceded motor manifestations by at least one year, with a combination of core features (fluctuating cognition with varied attention or alertness, recurrent well-formed visual hallucinations, or spontaneous features of parkinsonism) and suggestive features (REM sleep behaviour disorder, severe neuroleptic sensitivity, low dopamine transporter uptake in basal nuclei). None of the patients had neuroimaging evidence of focal cerebrovascular diseases or any other structural brain diseases that could account for the cognitive or language deficits.

Clinical assessment

After diagnostic confirmation, patients and caregivers were assessed for: patient age, gender, schooling, estimated age at dementia onset, sleep satisfaction and estimated daily length of sleep[19], use of any medications, and scores on the Neuropsychiatric Inventory[20], the Mini-Mental State Examination[21], the Clinical Dementia Rating sum-of-boxes[22], a 15-item clock drawing test (free drawing)[23], the Schwab & England scale[24], Lawton's Scale for Instrumental Activities of Daily Living[25], the Brazilian Version of the Zarit Caregiver Burden Interview[26], forward digit span and reverse digit span, the Movement Disorder Society – Unified Parkinson's Disease Rating Scale[27], and the Hoehn & Yahr stages in the off state[28].

In a second evaluation, patients with LBD were also assessed with the Hooper Visual Organization Test (HVOT)[29], verbal fluency (VF)[30], and the primer-level dictation section of the Boston Diagnostic Aphasia Examination (PLD-BDAE)[31,32], including primer words, regular phonics, and common irregular words. All cognitive assessments were conducted on weekdays at morning time, by two examiners (FCM and FFO).

The Schwab & England scale[24] was employed for overall performance in activities of daily living. A trichotomous version (1 = unable; 2 = able with help; 3 = able without help) of Lawton's Scale for Instrumental Activities of Daily Living[25] was employed, with scores for using the telephone, getting to places beyond walking distance, grocery shopping, meal preparation, housekeeping, doing handyman work, doing laundry, taking own medications, and handling finances; caregivers provided all information, with a total score of 9 to 27.

For the HVOT, each participant was presented with 30 figures of fragmented objects in ascending order of difficulty[29]. For the VF tasks, the patient should generate the largest possible number of words in one minute for each category, including words beginning with F, A and S (F-A-S), as well as all animals, fruits and grocery items that might be known[33]. In the PLD-BDAE, the patient writes regular and irregular words to dictation[31].

Statistical analyses

Fisher's exact test and the Mann-Whitney test were used for comparisons of neurological features between dementia syndromes. Simple linear regressions were employed for comparisons between test results. A multiple linear regression model was employed for associations between each visual organization or language test (HVOT, VF, and the PLD-BDAE) and the following independent variables: schooling and length of the dementia syndrome; p-values were corrected with the Bonferroni test. The threshold of significance was set at $p < 0.05$.

Ethical aspects

This study is part of the research project 064990/2013 approved by the Ethics Committee of *Hospital São Paulo*, Unifesp, in October 2013. All invited patients and their legal representatives agreed to participate on the research and signed the Informed Consent Form before the evaluation.

Results

Overall, 39 participants were recruited; between the first and the second assessments, three patients passed away (7.7%), and four patients did not complete the second evaluation (10.3%), resulting in a final sample of 32 patients – 19 women (59.4%) and 13 men (40.6%). Twenty-one patients were diagnosed with probable dementia with Lewy bodies, one patient was diagnosed with possible dementia with Lewy bodies, nine patients were diagnosed with probable Parkinson's disease dementia, and one patient was diagnosed with possible Parkinson's disease dementia. Nineteen patients with dementia with Lewy bodies (86.4%) had visual hallucinations, versus six patients with Parkinson's disease dementia (60.0%), $p = 0.165$. Sixteen patients with dementia with Lewy bodies (72.7%) had parkinsonism, versus ten patients with Parkinson's disease dementia (100.0%), $p = 0.142$. Moreover, fifteen patients with dementia with Lewy bodies had fluctuations (68.2%). Demographic data and test results for all patients with LBD are summarized in Table 1.

There was no statistically significant difference between patients with dementia with Lewy bodies and patients with Parkinson's disease

Table 1. Demographic data and test results

Variables, *n* = 32	Mean or *n* (%)	SD	Range
Age at examination (years-old)	75.84	9.1	54-89
Age at dementia onset (years-old)	71.14	9.8	50-87
Length of the dementia syndrome (years)	4.81	3.4	1-12
Schooling (years)	3.59	3.4	0-12
Sleep Satisfaction	23 (71.9%)	-	
Hours of Sleep	8.25	2.3	-4-13
Daily amount of different medications	5.03	2.6	0-13
Daily amount of pills/injections	7.42	5.4	0-25.5
Clinical Dementia Rating sum-of-boxes (0.0-18.0 points)	10.63	4.1	4.0-18.0
Neuropsychiatric Inventory (0-144 points)	41.25	19.5	7-84
Mini-Mental State Examination (0-30 points)	17.72	5.7	7-27
Clock Drawing Test (0-15 points)	5.16	4.1	0-15
Schwab & England scale (0%-100%)	56.56%	25.6%	10%-90%
Lawton's Scale for Instrumental Activities of Daily Living (9-27 points)	13.41	4.4	9-22
Brazilian Version of the Zarit Caregiver Burden Interview (0-56 points)	20.00	8.4	3-35
Forward Digit Span	4.72	1.3	3-8
Reverse Digit Span	2.25	0.7	1-3
MDS-UPDRS – Part I	19.53	5.5	6-30
MDS-UPDRS – Part II	17.97	11.9	0-42
MDS-UPDRS – Part III	33.38	26.5	1-99
MDS-UPDRS – Part IV	3.47	5.0	0-17
Hoehn & Yahr stage – OFF state (0-5)	2.88	1.6	0-5
Hooper Visual Organization Test	6.97	3.4	0-15
Verbal Fluency (F-A-S)	6.44	5.7	0-24
Verbal Fluency (animals)	6.78	4.1	0-18
Verbal Fluency (fruits)	5.59	2.4	0-10
Verbal Fluency (grocery items)	6.31	3.7	0-15
PLD-BDAE	5.06	5.6	0-16

