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ORIGINAL RESEARCH

Striato-nigro-striatal tract dispersion abnormalities in patients with chronic schizophrenia

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Abstract
The white matter connections between the midbrain dopamine neurons and the striatum are part of a neural system involved in reward-based learning, a process that is impaired in patients with schizophrenia. The striato-nigro-striatal (SNS) tract, which participates in this process, has not as yet been explored. The present study aimed to use diffusion MRI (dMRI) to delineate the SNS tract, and to compare the application of two dMRI measures, Tract Dispersion (TD), an index of white matter morphology, and Fractional Anisotropy (FA), an index of white matter integrity, to detect group differences between patients with chronic schizophrenia (CSZ) and healthy controls (HC). dMRI scans were acquired in 22 male patients with CSZ and 23 age-matched HC. Two-tensor tractography was used in addition to manually-delineated regions of interest to extract the SNS tract. A mixed-model analysis of variance was used to investigate differences in TD and FA between CSZ patients and HC. The associations between TD and behavioral measures were also explored. Patients and controls differed significantly in TD ($P = 0.04$), but not in FA ($P = 0.69$). The group differences in TD were driven by a higher TD in the right hemisphere in the CSZ group. Higher TD correlated significantly with poorer performance in the Iowa Gambling Task (IGT) when combining the scores of both groups. The findings suggest that dysconnectiviy of the SNS tract which is associated with schizophrenia, could arise from abnormalities in white matter morphology. These abnormalities may potentially reflect irregularities in brain development.

Keywords Diffusion MRI · Reward processing · Psychotic symptoms

Introduction

One of the challenges in schizophrenia (SZ) research is to elucidate the links between abnormal neurobiology and clinical symptoms. The dysconnection hypothesis of schizophrenia proposes that SZ is the result of an abnormal functional integration of neural systems (Friston 1998; Stephan et al. 2009) and has been put forward as an explanatory model to understand these links. Although this hypothesis was initially formulated with regard to functional

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dysconnectivities (Stephan et al. 2009), more recently there has been increasing evidence from structural brain imaging studies, based primarily upon microstructural changes in white matter, that support the presence of structural dysconnectivity in addition to functional dyconnectivity in SZ (Kubicki et al. 2007; Pettersson-Yeo et al. 2011). Most of the structural studies of white matter connections to gray matter regions have focused on an analysis of large neural systems such as the frontoparietal, frontotemporal, corticostriatal and thalamocortical tracts (Leroux et al. 2014; Quan et al. 2013; Seitz et al. 2016; Woodward et al. 2012). However, structural abnormalities of smaller networks that may also play a role in the pathophysiology of SZ, such as the striato-nigro-striatal (SNS) tract, have not as yet been explored.

The connections between the substantia nigra/ventral tegmental area complex (SN/VTA) and the striatum, which form the SNS tract, are part of a neural network involved in reward-based learning (Haber and Behrens 2014; Wise 2004). Certain symptoms in SZ have been conceptualized in terms of SNS-mediated abnormalities in reward processing, specifically incentive salience and reward-based learning (Ziauddeen and Murray 2010). Incentive salience refers to the ability to capture attention based on associations that predict positive or negative outcomes. Reward-based learning, on the other hand, refers to the process by which organisms use these associations to modify behavior when the outcome is better than expected. Evidence suggests that this type of learning is impaired in patients with SZ, resulting in abnormal responses towards reward-predicting stimuli (Gold 2012; Roiser et al. 2009). For example, Roiser et al. (2009) showed that patients with SZ who participated in a reward learning paradigm, exhibited a decreased reactivity towards reward-predicting stimulus compared to healthy controls. In addition, these abnormalities correlated with the severity of positive and negative symptoms. One explanation of reward processing abnormalities in SZ and its association with clinical symptoms is the presence of abnormal dopamine signaling (Kapur 2003; Ziauddeen and Murray 2010). Therefore, studying the connectivity of the SNS tract is important as it contains dopamine projections, and is one of the regions where the integration of information from brain structures that participate in reward-based learning occurs (Haber et al. 2000; Haber and Behrens 2014).

