Schizophrenia

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Altered white matter microstructure of language pathways and semantic cognition deficiencies in early psychosis

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Semantic language dysfunction is a hallmark of early psychosis, yet the underlying brain structural correlates are largely unexplored. In particular, it is unclear whether core deficits arise from disruptions to semantic representation, which refers to the stored knowledge of word meanings, or to semantic control, which entails top-down mechanisms that guide the retrieval and selection of context-appropriate semantic information. By dissociating semantic representation-related from semantic control-related performance, we aimed to identify the preferential impairment in early psychosis and its structural correlates in the ventral and dorsal language streams. We investigated $N = 120$ individuals across the psychosis spectrum: $N = 40$ individuals with early psychosis, $N = 40$ individuals with high schizotypy, and $N = 40$ individuals with low schizotypy. Participants with high and low schizotypy constituted the non-clinical comparison group. All participants completed tasks designed to isolate semantic representation-related and semantic control-related processes. Given the importance of accurate delineation, this study employed meticulous manual fiber tractography of diffusion tensor imaging (DTI) data to ensure reliable evaluation of ventral and dorsal pathway microstructure. Compared to individuals with high and low schizotypy, individuals with early psychosis showed pronounced deficits in semantic control-related performance, while the semantic representation-related measure remained largely intact. Mean diffusivity in the left inferior fronto-occipital fasciculus and left uncinate fasciculus was lower in the early psychosis group than in individuals with schizotypy. In the early psychosis group, fractional anisotropy in the left arcuate fasciculus was negatively correlated with semantic control-related performance, but no DTI measure was associated with the semantic representation-related measure. These results underscore semantic control-related performance as a core deficit in early psychosis and extend the conventional view that semantic processing is subserved primarily by ventral pathways. The arcuate fasciculus appears implicated in semantic control-related processes, indicating a more integrated interplay of dorsal and ventral streams in semantic language processing.

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INTRODUCTION

Semantic processing abnormalities manifest clinically as formal thought disorder as well as delusional phenomena and are considered core clinical features of schizophrenia[1–3]. Similar, albeit milder, semantic disruptions have been described in non-psychotic first-degree relatives of psychotic patients and individuals with schizotypy[4–6]. Schizotypy refers to a constellation of personality traits thought to arise from a similar combination of genetic, neurodevelopmental, and psychosocial factors as schizophrenia, placing schizotypy on a continuum with the disorder[6]. In schizophrenia-spectrum disorders, residual thought disorder often persists even during remission[7], and semantic-processing abnormalities are associated with social-functioning deficits[8], underscoring their central role in the disorder. Previous studies demonstrated that semantic-processing abnormalities in schizophrenia-spectrum disorders are reflected in disrupted functional coordination within semantic brain networks, including reduced small-world network organization and deficient inhibition of spreading activation[9–11]. Evidence additionally suggests that structural white matter pathway organization is linked to semantic processing abnormalities in schizophrenia[12].

Recent research indicates that formal thought disorder and delusions in schizophrenia correlate with altered white matter microstructure in the left dorsal language stream as well as in the left ventral language stream[13–16]. Moreover, altered microstructure of ventral language stream pathways has been linked to subclinical cognitive-perceptual (positive) symptoms of schizotypy in a multimodal lesion-mapping study[17]. During awake surgery, direct electrical stimulation of the inferior fronto-occipital fasciculus (IFOF), a principal component of the ventral language stream, elicits semantic paraphasias (using different but related words instead of intended ones) and impairs nonverbal semantic association tasks[18–20]. These observations underscore the essential role of the IFOF in semantic processing and suggest that alterations in this pathway could contribute to semantic anomalies in schizophrenia-spectrum disorders. Consistent with this idea, white matter microstructure of the ventral language stream, particularly the left IFOF, has been shown to be associated with semantic processing deficits in schizophrenia[21]. However, deficits in semantic processing may arise from disruptions in two complementary facets of meaning processing: semantic representation and semantic control[22]. Semantic representation refers