SD: standard deviation; MDS-UPDRS: Movement Disorder Society – Unified Parkinson's Disease Rating Scale; PLD-BDAE: primer-level dictation section of the Boston Diagnostic Aphasia Examination.

dementia regarding age (p = 0.291), gender (p = 0.999), schooling (p = 0.597), age at dementia onset (0.626), estimated length of sleep (p = 0.143), use of different medications (p = 0.067), or scores on the Neuropsychiatric Inventory (p = 0.655), the Mini-Mental State Examination (p = 0.382), the Clinical Dementia Rating sum-of-boxes (p = 0.291), the clock drawing test (p = 0.092), the Brazilian Version of the Zarit Caregiver Burden Interview (p = 0.871), forward digit span (p = 0.291), reverse digit span (p = 0.371), the HVOT (p = 0.855) or VF (p = 0.999), but patients with dementia with Lewy bodies were more satisfied with their sleep (p = 0.013).

Table 2 summarizes the results from simple linear regressions between visual organization and language test results for all patients with LBD. Visual organization was associated with category VF, whereas all language tests were correlated with each other, except for the association between VF (animals) and the PLD-BDAE.

Tables 3 and 4 list results from simple linear regressions regarding visual organization and language tests for predictions of associations with other neuropsychiatric features. Visual organization was associated with basic (but not instrumental) functionality, general cognitive tests, motor examination and the Neuropsychiatric Inventory total scores. All categories of VF were associated with general cognitive tests, and inversely associated with global dementia rating; however, only VF for F-A-S and for fruits was associated with the clock drawing test, only VF for F-A-S and for grocery items was associated with non-motor experiences of daily living, and only VF for fruits was associated with motor experiences of daily living and motor examination. All categories of VF were associated with forward digit span, except for fruits, the only category associated with reverse digit span. Sleep satisfaction was negatively associated with all categories of VF, except for fruits. The PLD-BDAE was associated with basic (but not instrumental) functionality, general cognitive tests, motor experiences of daily living and motor examination. Length of sleep, instrumental functionality, and caregiver distress regarding behavioural symptoms had no significant associations with visual organization or language tests.

Table 5 lists results from multiple linear regressions involving language and visual organization tests. Schooling did not affect performance in any test, while the length of the dementia syndrome was negatively associated with performance in the HVOT and VF (animals).

Table 2. Results from simple linear regressions for predictions between visual organization and language test results

Variable 1	Variable 2	Squared multiple R	*t*	F-ratio	p-value
HVOT	VF (F-A-S)	0.118	2.003	4.013	0.051
HVOT	VF (animals)	0.219	2.902	8.424	**0.007**
HVOT	VF (fruits)	0.366	4.160	17.307	**<0.001**
HVOT	VF (grocery items)	0.246	3.125	9.768	**0.004**
HVOT	PLD-BDAE	0.096	1.790	3.203	0.080
VF (F-A-S)	VF (animals)	0.453	4.983	24.826	**<0.001**
VF (F-A-S)	VF (fruits)	0.171	2.485	6.177	**0.018**
VF (F-A-S)	VF (grocery items)	0.445	4.909	24.096	**<0.001**
VF (F-A-S)	PLD-BDAE	0.213	2.851	8.126	**0.008**
VF (animals)	VF (fruits)	0.268	3.313	10.975	**0.003**
VF (animals)	VF (grocery items)	0.586	6.516	42.465	**<0.001**
VF (animals)	PLD-BDAE	0.045	1.185	1.404	0.244
VF (fruits)	VF (grocery items)	0.470	5.161	26.640	**<0.001**
VF (fruits)	PLD-BDAE	0.134	2.156	4.647	**0.037**
VF (grocery items)	PLD-BDAE	0.151	2.306	5.319	**0.027**

HVOT: Hooper Visual Organization Test; VF: verbal fluency; PLD-BDAE: primer-level dictation section of the Boston Diagnostic Aphasia Examination.

Table 3. Results from simple linear regressions for predictions between test results (with reference to visual organization and language functions)

Variable 1	Variable 2	Squared multiple R	*t*	F-ratio	p-value
HVOT	Clinical Dementia Rating sum-of-boxes	0.272	-3.352	11.234	**0.002**
HVOT	15-item Clock Drawing Test	0.217	2.880	8.293	**0.007**
HVOT	Forward Digit Span	0.046	1.208	1.459	0.235
HVOT	Reverse Digit Span	0.025	0.870	0.758	0.605
HVOT	Lawton's Scale for Instrumental Activities of Daily Living	0.079	1.604	2.573	0.116
HVOT	Schwab & England scale	0.212	2.839	8.058	**0.008**
HVOT	Mini-Mental State Examination	0.239	3.071	9.433	**0.005**
HVOT	MDS-UPDRS – Part I	0.015	-0.679	0.461	0.509
HVOT	MDS-UPDRS – Part II	0.092	-1.745	3.046	0.088
HVOT	MDS-UPDRS – Part III	0.136	-2.169	4.707	**0.036**
HVOT	Hoehn & Yahr stage – OFF	0.139	-2.198	4.833	**0.034**
VF (F-A-S)	Clinical Dementia Rating sum-of-boxes	0.239	-3.072	9.437	**0.005**
VF (F-A-S)	15-item Clock Drawing Test	0.164	2.429	5.900	**0.020**
VF (F-A-S)	Forward Digit Span	0.314	3.703	13.715	**0.001**
VF (F-A-S)	Reverse Digit Span	<0.001	0.116	0.013	0.904
VF (F-A-S)	Lawton's Scale for Instrumental Activities of Daily Living	0.057	1.351	1.826	0.184
VF (F-A-S)	Schwab & England scale	0.043	1.156	1.336	0.256
VF (F-A-S)	Mini-Mental State Examination	0.313	3.889	15.128	**<0.001**

