Research Paper

# Shape features of working memory-related deep-brain regions differentiate high and low community functioning in schizophrenia

Eva C. Alden [a,b], Matthew J. Smith [c], James L. Reilly [a], Lei Wang [a,d], John G. Csernansky [a], Derin J. Cobia [a,e,*]

[a] Northwestern University Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, 710 N Lake Shore Drive, Chicago, IL 60611, USA
[b] Division of Neurocognitive Disorders, Department of Psychiatry and Psychology, Mayo Clinic, 200 First Street SW, Rochester, MN 55904, USA
[c] School of Social Work, University of Michigan, 1080 South University Avenue, Ann Arbor, MI, USA
[d] Department of Psychiatry and Behavioral Health, Ohio State University Wexner Medical Center, Columbus, OH, USA
[e] Department of Psychology and Neuroscience Center, Brigham Young University, Provo, UT, USA

ABSTRACT

We have previously shown that schizophrenia (SCZ) participants with high community functioning demonstrate better verbal working memory (vWM) performance relative to those with low community functioning. In the present study, we investigated whether neuroanatomical differences in regions supporting vWM also exist between schizophrenia groups that vary on community functioning. Utilizing magnetic resonance imaging, shape features of deep-brain nuclei known to be involved in vWM were calculated in samples of high functioning (HF-SCZ, $n = 23$) and low functioning schizophrenia participants (LF-SCZ, $n = 18$), as well as in a group of healthy control participants (CON, $n = 45$). Large deformation diffeomorphic metric mapping was employed to characterize surface anatomy of the caudate nucleus, globus pallidus, hippocampus, and thalamus. Statistical analyses involved linear mixed-effects models and vertex-wise contrast mapping to assess between-group differences in structural shape features, and Pearson correlations to evaluate relationships between shape metrics and vWM performance. We found significant between-group main effects in deep-brain surface anatomy across all structures. Post-hoc comparisons revealed HF-SCZ and LF-SCZ groups significantly differed on both caudate and hippocampal shape, however, significant correlations with vWM were only observed in hippocampal shape for both SCZ groups. Specifically, more abnormal hippocampal deformation was associated with lower vWM suggesting hippocampal shape is both a neural substrate for vWM deficits and a potential biomarker to predict or monitor the efficacy of cognitive rehabilitation. These findings add to a growing body of literature related to functional outcomes in schizophrenia by demonstrating unique shape patterns across the spectrum of community functioning in SCZ.

## 1. Introduction

Schizophrenia is a severe and chronic mental illness that disrupts multiple aspects of community functioning (Bellack et al., 2007). There is growing evidence that treatments targeted to improve cognition can also improve the level of general functioning in individuals with schizophrenia. Further, among cognitive functions, working memory may be especially critical for enhancing community functioning (Kaneda et al., 2009; Subramaniam et al., 2014). In addition to functional deficits, schizophrenia has been associated with a variety of neuroanatomical changes as compared to healthy individuals (Olabi

et al., 2011). Some of the more common deep-brain abnormalities observed are in structures involved in working memory, including volume reductions in the hippocampus (Davidson and Heinrichs, 2003), caudate, and thalamus; as well as a volume increase in the globus pallidus (Erp et al., 2016; Wright et al., 2000). However, while structural brain changes in the structures that subserve working memory are reliably associated with schizophrenia, it is unknown what impact they have on the degree of community functioning.

Only recently has the relationship between neuroanatomical abnormalities and level of functioning been explored in schizophrenia. A systematic review by Wojtalik et al. found that of the >30,000 published

---

magnetic resonance imaging (MRI) articles on schizophrenia, only 39 discussed neuroimaging results in the context of functional outcomes (Wojtalik et al., 2017). Among these 39 studies, it was noted that better community functioning was associated with less cortical thinning (Prasad et al., 2005; Tully et al., 2014), as well as greater volume of the thalamus and hippocampus (Aoyama et al., 2011; Brambilla et al., 2013). Because of this work, targeted investigation of relationships between functional outcomes and the neurobiology of working memory in schizophrenia are timely.

Our group previously utilized multiple cluster analytic techniques that identified two distinct schizophrenia (SCZ) groups characterized by either high (HF-SCZ) or low (LF-SCZ) levels of community functioning, and a comparison of these groups across multiple cognitive domains revealed HF-SCZ demonstrated stronger verbal working memory performance (vWM) relative to LF-SCZ (Alden et al., 2015). Utilizing high-dimensional surface-mapping procedures, we now characterize the structural characteristics of deep-brain structures involved in vWM to determine whether a concomitant neurobiological heterogeneity among these functionally defined patient groups also exists. Regions of interest were selected a priori based on current theories of neural circuitry known to support working memory performance, and included the caudate nucleus, hippocampus, globus pallidus, and thalamus (Duff and Brown-Schmidt, 2012; Emch et al., 2019). We hypothesized the HF-SCZ group would demonstrate shape abnormalities in these structures intermediate to LF-SCZ and healthy comparison participants (CON), and that the degree of shape deformation in regions that differed between the SCZ groups would be directly correlated with deficits in vWM performance.

## 2. Methods

### 2.1. Participants

The present samples are composed of a subset of participants from a large longitudinal study of schizophrenia. Participants were those who had available and usable imaging data, which included 23 individuals with HF-SCZ, 18 with LF-SCZ, and 45 CON. These participants were previously classified by level of functioning through cluster analysis (Alden et al., 2015), details regarding clustering procedures can be found in the Supplemental Methods. In brief, SCZ participants met DSM-IV criteria for schizophrenia, but not schizoaffective disorder, confirmed using the Structured Clinical Interview for DSM-IV (First et al., 1996). Community functioning was assessed via three distinct measures of functioning, including the Brief UCSD Performance-based Skills Assessment (UPSA-B, Mausbach et al., 2007), Social Skills Performance Assessment (SSPA, Patterson et al., 2001), and Specific Levels of Functioning (SLOF, Schneider and Struening, 1983). The domain of vWM was assessed based on performance on the Letter-Number Sequencing and Digit Span subtests of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III, Wechsler, 1997). Informed consent was obtained from all participants, which contained a detailed description of all study procedures, as well as any possible risks and/or benefits. All data were collected according to ethical guidelines as outlined by the Declaration of Helsinki; all procedures were approved by the Northwestern University Feinberg School of Medicine Institutional Review Board.(WAIS-III, Wechsler, 1997).

### 2.2. Image acquisition

All MR scans were collected using a 3T TIM TRIO system (Siemens Medical Systems) equipped with actively shielded gradients, echo-planar capability, and 12-channel head coils. Two high-resolution 3D T1-weighted MPRAGE volumes optimized for gray-white contrast [TE = 3.16 ms, TR = 2400 ms, $1 \times 1 \times 1$ mm voxels] were acquired and each subject were aligned and averaged to create a low-noise image volume (Buckner et al., 2004).