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to stored knowledge about words and concepts, encompassing the fundamental meanings that accumulate over a lifetime[23]. In contrast, semantic control involves the goal-directed retrieval, selection, and integration of relevant semantic information from these stores, while inhibiting competing or irrelevant associations[22]. For example, whereas an intact semantic representation allows an individual to know that a "palm" can refer to both a part of the hand and a type of tree, semantic control determines which meaning is contextually appropriate when the individual hears the word "palm" in conversation. Recent studies using spectral dynamic causal modeling (DCM) primarily suggest impaired semantic control in psychosis, characterized by aberrant fronto-temporal regulation of semantic activation and contextual processing[24,25]. While further insights into the organization of semantic representation and control have emerged from neurology and neurosurgery[26], their precise structural correlates remain poorly understood, particularly within schizophrenia-spectrum disorders. The white matter pathways that support semantic representation and control-related performance are thought to be principally located within the ventral language stream, which includes both an indirect route comprising the inferior longitudinal fasciculus (ILF) and the uncinate fasciculus (UF), and a direct route via the IFOF[27].

The present study aims to clarify how perisylvian white matter microstructure relates to specific dimensions of semantic cognition, namely, semantic representation-related and semantic control-related performance, in individuals with early psychosis. We hypothesized that deficits in semantic representation and control-related performance are associated with altered white matter microstructure of ventral language stream components, thereby illuminating the neural characteristics of language disturbances commonly observed in the early stages of schizophrenia-spectrum disorders.

MATERIAL AND METHODS

Subjects

As part of the VELAS (Ventral language stream in schizophrenia with regard to semantic and visuo-spatial processing anomalies) study[28–30], 12 female and 28 male (total $N = 40$) early psychosis patients and 41 female and 39 male (total $N = 80$) individuals with high ($N = 40$) and low ($N = 40$) schizotypy, matched for age and education, were included in this study. Early psychosis was defined as no more than five years since the first psychotic episode. This time frame was chosen to minimize confounds from illness chronicity and prolonged antipsychotic exposure and to examine language-network alterations closer to illness onset[31]. Subjects were recruited from the inpatient and outpatient departments of the Psychiatric Hospital of the University of Zurich, Switzerland. Patients fulfilled the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria for a psychotic disorder: schizophrenia (F20; $N = 22$), acute and transient psychotic disorder (F23; $N = 10$), schizoaffective disorder (F25; $N = 5$), recurrent depressive disorder or current episode severe with psychotic symptoms (F33.3; $N = 3$). Individuals with schizotypy were recruited through an online pre-assessment, which was spread over different platforms and noticeboards of Swiss universities and colleges, common Swiss public platforms, a mailing list of students of psychology, tweets by the research team and direct contact of different schools and educational institutions of various levels. For the pre-assessment, an online schizotypy screening ($N = 1062$) was conducted using the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)[32] and Multidimensional Schizotypy Scale (MSS)[33]. Using model-based clustering (mclust in R) according to Scrucca et al.[34], we identified five (MSS) and four (O-LIFE) schizotypy clusters. Using the predict.Mclust function[34], we determined which cluster each of the 40 patients would most likely belong to based on their schizotypy scores. This showed that all patients would most likely belong to MSS clusters 3–5 and O-LIFE clusters 2–4, i.e., clusters with higher schizotypy scores. 40 healthy controls from the same clusters, i.e., matching the patients in schizotypy (in addition to age and education), were selected for the "high schizotypy" group. 40 healthy controls from MSS clusters 1–2 and O-LIFE cluster 1, i.e., with lower schizotypy scores (matching the patients in age and education) were selected for the "low schizotypy" group. To be included, all subjects had to be aged 14 – 40 years and right-handed as determined by the short form of the Edinburgh handedness inventory[35]. The a priori age window was chosen to capture late adolescence through early to mid-adulthood, when risk for first-episode psychosis is highest, while avoiding older ages in which age-related white-matter decline accelerates. Although recruitment targeted ages 14–40 years, the analyzed sample spanned 17–39 years. This range lies within a period of relative white-matter stability, after the marked developmental increases of adolescence and before the accelerated declines that typically begin after age 50[36]. To account for developmental effects within this range, age was included as a continuous covariate in all primary models. Participants aged 14–17 years were not represented in the analyzed sample, and inclusion of this band would likely have introduced greater developmental confounding. Participants with a current substance use disorder (excluding nicotine) were excluded. Exclusion criteria also included past or current neurological or ophthalmological disorders, history of head trauma with concurrent loss of consciousness, and current pregnancy. Exclusion criteria limited to control subjects were a history of any psychiatric disorder. All language assessments were administered in German, and fluency in German as well as German as a native language were therefore required inclusion criteria. All but 6 patients were under antipsychotic pharmacotherapy. All participants provided written informed consent, the ethics committee of Kantonale Ethikkommission Zürich gave ethical approval for this work (KEK-ZH 2020/01049), and the study adhered to the Declaration of Helsinki.