The dysconnection hypothesis of schizophrenia is a useful explanatory framework to understand the links between clinical symptoms, reward processing abnormalities and abnormal neurobiology. Within this framework, structural abnormalities in the SNS tract may alter connections between the substantia nigra and striatum and therefore result in aberrant reward-based learning and clinical symptoms. Diffusion-Weighted Imaging (DWI) provides a means to study white matter networks in vivo (Basser and Pierpaoli 1996; Beaulieu 2002) and may, therefore, provide evidence in support of structural processes of dysconnectivity. DWI is sensitive to the rate and direction of water permeability and offers information about white matter microstructure. However, the use of standard DWI measures such as fractional anisotropy (FA) and mean diffusivity (MD) have limitations. This is because changes in FA and MD may reflect a combination of factors including myelin damage, axonal membrane disruptions, abnormal packing of axons, (Beaulieu 2002; Kubicki et al. 2007) and fiber tract geometry **(**Savadjiev et al. 2010**;** Whitford et al. 2011**).** Hence, there is a need to use a more specific measure to study white matter.

Given the potential limitations of the conventional DWI indices, in the present study we used an index of fiber geometry, called Tract Dispersion (TD), as an additional measure of white matter structure. Introduced by Savadjiev et al. (2014a), this measurement reflects the degree to which tracts deviate from being parallel, as in the case of fanning fibers, thereby providing information about a macrostructural feature of white matter. Furthermore, TD and other related indices of white matter geometry have been proposed to reflect changes that take place in neurodevelopment (Savadjiev et al. 2014a, 2014b, 2016). As axons develop from cells in the gray matter, it is thought that the spatial layout of these axons depends on the degree of spread of the neuronal cell bodies in the gray matter structure from which they originate (López-Bendito et al. 2006). We thus expect that abnormalities in the distribution of neurons at a macroscopic scale in a given gray matter area to be reflected by abnormalities in the spread of the associated white matter fibers, as measured by TD. Furthermore, it is also known that axonal input from distant gray matter regions is important for the development of cortical morphology. In experiments with monkey brains in utero, it has been shown that the surgical removal of part of the cortex produces changes in cortical morphology (area, volume, sulco-gyral pattern) in cortical regions distant from the operation site, possibly due to lack of axonal input that would normally be incoming from the removed cortex (Dehay et al. 1996; Goldman-Rakic 1980; Goldman-Rakic and Rakic 1984).

SZ is a disorder with a likely neurodevelopmental component as several genes known to play a key role in brain development are also candidate genes for SZ (Lewis and Levitt 2002; Rapoport et al. 2012). Variations in nucleotides can change the functionality of such candidate genes (Law et al. 2007) and could predispose to SZ by their effect on neurodevelopment. Therefore, we hypothesize that in SZ, changes in normal neurodevelopmental processes could impact the development of sub-cortical gray matter structures, and its connections to other brain structures, such as the SNS tract.

The first goal of this study was to use DWI to delineate and extract the SNS tract, a white matter bundle that connects the substantia nigra/ventral tegmental area complex (SN/VTA) with the striatum. Our second goal was to evaluate the differences in the structural connectivity of the SNS tract as assessed with TD, in a group of patients with chronic schizophrenia and healthy controls. A comparison between TD and a well-established DWI metric, Fractional Anisotropy (FA), was made in order to test the hypothesis that changes in TD detect subtle white matter neurodevelopmental abnormalities in SZ, that may not be detected with FA. The third goal of this study was to evaluate the associations between TD and clinical and cognitive measures. We hypothesized that the severity of symptoms, along with worse performance on cognitive tasks, would be correlated with abnormal TD values.