Variable 1	Variable 2	Squared multiple R	*t*	F-ratio	p-value
VF (F-A-S)	MDS-UPDRS – Part I	0.235	-3.039	9.236	**0.005**
VF (F-A-S)	MDS-UPDRS – Part II	0.030	-0.961	0.923	0.654
VF (F-A-S)	MDS-UPDRS – Part III	0.056	-1.332	1.775	0.190
VF (F-A-S)	Hoehn & Yahr stage – OFF	0.003	0.325	0.106	0.746
VF (ANIMALS)	Clinical Dementia Rating sum-of-boxes	0.208	-2.811	7.901	**0.008**
VF (ANIMALS)	15-item Clock Drawing Test	0.019	0.773	0.598	0.549
VF (ANIMALS)	Forward Digit Span	0.274	3.366	11.329	**0.002**
VF (ANIMALS)	Reverse Digit Span	0.005	-0.398	0.158	0.696
VF (ANIMALS)	Lawton's Scale for Instrumental Activities of Daily Living	0.054	1.310	1.715	0.198
VF (ANIMALS)	Schwab & England scale	0.081	1.627	2.648	0.110
VF (ANIMALS)	Mini-Mental State Examination	0.192	2.670	7.127	**0.012**
VF (ANIMALS)	MDS-UPDRS – Part I	0.077	-1.587	2.517	0.119
VF (ANIMALS)	MDS-UPDRS – Part II	0.017	-0.723	0.523	0.518
VF (ANIMALS)	MDS-UPDRS – Part III	0.056	-1.334	1.780	0.189
VF (ANIMALS)	Hoehn & Yahr stage – OFF	<0.001	-0.081	0.007	0.934
VF (FRUITS)	Clinical Dementia Rating sum-of-boxes	0.222	-2.929	8.580	**0.006**
VF (FRUITS)	15-item Clock Drawing Test	0.154	2.338	5.468	**0.025**
VF (FRUITS)	Forward Digit Span	0.070	1.498	2.244	0.141
VF (FRUITS)	Reverse Digit Span	0.184	2.597	6.745	**0.014**
VF (FRUITS)	Lawton's Scale for Instrumental Activities of Daily Living	0.108	1.905	3.629	0.063
VF (FRUITS)	Schwab & England scale	0.205	2.780	7.729	**0.009**
VF (FRUITS)	Mini-Mental State Examination	0.231	3.006	9.037	**0.005**
VF (FRUITS)	MDS-UPDRS – Part I	0.038	-1.083	1.173	0.287
VF (FRUITS)	MDS-UPDRS – Part II	0.128	-2.096	4.392	**0.042**
VF (FRUITS)	MDS-UPDRS – Part III	0.187	-2.626	6.899	**0.013**
VF (FRUITS)	Hoehn & Yahr stage – OFF	0.075	-1.562	2.439	0.125
VF (GROCERY ITEMS)	Clinical Dementia Rating sum-of-boxes	0.311	-3.680	13.546	**0.001**
VF (GROCERY ITEMS)	15-item Clock Drawing Test	0.095	1.780	3.168	0.082
VF (GROCERY ITEMS)	Forward Digit Span	0.452	4.976	24.761	**<0.001**
VF (GROCERY ITEMS)	Reverse Digit Span	0.065	1.442	2.080	0.156
VF (GROCERY ITEMS)	Lawton's Scale for Instrumental Activities of Daily Living	0.078	1.598	2.555	0.117
VF (GROCERY ITEMS)	Schwab & England scale	0.111	1.941	3.766	0.059
VF (GROCERY ITEMS)	Mini-Mental State Examination	0.330	3.843	14.773	**<0.001**
VF (GROCERY ITEMS)	MDS-UPDRS – Part I	0.134	-2.153	4.637	**0.037**
VF (GROCERY ITEMS)	MDS-UPDRS – Part II	0.046	-1.209	1.461	0.235
VF (GROCERY ITEMS)	MDS-UPDRS – Part III	0.075	-1.558	2.428	0.126
VF (GROCERY ITEMS)	Hoehn & Yahr stage – OFF	0.011	-0.567	0.321	0.582
PLD-BDAE	Clinical Dementia Rating sum-of-boxes	0.159	-2.380	5.665	**0.022**
PLD-BDAE	15-item Clock Drawing Test	0.420	4.663	21.745	**<0.001**
PLD-BDAE	Forward Digit Span	0.114	1.966	3.867	0.056
PLD-BDAE	Reverse Digit Span	0.092	1.744	3.042	0.088
PLD-BDAE	Lawton's Scale for Instrumental Activities of Daily Living	0.025	0.881	0.776	0.611
PLD-BDAE	Schwab & England scale	0.114	1.967	3.870	0.056
PLD-BDAE	Mini-Mental State Examination	0.300	3.590	12.890	**0.001**
PLD-BDAE	MDS-UPDRS – Part I	0.052	-1.287	1.657	0.205
PLD-BDAE	MDS-UPDRS – Part II	0.154	-2.338	5.468	**0.025**
PLD-BDAE	MDS-UPDRS – Part III	0.274	-3.364	11.316	**0.002**
PLD-BDAE	Hoehn & Yahr stage – OFF	0.128	-2.098	4.401	**0.042**

HVOT: Hooper Visual Organization Test; VF: verbal fluency; PLD-BDAE: primer-level dictation section of the Boston Diagnostic Aphasia Examination; MDS-UPDRS: Movement Disorder Society – Unified Parkinson's Disease Rating Scale.

