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Testing Trait Depression as a Potential Clinical Domain in Schizophrenia

Joshua Chiappelli[a], **Peter Kochunov**[a], **Katherine DeRiso**[a], **Kavita Thangavelu**[a], **Hemalatha Sampath**[a], **Florian Muellerklein**[a], **Katie L. Nugent**[a], **Teodor T. Postolache**[a], **William T. Carpenter Jr.**[a], and **L. Elliot Hong**[a]

[a] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

The DSM-5 includes depression as a dimension of psychosis. We tested whether persistent experience of depression, called 'trait depression', is a clinical feature separate from psychosis and several well-known, trait-like deficits of schizophrenia. 126 individuals with schizophrenia and 151 control participants completed the Maryland Trait and State Depression questionnaire, with a subset completing measures of cognition and functional capacity, and diffusion tensor imaging (n=73 patients and 102 controls for imaging analysis). Subjectively experienced, longitudinal trait depression is significantly higher in patients with schizophrenia compared with controls. Higher trait depression scores were associated with more severe psychosis. Surprisingly, individuals with higher trait depression manifested less cognitive and global functioning deficits. In addition, trait depression scores were positively associated with fractional anisotropy of white matter. Trait depression appears to be a highly relevant clinical domain in the care of patients with schizophrenia that also has distinct relationships with some other known traits of the disease. Trait depression may be an important contributor to the clinical heterogeneity of schizophrenia.

Keywords

Depression; Schizophrenia; White Matter; Cognition

Address: P.O. Box 21247, Baltimore, MD 21228 Fax (410) 402 6077, Phone (410) 402 6827 jchiappelli@mprc.umaryland.edu.

Contributors

Joshua Chiappelli contributed to data analysis and prepared the first draft of the manuscript. Peter Kochunov contributed to study design and data analysis. Katherine DeRiso, Kavita Thangavelu, Hemalatha Sampath, and Florian Muellerklein oversaw protocol implementation and data management. Katie Nugent, Teodor Postolache, and William Carpenter Jr. contributed to data analysis, writing and editing. Elliot Hong served as principal investigator and assisted in all stages of design, analysis and writing. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare no conflict of interest.

Introduction

Depression is common during the course of schizophrenia, reported in prodromal state (Häfner et al., 2013), first episode psychosis (Sönmez et al., 2013), and during and following acute episodes (McGlashan and Carpenter, 1976). Depressive symptoms are associated with higher risk of suicidal attempts and ideation in schizophrenia (Andriopoulos et al., 2011; Upthegrove et al., 2010). Despite the clinical importance of depression in the care of schizophrenia patients, depressive symptoms are often not considered core pathology in schizophrenia. Instead, depression has been viewed from a categorical perspective and used to delineate the boundary between affective and non-affective psychoses. The DSM-5 includes depression as a dimension of psychosis, inviting a re-examination of its role in schizophrenia using modern phenomenological concepts and technology. Previous studies compared current depressive symptoms to other features in schizophrenia and typically found that depression showed no significant association with cognitive deficits in patients. For example, a study by Bowie and colleagues employed Beck's Depression Inventory and showed that the depressive symptoms had no relationship with neuropsychological performance or laboratory assessment of functional capacity (Bowie et al., 2006). Similar results were observed when the Calgary Depression Scale for Schizophrenia was used (Tanaka et al., 2012). Several more studies linked depressive symptoms to awareness of negative symptoms and functional deficits but not to the deficits themselves (Liddle et al., 1993; Maggini and Raballo, 2006). The common interpretation is that better insight into the illness and the associated deficits and stigma contributes to depression formation in schizophrenia patients (Crumlish et al., 2005; Delaney et al., 2012; Drake et al., 2004; Moore et al., 1999; Staring et al., 2009). However, this argument considers only the current experience of depression.