Behavioral data acquisition

Symptom assessments. Assessment of schizophrenia psychopathology was conducted on the day of testing and included the O-LIFE[32], MSS[33], and Positive and Negative Syndrome Scale (PANSS)[37], which were administered to all participants in all three groups.

Neuropsychological assessments. Participants completed a picture naming task (DO80) to assess neuropsycholinguistic impairment[38]. On the DO80 picture-naming test, we quantified paraphasias, defined as erroneous word productions during speech or naming. We distinguished semantic paraphasias (substituting a word with a related meaning; e.g., 'knife' for 'fork') from phonemic paraphasias (sound-based errors; e.g., 'bork' for 'fork')[39]. Additionally, we applied the multiple-choice word test (MWT-B), which samples crystallized vocabulary under low competition demands, to evaluate semantic representation-related performance[40]. Verbal fluency tasks[41,42] as well as the Camel and Cactus Test (CCT), which requires matching an image with a matching image from a selection of four images based on their semantic association, to measure semantic control-related performance[43]. Category verbal fluency and the Camel and Cactus Test (CCT) place demands on top-down, context-guided retrieval and selection among competing semantic representations, rather than straightforward knowledge access, thereby emphasizing the control component of semantic cognition. In the CCT, participants select the context-appropriate associate while suppressing irrelevant competitors, and in category verbal fluency, they strategically search semantic memory, cluster related items, shift between clusters, and inhibit

repetitions or off-category responses[22,43,44]. Visual stimuli for the CCT were generated on a screen using custom scripts based on the PsychoPy software suite[45]. In our PsychoPy implementation of the Camel-and-Cactus Test (CCT), each trial began with a one-second central white fixation cross, after which the CCT target image display appeared and remained onscreen until the participant responded via keypress, then the next trial commenced. Each trial presented a target image at the top center and four candidate associates below in a 2 × 2 grid (Supplementary Fig. 1). One option was the correct semantic associate, and three were foils matched on basic category. The position of the correct option was counterbalanced across the four locations, and trial order (3 practice items, 64 test items) was randomized. For the CCT, outcome measures were accuracy (number of correct selections) and response time per trial. For category fluency, the outcome measure was the total number of correct items generated in 60 seconds, and repetitions as well as off-category responses were excluded. It is important to note that performance on verbal fluency tasks and CCT engages executive control, processing speed, and attention in addition to semantic control, and performance on the MWT-B primarily reflects crystallized vocabulary. Accordingly, these tasks provide proxy measures rather than process-pure indices of semantic control and semantic representation. Importantly, we controlled for the effects of executive functions, processing speed, and attention, which have been shown to be relevant for semantic processing[46] and were therefore included as covariates in all behavioral tests. These were assessed using the Victoria Stroop[47], the Trail Making Test (TMT) A and B[48], as well as the digit span forward and backward[49].

MRI data acquisition. Imaging was performed on a Philips Achieva 3.0 T magnetic resonance scanner with a 32-channel SENSE head coil (Philips, Best, The Netherlands). 3D-T1-weighted images with a voxel resolution of $1mm^3$ as well as diffusion weighted imaging (DWI) with 64 non-collinear directions (3000 s/mm^2) and one b0 (0 s/mm^2), were acquired with a voxel resolution of 1.96 × 1.96 x 2 mm^3.

Diffusion tensor imaging. We used DWI to perform diffusion tensor imaging (DTI). First, we used HD-BET, a high-quality deep learning based algorithm, for brain extraction using the T1-weighted images[50]. Second, for the computation of the diffusion tensor out of DWI, we used ExploreDTI 4.8.6[51]. We applied a subject motion and distortion correction to DWI data (reference volume: b0 image). Second, we warped the resulting data to the brain-extracted T1 volumes using an EPI correction[52]. We performed whole-brain deterministic tractography with a diffusion tensor model[53]. Tract termination criteria were set to fractional anisotropy < 0.2 and tract angle > 45 degrees.