Methods

Participants

Twenty-two male patients with chronic schizophrenia (CZS) were recruited from the Veteran's Affairs (VA) Boston Healthcare System (Brockton Division). Twenty-three male healthy controls (HC) were recruited through local newspaper advertisements (see Supplementary Material for inclusion and exclusion criteria). Table 1 summarizes the demographic characteristics of the sample. Patients and controls were matched for age, handedness, parental socioeconomic status, and estimated premorbid IQ. The study was approved by the local Institutional Review Board. All study participants signed informed consent prior to participation in the study.

Imaging analysis

Image acquisition and processing

Images were obtained on a single 3-Tesla whole body MRI Echo speed system General Electric scanner (GE Medical Systems, Milwaukee) at the Brigham and Women's Hospital, Boston, MA. Diffusion weighted images were acquired using an echo planar image sequence with the following parameters: TR/TE = 1700 ms/78 ms; 51 gradient directions with b = 900 s/mm^2; 8 directions with b = 0 s/mm^2. Each volume consisted of 85 axial slices of 1.7 mm thickness, and an acquisition matrix of 144 × 144 in a field of view of 240x240mm^2, resulting in 1.7mm^3 isotropic voxels. The pre-processing steps included motion and eddy current correction using an affine registration algorithm in FSL (http://www.fmrib.ox.ac.uk/fsl). Diffusion tensor images were estimated from the Diffusion-Weighted Images in Slicer Version 2.8

Table 1 Sample Characteristics

Variable	CSZ patients (n = 22)	HC (n = 23)	CSZ vs. HC	
			t-value	p-value
Age (years)	45.40 (1.95)	40.47 (2.49)	−1.54	0.13
Gender	100% Male	100% Male	–	–
Education (years)	12.00 (4.30)	13.00 (5.49)	0.67	0.5
Parental SES	2.59 (1.18)	2.48 (1.23)	−0.31	0.57
Age-of-onset (years)	18.85 (11.86)	–	–	–
Medication dosage (CPZ Equivalent)	422.05 (293)	–	–	–
Duration-of-illness (years)	16.22 (12.39)	–	–	–
Premorbid IQ (WRAT-3 Reading)	93.82 (11.69)	103.09(27.03)	1.48	0.14
SAPS Global Score	8.71 (3.85)	–	–	–
SANS Global Score	10.97 (6.97)	–	–	–
WCST Perseverative Responses	23.30 (17.82)	14.38 (13.69)	−1.53	0.13
WCST Perseverative Errors	20.20 (14.68)	13.62 (11.82)	−1.35	0.18
WCST Non-perseverative Errors	18.60 (11.00)	13.23 (12.83)	−1.28	0.20
IGT Total Amount Lost	9409 (2207)	9040 (1956)	−0.44	0.66
IGT Number Times Lost	31.05 (7.95)	26.10 (4.60)	−1.80	0.08
IGT Average Loss Amount	313.04 (107.5)	360.64 (122.13)	0.82	0.41
IGT Total Amount Earned	−1224 (1404)	−854 (347)	0.72	0.47
Mean striatum volume (mm^3)	10,509 (1218)	10,269 (774)	−0.02	0.83
Mean substantia nigra volume (mm^3)	816 (258)	867 (260)	−0.20	0.84

Values show the mean and standard deviation. CSZ: chronic schizophrenia, HC: healthy controls. SES: Socioeconomic status, CPZ: Chlorpromazine, WRAT-3: Wide range achievement test, WCST: Wisconsin card sorting test, IGT: Iowa gambling task (http://www.slicer.org), based on the weighted-least-squares estimation.

Region-of-interest definition and tractography

The SNS tract was identified on the basis of connections between the SN/VTA and the striatum. The name striato-nigro-striatal reflects the presence of bi-directional projections between the SN/VTA and the striatum. Haber et al. (2000) have suggested that these projections follow a spiraling pattern. We used this name to be consistent with previous descriptions of this tract (Haber et al. 2000; Haber and Knutson 2010). The SN/VTA complex and striatum were outlined manually as automatic segmentation for these regions is not optimal. The SN/VTA was delineated on T2-weighted images, as the iron contained in the DA neurons attenuates the MRI signal (Fig. 1a). Intraclass correlation coefficients (ICC) were calculated for the volume measures by two raters for 6 cases. For left and right SN and total SN ICC was >0.98. The total striatum is comprised of, and can be parcellated into, the caudate, putamen and ventral striatum, which includes the nucleus accumbens. For this study, the entire unparcellated striatum was delineated. A description of the manual delineation of the striatum is included in Levitt et al. (2013).