Indeed, most if not all studies in schizophrenia have employed instruments that measure only current or very recent depressive symptoms, and neglect the longitudinally experienced, ‘trait’ aspects of depression. We used the Maryland Trait and State Depression (MTSD) Scale that was developed to provide a tool to overcome this limitation (Chiappelli et al., 2014). This is a self-rated scale performed in an interview setting, with some items assessing the frequency of depressive symptoms experienced over the course of adult life, and other items asking specifically about depressive symptoms experienced in the past week. Factor analysis revealed that depression symptoms captured by MTSD in both schizophrenia patients and controls were segregated into two domains: trait (symptoms experienced frequently throughout adult life) and state (current symptoms) depression. Trait depression reported by the patients through MTSD was distinct from their negative symptoms evaluated during the same session; depression and negative symptoms may overlap in observable behaviors, such as psychomotor retardation, but trait depression involves the tendency to experience negative emotions and distressing thoughts, whereas negative symptoms are characterized by apparent deficits in motivation and affect regardless of negative inner experience (Chiappelli et al., 2014). Most importantly, the initial work on the MTSD taught us that trait depression is a prominent feature in the presentation of schizophrenia patients – when we ask our patients. The immediate question then becomes

whether trait depression is a distinct clinical domain or if it is biologically linked to other core or trait-like features of schizophrenia.

If trait depression is measuring a stable feature in some patients with schizophrenia, we hypothesized that it should either associate with other trait-like features of schizophrenia, or represent a separate, trait-like clinical domain. Here, we examined the relationship between trait depression and three well-replicated, relatively persistent behavioral and brain structure abnormalities in schizophrenia: 1) cognitive deficits, particularly in processing and speed and working memory, are among the most prominent, well-replicated, trait-like clinical deficits in schizophrenia (Barder et al., 2013; Bonner-Jackson et al., 2010; Hoff et al., 2005; Roalf et al., 2013); 2) functional capacity impairment as measured with the UCSD Performance Based Skills Assessment, which is a well-recognized feature of schizophrenia that is relatively stable over time (Harvey et al., 2012; Light et al., 2012) and 3) white matter integrity as measured by the fractional anisotropy (FA) derived from diffusion tensor imaging (DTI); one of the most replicated brain structural abnormalities in schizophrenia (Ellison-Wright and Bullmore, 2009; Yao et al., 2013). We expected that this effort would yield clues on the possible biological and functional underpinnings of trait depression, paving the way to use this novel phenomenological approach to parse some of the clinical heterogeneity of the disorder.

Methods

Participants

Individuals with schizophrenia were recruited from the Maryland Psychiatric Research Center and the neighboring community mental health clinics. Community comparison participants were recruited from advertisements in local media. A total of 277 participants (126 patients and 151 controls) participated in the study and completed MTSD assessment. Among them, 118 patients and 151 controls completed cognitive and functional assessments; within which 73 patients and 102 controls completed a MRI scan for DTI. All participants were assessed with the Structured Clinical Interview for DSM Disorders (SCID). Among the patient sample, 22 met criteria for schizoaffective disorder, and an additional 19 had a past history of at least one episode of major depressive disorder.

Of the 277 participants in this study, 197 (71.4%) were previously included in the initial psychometric and factorial analysis of the MTSD (Chiappelli et al., 2014). For the patients, 9 were not on antipsychotic medication at time of the study; 15 were taking clozapine, 16 were taking a typical antipsychotic, 49 were taking an atypical antipsychotic, and the rest were on two or more antipsychotic medications. There were also 44 patients who were taking an antidepressant medication at time of study. Current psychosis severity was assessed using the psychosis subscale in the Brief Psychiatric Rating Scale (BPRS), which includes clinician ratings for conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. The relative independence between trait depression and negative symptoms was previously reported (Chiappelli et al., 2014) and is not repeated here.

MTSD assessments

The Maryland Trait and State Depression (MTSD) questionnaire consists of 36 items asking participants to rate frequency of depressive symptoms over the past week ('State' questions) or throughout their adult lives excluding the past week ('Trait' questions). This questionnaire has been demonstrated to have suitable psychometric properties and construct validity, in particular in its ability to distinguish depressive from negative symptoms (Chiappelli et al., 2014). The scale and user instructions are available to download at http://www.mdbrain.org/MTSD_instructions_and_scale.pdf.