Manual tractography. For the segmentation of specific bilateral tracts, manual tractography was performed. We used region-of-interest (ROI) masks for the selection of specific fibers of the whole brain DTI dataset.

To reconstruct the arcuate fasciculus (AF) (Fig. 2a), the first ROI was positioned around the deep white matter at the fronto-parietal junction, where the AF appears as a green layer in the coronal plane of the directionally encoded tensor (DET) map, situated laterally to the blue fibers of the corona radiata. The second ROI is placed around the descending segment of the superior longitudinal fasciculus in the posterior temporal lobe, visible as a blue structure lateral to the splenium of the corpus callosum in the transverse plane of the DET map[54].

To track the IFOF (Fig. 2b), the first ROI is placed around the entire frontal lobe on a coronal slice at the level of the precentral sulcus. The second coronal ROI is positioned to encompass the entire hemisphere at the junction of the parieto-occipital and calcarine sulci, identified on the mid-coronal slice, following the approach of Smits et al.[54] with slight modifications.

The UF (Fig. 2d) is tracked by selecting the most posterior coronal slice where the temporal lobe is distinct from the frontal lobe. The first ROI encompasses the entire temporal lobe, while the second ROI includes the full set of projections toward the frontal lobe, appearing green on the DET map[55].

To track the ILF (Fig. 2c), the first ROI is positioned within the white matter of the anterior temporal lobe, just anterior to the temporal horn of the ventricular system. The second ROI is placed in the coronal plane at the level of the preoccipital notch[56].

To track the corticospinal tract (CST), the first transversal ROI was placed at the level of the pons, with the identification of CST (Fig. 2e) fibers facilitated by the DET map, where the pyramidal tract appears blue. The second ROI was positioned in the axial plane around the precentral gyrus, at the base of the precentral and central sulci[57].

After generating the fiber tracts based on the described ROIs, we manually removed fibers that belonged to neighboring fiber systems using carefully placed regions of avoidance. Finally, mean values of fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity were extracted from reconstructed tracts using in-house software.

Statistical analysis. Group comparisons of white-matter fiber pathways and behavioral test outcomes used ordinary least squares linear regression, and all models were adjusted for age, sex, education, attention, processing speed, and executive function. Coefficients within models were compared using Wald tests, and coefficients between models were compared using seemingly unrelated estimation adjusted as above. Group comparisons of semantic processing were conducted using random-effects multinomial logistic regression models, adjusted as above, reporting relative-risk ratios (RRR). Response latencies were assessed using multilevel mixed-effects linear regression models with a clustered sandwich estimator, adjusted as above. The association between white matter microstructure and impairments in semantic processing was analyzed using negative binomial regression models, reporting incidence-rate ratios (IRR) and random-effects multinomial logistic regression models, as appropriate and as adjusted as above. Coefficients between models were compared using seemingly unrelated estimation adjusted as above. All tests were performed using Stata version 18 (StatCorp, Texas). Estimates were considered statistically significant when $p < 0.05$. Unless otherwise stated, two-tailed hypothesis testing was used, and unadjusted p values were reported.

RESULTS

Demographic and global brain measures

Table 1 summarizes the demographic characteristics and clinical data for individuals with psychosis as well as for individuals with low and high schizotypy. Compared to controls, the patient group included a higher percentage of males, although this difference was not statistically significant (chi2 = 5.34, $p = 0.07$). There was also no significant difference in age between the groups (ANOVA: $F = 2.94$, $p = 0.06$). Compared with individuals with low and high schizotypy, the early psychosis group showed higher PANSS Total and Positive, Negative, and General subscale scores (Welch's unequal-variance t-tests; early psychosis vs low and vs high schizotypy: $t > 6.5$, $p < 5 \times 10^{-8}$ in each case). All bilingual participants completed testing in German (a native language for all). One participant each reported Dutch, Swahili, Italian, Brazilian Portuguese, or Albanian as their other native language, and the remainder reported English. Behavioral data for different language tasks is presented in Supplementary Table 1.