Whole-brain tractography was computed using the multi-fiber tracking method of Malcolm et al. (2010). The fibers ending in the SN and the striatum ROIs in each hemisphere were then extracted for further analysis (see Fig. 1).

dMRI measures

For each tract under investigation in this study, we computed the measure of TD, introduced by Savadjiev et al. (2014a). At each point along each fiber, this measurement reflects the degree to which tracts deviate from being parallel, as in the case of fanning fibers. More specifically, at each point along each fiber, this method computes the variation of a fiber's tangent vector in all directions orthogonal to the curve, which leads to a measure of local white matter dispersion. In the present study, we computed TD using a scale parameter of 8.5 mm (see Savadjiev et al. (2014a) for further technical and implementation details). The TD measure is computed using tractography as input. As such, the stability and reproducibility of TD are essentially those of the tractography algorithm. If the same tractography input is used, TD values will also be the same, regardless of how many times the process is repeated. As for the reproducibility of tractography, it depends on the specific algorithm used (Guevara et al. 2017**;** Tensaouti et al. 2011**;** Wakana et al. 2007). Specifically, our tractography algorithm has shown good reproducibility when different MRI acquisition parameters are used (Rathi et al. 2014**).**

As an illustration, Fig. 1b shows a fiber tract colored by the TD measure. In addition to computing the TD measure, we also computed the Fractional Anisotropy (FA) along each individual fiber under investigation. Both the TD and FA measurements were then used in a statistical analysis framework as described below in Section 2.4.

Clinical and cognitive measures

A licensed clinical psychologist (PGN) and trained research assistants conducted all clinical and cognitive assessments. Symptom severity was assessed with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984a, b) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1984a; b). In addition to the total scores of the SANS and SAPS, global ratings were examined. The Iowa Gambling Test (Bechara et al. 1994) and the Wisconsin Card Sorting Tests (Heaton et al. 1993) were employed as a measures of reward-based learning. We selected the IGT to probe neuropsychological correlates of SNS because it is a task that simulates real-life decision-making by modulating the frequency and magnitude of potential rewards and punishments (Bechara et al. 1994). It has been