Assessment of cognition and functional capacity

Cognition testing included the Digit Symbol Coding task of the WAIS-3 (Wechsler, 1997) and the Digit Sequencing task from the Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004), to assess processing speed and working memory, respectively. While the cognitive deficit in schizophrenia encompasses multiple domains, deficits in processing speed (Dickinson et al., 2007; Dickinson et al., 2008; Knowles et al., 2010) and working memory (Forbes et al., 2009; Keefe et al 2004) are particularly severe. Scores were calculated as t scores according to population norms based on age for the Digit Symbol Coding task, and age and sex for the Digit Sequencing task (Keefe et al., 2008). The UCSD Performance-based Skills Assessment (UPSA-2) was used to measure functional capacity. UPSA-2 uses role-play to assess functioning across five domains: organization/planning, financial skills, communication skills, transportation, and household skills, and is a validated tool to assess community functional capacity in schizophrenia patients (Bowie et al., 2006). The UPSA-2 also shows considerable stability over time, indicating it measures a trait-like characteristic in schizophrenia patients (Leifker et al., 2010). The total score was used as a measure of community functional capacity.

Assessment of cerebral white matter integrity

Diffusion tensor data were collected at the University of Maryland Center for Brain Imaging Research using a Siemens 3T TRIO MRI (Erlangen, Germany) system equipped with a 32-channel phase array head coil. The high-angular resolution diffusion imaging (HARDI) DTI data were collected using a single-shot, echo-planar, single refocusing spin-echo, T2-weighted sequence with a spatial resolution of 1.7×1.7×3.0 mm. The sequence parameters were: TE/TR=87/8000ms, FOV=200mm, axial slice orientation with 50 slices and no gaps, five b=0 images and 64 isotropically distributed diffusion weighted directions with b= 700 s/mm2. These parameters maximized the contrast to noise ratio for FA measurements (Kochunov et al., 2012). A tract-based spatial statistics (TBSS) method, distributed as a part of FMRIB Software Library (FSL) package, was used for tract-based analysis of diffusion anisotropy (Smith et al 2006). The population-based, 3D, DTI cerebral white matter tract atlas developed in Johns Hopkins University and distributed with the FSL package (Wakana et al., 2004) was used to calculate population average FA values along the spatial course of major white matter tracts. First, fractional anisotropy (FA) images were created by fitting the diffusion tensor to the motion and eddy current diffusion data. RMSDIFF (Smith et al., 2006) was used to estimate the root mean square (RMS) movement distance between diffusion sensitized and b=0 images. All data passed QA control of <3mm accumulated

motion during the scan. There were no difference in the average motion per TR between patients and controls (0.42±0.21 vs. 0.43±0.20, for patients and controls, respectively). In the next step, all FA images were globally spatially normalized to the Johns Hopkins University (JHU) (Wakana et al., 2004) and then nonlinearly aligned to a group-wise, minimal-deformation target (MDT) brain using the FLIRT method (Kochunov et al., 2001; Smith et al., 2006). Next, individual FA images were averaged to produce a group-average anisotropy image. This image was used to create a group-wise skeleton of white matter tracts. The skeletonization procedure was a morphological operation, which extracts the medial axis of an object. Finally, FA images were thresholded at FA=0.20 level to eliminate non-white matter voxels and FA values were projected onto the group-wise skeleton of white matter structures. This step accounts for residual misalignment among individual white matter tracts. FA values were assigned to each point along a skeleton using the peak value found within a designated range perpendicular to the skeleton. This processing was performed under two constraints. A distance map was used to establish search borders for individual tracts. The borders were created by equally dividing the distance between two nearby tracts. Secondly, a multiplicative 20mm full width at half-max Gaussian weighting was applied during the search to limit maximum projection distance from the skeleton. The average FA from whole brain white matter was used as the primary measure. The FA from the fourteen major tracts were used for exploratory analyses.

Data analysis

One-way ANOVA was used for group comparisons of clinical and trait measures that had a normal distribution, and Kruskal-Wallis test used for measures with non-normal distribution. MTSD means had a non-normal distribution as determined by the one-sample Kolmogorov-Smirnov test, therefore Spearman's correlations were used to compare depression severity with other trait measures. Correction for multiple comparisons was done using the method of Benjamini and Hochberg (1995). All tests were two-tailed.