### 2.3. Surface mapping

Surface features of the caudate, globus pallidus, hippocampus, and thalamus were derived through application of FreeSurfer-initiated large-deformation high-dimensional brain mapping (Csernansky et al., 2004; Khan et al., 2008). This atlas-based transformation technique uses a template image of each structure, which is first aligned with the target brain regions with the segmentation image of each subject via anatomical landmarks, then subsequently warped onto the target via diffeomorphic mapping of voxel intensities. The diffeomorphic transformations allow individual surface points to independently match, therefore preserving the unique surface features. Finally, surfaces were generated by superimposing a tessellated graph over each subject's image (Khan et al., 2008).

### 2.4. Statistical analysis

Between-group differences in demographics and cognition were assessed with chi-square and analysis of variance (ANOVA) models while independent samples *t*-tests were used to evaluate differences in antipsychotic medication between SCZ groups. Repeated measures multivariate analysis of covariance models (RM-MANCOVA) were used to assess the overall effect of group status on the volume of each brain structure across right and left hemisphere, which included supratentorial volume (derived from FreeSurfer) as a covariate to account for the global effects of whole brain volume. If a model was significant for the group effect, then follow-up one-way RM-ANCOVA models were conducted as a post hoc analysis to assess each specific group contrast.

Principal component analysis (PCA) was employed to assess localized shape differences by reducing shape dimensions into the first 10 eigenvectors per hemisphere, which accounted for ~80% of the total shape variance (Grenander and Miller, 1998). To evaluate group differences, linear mixed effects models were conducted given the non-independent eigenvalues generated by the PCA, as well as the capability to account for multilevel hierarchically nested data. Mixed effects analyses were first performed to test a main, or fixed, effect of group – CON, HF-SCZ, and LF-SCZ – on shape of deep-brain structures. For shape, data levels included hemisphere and eigenvector. Pairwise post-hoc comparisons were then conducted to evaluate the specific between-group differences for each group.

Vertex-wise studentized-t surface maps were also generated for each group comparison (CON vs. HF-SCZ, CON vs. LF-SCZ, and HF-SCZ vs. LF-SCZ) on all structures to examine regional differences in shape deformation. Perpendicular change was given either a positive or negative sign, corresponding to outward and inward deformation, respectively. Previous work from our group revealed these surface displacements are representative estimates of localized volume loss or exaggeration of deep-brain nuclei (Hanko et al., 2019).

Individual scores for each subject that represent unique variation in the shape across both left and right hemispheres were generated using xBeta residuals, which represent a maximum likelihood estimate statistic for group classification derived from logistic regression (Smith et al., 2014). The model was set such that the contrast compared healthy subjects to all schizophrenia subjects in order to create one xBeta per individual. The first 10 eigenvectors from each hemisphere (for a total of 20) from each structure (caudate, globus pallidus, hippocampus, and thalamus) were input into the predictive model. Bivariate Pearson correlations were then performed to evaluate the relationship between vWM performance and xBeta scores.

## 3. Results

### 3.1. Participant characteristics

There were no differences in age, gender, parental socioeconomic status, and race across CON, HF-SCZ, and LF-SCZ. There was a

significant overall group effect for vWM ($F_{2,80} = 14.481$, $p = 0.00$), with CON demonstrating better vWM performance than both HF-SCZ and LF-SCZ. The difference in vWM performance between HF-SCZ and LF-SCZ was not statistically significant ($p = 0.17$), but demonstrated a large effect size ($d = 2.91$) suggesting that there was substantial variability within and between the two SCZ groups. Regarding measures of functioning in the schizophrenia subgroups, HF-SCZ demonstrated significantly stronger performance relative to LF-SCZ on the SLOF ($F_{1,39} = 25.23$, $p < 0.001$), SSPA ($F_{1,39} = 7.52$, $p = 0.009$), and UPSA-B ($F_{1,39} = 43.3$, $p < 0.001$). There were no significant differences in duration of illness ($t_{39} = -1.42$, $p = 0.40$) or the level of antipsychotic medications (chlorpromazine equivalents) ($t_{39} = -0.858$, $p = 0.16$); see Table 1 for details.

### 3.2. Volume analysis

Significant main effects for group were observed in the globus pallidus ($F_{2,82} = 4.56$, $p = 0.01$) and hippocampus, ($F_{2,82} = 5.18$, p = 0.01), but not for the caudate or thalamus. Post-hoc RM-ANCOVAs demonstrated that HF-SCZ had significantly lower volumes than CON in both the hippocampus ($F_{1,65} = 8.90$, $p = 0.004$) and globus pallidus ($F_{1,65} = 8.64$, $p = 0.01$). There were no significant differences in volume between LF-SCZ and CON in either the globus pallidus ($F_{1,60} = 3.34$, $p = 0.07$) or hippocampus ($F_{1,60} = 2.51$, $p = 0.19$). There were also no significant volumetric differences between HF-SCZ and LF-SCZ in the globus pallidus ($F_{1,38} = 0.43$, $p = 0.52$) or hippocampus ($F_{1,38} = 2.23$ $p = 0.14$); see Table 2 for details.

**Table 1**
Demographic and clinical characteristics of study samples.

| | CON (n = 45) | HF-SCZ (n = 23) | LF-SCZ (n = 18) | Statistic |
|---|---|---|---|---|
| Demographics | | | | |
| Age, mean years (SD) | 31.70 (8.64) | 33.74 (5.44) | 31.56 (7.74) | $F_{2,83} = 0.61$, $p = 0.54$ |
| Gender (% male) | 51.1% | 60.9% | 72.2% | $X^2_2 = 2.45$, $p = 0.29$ |
| Average SES, mean (SD)[a] | 28.49 (9.68) | 25.75 (10.15) | 22.78 (8.13) | $F_{2,83} = 2.39$, $p = 0.10$ |
| Race % Caucasian | 46.7% | 39.1% | 38.9% | $X^2_8 = 6.68$, $p = 0.57$ |
| % African-American | 37.8% | 52.2% | 44.4% | |
| % Asian | 6.7% | 4.3% | 0% | |
| % other | 8.9% | 4.3% | 11.1% | |
| Chlorpromazine equivalent (mg), mean (SD) | – | 546.98 (489.16) | 509.51 (409.64) | $t_{39} = -1.42$, $p = 0.16$ |
| Duration of illness, mean years (SD) | – | 12.55 (6.37) | 14.48 (8.09) | $t_{39} = -0.858$, $p = 0.40$ |
| Verbal working memory | 0.01 (0.14) | −0.73 (0.20) | −1.27 (0.17) | $F_{2,80} = 14.48$, $p < 0.001$[†,**] |
| Measures of functioning (total scores) | | | | |
| Specific Levels of Functioning (SLOF) | – | 132.74 (9.2) | 115.5 (12.8) | $F_{1,39} = 25.23$, $p < 0.001$** |
| Social Skills Performance Assessment (SSPA) | – | 3.51 (0.64) | 2.93 (0.72) | $F_{1,39} = 7.52$, $p = 0.009$* |
| Brief UCSD Performance-Based Skills Assessment (UPSA-B) | – | 83.17 (9.7) | 63.66 (9.0) | $F_{1,39} = 43.3$, $p < 0.001$** |

[a] CON $n = 43$, HF-SCZ $n = 22$.
[†] CON > HF-SCZ, CON > LF-SCZ (Bonferroni corrected).
[*] $p < 0.01$.
[**] $p < 0.001$.