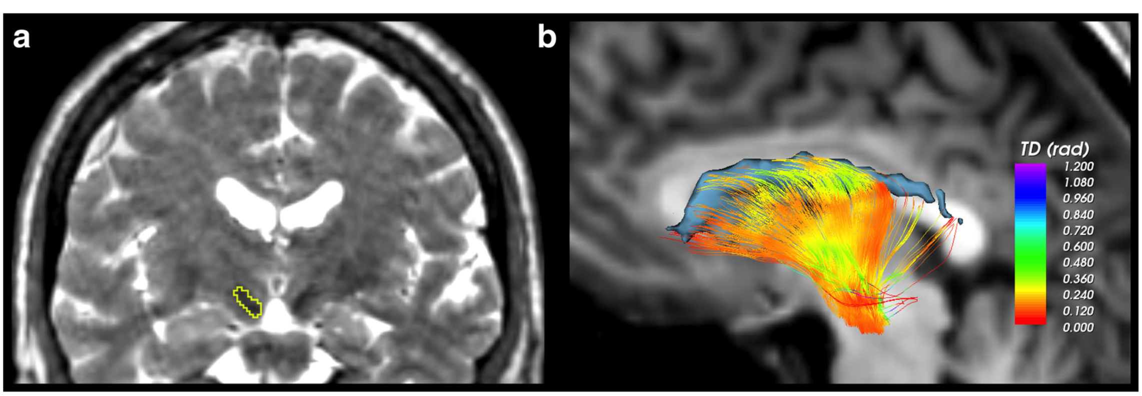

Fig. 1 Extraction of the SNS tract. **a** Delineation of the substantia nigra/VTA complex (SN/VTA) (in yellow) on a T2-weighted coronal image. **b** A lateral view of a 3D rendering of the SNS tract connecting the manually delineated striatum (in blue) and the SN/VTA superimposed on a diffusion-weighted sagittal image. Only the caudate nucleus is shown here to allow complete visualization of the SNS tract. The tract is colored by TD values; yellow/green areas have higher TD, and red/orange areas have lower TD

suggested that performance during the IGT is highly dependent on the ability to learn to sacrifice immediate rewards in favor of long-term benefits, which is highly influenced by emotional factors related to reward processing (Bechara et al. 2000). Consistent with these concepts, several authors have used the IGT to explore reward-based learning deficits in schizophrenia (Kester et al. 2006; Lee et al. 2007; Nestor et al. 2014; Shurman et al. 2005). Similarly, the WCST has been associated with a number of cognitive domains including working memory, cognitive flexibility and abstract thinking. Performance on this test does depend on the ability to learn from positive and negative rewards. Lastly, this test has also been used to study reward-based learning in patients with schizophrenia (Cella et al. 2014; Farreny et al. 2016; Prentice et al. 2008). Therefore, we believe that the IGT and WCST are related to reward-based learning and may potentially be associated with measures of structural connectivity in the SNS tract. All tests were part of an extensive neuropsychological test battery of the Boston Center for Intervention Development and Applied Research study (CIDAR) study (www. bostoncidar.org, accessed October 2016).

Statistical analysis

Statistical analyses were performed on the Statistical Package for the Social Sciences Version 19.

Group differences

A mixed-model analysis of covariance (ANCOVA) was used to investigate differences in TD and FA between CSZ patients and HC. We conducted two separate ANCOVAs (1 for TD and 1 for FA). TD and FA were entered as the dependent variables in separate models, 'hemisphere' (left-right) as the 'within-subject' variable, and 'group' (CSZ and HC) as the 'between-subject' variable. 'Age', 'mean striatum volume' and 'mean SN volume' were entered as covariates.

Clinical and cognitive measures

We conducted Spearman's correlations to investigate the associations between TD and total SANS and SAPS scores, and cognitive variables. Spearman rank-order correlations were used instead of Pearson correlations because clinical symptoms and cognitive scores are ordinal rather than continuous variables, and they were not normally distributed (as evaluated with the Shapiro-Wilk Test).

For the cognitive variables, composite measures of the Wisconsin Card Sorting Test (WCST) and the Iowa Gambling Test (IGT) were obtained with a principal component analysis (PCA) in order to reduce the dimensionality of the data (Table S1, Supplementary Material). Factor loadings of the composites of the WCST and IGT were extracted and correlated with TD. For all analyses, P values <0.05 were considered significant.

Additional analyses

We used Spearman's correlations to investigate the associations between TD and FA, between dMRI measures and striatum volume and patient's chlorpromazine-equivalent (CPZ) medication dosage. Spearman's correlations were used in this case because CPZ medication dosage was not normally distributed.

Results

Group differences

The mixed-model ANCOVA for TD showed a significant main effect of Group, $F_{(1,39)} = 4.46$, $P = 0.04$. No significant main effect of Hemisphere, $F_{(1,39)} = 2.17$, $P = 0.14$, or an interaction effect of Hemisphere x Group, $F_{(1,39)} = 1.22$, $P = 0.27$, was observed (Fig. 2a). Post-hoc t tests showed a significant difference in TD in the right hemisphere, $t(45) = -2.16$, $P = 0.03$, but not in the left hemisphere, $t(45) = -0.47$, $P = 0.63$. The FA analysis did not reveal a main effect of Group, $F_{(1,39)} = 0.15$, $P = 0.69$. The main effect of Hemisphere, $F_{(1,39)} = 2.10$, $P = 0.15$, and the interaction Group x Hemisphere, $F_{(1,39)} = 2.19$, $P = 0.14$, were also non-significant (Fig. 2b).