Results

Relationship of Trait and State Depression to Psychosis, Cognition and Functional Capacity Schizophrenia patients and controls were matched in age but there were significantly more smokers (p=0.007) and lower education levels in patients compared with controls (Table 1). Patients had significantly higher MTSD trait (χ^2=16.48, p<0.001; Cohen's *d*=0.49) and state (χ^2=33.49, p<0.001; Cohen's *d*=0.68) scores compared with controls (Table 1). Patients also showed significantly impaired cognition (processing speed and working memory) and functional capacity (UPSA-2; Table 1). Patients with schizoaffective disorder and/or a history of at least one episode of MDD had significantly higher MTSD trait and state scores compared to schizophrenia patients without a history of MDD; however, these subgroups did not significantly differ on measures of cognition, functional capacity, or whole brain average FA (Supplementary Table 1). The following analyses include all patients combined in one group.

We found that the severity of trait and state depression measures were significantly and positively associated with BPRS psychosis score (rho=.246, p=.005, rho=.312, p<.001

respectively) in patients with schizophrenia. However, there were no indications that more severe trait depression was related to more severe deficits in any cognitive measures. Instead, the MTSD trait score had positive and significant correlations with working memory (rho=0.186, p=.044), processing speed (rho=0.206, p=.024), and functional capacity (rho=0.220, p=.017) in patients. The MTSD state score did not show any significant associations with cognition or functional capacity measurements. There were no significant correlations between depression state and trait scores and cognition or functional capacity in controls (Table 2).

Relationship of depressive symptoms to white matter integrity

Whole brain average FA was greater in healthy controls than schizophrenia patients (F=11.86, p=.001). The same trend was observed in individual tracts, with FA being statistically greater in controls than patients in all tracts (p=.001 to .024) except corticospinal tract, cingulum and inferior fronto-occipital tract (p=.051 to .711).

In patients, greater trait depression was significantly and positively associated with the whole brain average FA values and FA values for four white matter tracts – the corona radiata, thalamic radiation, superior longitudinal fasciculus, and superior fronto-occipital tract (Table 3). Significantly ($p<0.05$) positive associations were found between MTSD trait scores and FA of four additional tracts, including body of corpus callosum, fornix, internal capsule and sagittal striatum, although these associations were not significant after correcting for multiple tests. MTSD state scores showed no significant association with FA in any tracts after correction for multiple comparisons. In contrast, FA values were not associated with psychosis severity (r=-.130 to .008, all p>.290) (Table 4). In controls, the whole-brain average FA value was not significantly associated with MTSD trait (rho=-.041, p=.667) or MTSD state (rho=.010, p=.914). However, the average FA value for the cingulum was negatively correlated with trait depression in normal controls (rho=-.278, p=.003) and this was the only relationship that was significant after correction for multiple comparisons. None of the other 14 tracts including the whole brain FA was significantly associated with trait (rho=-.174 to .022, all p>.065) or state depression (rho=-.117 to .184, all p>.051) in controls.

Using the strongest correlation between trait depression and FA, for that of the SLF (Figure 1), partial correlations were calculated to examine if the relationship is mediated by cognition (mean of the z scores of working memory and processing speed). The partial correlation between MTSD-Trait and SLF FA controlling for the combined cognitive score was .234 (p=.063), suggesting that part of the relationship between trait depression and white matter integrity is mediated by cognition. In contrast, partial correlations between whole brain average FA and cognition remained significant even controlling for state (r=.356, p=.004) or trait depression (r=.359, p=.004).