**Table 2**
Group differences in volume (mean, SD in mm³).

| | CON (n = 45) | HF-SCZ (n = 23) | LF-SCZ (n = 18) | ANOVA |
|---|---|---|---|---|
| Caudate | | | | $F(2,82) = 0.07$, $p = 0.93$ |
| Left | 3534.35 (405.5) | 3469.04 (431.4) | 3575.30 (330.2) | |
| Right | 3478.27 (408.4) | 3421.16 (440.8) | 3513.50 (399.9) | |
| Globus pallidus | | | | $F(2,82) = 4.56$ $p = 0.01$[a] |
| Left | 1694.93 (202.0) | 1757.34 (192.7) | 1765.68 (155.2) | |
| Right | 1679.79 (184.2) | 1743.04 (185.1) | 1737.76 (165.2) | |
| Hippocampus | | | | $F(2,82) = 5.18$ $p = 0.01$[b] |
| Left | 2386.21 (307.5) | 2182.23 (193.3) | 2286.81 (219.4) | |
| Right | 2824.10 (373.1) | 2589.62 (254.3) | 2714.74 (240.3) | |
| Thalamus | | | | $F(2,82) = 0.16$ $p = 0.86$ |
| Left | 7347.88 (679.6) | 7191.82 (625.4) | 7244.69 (624.7) | |
| Right | 7157.27 (631.0) | 7043.13 (633.0) | 7122.26 (581.7) | |

[a] CON < HF-SCZ.
[b] CON > HF-SCZ.

### 3.3. Shape analysis

#### 3.3.1. Caudate

Linear mixed effects analysis revealed the overall model was significant ($F_{59,1660} = 4.409$, $p = 0.00$), with a significant group-by-eigenvector interaction ($F_{18,1660} = 1.87$, $p = 0.02$). There were no main effects for group ($F_{2,1660} = 0.965$, $p = 0.381$) or hemisphere ($F_{1,1660} = 0.746$, $p = 0.388$). Bonferroni corrected post-hoc comparisons revealed significant group-by-eigenvector interactions regarding CON vs. HF-SCZ ($t_{1660} = 1.99$, $p = 0.05$; $d = 0.51$), CON vs. LF-SCZ ($t_{1660} = -2.38$, $p = 0.03$; $d = -0.67$), and HF-SCZ vs. LF-SCZ ($t_{1660} = -3.73$, $p = 0.00$; $d = -1.18$). Inspection of vertex-wise surface contrast maps (Fig. 1) revealed both HF-SCZ and LF-SCZ groups were characterized by significant inward deformation on the posterior ventral and anterior lateral surfaces of the caudate relative to CON. Relative to LF-SCZ, HF-SCZ demonstrated small regions of inward deformation in dorsolateral and medial regions of only the right caudate.

#### 3.3.2. Globus pallidus

Linear mixed effects analysis revealed the overall model was significant ($F_{59,1660} = 10.14$, $p = 0.00$), with a significant group-by-eigenvector interaction ($F_{18,1660} = 2.225$, $p = 0.00$). There were no main effects for group ($F_{2,1660} = 0.90$, $p = 0.409$) or hemisphere ($F_{1,1660} = 2.714$, $p = 0.100$). Bonferroni corrected post-hoc comparisons revealed significant group-by-eigenvector interactions between CON vs. HF-SCZ ($t_{1660} = -2.97$, $p = 0.01$; $d = -0.76$) and CON vs. LF-SCZ ($t_{1660} = -3.42$, $p = 0.00$; $d = -0.95$). There were no significant differences between HF-SCZ and LF-SCZ ($t_{1660} = -0.61$, $p = 0.54$, $d = -0.19$). Inspection of vertex-wise surface contrast maps (Fig. 2) revealed HF-SCZ and LF-SCZ were characterized by significant outward deformation on the dorsal and ventral surfaces of the globus pallidus relative to CON.