Clinical and cognitive measures

Because TD in CSZ patients was significantly higher than in HCs, we expected to observe associations between higher TD and worse symptoms severity, as well as worse performance in cognitive tests. Given that the group analysis did not show a significant Hemisphere by Group interaction, and in order to decrease the probability of a type I error by reducing the number of tests, TD values from the left and right hemispheres were combined and correlated with behavioral measures.

There were no significant associations between mean TD and the total scores of the SAPS, $\rho = -0.11$, $P = 0.61$ and the SANS, $\rho = 0.20$, $P = 0.36$. The analysis of the SANS subscales showed a significant correlation between mean TD with Global Measure of Apathy, $\rho = 0.47$, $P = 0.02$. This indicates that the severity of apathy is associated with higher TD values, consistent with our hypotheses. However, this association did not survive Bonferroni correction for multiple comparisons ($P = 0.001$). There were no significant associations between mean TD and the SAPS subscales.

The analysis of the cognitive measures did not show significant correlations between the composite scores of the IGT and the WCST, when looking at patients and HCs separately.

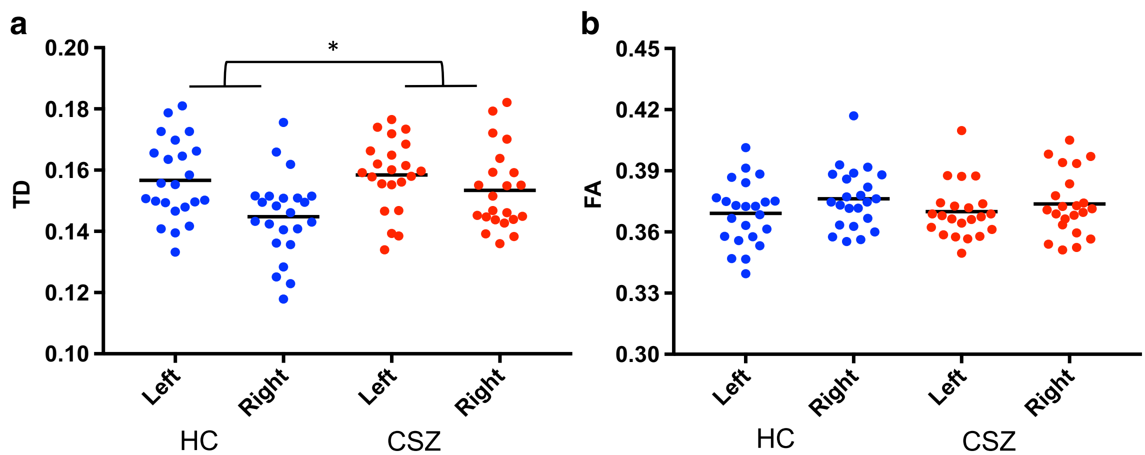

Fig. 2 Group differences in dMRI measures. Group differences in Total Dispersion (TD) (**a**) and Fractional Anisotropy (FA) (**b**) in the SNS tract. Red dots represent patients with chronic schizophrenia (CSZ); blue dots healthy controls (HC). Black brackets show significant comparisons. *$p < 0.05$

To increase the power of this analysis and because reward-based learning is a behavior observed across healthy and diseased individuals, we combined the scores of the two groups. As expected, there was a significant association between higher TD values and worse performance in the IGT, $\rho = -0.47$, $P = 0.01$ (Fig. 3). This association remained significant after Bonferroni correction for multiple comparisons.

Additional analyses

There were no significant correlations between TD and FA in CSZ or in HCs. There were no significant correlations between CPZ medication dosage and TD, $r = 0.14$, $P = 0.53$. Also, we did not find significant associations between striatal volumes and CPZ medication dosage, $r = -0.24$ $P = 0.26$.