Table 1. Sample Characteristics.

	Low schizotypy ($n = 40$)	High schizotypy ($n = 40$)	Patient ($n = 40$)
Sex, *n* (%)			
Female	22 (55)	19 (47.5)	12 (30)
Male	18 (45)	21 (52.5)	28 (70)
Age [years], *M* (*SD*)	25.1 (3.8)	27.5 (4.6)	27.2 (5.7)
Education, *n*			
Secondary School	0	0	8
Vocational Training	11	10	17
Higher Vocational Training	3	2	0
Baccalaureate ("Matura")	11	9	3
University (Bachelor's, incl. Applied Sciences)	11	12	5
University (Master's / Doctorate)	4	7	7
First language, *n* (%)			
German	31 (77.5)	–	7 (17.5)
Bilingual	8 (20)	–	–
Other	1 (2.5)	–	31 (77.5)
Diagnosis, *n* (%)			
Schizophrenia (F20)	–	–	22 (55)
Acute and transient psychotic disorder (F23)	–	–	10 (25)
Schizoaffective disorder (F25)	–	–	5 (12.5)
Recurrent depressive disorder with severe psychotic symptoms (F33.3)	–	–	3 (7.5)
Age onset [years], *M* (*SD*)	–	–	26.2 (7.1)
Duration of illness [weeks], *M* (*SD*)	–	–	128.6 (119.7)
No. of episodes, *n* (%)			
1	–	–	22 (55)
2	–	–	12 (30)
3	–	–	5 (12.5)
4	–	–	1 (2.5)
Type of antipsychotic therapy, *n* (%)			
None	40 (100)	40 (100)	6 (15)
Current antipsychotic monotherapy	–	–	27 (67.5)
Current intake of 2 antipsychotics	–	–	7 (17.5)
Duration of antipsychotic medication [weeks], *M* (*SD*)	–	–	56.9 (88.5)
PANSS Total	32.13 (5.36)	32.75 (3.66)	61.73 (14.7)
PANSS Positive	7.4 (1.6)	8.15 (1.49)	14.18 (5.61)
PANSS Negative	8.1 (1.75)	7.58 (0.81)	17.08 (6.07)
PANSS General	16.63 (2.77)	17.03 (2.42)	30.48 (6.75)

Group comparisons of semantic processing

Individuals with early psychosis showed significantly more semantic and phonemic paraphasias in the DO80 than both schizotypy controls (RRR 1.419, 95% CI [1.143, 1.762], $p = 0.002$ and 4.448, [1.523, 12.990], $p = 0.006$, respectively), as calculated with random-effects multinomial logistic regression models. With regard to semantic representation-related performance, there was no difference between individuals with early psychosis and with schizotypy (Fig. 1). By contrast, there were significant differences with regard to semantic control-related performance, where patients with early psychosis named significantly fewer items within one minute than schizotypy controls in the domains clothing and food (clothing: IRR: 0.832, 95% CI: 0.75, 0.922, $p < 0.001$; food: IRR: 0.899, 95% CI: 0.815, 0.991, $p = 0.03$) but not in the domain animals (Fig. 1). In the CCT, patients showed a significantly longer response latency than schizotypy controls (1.295, 95% CI [0.682, 1.908], $p < 0.001$). This increased response latency was more pronounced compared with controls with low schizotypy (1.517, 95% CI [0.882, 2.152], $p < 0.001$).

Group comparisons of white matter fiber pathways

DTI metrics on ventral and dorsal language streams are shown in Supplementary figs. 2 and 3 and language-related white matter pathways investigated with manual fiber tractography are illustrated in Fig. 2. With regard to the ventral language stream, early psychosis patients had lower mean diffusivity than controls with regard to the left IFOF (−0.486 standard deviation, 95% CI [−0.913, −0.058], $t = -2.251$, $p = 0.026$) and the left UF (−0.796 standard deviation, 95% CI [−1.199, −0.392], $t = -3.909$, $p < 0.001$) as calculated by regression models of the mean diffusivity adjusted for age, gender, education, attention, and executive functions. The difference between early psychosis and high schizotypy was significantly greater than between early psychosis and low schizotypy for the left UF ($F = 4.895$, $p = 0.029$) as established by a Wald test. Although no significant results were found in relation to the left AF per se, there were no significant differences of the mean diffusivity measures between the IFOF and the AF. In contrast, there was a significant difference in mean diffusivity measures between the UF and the AF (chi2(1) = 4.15,