#### 3.3.3. Hippocampus

Linear mixed effects analysis revealed the overall model was significant ($F_{59,1660} = 12.400$, $p = 0.00$), with a significant group-by-eigenvector interaction ($F_{18,1660} = 2.80$, $p = 0.00$). There were significant main effects for group ($F_{2,1660} = 3.387$, $p < 0.050$) and hemisphere ($F_{1,1660} = 13.884$, $p < 0.001$). Bonferroni corrected post-hoc
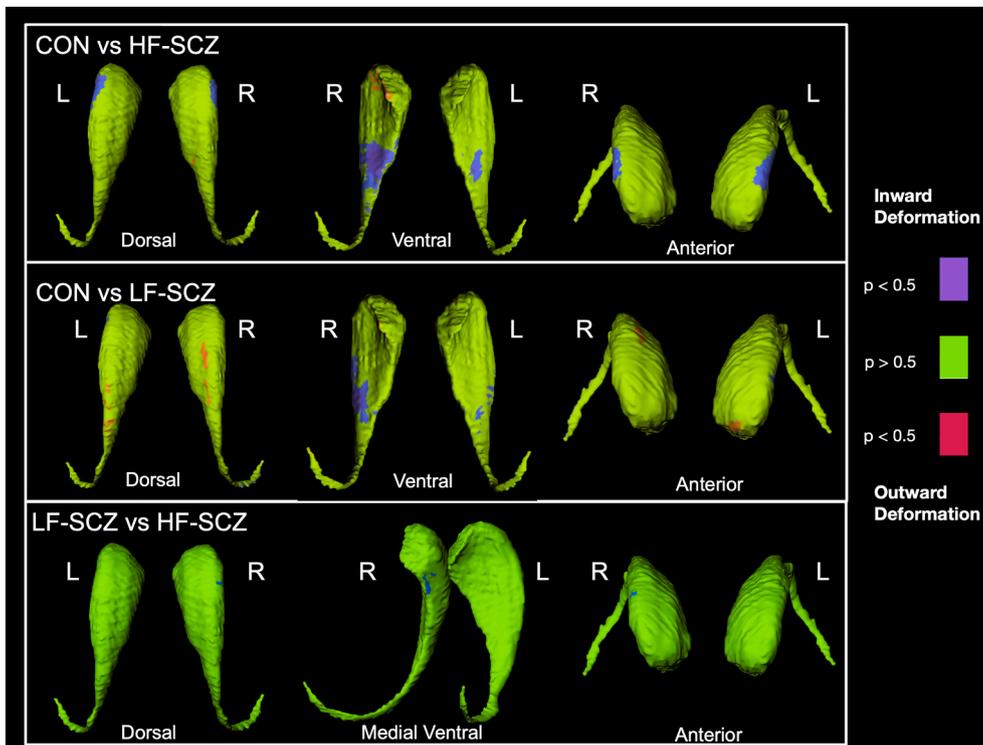
**Fig. 1.** Caudate nucleus surface shape contrast t-maps between: high community functioning schizophrenia (HF-SCZ) patients and control (CON) participants; low community functioning schizophrenia (LF-SCZ) patients and CON participants; HF-SCZ and LF-SCZ patients. Studentized-t values with cooler colors ($t < 0$) indicate inward shape differences and warmer colors ($t > 0$) indicate outward shape differences.
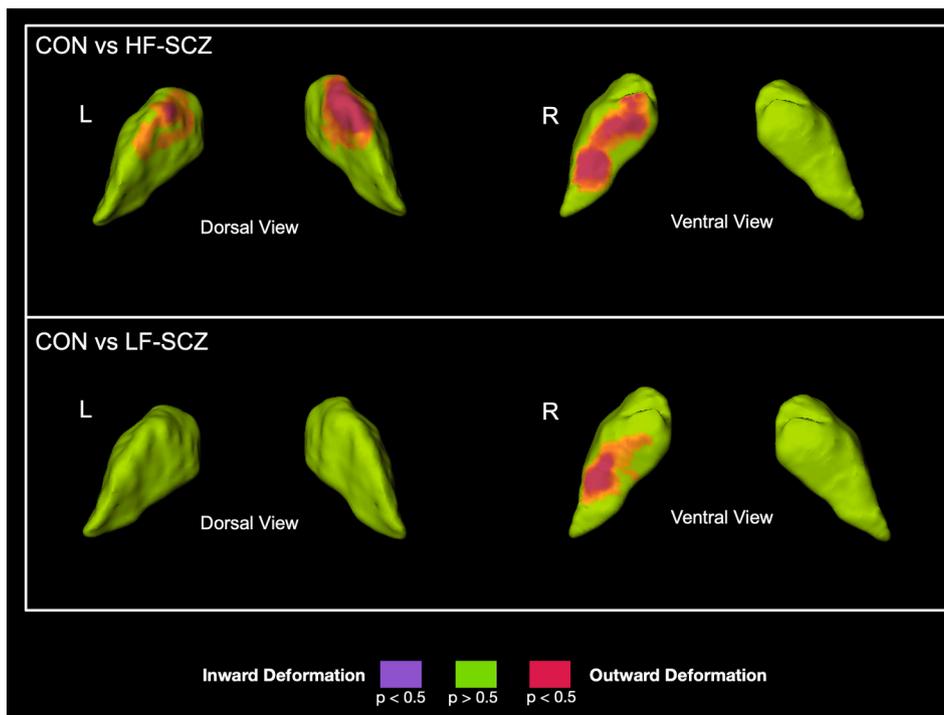


**Fig. 2.** Globus pallidus surface shape contrast t-maps between: high community functioning schizophrenia (HF-SCZ) patients and control (CON) participants; low community functioning schizophrenia (LF-SCZ) patients and CON participants. Studentized-t values with cooler colors ($t < 0$) indicate inward shape differences and warmer colors ($t > 0$) indicate outward shape differences.

comparisons revealed significant group-by-eigenvector interactions between CON vs. HF-SCZ ($t_{1660} = 5.69, p = 0.00; d = 1.46$), CON vs. LF-SCZ ($t_{1660} = 2.42, p = 0.03; d = 0.67$), and HF-SCZ vs. LF-SCZ ($t_{1660} = -2.49$, $p = 0.03; d = -0.78$). Inspection of the vertex-wise surface contrast maps (Fig. 3) revealed HF-SCZ showed greater inward deformation on the dorsolateral and ventral surfaces of the hippocampus compared to
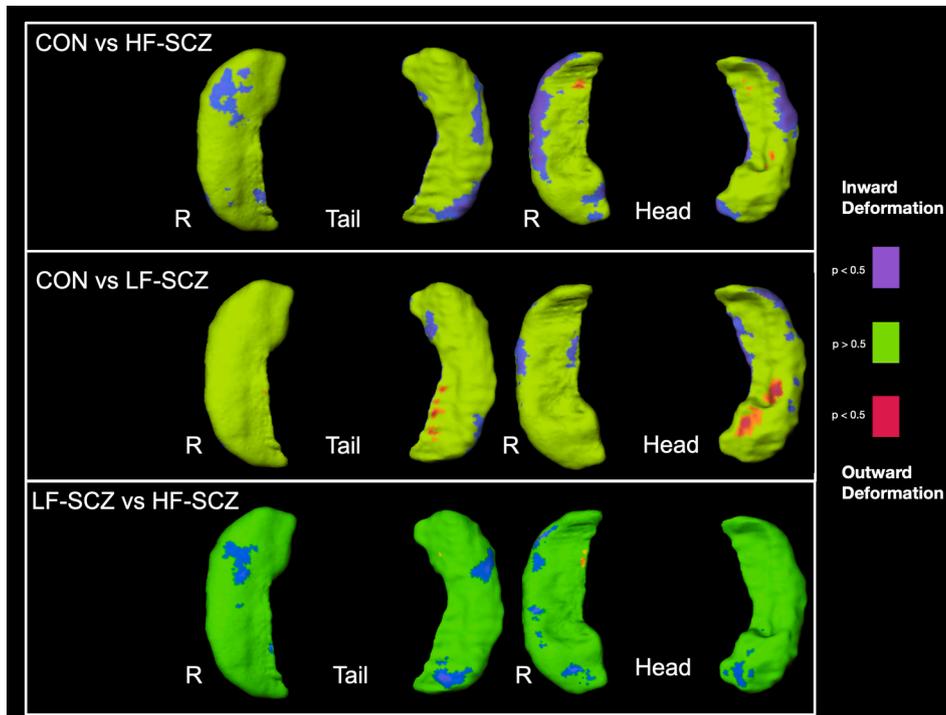
**Fig. 3.** Hippocampal surface shape contrast t-maps between: high community functioning schizophrenia (HF-SCZ) patients and control (CON) participants; low community functioning schizophrenia (LF-SCZ) patients and CON participants; HF-SCZ and LF-SCZ patients. Studentized-t values with cooler colors ($t < 0$) indicate inward shape differences and warmer colors ($t > 0$) indicate outward shape differences.

CON, while LF-SCZ had a similar, but attenuated pattern of inward deformation as well as outward deformation in left dorsal anterior and ventral posterior regions compared to CON. HF-SCZ also demonstrated significant bilateral inward deformation along the anterior and lateral dorsal, as well as anterior and posterior ventral surface of the hippocampus relative to LF-SCZ.