Discussion

In this study, associations among neuropsychiatric features of patients with LBD could be more accurately evaluated by specific tests. Knowledge of less studied clinical features, such as language disorders in LBD, can be useful to promote deinstitutionalized care and caregiver education.

Visual organization and PLD-BDAE test results were not significantly correlated, suggesting that the HVOT does not predict performance in the PLD-BDAE; in other words, this finding confirms that impairment of language may be a primary feature of LBD, and not necessarily secondary to cognitive deficits[34]. Nonetheless, VF and visuospatial abilities were concurrently associated in LBD. Visual organization is related to the frontal-subcortical circuitry that is

affected early in the course of LBD[35]. Moreover, poor VF is associated with incident dementia in Parkinson's disease, and could be due to impaired self-generated search[13]. Nevertheless, other studies have found that naming tests can be the best predictor of performance in the HVOT[35]. Patients with dementia with Lewy bodies have disproportionate deficits in visuospatial skills, attention and letter fluency[36]. Visuospatial processing, attention and executive functions in Parkinson's disease dementia have also been described to be similar to dementia with Lewy bodies[37].

Impaired connectivity with the frontal cortex leads to severely impaired grammatical expression in patients with LBD: failing to complete sentences, omitting the verb phrase, perseveration,

Table 4. Results from simple linear regressions for predictions between visual organization and language tests, features of sleep and neuropsychiatric inventory test results

Variable 1	Variable 2	Squared multiple R	t	F-ratio	p-value
HVOT	12-item Neuropsychiatric Inventory total scores	0.152	2.323	5.396	**0.026**
HVOT	12-item Neuropsychiatric Inventory – caregiver distress total scores	0.084	1.663	2.765	0.103
HVOT	Sleep satisfaction	0.017	-0.712	0.507	0.511
HVOT	Hours of sleep	0.051	-1.270	1.613	0.211
VF (F-A-S)	12-item Neuropsychiatric Inventory total scores	0.097	-1.791	3.208	0.080
VF (F-A-S)	12-item Neuropsychiatric Inventory – caregiver distress total scores	0.011	-0.589	0.347	0.567
VF (F-A-S)	Sleep satisfaction	0.170	-2.479	6.146	**0.018**
VF (F-A-S)	Hours of sleep	0.019	-0.769	0.592	0.546
VF (ANIMALS)	12-item Neuropsychiatric Inventory total scores	0.008	-0.505	0.255	0.623
VF (ANIMALS)	12-item Neuropsychiatric Inventory – caregiver distress total scores	<0.001	-0.097	0.009	0.920
VF (ANIMALS)	Sleep satisfaction	0.140	-2.213	4.899	**0.033**
VF (ANIMALS)	Hours of sleep	0.051	-1.273	1.621	0.210
VF (FRUITS)	12-item Neuropsychiatric Inventory total scores	0.005	0.383	0.147	0.706
VF (FRUITS)	12-item Neuropsychiatric Inventory – caregiver distress total scores	0.005	0.383	0.146	0.706
VF (FRUITS)	Sleep satisfaction	0.100	-1.825	3.330	0.075
VF (FRUITS)	Hours of sleep	0.060	-1.381	1.907	0.174
VF (GROCERY ITEMS)	12-item Neuropsychiatric Inventory total scores	<0.001	-0.080	0.006	0.934
VF (GROCERY ITEMS)	12-item Neuropsychiatric Inventory – caregiver distress total scores	0.025	0.873	0.763	0.607
VF (GROCERY ITEMS)	Sleep satisfaction	0.166	-2.441	5.957	**0.020**
VF (GROCERY ITEMS)	Hours of sleep	0.025	-0.873	0.762	0.606
PLD-BDAE	12-item Neuropsychiatric Inventory total scores	0.002	-0.269	0.073	0.785
PLD-BDAE	12-item Neuropsychiatric Inventory – caregiver distress total scores	0.011	-0.567	0.322	0.581
PLD-BDAE	Sleep satisfaction	<0.001	0.039	0.001	0.968
PLD-BDAE	Hours of sleep	0.010	0.540	0.291	0.600

HVOT: Hooper Visual Organization Test; VF: verbal fluency; PLD-BDAE: primer-level dictation section of the Boston Diagnostic Aphasia Examination.

Table 5. Multiple linear regressions for visual organization and language test results*

Variable (units)	Coefficient**	Coefficient** for schooling	Coefficient** for the length of dementia	Adjusted squared multiple R	*t*	F-ratio	p-value** for the regression
HVOT	8.259 (p < 0.001)	0.210 (p = 0.242)	-0.425 (p = 0.025)	0.113	7.591	2.980	0.067
VF (F-A-S)	6.783 (p = 0.001)	0.3 (p = 0.341)	-0.296 (p = 0.358)	0.000	3.534	0.716	0.497
VF (animals)	8.508 (p < 0.001)	0.146 (p = 0.504)	-0.468 (p = 0.042)	0.075	6.363	2.259	0.123
VF (fruits)	6.615 (p < 0.001)	-0.096 (p = 0.463)	-0.141 (p = 0.292)	0.009	8.312	1.143	0.333
VF (grocery items)	7.295 (p < 0.001)	0.093 (p = 0.643)	-0.273 (p = 0.191)	0.000	5.891	0.903	0.416
PLD-BDAE	3.889 (p = 0.048)	0.443 (p = 0.155)	-0.087 (p = 0.781)	0.004	2.067	1.069	0.356

*Multiple linear regressions for each of the listed dependent variables in relation to the following factors (2 degrees of freedom): schooling (years) and estimated length of the dementia syndrome (years).