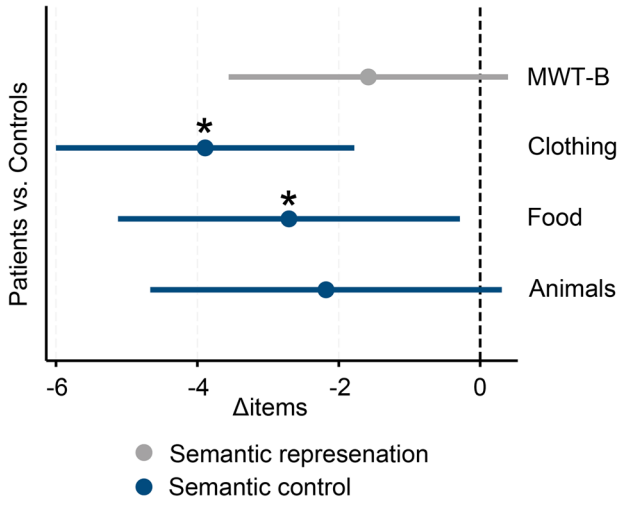

Fig. 1 Group differences in semantic representation and control-related performance between individuals with early psychosis and schizotypy. The semantic representation-related measure did not differ significantly between groups. However, individuals with early psychosis exhibited significantly reduced semantic control-related performance compared to schizotypy controls, as reflected in fewer items named within one minute in the clothing and food domains, but not in the animal domain. Differences shown are average marginal effects based on estimates from negative binomial regression models reported above. Error bars represent 95% confidence intervals. Asterisks indicate $p < 0.05$.

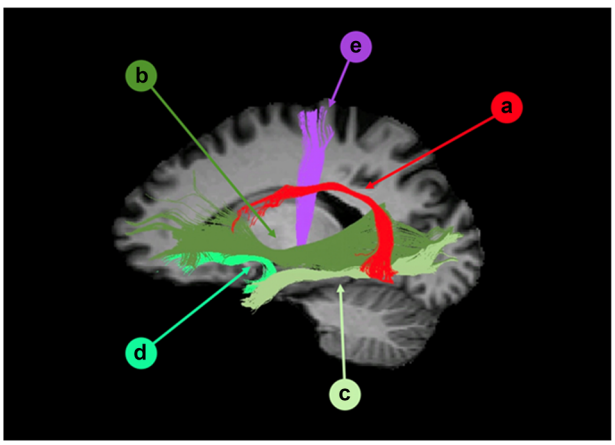

Fig. 2 DTI-based manual fiber tractography of language-related white matter pathways. Results from one representative individual with early psychosis are illustrated (left lateral view). Language processing mainly relies on a dual-stream architecture: a dorsal stream – including the arcuate fasciculus (**a**) – and a ventral stream. The latter depends on a direct pathway, the inferior fronto-occipital fasciculus (**b**), and an indirect pathway, formed by the inferior longitudinal fasciculus (**c**) and uncinate fasciculus (**d**). The corticospinal tract (**e**) is also shown.

$p = 0.042$), as found with seemingly unrelated estimation adjusted as above. No significant group differences were found with regard to the CST.

Association of tract microstructure with impairments in semantic processing

Diffusion measures fractional anisotropy and mean diffusivity of the tracts examined showed no significant ($p < 0.05$) association with the semantic representation-related measure either within the patient group or within the control group. In contrast, fractional anisotropy measures were negatively associated with verbal fluency as measured with naming items within one minute with regard to the left AF (clothing: IRR 0.911, 95% CI [0.842, 0.956], $p = 0.022$; animal: IRR 0.896, 95% CI [0.821, 0.978], $p = 0.014$) in early psychosis patients, using negative binomial regression models as appropriate and as adjusted as above (Fig. 3a, b).