Potential clinical confounding factors

We considered the potential impact of medications by examining the association between chlorpromazine dose equivalents (CPZ) of antipsychotic medication, depression scores, and FA values for patients. This revealed only one significant correlation surviving correction

for multiple comparisons: a negative correlation between CPZ and FA of the genu of the corpus callosum (rho=-.396, p=.001). CPZ was not associated with trait depression (rho=-.093, p=327) nor state depression (rho=-.109, p=.251). We also examined the potential confounding effect of antidepressant use. Patients taking antidepressants had higher trait depression (χ^2=5.34, p=.021) but not state depression (χ^2=2.77, p=.096) than patients not on antidepressants. However, patients taking antidepressants did not have higher whole-brain average FA values (t=.674, p=.502). Patients who smoke did not differ from patients who were nonsmokers in trait depression (F=.010, p=.922) nor state depression (F=.183, p=.670). Finally, we also examined the correlations of FA with psychosis, working memory, processing speed, and UPSA-2 (Table 4). Processing speed showed the most robust correlations with FA of multiple tracts in the white matter even after corrections for multiple comparisons.

Discussion

We found that subjectively reported trait depression is prominent in patients with schizophrenia, but greater trait depression did not correspond to more severe deficits in several cognitive and biological markers associated with schizophrenia. If anything, trait depression was associated with slightly higher cognitive and functional capacity, and greater white matter integrity in individuals with schizophrenia.

These findings appear paradoxical, especially when examined in comparison to major depressive disorder (MDD). In MDD, severity of depression is associated with worse cognition (Lee et al., 2012; Snyder, 2013), and modest cognitive deficits are still apparent in euthymic periods (Bora et al., 2013). In mood disorders trait depression is more closely linked to cognitive impairment than state depression (Sarapas et al., 2012). In comparison, our results indicate that trait depression is associated with less cognitive impairment in schizophrenia. Individuals with MDD also tend to exhibit decreased FA in white matter tracts compared to individuals without MDD (Liao et al., 2013), particularly in the SLF, where greater severity of depressive symptoms correlates with more reduction in FA values (Murphy and Frodl, 2011). In our study the results show an opposite trend as trait depression in schizophrenia is associated with higher FA, with the trend strongest in the SLF (Figure 1). Therefore, there appeared consistently “paradoxical” findings on how trait depression in schizophrenia is related to cognition, function, and white matter integrity, as compared with how depression in MDD is related to these measures. We believe these observations raise an interesting question on whether trait depression is a relatively separate clinical domain compared to depression in MDD or these other trait-like clinical and biological measures in schizophrenia. That the FA of the SLF in particular showed the strongest relationship to trait depression is intriguing, as this tract exhibits delayed maturation relative to other tracts in the brain, remaining plastic through adolescence (Lebel and Beaulieu, 2011); additionally, SLF FA may be influenced by the same genetic factors contributing to working memory (Karlsgodt et al., 2010).

Our observations are in fact consistent with research done in deficit vs. nondeficit syndrome schizophrenia. Individuals with deficit syndrome are characterized by persistent negative symptoms and more severe cognitive deficits, and tend to have less depression when

compared with patients without deficit syndrome, who tend to have high levels of depression and better cognitive functioning (Cohen et al., 2007; Kirkpatrick et al., 2001). Longitudinal studies have also found that presence of depression is a good prognostic indicator for persons with chronic schizophrenia (McGlashan, 1988). Additionally, in individuals with chronic schizophrenia with overall very poor functioning, depression was found to be associated with higher social and cognitive functioning (Rieckmann et al., 2005). These previous data suggest that, after all, it may not be surprising that trait depression in schizophrenia is associated with relatively preserved cognitive ability and functional capacity, despite the fact that depression in schizophrenia is associated with other significantly negative social and clinical consequences (Conley et al., 2007).

Our data may support the 'affective pathway' to psychosis as conceptualized by Myin-Germeys and van Os (2007). This theory predicts that heightened affective reactivity to stress contributes to expression of positive symptoms of schizophrenia in a pathway independent of cognitive deficits, and may in fact be associated with a good-outcome type of psychosis (Myin-Germeys and van Os 2007). Given the clear association between stress exposure and risk of depression (Vinkers et al., 2014), it is possible that trait depression reflects chronically heightened affective reactivity, and in this context the association between trait depression and positive symptoms reported here is consistent with the affective pathway theory. Alternatively, our results can be interpreted as representing the influence of insight, in that preserved cognitive ability may be associated with better recognition of the limitations posed by severe mental illness, which may in turn induce symptoms of depression. This hypothesis is not incompatible with the affective pathway theory, but further work is necessary to clarify the complex interactions of clinical insight, cognition, depression, and positive symptoms of psychosis.