### 3.3.4. Thalamus

Linear mixed effects analysis revealed the overall model was significant ($F_{59,1660} = 6.49$, $p = 0.00$), with a significant group-by-eigenvector
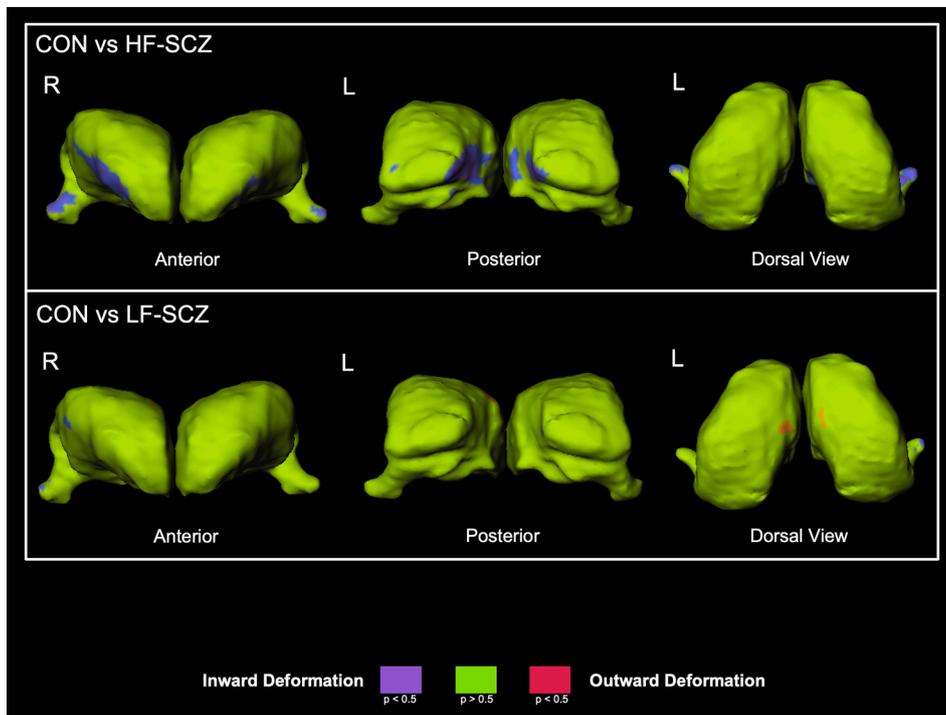


**Fig. 4.** Thalamic surface shape contrast t-maps between: high community functioning schizophrenia (HF-SCZ) patients and control (CON) participants; low community functioning schizophrenia (LF-SCZ) patients and CON participants. Studentized-t values with cooler colors ($t < 0$) indicate inward shape differences and warmer colors ($t > 0$) indicate outward shape differences.

interaction ($F_{18,1660} = 1.62$, $p = 0.05$). There were no main effects for group ($F_{2,1660} = 0.246$, $p = 0.782$) or hemisphere ($F_{1,1660} = 2.496$, $p = 0.114$). There was a significant group-by-eigenvector interaction between CON and HF-SCZ ($t_{1660} = 5.69$, $p = 0.00$; $d = -0.84$), but not CON and LF-SCZ ($t_{1660} = 5.69$, $p = 0.17$; $d = -0.48$) or HF-SCZ and LF-SCZ ($t_{1660} = 5.69$, $p = 0.25$; $d = 0.36$). Inspection of vertex-wise surface contrast maps (Fig. 4) revealed HF-SCZ showed greater inward deformation along lateral and medial aspects of the thalamus, as well as lateral geniculate nuclei. In LF-SCZ, only very mild inward deformation was observed in lateral aspects of the right thalamus, and outward deformation in medial regions.

### 3.4. Relationships between shape and verbal working memory performance

Guided by the significant results in the HF-SCZ vs. LF-SCZ contrasts above, correlation analyses were conducted between caudate and hippocampal shape with vWM performance in the SCZ groups. Significant inverse correlations between hippocampal shape and vWM were observed in both HF-SCZ ($r = -0.43$, $p = 0.04$) and LF-SCZ ($r = -0.53$, $p = 0.02$), which indicated that poorer vWM was associated with greater abnormal hippocampal shape deformation in these groups (Fig. 5). Correlations between vWM and caudate shape were non-significant for both groups.

### 4. Discussion

The overarching aim of the study was to characterize neuroanatomical differences in schizophrenia subgroups with either high or low community functioning relative to healthy individuals. Previous normative literature on measures of functioning utilized in this study support the classification of high and low functioning given to our schizophrenia subgroups, in particular the HF-SCZ group was performing in a range consistent with healthy individuals (Harvey et al., 2016; Miller et al., 2021). We found that shape of all deep-brain regions was significantly altered in HF-SCZ and LF-SCZ as compared to CON, but only hippocampal and caudate shape differentiated HF-SCZ from LF-SCZ. Furthermore, correlation analyses revealed that abnormal shape of the hippocampus alone was related to poorer vWM performance in both HF-SCZ and LF-SCZ. These findings suggest that selective aspects of the global deep-brain structural abnormalities commonly observed in schizophrenia contribute to the cognitive substrate of functional outcomes in this illness.

Our findings of shape differences for the globus pallidus and



**Fig. 5.** Hippocampal shape progressing from healthy control (CON) to schizophrenia (SCZ) correlated with poorer verbal working memory performance in both high (HF-SCZ: $r = -0.43$, $p = 0.04$) and low community functioning (LF-SCZ: $r = -0.53$, $p = 0.02$) schizophrenia groups.

thalamus in both SCZ subgroups relative to CON are largely congruent with prior studies of shape alterations in the basal ganglia (Shepherd et al., 2012). With respect to the observed outward deformation in the globus pallidus, previous work indicates this may be a function of medication side-effects (Erp et al., 2016; Staal et al., 2000), as research has consistently demonstrated this is an effect of long-term antipsychotic use on basal ganglia structures (Mamah et al., 2008; Vernon et al., 2012). In both SCZ groups exaggerated outward deformation was noted relative to CON, but the pattern appeared more extensive in the HF-SCZ group. Regarding the thalamus, the shape abnormalities we observed across both SCZ groups occurred in ventral lateral and mediodorsal regions, which are reflective of the current literature on thalamic dysfunction in schizophrenia (Alemán-Gómez et al., 2020; Steullet, 2020). No statistically significant differences were noted between the HF-SCZ and LF-SCZ, although LF-SCZ appeared to have a more attenuated thalamic pattern overall compared to CON, suggesting this region may be less involved in the expression of the unique characteristics of this group.