**All p-values have been corrected with the Bonferroni test.

SD: standard deviation; HVOT: Hooper Visual Organization Test; VF: verbal fluency; PLD-BDAE: primer-level dictation section of the Boston Diagnostic Aphasia Examination.

requiring additional time to plan sentences[34]. We observed similar errors in the narrative discourse of our patients, but it should be noted that cortical involvement may occur earlier in dementia with Lewy bodies compared to Parkinson's disease dementia[38].

Cognitive and functional tests are usually correlated with one another in all stages of AD[23]. In our study with patients with LBD, we found that the higher the Clinical Dementia Rating sum-of-boxes scores, the lower were language and visuospatial test results. Likewise, language and visuospatial test results followed Mini-Mental State Examination scores. This could be helpful for differential diagnoses, since visuospatial abilities are more impaired in LBD than in other dementia syndromes[39]. In comparison with AD, patients with LBD have better contextual verbal delayed recall and recognition, and less short-term memory deficits, but worse letter fluency deficits and qualitative measures of executive functioning, and worsening visuoperception following overall cognitive decline[37,40].

The Hoehn and Yahr stages grade severity of parkinsonism[28], while the clock drawing test is a measure of visuospatial dysfunction also useful for screening cognitive impairment[23]. When performances in the HVOT and in the PLD-BDAE were worse, patients also had more severe parkinsonism and lower scores in the clock drawing test. It has been shown that patients with LBD who lose more motor function also have the greatest visuospatial impairment[13].

Only VF had a negative association with sleep satisfaction, but not with length of sleep, suggesting that sleep satisfaction may be inversely correlated with the stage of LBD. Sleep disorders occur in three quarters of autopsy-confirmed cases of dementia with Lewy bodies, but may not necessarily correlate with sleep satisfaction; in addition to attentional, executive functioning, and visuospatial impairments, the presence of impaired verbal learning helps identify prodromal dementia with Lewy bodies in patients with sleep disorders[41]. Moreover, it has been shown that the severity of psychotic symptoms in patients with Parkinson's disease is directly associated with the severity of cognitive impairment and sleep disturbances[42].

In our analyses, only the HVOT was associated with total scores of the Neuropsychiatric Inventory. Behavioural symptoms may affect sustained attention and, therefore, cognitive functioning[43]. Despite the increased frequency of visual hallucinations in LBD when compared to other dementia syndromes, they also lead to worse prognosis[8]. Still regarding neuropsychiatric symptoms, caregiver distress had no significant associations with visual organization or language tests, possibly representing low sensitivity to score variations in these tests.

All categories of VF were associated with forward digit span, except for fruits, the only category associated with reverse digit span. These findings suggest that attention and executive functions are important for most forms of category VF, but working memory might not decline concurrently.

Visual organization and language performance were not affected by education. This could be due to the cross-sectional nature of our study, but also to the fact that mechanisms of neurodegeneration supersede protective factors in these patients.

The length of the dementia syndrome was negatively associated with visual organization and VF for animals, an important finding to be correlated with the rapid cognitive decline usually found in patients with LBD[12]. On the other hand, instrumental functionality had no significant associations with visual organization or language tests, possibly due to the fact that instrumental functional decline occurs earlier, while visuospatial and language decline happen throughout the course of LBD.

The most important limitations of our study comprise its small sample size, its cross-sectional nature, and the fact that all patients were recruited from a single centre, thus limiting generalizability. Also, the size of our sample did not allow stratification into patient groups according to diagnoses (dementia with Lewy bodies or Parkinson's disease dementia), but pathophysiology is similar for these two diseases[16,37], and our results were mostly unaffected by this choice. Furthermore, the wide age range of the patients (spanning 45 years) could have affected our results due to the fact that young and older adults use different strategies to accommodate to impairments in executive function[44] but, considering that all patients were over 50 years-old and had at least one year of dementia diagnosis, we believe this to be unlikely.

We conclude that language and visual organization tend to follow motor skills and general cognitive performance in patients with LBD. Whereas visual organization did not predict performance in the PLD-BDAE, visuospatial abilities and VF were concurrently associated, suggesting that features of linguistic impairment in LBD may be attributed to components of cognition and language. Moreover, only visual organization was associated with behavioural performance, suggesting that neuropsychiatric symptoms are differentially associated with visual organization in comparison with linguistic features in LBD. Future studies should address neuropsychiatric correlations in prospective assessments.

Conflicts of interest

The authors report no conflicts of interest related to this paper.

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Brief report

Social communication impairments and restricted, repetitive patterns ("Kodawari") considered from the "Comprehension" section of the WISC-IV in autism spectrum disorder

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Abstract

Background: Many studies have used the Wechsler Intelligence Scale (WISC) to examine the characteristics of autism spectrum disorder (ASD). However, most studies have been based on profile analysis, not on content analysis. **Objective:** The objective of the present study was to apply the WISC-IV to clinical assessment of ASD and clarify how the characteristics of the disorder were reflected in specific items. **Methods:** The study participants were 20 patients aged 5-16 years diagnosed with ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). We recruited 20 patients with attention-deficit/hyperactivity disorder (ADHD) and 20 patients with other disorders (neurotic disorders) as controls. We then compared the scores of the ninth item of the WISC-IV ("Comprehension") among the three groups. **Results:** The differences observed between the ASD vs. the other disorders group were not significant by the standard scoring method. Thus, a two-level scoring method of 0 and ≥1 point was adopted. As a result, significantly more participants in the ASD group scored 0 points compared with the ADHD and other disorders groups. **Discussion:** The results of the present study revealed that a characteristic of ASD appeared in the ninth item of "Comprehension" on the WISC-IV.

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Keywords: Autism spectrum disorder, attention-deficit/hyperactivity disorder, content analysis, DSM-5, WISC.