Despite the associations of trait depression with relatively preserved neuropsychological functioning and white matter integrity, depression remains a clinically grave phenomenon in schizophrenia, as greater levels of depression predict lower psychological feelings of well-being (Strauss et al., 2012), worse subjective quality of life (Narvaez et al., 2008), and suicidal ideation (Upthegrove et al., 2010), and must be closely monitored and treated. Within the chronic course of schizophrenia, capacity for understanding of self, insight into illness, and recognition of stigma surrounding the disorder, may be markers of preserved cognitive function, but also a risk factor for longitudinally experienced depression. In this context, further study of the neurobiology of trait depression as compared with state depression, and the neurobiology of depression in schizophrenia versus depression in MDD, may offer new ways to reduce clinical heterogeneity and improve individualized treatment planning.

An important limitation of this study is a potential recall bias inherent in our measure of trait depression. As the MTSD-Trait scale requires a retrospective assessment of experience of depressive symptoms, individuals with better memory may be more able to recall such symptoms. However, we would expect this bias to be present in the community sample used as a control group in our study, but within that sample there was no association between trait depression and cognitive performance (Table 2). Another limitation is that some of the individuals with schizophrenia who participated in this study were taking antidepressants,

and these patients had higher levels of trait depression. However, there was no evidence that patients taking antidepressants had higher levels of cognitive performance or white matter FA, arguing against the possibility that the associations of these measures with trait depression could be attributed to antidepressant use.

To summarize, the longitudinal experience of depression is related to more severe psychosis yet less deficit in several trait-like clinical features of schizophrenia. Furthermore, trait depression in schizophrenia appeared to be distinct from how trait depression is related to cognition in patients with major depression. We also replicated previous findings that state depression has essentially no relationship with cognitive impairment in schizophrenia. However, the neurobiology of trait depression, and its biological convergence and divergence from state depression require further investigation. These results may also have implications for the ongoing efforts to identify domains of psychopathology that cut across traditional diagnostic boundaries (Insel et al., 2010). Schizophrenia and affective disorders overlap in several symptom domains, including depressive symptoms and cognitive deficits (Harvey, 2011); however, there appear to be distinct patterns in how trait depression is related to cognition and white matter integrity in these disorders. This underscores the importance of developing constructs that account for different pathophysiological pathways to similar symptom domains. The current analysis lends validity to the proposal that trait depression could be a clinical domain unlike other clinical or biological measures commonly included in the discourse of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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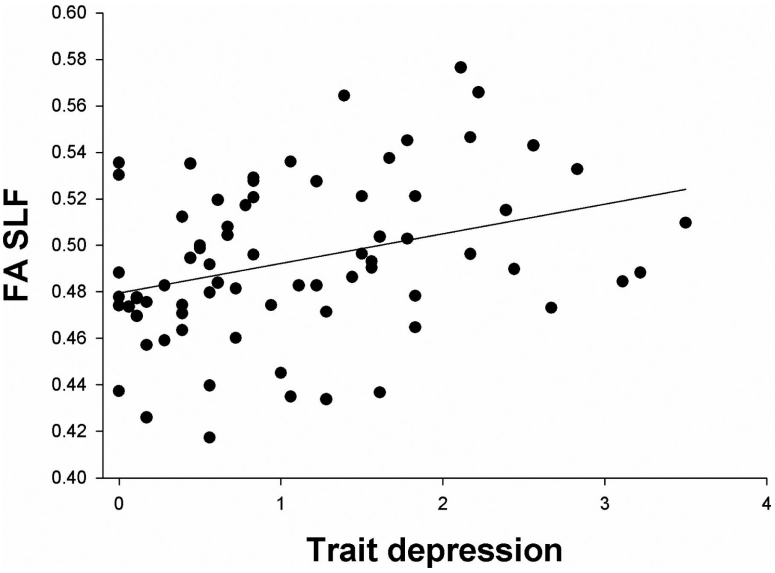

Figure 1.