Discussion

In this study, we used DTI to delineate and to extract the SNS tract in a group of patients with CSZ and HC. To the best of our knowledge, this is the first DTI study that has used TD to investigate the geometry of the SNS tract in patients with CSZ. We tested the hypothesis that changes in TD detect subtle white matter neurodevelopmental abnormalities in SZ that may not be detected with FA. We also predicted that the severity of symptoms and performance in cognitive tasks would be correlated with abnormal TD values. We observed that while patients with CSZ exhibited abnormal TD they did not exhibit abnormalities in FA. We also found a significant association between higher TD values and worse performance in the IGT when collapsing both groups. Finally, we observed an association between higher TD and worse severity of apathy in the patient group.

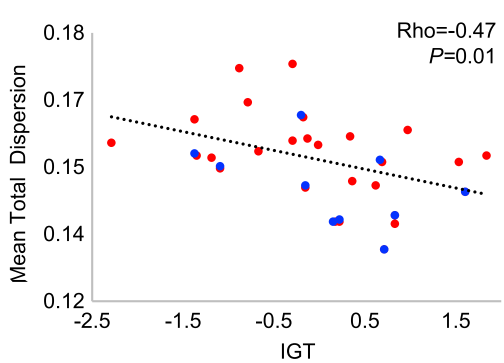

Fig. 3 Associations between mean TD and the IGT. Red dots represent patients with chronic schizophrenia (CSZ); blue dots healthy controls (HC)

Abnormal TD as a marker of atypical neurodevelopment

The findings of abnormal TD but not FA supports the notion that TD may detect subtle white matter changes in SZ that may not be detected with FA. Moreover, because TD is a measure of white matter morphology, and as changes in the morphological features of the brain have been associated with abnormal neurodevelopment, this finding suggests a neurodevelopmental component in the pathophysiology of SZ. This is consistent with previous work demonstrating the existence of white matter dispersion abnormalities at different stages of this disease (Savadjiev et al. 2010, 2014a, 2014b, 2016; Whitford et al. 2011). For example, Whitford et al. (2011) found abnormal white matter geometry in the genu of the corpus callosum in patients with CSZ, a finding that was also reported by Savadjiev et al. in a study on early onset SZ (Savadjiev et al. 2014b). Furthermore, a reversal pattern of normal sexual dimorphism, (i.e. higher dispersion in males with schizophrenia) which was present in the early onset group, was also found in a recent study of non-psychotic high-risk subjects (Savadjiev et al. 2016). The direction of dispersion changes is not consistent across studies. However, this is congruent with the idea that dispersion changes are dependent on the underlying tract geometry of the region under evaluation. That is, depending on the specific tract under investigation, TD could differ from normal subjects in either direction (i.e. higher or lower); but, in either case, appropriate brain wiring connectivity between grey matter structures would differ, causing dysfunction. This evidence also suggests that the abnormalities in TD observed in the SNS tract are an example of a more general disruption of abnormal tract geometry in schizophrenia, although further research is warranted.

The associations between SNS tract morphology and reward-based learning

The finding of abnormal TD in the SNS tract in the CSZ group is consistent with the role of the SNS tract in the pathophysiology of SZ. Furthermore, the significant correlation between TD and the IGT composite score highlights the importance of the SNS tract in reward-based learning, although the absence of a similar correlation with the WCST composite score supports that our finding should be interpreted as exploratory. From a neurobiological perspective, the connections between the midbrain dopamine neurons, the ventral striatum and the prefrontal cortex mediates the motivational and cognitive aspects of reward (Haber et al. 2000; Haber and Behrens 2014). Functional imaging studies in SZ have shown that the degree of impairment in reward-based learning and the severity of negative symptoms is associated with hypoactivation in the reward system, specifically in the ventral striatum (Juckel et al. 2006; Mucci et al. 2015; Radua et al. 2015). Therefore, our finding of higher dispersion in the SNS tract, might suggest a lack of effective communication at the level of synapses between SN/VTA and the striatum. This, in turn, may result in abnormalities in reward-based learning.