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[1], autism spectrum disorder (ASD) is diagnosed as (A) persistent deficits in social communication and social interaction across multiple contexts, and (B) restricted, repetitive patterns of behavior, interests, or activities. Many studies have used the Wechsler Intelligence Scale (WISC) to examine the characteristics of ASD. Most of those investigations analyzed score profiles from the WISC-III[2] or WISC-IV[3].

However, it has been noted that the characteristics of ASD are not clarified based on a profile analysis as the intelligence score increases[4]. With this background, Kuroda *et al.*[5] analyzed results from the WISC-III for three boys (intelligence quotient [IQ] > 100) diagnosed with pervasive developmental disorder (PDD) according to the DSM-IV. They summarized their findings as follows: 1) difficulties with understanding the minds of others, 2) qualitative impairments in communication, 3) perseveration, 4) weak central coherence, and 5) visualization (over-concrete thinking). However, they did not focus on a specific item; rather, they attempted to identify various characteristics in various items. For clinical application, we considered that it might be more practical to clarify which characteristics appear in which items. Therefore, to identify useful items for the diagnosis of ASD, we examined whether the characteristics of ASD appear in specific items. We also considered the future possibilities and usefulness of such research methods.

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Methods

Participants

The study participants were 20 patients aged 5-16 years who had visited our clinic between January 1, 2014 and December 31, 2017 and been diagnosed with ASD according to the DSM-5. All patients had an IQ ≥ 80 according to the WISC-IV. It was considered best to select controls from clinical cases in which a differential diagnosis was problematic. Therefore, we also recruited 20 age matched patients with attention- deficit/hyperactivity disorder (ADHD) and 20 age-matched patients with other disorders (e.g., anxiety disorders, obsessive-compulsive and related disorders, stressor-related disorders, dissociative disorders, somatic symptom and related disorders) as controls.

Other disorders were so-called neurotic disorders according to the tenth revision of the International Classification of Diseases[6].

No significant differences in age, IQ, or male-female ratio were observed between the ASD and other groups (Table 1).

Table 1. Baseline characteristics of participants

	ASD	ADHD	Other disorders
N	20	20	20
Sex (M/F)	13/7	17/3	8/12
Mean age (SD) in years	10.83 (3.67)	10.80 (2.50)	11.15 (3.01)
Mean IQ (SD)	92.10 (12.86)	92.35 (10.16)	98.45 (10.65)

No significant differences in age, IQ, or male-female ratio were observed between the ASD and other groups.

Measurement

Since no prior research has examined the characteristics of ASD for specific items of the WISC-IV, we chose a specific item of the WISC-IV based on the diagnostic criteria for ASD in the DSM-5 and the psychologist's experience that patients with ASD were not good at making apologies for others, and then compared and examined the scores among the three groups. Since the independence between the items could not be assured, it was judged that a multivariate analysis was not appropriate.

The essence of item A of the diagnostic criteria for ASD in the DSM-5 is "a lack of a viewpoint of others". Regarding the associated question, the ninth item of the "Comprehension" section asks about the reasons why we apologize when we hurt the feelings of others. We chose this item because it refers to making an apology to another person, which means that we must think about that person's feelings and about maintaining or repairing our relationship. We thought that this item would make it relatively easy to assess the presence or absence of a viewpoint of others.

Next, the essence of item B of the DSM-5 diagnostic criteria is so-called "Kodawari", a Japanese word meaning restricted, repetitive, and stereotyped patterns of thinking and behavior. This is a characteristic observed as a way of answering many items, rather than a specific one. However, the ninth item of the "Comprehension" section is appropriate for evaluating "Kodawari" because it asks for multiple reasons, which patients with "Kodawari" may not be able to do because they have difficulty switching viewpoints.

There are three general criteria for scoring the ninth item; these are "General criterion A: Contents about human relations", "General criterion B: Contents about reflection", and "General criterion C: Contents about sympathy". Regarding scores, 2 points are awarded for answering two or more of these items, 1 point is awarded for answering one item, and 0 points are awarded for not answering any items.

Data were collected and statistically analyzed according to the following procedure:

1) First, we adopted standard (general) scoring, i.e., three stages of 0, 1, and 2 points, and then aggregated and examined the distribution of scores between the ASD vs. ADHD groups and the ASD vs. other disorders groups. 2) Next, if the comparison of one or the other was not statistically significant, we adopted scoring that emphasized the differences between lower scores, i.e., 0 points and ≥1 point, because clinical psychologists find that patients with ASD are particularly bad at recognizing the emotions of others.

Statistical analyses

For the statistical analysis, Fisher's exact test was conducted using Statcel software (2nd ed.; OMS Publishing Inc., Saitama, Japan)[7].

Results

When the three levels of 0, 1, and 2 were adopted, significant differences were found in the score distribution of the ninth item of the "Comprehension" section between the ASD vs. ADHD groups. Similar results were observed for the ASD vs. the other disorders groups, but these differences were not significant.

Since the differences observed between the ASD vs. the other disorders groups were not significant, a two-level scoring method of 0 and ≥1 point was adopted. As a result, significantly more participants in the ASD group scored 0 points for the ninth item of the "Comprehension" section compared with the ADHD and other disorders groups (Table 2).

Table 2. Scores for the ninth item between the ASD *vs.* ADHD groups and the ASD vs. other disorders group when emphasizing the difference between lower scores

	0 points	≥1 point	Total
ASD	9	11	20
ADHD	3	17	20
Other disorders	3	17	20

Discussion

Previous studies have evaluated the cognitive characteristics of ASD through investigating biases between abilities by conducting a profile analysis, such as difference in WISC-III or WISC-IV subtest scores. Oliveras-Rentas *et al.*[8] investigated 56 cases with high-functioning ASD, and found that the results of the WISC-IV were strong for "Matrix Reasoning" and "Similarities" and weak for "Comprehension", "Coding", and "Symbol Search". They said that "Comprehension" was correlated negatively with social symptoms and "Coding" and "Symbol Search" were sections comprising the Processing Speed Index. However, it has also been reported that it is difficult to identify specific profiles of the WISC in individuals with higher IQ scores, such as those with high-functioning ASD with above-average intelligence[4]. Therefore, it is difficult to determine whether patients have ASD from a profile analysis.