The literature regarding alterations of the caudate in schizophrenia is generally consistent with our findings; however, the direction of the effect is mixed depending on method and sample composition. Inward shape deformation has been observed in multiple studies (Cobia et al., 2021; Mamah et al., 2016, 2007), while surface expansion and thickening were noted in a recent meta-analysis of schizophrenia (Gutman et al., 2021). Both SCZ groups showed greater hippocampal abnormalities relative to CON, with significant inward deformations, but additional outward deformations, in left dorsal and ventral regions for the LF-SCZ group. In the SCZ group comparisons, significant inward deformation was noted in the HF-SCZ relative to LF-SCZ group only in the caudate and hippocampus; furthermore, qualitative review of the shape maps for all structures revealed a greater degree of shape abnormality in HF-SCZ relative to CON than LF-SCZ. Given that prior studies identify inward deformation of deep-brain structures as a core feature of schizophrenia (Csernansky et al., 2002; Gutman et al., 2021; Wang et al., 2008), our results suggest HF-SCZ may represent a more typical neurobiological form of schizophrenia relative to LF-SCZ. Our expectation was that HF-SCZ would demonstrate brain abnormalities intermediate to CON and LF-SCZ. However, the findings indicate the opposite suggesting different brain regions, or imaging features, may better represent the poorer community functioning in LF-SCZ. In a recent study using these same groups, we also found that HF-SCZ demonstrated intermediate BOLD activation between CON and LF-SCZ during a social skills task involving facial affect perception (Karpouzian et al., 2017), suggesting social perception and social skills may play a role in supporting elevated community-based functioning in schizophrenia. However, novel machine learning approaches to studying general functional outcomes in psychosis do reinforce the importance of deep brain structures, including the hippocampus, in predicting long-term outcome and resilience (Kambeitz-Ilankovic et al., 2016; de Wit et al., 2016a, 2016b).

Consistent with prior work that suggests that smaller hippocampal volumes are associated with poorer working memory performance (Guo et al., 2014), we observed that greater surface abnormalities in the hippocampus were associated with poorer verbal working memory performance in both SCZ groups. Other studies have shown that overactivation of the hippocampus is strongly associated with schizophrenia (Wible, 2013), and that greater intrinsic activity in the hippocampus is inversely correlated with verbal working memory performance (Tregellas et al., 2014). Collectively, the literature suggests the hippocampus is an important substrate for working memory (Cave and Squire, 1992; Duff and Brown-Schmidt, 2012), although structural integrity alone may not completely explain differences in performance among those with high or low functional capacity. Indeed, some recent work utilizing path analysis discovered that a unique combination of cognition, vocal emotional output, mood, and negative symptoms were strong "bottom-up" predictors of functional outcome in schizophrenia (Luo et al., 2021).
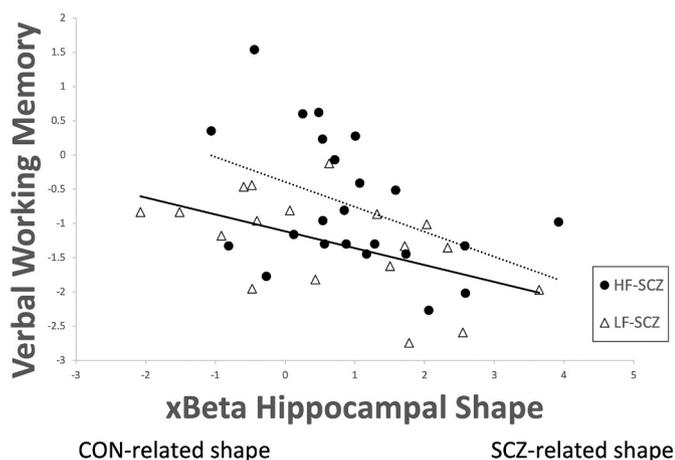
The limitations of this study include 1) the number of subjects per group is relatively small, with unequal numbers in the SCZ groups, and replication with larger samples are needed and 2) the cross-sectional design only assesses cluster classification from an initial time point and long-term stability of these groupings can be determined with longitudinal models. Future studies of functional outcomes in SCZ would benefit from the inclusion of known "facilitators" of functional recovery, such vocational rehabilitation (Vita et al., 2011), cognitive enhancement therapy (Eack et al., 2010), and cognitive remediation therapy (Twamley et al., 2012). Other factors known to impact level of functioning such as social supports, family involvement, coping style, and emotion regulation should also be evaluated.

In summary, we found that unique surface anatomy alterations in the caudate, hippocampus, globus pallidus, and thalamus defined functionally-defined schizophrenia subgroups relative to healthy individuals, and that patient groups with high and low levels of community functioning specifically differed in hippocampal shape. Furthermore, hippocampal abnormalities in the schizophrenia groups were related to worse verbal working memory performance. These findings add to a growing body of literature related to functional outcomes in schizophrenia by highlighting differential patterns of shape deformation that are correlated with verbal working memory performance in the context of community functioning.

## Funding sources

## CRediT authorship contribution statement

**Eva Alden, Matthew J. Smith** and **Derin Cobia**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration and Writing – Original Draft. **James L. Reilly**: Conceptualization, Writing – Review & Editing; **John G. Csernansky, Lei Wang**: Resources, Writing – Review & Editing, Supervision, Funding Acquisition.

## Declaration of competing interest

Dr. Csernansky currently serves on a DSMB for a study sponsored by Sunovion, Inc. that is unrelated to the present study. Dr. Smith receives royalties from SIMmersion, LLC, for sales of a job interview intervention. Dr. Cobia currently serves as a consultant for Sage Pharmaceuticals on a project unrelated to the present study. Drs. Alden, Reilly, and Wang report no financial relationships with commercial interests. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

## Acknowledgments

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.scog.2022.100250.

## References

Alden, E.C., Cobia, D.J., Reilly, J.L., Smith, M.J., 2015. Cluster analysis differentiates high and low community functioning in schizophrenia: subgroups differ on working memory but not other neurocognitive domains. Schizophr. Res. 168, 273–278.

Alemán-Gómez, Y., Najdenovska, E., Roine, T., Fartaria, M.J., Canales-Rodríguez, E.J., Rovó, Z., Hagmann, P., Conus, P., Do, K.Q., Klauser, P., Steullet, P., Baumann, P.S., Cuadra, M.B., 2020. Partial-volume modeling reveals reduced gray matter in specific thalamic nuclei early in the time course of psychosis and chronic schizophrenia. Hum. Brain Mapp. 41 (14), 4041–4061. https://doi.org/10.1002/hbm.25108.

Aoyama, N., Théberge, J., Drost, D.J., Manchanda, R., Northcott, S., Neufeld, R.W.J., Menon, R.S., Rajakumar, N., Pavlosky, W.F., Densmore, M., Schaefer, B., Williamson, P.C., 2011. Grey matter and social functioning correlates of glutamatergic metabolite loss in schizophrenia. Br. J. Psychiatry 198, 448–456.

Bellack, A.S., Green, M.F., Cook, J.A., Fenton, W., Harvey, P.D., Heaton, R.K., Laughren, T., Leon, A.C., Mayo, D.J., Patrick, D.L., Patterson, T.L., Rose, A., Stover, E., Wykes, T., 2007. Assessment of community functioning in people with schizophrenia and other severe mental illnesses: a white paper based on an NIMH-sponsored workshop. Schizophr. Bull. 33, 805–822.