No significant correlations between IFOF, UF or ILF and semantic fluency were found in patients with psychosis. Furthermore, in this group, the majority of differences in the associations of fractional anisotropy measures (IFOF, UF, ILF, and AF) with semantic fluency were not significant. Exceptions were AF vs. ILF in relation to clothing and animal naming, where significant differences were found (chi2(1) = 5.80, $p = 0.016$ and chi2(1) = 5.35, $p = 0.021$ respectively), as established with seemingly unrelated estimation adjusted as above. No significant group differences were found regarding the corticospinal tract.

DISCUSSION

Our study provides novel insights into the neural and behavioral aspects of semantic processing in early psychosis. By separating semantic representation-related from semantic control-related performance and linking these to DTI measures of language stream components, our findings advance the understanding of semantic processing in psychosis. Importantly, this study employed the meticulous procedure of manual fiber tractography on DTI data to reliably assess the integrity of ventral and dorsal pathways.

Individuals with early psychosis showed impairments in semantic control-related performance, such as reduced verbal fluency and longer response times in a semantic association task, compared to individuals with schizotypy. Adjusting for executive function, processing speed, and attention suggests that these deficits extend beyond general cognitive impairments, highlighting a distinct disruption in semantic control-related performance. Because attention, processing speed, and executive function are broadly impaired in psychosis[41] and overlap with semantic control, fully disentangling semantic-control deficits from general cognitive impairments is difficult, even though our covariate adjustment likely removes shared variance with the target processes. Our findings of impaired verbal fluency and prolonged response latencies in schizophrenia are consistent with previous reports in the literature[58–60]. However, we found no significant differences in semantic representation-related performance between the groups, suggesting that a primary challenge in early psychosis may lie in handling and manipulating semantic information[61,62]. Because semantic control supports lexical selection, suppression of competitors, and context-appropriate meaning[22], this disturbance is expected to generalize to everyday language use and contribute to disturbances commonly observed in psychosis, including reduced spontaneous fluency and incoherence. Clinically, this profile suggests that remediating communication difficulties in early psychosis may require interventions that strengthen semantic control, for example, by training retrieval strategies and error monitoring in connected speech.

In our DTI analysis, we observed reduced mean diffusivity for the left IFOF and left UF in individuals with early psychosis compared to individuals with schizotypy. This finding was unexpected and contrasts with prior studies reporting increased mean diffusivity in ventral language stream components of psychosis patients[21,63]. However, it aligns with recent evidence suggesting that white matter abnormalities in ventral language stream components show high variability in psychosis patients[31]. Lower mean diffusivity, as observed in this study, may reflect greater fiber density or axonal integrity, potentially driven by compensatory neurodevelopmental mechanisms during the early stages of psychosis. In contrast, reductions in fiber density,

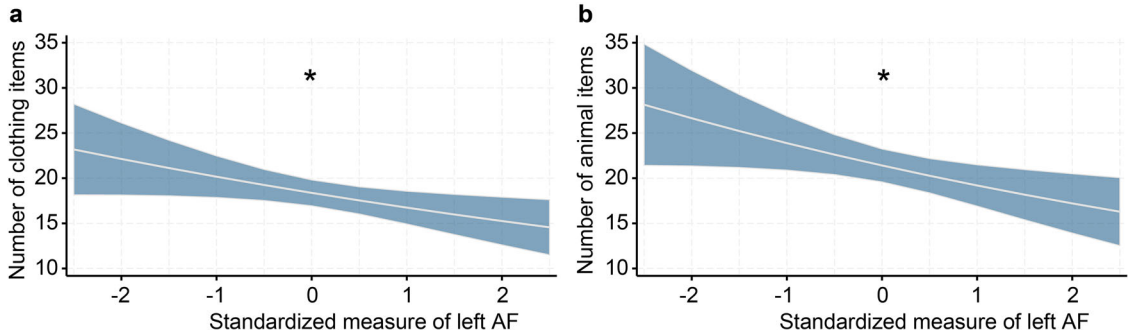

Fig. 3 Association between white matter integrity of the arcuate fasciculus and verbal fluency. a In individuals with early psychosis, fractional anisotropy of the left arcuate fasciculus was negatively associated with the number of clothing items named within one minute. **b** A similar negative association was observed for animal items. Standardized measure: z-transformed values of left AF. Shown are predictive margins based on estimates from negative binomial regression models reported above. Shaded areas represent 95% confidence intervals. $P < 0.05$.