Kuroda *et al.*[5] analyzed the WISC-III scores of three high-functioning patients with PDD in detail. They found in the "Comprehension" section that patients with ASD often failed to recognize the emotions of others. Based on the findings of Kuroda *et al.*[5] and our own daily clinical experience, we focused specifically on the ninth item of the WISC-IV with the aim of aiding the diagnosis of highly-functional ASD. Based on our clinical experience that patients with high-functioning ASD are particularly bad at recognizing the emotions of others, an analysis was added that emphasized the differences in lower scores. Significantly lower scores were found in the ASD group compared to both the ADHD and other disorders groups.

This result suggests that patients in the ADHD and other disorders groups can express "human relations", "reflection", and "sympathy" to varying degrees on the ninth item of the "Comprehension" section in the WISC-IV. However, patients with ASD find this more difficult, and these results support our hypothesis.

It is relatively easy for general clinicians to ask whether patients are frequently isolated and pay attention to specific things in daily life when diagnosing high-functioning ASD in daily clinical practice. However, it is difficult for non-experts to identify psychological characteristics

in daily practice. The ninth item of the "Comprehension" section is a relatively simple question. It asks respondents the reasons why they apologize when they hurt the feelings of others. Moreover, the scoring method is straightforward. The results of the present study may have clinical significance, as they suggest the possibility of a simple psychological evaluation method for daily clinical practice.

A limitation of the present study was that only the ninth item of the "Comprehension" section in the WISC-IV was used. No other items were considered. Takekoh *et al.*[9] suggested that persistence (similar to "Kodawari") was observed for "Cancellation" in the WISC-IV. Other items in the WISC-IV should be investigated in a future study.

Conclusion

A content analysis of the ninth item of the "Comprehension" section in the WISC-IV seemed to reflect "a lack of a viewpoint of others" and to be related to the characteristic of "limited repetitive pattern ("Kodawari")" in the ASD group. Significant differences were observed in the scores between the ASD vs. the ADHD and other disorders groups when we used a scoring method emphasizing the differences between lower scores.

These findings suggest that the characteristics of ASD could be grasped more easily by focusing on the ninth item of the "Comprehension" section.

Portions of this paper were presented by N.S. at the 38th Annual Meeting of the Japanese Society for Psychiatric Diagnosis (Kawagoe, 2018).

Ethical approval

This study was approved by the IRB of Saitama Medical University Hospital.

Disclosure

The authors declare no conflicts of interests.

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Serotonin syndrome associated with methadone and milk thistle seeds: a case report

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Abstract

Background: Serotonin syndrome is rarely, potentially life threatening condition, associated with use of serotonin acting medications and psychoactive drugs. In the majority of cases the symptoms occur soon after the initiation of a new drug or a change in the dose. **Objective:** To present a case report and to describe the possible mechanism of development of serotonin syndrome during the interactions between milk thistle seeds and methadone on hepatic cytochrome enzyme system P450. **Methods:** A case report of a young man on regular therapy with methadone, who develop a serotonin syndrome after ingestion a high dose of milk thistle seeds. **Results:** Commercial preparations of milk thistle include the extract silibinin, which exhibits no beneficial or harmful drug interactions at normal doses, but at higher concentrations it can lead to dose-dependent effects on methadone metabolism, through inhibition of CYP3A4 and P-glycoprotein. As a result, it may lead to enhanced serotonin re-uptake inhibition and increased serotonin activity. **Discussion:** Milk thistle is widely used and recommended for detoxification, but it may have serious and life threatening interactions with psychotropic drugs and psychoactive substances when used in high doses.

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Keywords: Serotonin syndrome, milk thistle, silymarin, methadone, interaction, cytochrome P450.

Introduction

Serotonin syndrome (SS) is a rare, potentially life threatening, condition, associated with the use of serotonin-acting medications and psychoactive drugs. The mechanism of the formation of SS is via postsynaptic hyperstimulation of 5-hydroxytryptamine (5-HT) 2A and 1A serotonin receptors in the central and peripheral nervous system. In the majority of cases the symptoms occur soon after the initiation of a new drug or a change in the dose. The classic triad of symptoms are: altered mental status (confusion, excitement, agitation, hallucinations), autonomic dysfunction (tachycardia, tachypnea, fever, diaphoresis) and neuromuscular abnormalities (tremor, hyperreflexia, clonus, myoclonus). SS is usually self-limited once the iniciting drug has been discontinued[1,2].

Case report

A 51-years old male with psychoactive substance use disorder, who was on methadone substitution therapy (200 mg daily) for 15 years, was admitted to a psychiatric unit for confusion and fluctuating levels of agitation. Before the admission he had been observed at the emergency department after experiencing restlessness, palpitations, dyspnea and resting tremor in the last 24 hours. ECG, laboratory tests and physical examination did not show any abnormalities, except high blood pressure (200/120 mmHg), and tachycardia and tachypnea. He admitted using milk thistle seeds regularly for some time, but in the last three days he took a full fist of seeds daily in an attempt to "detoxify" his liver because of regular alcohol consumption. At the emergency department he was disoriented, confused and agitated, with hallucinations and he was consequently transferred to the psychiatric ward. Upon admission he was still confused, with high blood pressure and tachycardia. Restlessness, hallucinations and neuromuscular symptoms (tremor of the hands and jaw, myoclonus, hyperreflexia) were also observed. Alcohol and drug screening-tests were negative. Supportive measures and a sedative agents were introduced (lorazepam 2.5 mg). After three hours, the symptoms resolved completely.