Brambilla, P., Perlini, C., Rajagopalan, P., Saharan, P., Rambaldelli, G., Bellani, M., Dusi, N., Cerini, R., Mucelli, R.P., Tansella, M., Thompson, P.M., 2013. Schizophrenia severity, social functioning and hippocampal neuroanatomy: three-dimensional mapping study. Br.J. Psychiatry 202, 50–55.

Buckner, R.L., Head, D., Parker, J., Fotenos, A.F., Marcus, D., Morris, J.C., Snyder, A.Z., 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. NeuroImage 23 (724), 738.

Cave, C.B., Squire, L.R., 1992. Intact verbal and nonverbal short-term memory following damage to the human hippocampus. Hippocampus 2, 151–163.

Cobia, D., Rich, C., Smith, M.J., Mamah, D., Csernansky, J.G., Wang, L., 2021. Basal ganglia shape features differentiate schizoaffective disorder from schizophrenia. Psychiatry Res. Neuroimaging 317, 111352.

Csernansky, J.G., Wang, L., Jones, D., Rastogi-Cruz, D., Posener, J.A., Heydebrand, G., Miller, J.P., Miller, M.I., 2002. Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. Am. J. Psychiatry 159 (2000), 2006.

Csernansky, J.G., Wang, L., Joshi, S.C., Ratnanather, J.T., Miller, M.I., 2004. Computational anatomy and neuropsychiatric disease: probabilistic assessment of variation and statistical inference of group difference, hemispheric asymmetry, and time-dependent change. NeuroImage 23 (Suppl. 1), S56 68.

Davidson, L.L., Heinrichs, R.W., 2003. Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis. Psychiatry Res. Neuroimaging 122 (69), 87.

Duff, M.C., Brown-Schmidt, S., 2012. The hippocampus and the flexible use and processing of language. Front. Hum. Neurosci. 6, 69.

Eack, S.M., Hogarty, G.E., Cho, R.Y., Prasad, K.M.R., Greenwald, D.P., Hogarty, S.S., Keshavan, M.S., 2010. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch. Gen. Psychiatry 67 (674), 682.

Emch, M., von Bastian, C.C., Koch, K., 2019. Neural correlates of verbal working memory: an fMRI meta-analysis. Front. Hum. Neurosci. 13, 180.

Erp, T.van, Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D. W., Cannon, D.M., Corvin, A., Machielsen, M.W.J., Koenders, L., Haan, L.de, Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., Haren, N. E.M.van, Pol, H.E.Hulshoff, Pol, H.E.H., Ophoff, R.A., Kahn, R.S., Roiz-Santiáñez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jönsson, E.G., Dimitrova, R., Bois, C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P.M., Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol. Psychiatry 21, 547–553.

First, M.B., Gibbon, M., Spitzer, R.L., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders-Research Version. Biometrics Research, New York.

Grenander, U., Miller, M.I., 1998. Computational anatomy: an emerging discipline. Q. Appl. Math. 56, 617–694.

Guo, X., Li, J., Wang, J., Fan, X., Hu, M., Shen, Y., Chen, H., Zhao, J., 2014. Hippocampal and orbital inferior frontal gray matter volume abnormalities and cognitive deficit in treatment-naive, first-episode patients with schizophrenia. Schizophr. Res. 152, 339–343.

Gutman, B.A., van Erp, T.G.M., Alpert, K., Ching, C.R.K., Isaev, D., Ragothaman, A., Jahanshad, N., Saremi, A., Zavaliangos-Petropulu, A., Glahn, D.C., Shen, L., Cong, S., Alnæs, D., Andreassen, O.A., Doan, N.T., Westlye, L.T., Kochunov, P., Satterthwaite, T.D., Wolf, D.H., Huang, A.J., Kessler, C., Weideman, A., Nguyen, D., Mueller, B.A., Faziola, L., Potkin, S.G., Preda, A., Mathalon, D.H., Bustillo, J., Calhoun, V., Ford, J.M., Walton, E., Ehrlich, S., Ducci, G., Banaj, N., Piras, Fabrizio, Piras, Federica, Spalletta, G., Canales-Rodríguez, E.J., Fuentes-Claramonte, P., Pomarol-Clotet, E., Radua, J., Salvador, R., Sarró, S., Dickie, E.W., Voineskos, A., Tordesillas-Gutiérrez, D., Crespo-Facorro, B., Setién-Suero, E., van Son, J.M., Borgwardt, S., Schönborn-Harrisberger, F., Morris, D., Donohoe, G., Holleran, L.,

Cannon, D., McDonald, C., Corvin, A., Gill, M., Filho, G.B., Rosa, P.G.P., Serpa, M.H., Zanetti, M.V., Lebedeva, I., Kaleda, V., Tomyshev, A., Crow, T., James, A., Cervenka, S., Sellgren, C.M., Fatouros-Bergman, H., Agartz, I., Howells, F., Stein, D. J., Temmingh, H., Uhlmann, A., de Zubicaray, G.I., McMahon, K.L., Wright, M., Cobia, D., Csernansky, J.G., Thompson, P.M., Turner, J.A., Wang, L., 2021. A meta-analysis of deep brain structural shape and asymmetry abnormalities in 2,833 individuals with schizophrenia compared with 3,929 healthy volunteers via the ENIGMA Consortium. Hum. Brain Mapp. 43, 352–372.

Hanko, V., Apple, A.C., Alpert, K.I., Warren, K.N., Schneider, J.A., Arfanakis, K., Bennett, D.A., Wang, L., 2019. In vivo hippocampal subfield shape related to TDP-43, amyloid beta, and tau pathologies. Neurobiol. Aging 74 (171), 181.

Harvey, P.D., Aslan, M., Du, M., Zhao, H., Siever, L.J., Pulver, A., Gaziano, J.M., Concato, J., 2016. Factor structure of cognition and functional capacity in two studies of schizophrenia and bipolar disorder: implications for genomic studies. Neuropsychology 30, 28–39.

Kambeitz-Ilankovic, L., Meisenzahl, E.M., Cabral, C., von Saldern, S., Kambeitz, J., Falkai, P., Möller, H.-J., Reiser, M., Koutsouleris, N., 2016. Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification. Schizophr. Res. 173, 159–165.

Kaneda, Y., Jayathilak, K., Meltzer, H.Y., 2009. Determinants of work outcome in schizophrenia and schizoaffective disorder: role of cognitive function. Psychiatry Res. 169, 178–179.

Karpouzian, T.M., Schroeder, M.P., Abram, S.V., Wanar, H., Alden, E.C., Eack, S.M., Csernansky, J.G., Smith, M.J., 2017. Neural correlates of preserved facial affect perception in high functioning schizophrenia. Psychiatry Res. Neuroimaging 266 (83), 85.