Scatterplot of relationship between trait depression and fractional anisotropy (FA) of the superior longitudinal fasciculus (SLF) in schizophrenia patients.

Table 1

Group differences in demographic, clinical and neuropsychological variables.

	Schizophrenia	Control	Test statistic	p value
Total N	126	151	n/a	n/a
Age [years](±sd)	37.9 (13.3)	35.8(13.8)	t=1.25	.214
%Male	55.5	34.4	$\chi 2$=12.5	.002
%Smoker	43.7	27.8	$\chi 2$=7.36	.007
CPZ [mg]	542	n/a	n/a	n/a
MTSD-Trait	1.11	0.70	χ^2=16.48	<.001
MTSD-State	0.92	0.43	χ^2=33.49	<.001
Working memory	36.6	45.4	t=5.67	<.001
Processing speed	7.4	10.5	t=8.01	<.001
Functional capacity	86.7	101.5	t=8.31	<.001

CPZ = chlorpromazine dose equivalent of antipsychotic medication. Working memory was assessed using the Digit Sequencing task from the Brief Assessment of Cognition in Schizophrenia, processing speed was assessed with the Digit Symbol Coding task (WAIS-3), and functional capacity was measured using the UPSA-2.

Table 2

Correlation coefficients between MTSD Trait and State scales and measure of working memory, processing speed, and functional capacity (UPSA-2 Total).

	Controls (n=151)		Patients (n=118)	
	MTSD-Trait	**MTSD-State**	**MTSD-Trait**	**MTSD-State**
BPRS Psychosis	n/a	n/a	.246*	.312*
Working memory	−.016	−.069	.186*	.090
Processing speed	−.081	−.110	.200*	.084
Functional capacity	.033	.010	.217*	.080

*significant after Benjamini and Hochberg correction for multiple comparisons ($p<.05$)

Table 3

Correlations of MTSD scores with FA of white matter tracts in individuals with schizophrenia (n=73).

White matter tract	MTSD-Trait	MTSD-State
Average FA	.241*	.228
Genu of CC	.176	.189
Body of CC	.241*	.275*
Splenium of CC	.124	.138
Fornix	.249*	.288*
Corticospinal	.052	−.005
Internal capsule	.262*	.183
External capsule	.219	.167
Corona radiata	.340*†	.320*
Thalamic radiation	.341*†	.258*
Sagittal striatum	.303*	.311*
Cingulum	.195	.181
SLF	.367*†	.275*
SFO	.346*†	.276*
IFO	.064	.017

CC=corpus callosum; SLF=superior longitudinal fasciculus; SFO=superior fronto-occipital fasciculus; IFO=inferior fronto-occipital fasciculus.

* p<.05 – nominally significant

† significant after correction for multiple comparisons using method of Benjamini and Hochberg (1995)

Table 4

Correlation coefficients between symptom and cognitive measures and FA values in individuals with schizophrenia.

White matter tract	BPRS-Psychosis	Processing speed	Working memory	Functional capacity
Average FA	−.112	.443*	.261*	.333*
Genu of CC	.008	.272*	.176	.241
Body of CC	−.014	.427*†	.289*	.328*
Splenium of CC	−.004	.407*†	.216	.177
Fornix	−.024	.363*†	.075	.206
Corticospinal	−.130	.310*†	.208	.238
Internal capsule	−.125	.412*†	.303*	.387*†
External capsule	−.086	.339*†	.263*	.314*
Corona radiata	−.069	.363*†	.203	.375*†
Thalamic radiation	−.036	.304*†	.252*	.383*†
Sagittal striatum	−.049	.436*†	.289*	.417*†
Cingulum	−.111	.383*†	.300*	.270*
SLF	−.034	.384*†	.266*	.410*†
SFO	.019	.313*†	.159	.327*
IFO	−.013	.166	.114	.038

* $p<.05$ – nominally significant

† significant after correction for multiple comparisons using method of Benjamini and Hochberg (1995)