Discussion

A possible mechanism of the development of SS was through interaction on the hepatic drug-metabolizing enzyme system cytochrome P450. Methadone is a serotonin re-uptake inhibitor, metabolized by cytochrome P450, mostly by CYP3A4[3]. *In vitro* studies of methadone show a greater tendency toward serotonin reuptake inhibition compared with other opiates, which may explain methadone-mediated precipitation of SS[4]. Milk thistle is widely used for several medical conditions, especially for liver diseases. Commercial preparations of milk thistle include the extract silymarin, consisting of various flavonolignans, including silibinin, which have been shown to inhibit the in vitro activity of several cytochrome P450 enzymes including CYPP3A4[5]. Silibinin exhibits no harmful drug interactions at normal doses (200-900 mg/day), but at higher concentrations it can lead to clinical important drug-drug interactions through inhibition of CYP3A4 and P-glycoprotein[6]. Results from in vitro studies on rats have indicated dose-dependent effects of silibinin on methadone metabolism, resulting in 50 to 100 percent reduction in methadone metabolism, which can lead to enhanced serotonin re-uptake inhibition and increased serotonin activity[7,8].

Conclusion

The interactions between milk thistle seeds and methadone need further investigations and more attention is recommended in patients on long-therm methadone therapy using milk thistle to treat liver diseases.

Conflict of interest

Nothing to declare.

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Evidence for a distinct depression-type schizophrenia: a pilot study

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Dear Editor,

Reciprocity of depressive and psychotic symptoms in patients with schizophrenia and major depression disorder (MDD), respectively, complicates differential psychiatric diagnosis. Notably, 60%-70% of schizophrenia patients experience moderate to severe depressive symptoms[1-3]. Indeed, schizophrenia and MDD have been proposed to be variants of the same disorder, namely major psychiatric disorder[1]. Notwithstanding, distinct functional brain characteristics of these two patient groups have been demonstrated[2]. Additionally, patients with schizophrenia and MDD have been reported to have reduced and increased corpus callosum (CC) sizes, respectively[3-5]. Thus, we have hypothesized that there may be a depressive-type schizophrenia.

This study was approved by the ethical committee of The Tianjin Mental Health Center. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from participants and their guardians.

We used magnetic resonance imaging (MRI) and tract-based spatial statistics (TBSS) to compare the CCs of first-episode drug-naïve schizophrenia patients with (FE-SCZ-D) versus without (FE-SCZ-nD) depressive symptoms (N = 15/group), matched for demographics and symptom severity, and 20 healthy controls (HCs) who served as a reference group. None of the participants had a family history of mental illness. Their mean ages ± standard deviations (SDs) by group were: FE-SCZ-D, 24.5 ± 4.5 years; FE-SCZ-nD, 23.5 ± 2.5 years; and HC, 24.5 ± 3.5 years (R = 0.557; p = 0.405). The gender ratios of the groups were (males/females): FE-SCZ-D, 8/7; FE-SCZ-nD, 9/6; and HC, 7/8 (p = 0.265). The FE-SCZ-D and FE-SCZ-nD groups had mean (±SD) illness durations of 2.3 ± 1.2 months and 2.8 ± 1.4 months, respectively (R = 0.362; p = 0.265). The FE-SCZ-D and FE-SCZ-nD groups had mean (±SD) Positive and Negative Syndrome Scale scores of 80.0 ± 19.0 and 82.6 ± 17.7, respectively (R = 0.523; p = 0.799), and they had mean (±SD) Calgary Depression Scale for Schizophrenia scores of 15.5 ± 1.5 and 0.0 ± 0.0, respectively. This pilot study was completed from January 1st to December 31st of 2018. All participants volunteered and gave written informed consent; the Wenzhou Seventh People's Hospital provided ethics approval.

TBSS analysis of MRI data showed more pronounced CC reductions in the FE-SCZ-nD group than in the FE-SCZ-D group; both schizophrenic patient groups had reduced CCs relative to HCs (Figure 1). Hence, the presence of depressive symptoms seemed to

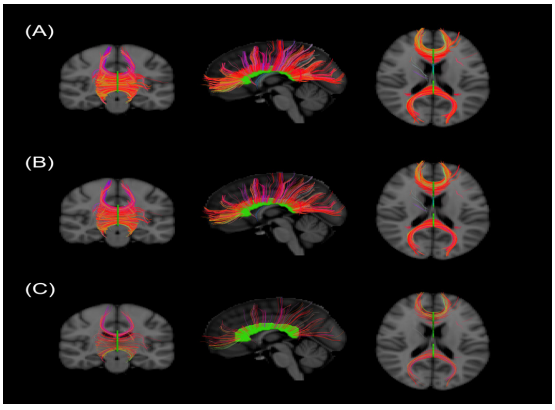

Figure 1. TBSS-based comparison of MRI examinations of white matter structures, especially CC connections, between a HC reference group (**A**), FE-SCZ-D patients (**B**), and FE-SCZ-nD patients (**C**).

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counter, or perhaps be a protective factor against, CC reduction in patients with schizophrenia. These findings are consistent with our hypothesis that there may be a distinct depression-type schizophrenia.

Limitations of this study included a small sample size, all patients being inpatients (due to imperative auditory hallucinations) who refused antipsychotic treatment prior to hospitalization, participant loss (6 per patient group) due to MRI noncompliance, and limited-resolution images. Larger-cohort and multi-center studies with more subtle neuroimaging are needed to clarify brain alterations related to psychosis and depressiveness.

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Conflict of interests

None.

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