Khan, A.R., Wang, L., Beg, M.F., 2008. FreeSurfer-initiated fully-automated subcortical brain segmentation in MRI using Large Deformation Diffeomorphic Metric Mapping. NeuroImage 41 (735), 746.

Luo, H., Zhao, Y., Fan, F., Fan, H., Wang, Y., Qu, W., Wang, Z., Tan, Y., Zhang, X., Tan, S., 2021. A bottom-up model of functional outcome in schizophrenia. Sci. Rep. UK 11, 7577.

Mamah, D., Wang, L., Barch, D.M., de Erausquin, G.A., Gado, M., Csernansky, J.G., 2007. Structural analysis of the basal ganglia in schizophrenia. Schizophr. Res. 89 (59), 71.

Mamah, D., Harms, M.P., Wang, L., Barch, D.M., Thompson, P., Kim, J., Miller, M.I., Csernansky, J.G., 2008. Basal ganglia shape abnormalities in the unaffected siblings of schizophrenia patients. Biol. Psychiatry 64 (111), 120.

Mamah, D., Alpert, K.I., Barch, D.M., Csernansky, J.G., Wang, L., 2016. Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. Neuroimage Clin. 11 (276), 286.

Mausbach, B.T., Harvey, P.D., Goldman, S.R., Jeste, D.V., Patterson, T.L., 2007. Development of a brief scale of everyday functioning in persons with serious mental illness. Schizophr.Bull. 33, 1364–1372.

Miller, M.L., Strassnig, M.T., Bromet, E., Depp, C.A., Jonas, K., Lin, W., Moore, R.C., Patterson, T.L., Penn, D.L., Pinkham, A.E., Kotov, R.A., Harvey, P.D., 2021. Performance-based assessment of social skills in a large sample of participants with schizophrenia, bipolar disorder and healthy controls: correlates of social competence and social appropriateness. Schizophr. Res. 236, 80–86.

Olabi, B., Ellison-Wright, I., McIntosh, A.M., Wood, S.J., Bullmore, E., Lawrie, S.M., 2011. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol. Psychiatry 70.

Patterson, T.L., Moscona, S., McKibbin, C.L., Davidson, K., Jeste, D.V., 2001. Social skills performance assessment among older patients with schizophrenia. Schizophr. Res. 48, 351–360.

Prasad, K.M.R., Sahni, S.D., Rohm, B.R., Keshavan, M.S., 2005. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. Psychiatry Res. Neuroimaging 140, 147–155.

Schneider, L.C., Struening, E.L., 1983. SLOF: a behavioral rating scale for assessing the mentally ill. Soc. Work. Res. Abstr. 19, 9–21.

Shepherd, A.M., Laurens, K.R., Matheson, S.L., Carr, V.J., Green, M.J., 2012. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci. Biobehav. Rev. 36, 1342–1356.

Smith, M.J., Cobia, D.J., Wang, L., Alpert, K.I., Cronenwett, W.J., Goldman, M.B., Mamah, D., Barch, D.M., Breiter, H.C., Csernansky, J.G., 2014. Cannabis-related working memory deficits and associated subcortical morphological differences in healthy individuals and schizophrenia subjects. Schizophr.Bull. 40, 287–299.

Staal, W., Pol, H.H., Schnack, H., Hoogendoorn, M., Jellema, K., Kahn, R., 2000. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. Am. J. Psychiatry 157 (416), 421.

Steullet, P., 2020. Thalamus-related anomalies as candidate mechanism-based biomarkers for psychosis. Schizophr. Res. 226, 147–157.

Subramaniam, K., Luks, T.L., Garrett, C., Chung, C., Fisher, M., Nagarajan, S., Vinogradov, S., 2014. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. NeuroImage 99 (281), 292.

Tregellas, J.R., Smucny, J., Harris, J.G., Olincy, A., Maharajh, K., Kronberg, E., Eichman, L.C., Lyons, E., Freedman, R., 2014. Intrinsic hippocampal activity as a biomarker for cognition and symptoms in schizophrenia. Am. J. Psychiatry 171, 549–556.

Tully, L.M., Lincoln, S.H., Liyanage-Don, N., Hooker, C.I., 2014. Impaired cognitive control mediates the relationship between cortical thickness of the superior frontal gyrus and role functioning in schizophrenia. Schizophr. Res. 152, 358–364.

Twamley, E.W., Vella, L., Burton, C.Z., Heaton, R.K., Jeste, D.V., 2012. Compensatory cognitive training for psychosis: effects in a randomized controlled trial. J. Clin. Psychiatry 73 (1212), 1219.

Vernon, A.C., Natesan, S., Crum, W.R., Cooper, J.D., Modo, M., Williams, S.C.R., Kapur, S., 2012. Contrasting effects of haloperidol and lithium on rodent brain structure: a magnetic resonance imaging study with postmortem confirmation. Biol. Psychiatry 71, 855–863.

Vita, A., Peri, L.D., Barlati, S., Cacciani, P., Deste, G., Poli, R., Agrimi, E., Cesana, B.M., Sacchetti, E., 2011. Effectiveness of different modalities of cognitive remediation on symptomatological, neuropsychological, and functional outcome domains in schizophrenia: a prospective study in a real-world setting. Schizophr. Res. 133, 223–231.

Wang, L., Mamah, D., Harms, M.P., Karnik, M., Price, J.L., Gado, M.H., Thompson, P.A., Barch, D.M., Miller, M.I., Csernansky, J.G., 2008. Progressive deformation of deep brain nuclei and hippocampal-amygdala formation in schizophrenia. Biol. Psychiatry 64, 1060–1068.

Wechsler, D., 1997. Wechsler Adult Intelligence Scale, Third edition. The Psychological Corporation.

Wible, C.G., 2013. Hippocampal physiology, structure and function and the neuroscience of schizophrenia: a unified account of declarative memory deficits, working memory deficits and schizophrenic symptoms. Behav. Sci. 3, 298–315.

de Wit, S., Wierenga, L.M., Oranje, B., Ziermans, T.B., Schothorst, P.F., van Engeland, H., Kahn, R.S., Durston, S., 2016a. Brain development in adolescents at ultra-high risk for psychosis: longitudinal changes related to resilience. Neuroimage Clin. 12, 542–549.

de Wit, S., Ziermans, T.B., Nieuwenhuis, M., Schothorst, P.F., van Engeland, H., Kahn, R. S., Durston, S., Schnack, H.G., 2016b. Individual prediction of long-term outcome in adolescents at ultra-high risk for psychosis: applying machine learning techniques to brain imaging data. Hum. Brain Mapp. 38, 704–714.

Wojtalik, J.A., Smith, M.J., Keshavan, M.S., Eack, S.M., 2017. A systematic and meta-analytic review of neural correlates of functional outcome in schizophrenia. Schizophr.Bull. 43, 1329–1347.

Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W.R., David, A.S., Murray, R.M., Bullmore, E. T., 2000. Meta-analysis of regional brain volumes in schizophrenia. Am. J. Psychiatry 157 (16), 25.