The associations between abnormal SNS tract morphology and apathy severity

Although the finding regarding the association between TD and apathy did not survive correction for multiple comparisons, it is worthy of discussion. Negative symptoms are a common complaint among patients with SZ, who often report an inability to experience pleasure, social withdrawal and a reduction in emotional and verbal expression (Deserno et al. 2016). They can be grouped into two domains: avolitional and expressive deficits (Blanchard and Cohen 2006; Kaiser et al. 2016). These domains are hypothesized to involve different neural systems, so that avolition deficits, including apathy, would be much strongly associated with deficits within the reward-system, while expressive deficits, such as alogia, would be linked to abnormalities in regions involved in motor function and language expression (Kaiser et al. 2016).

Specifically, we found a correlation between higher TD and the severity of apathy, which is defined as a lack of drive and motivation. This finding is linked to the idea that negative symptoms in SZ are related to abnormalities in neurobiological systems underlying motivational and reward processes. Indeed, associations between the inability to learn from rewarding feedback and negative symptoms have been reported in a number of studies (Juckel et al. 2006; Roiser et al. 2009; Somlai et al. 2011); Yilmaz et al. 2012). A link between negative symptoms and premorbid symptoms in schizophrenia has also been proposed (Andreasen 2010; Levitt et al. 1994), which may suggest an association between negative symptoms and early neurodevelopmental changes. Although our finding did not survive Bonferroni correction, possibly due to the small sample size, it is consistent with the hypothesis that negative symptoms in SZ may arise from the disruption of neural networks involved in representing values and using them for decision-making (Deserno et al. 2016; Ziauddeen and Murray 2010). Future studies with larger sample sizes are needed to confirm this finding.

Limitations

There were several limitations in this study. First, the group differences in TD are significant at the 0.05 level, but not at the 0.01 level, which limit the generalizability of the findings. Second, the correlation between TD and the IGT scores was only detectable after averaging the scores of CSZ and HCs. We agree that combining performance of behavioral measures is not ideal in studies comparing different groups. We now qualify this finding as exploratory and note that it is clearly limited by the fact that it is based on the aggregate sample combining patient and control groups. We provide further context for this finding by noting in light of the relative novelty of the TD measure there is a need for examining its neuropsychological correlates in larger patient samples with greater statistical power than that of our current study. That we did find such a highly statistically significant, Bonferroni-corrected correlation for the combined sample, does underscore the need for future studies to examine the IGT as a potential neuropsychological probe of SNS tract dispersion. In addition, we note that we did not find significant differences in IGT performance between patients and controls (See Table 1). This finding raises an important theoretical and empirical question as to the role of SNS tract dispersion in the computation and implementation of basic cognitive and affective processes related to decision making as assessed by the IGT. We also implemented this approach in order to address the possibility of a type 2 error. That we did not similarly find a correlation between SNS tract dispersion and the WCST composite score supports that further studies with larger samples are warranted. Third, in this study we included only male patients, to control for the confound of gender, because it has been shown that white matter dispersion is sexually dimorphic (Savadjiev et al. 2014b; Savadjiev et al. 2016). Thus, this study should also be repeated in female subjects in order to extend the generalizability of its findings.

Conclusion

Our findings showed that a novel neuroimaging measure of macrostructural white matter tract morphology, TD, revealed abnormalities in the SNS tract in patients with CSZ, that were not evident with the use of a less specific measure of white matter microstructure, FA. These abnormalities may potentially indicate the presence of irregularities in brain development. The association between TD with a composite score of the IGT highlights the potential role of the SNS tract in reward processing.

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Compliance with ethical standards

Conflict of interest Ana Maria Rivas-Grajales, Peter Savadjiev, Marek Kubicki, Paul G. Nestor, Margaret Niznikiewicz, Robert W. McCarley, Carl-Fredrik Westin, Martha E. Shenton and James J. Levitt declare that they have no conflicts of interest.

Human and animal rights 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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