possibly linked to excitotoxic processes[64], might become more prominent in later stages of the disorder[65]. These findings underscore the heterogeneity of psychosis and emphasize the need to account for stage-specific and individual differences when interpreting microstructural white matter alterations. Instead of serving as uniform indices of semantic processing in psychotic disorders, white-matter measures may be more useful for stage-sensitive, patient-level longitudinal monitoring of microstructural change in the language network. Combining diffusion-derived indices of white matter microstructure with myelin-sensitive macromolecular measures may thereby enhance interpretability. Prior multimodal work reported co-localized reductions in the myelin-sensitive magnetization transfer ratio and FA within the IFOF in chronic schizophrenia[66]. Although we observed no FA group difference in the IFOF, subtle myelin-sensitive abnormalities cannot be excluded because diffusion and magnetization transfer measure partially distinct tissue properties.

Interestingly, fractional anisotropy in the left AF, a key component of the dorsal language stream, was negatively correlated with verbal fluency in the early psychosis group. This association suggests that lower fractional anisotropy, typically indicative of reduced structural integrity, may mitigate dysregulation of the AF in early psychosis. A contribution of dysregulated fronto–temporal interactions via the arcuate fasciculus to semantic-control deficits would also align with recent spectral dynamic causal modeling studies that suggest aberrant fronto–temporal regulation of semantic activation and contextual processing in early psychosis[24,25]. In addition to semantic abnormalities, auditory verbal hallucinations in schizophrenia also converge on perisylvian language systems, including superior temporal and inferior frontal regions connected by the arcuate fasciculus[67]. Although both schizophrenia and schizotypy show structural and functional frontotemporal alterations, these are generally less severe in schizotypy, particularly in frontal regions[67–70]. Loss of this relatively preserved frontal capacity may intensify dysregulation of the arcuate fasciculus and, consistent with our findings, exacerbate semantic-control deficits. We speculate that this cascade promotes formal thought disorder and auditory verbal hallucinations, thereby contributing to frank psychosis, possibly via glutamatergic mechanisms linking language-network pathology across these phenomena[67].

We did not find significant correlations between ventral language stream DTI measures and semantic control-related performance, which may be attributable to the limited sample size. Interestingly, the implication of the left AF in semantic control-related performance in our early psychosis cohort suggests that semantic processing in psychosis may not be restricted to the ventral stream[71]. Our findings indicate that, within the context of psychosis, a strict anatomical separation between phonological processes (dorsal pathway) and conceptually driven language production (ventral pathway) may not exist in such a clear-cut form. This interpretation is consistent with the WEAVER++/ARC model[72], which posits that both phonological and semantic processes can be mediated through the AF and therefore do not exhibit a complete anatomical dissociation, also in psychosis. Our dorsal/ventral tract findings also align with E/I models in which microcircuit inhibitory deficits disrupt salience/executive–temporal interactions, yielding frontotemporal dysconnectivity and language disorganization[73]. Although diffusion MRI does not index E/I directly, the selective changes in semantic control relative to representation accord with this framework.

This study has several limitations. First, it is cross-sectional and cannot determine whether the observed white-matter differences between early psychosis and schizotypy are consequences of psychotic episodes or reflect pre-existing group differences. Longitudinal studies in schizotypy and early-psychosis cohorts are needed to delineate the onset and trajectory of these differences. Second, our behavioral measures are not process-pure: the VFT and CCT engage executive control, processing speed, and attention in addition to semantic control, and the MWT-B primarily indexes crystallized vocabulary rather than isolated semantic representation. Accordingly, construct-specific conclusions regarding semantic representation versus semantic control should be considered in light of this caveat. To address this limitation, we statistically accounted for the influence of executive functions, processing speed, and attention. Third, our manual tractography targeted perisylvian language pathways and did not reconstruct other association tracts, including the cingulum bundle, whose microstructure has been linked to conceptual disorganization in early psychosis[74].

Still, our findings have important implications for understanding the neural basis of language dysfunction in psychosis. By disentangling semantic representation-related from semantic control-related performance, we highlight the importance of semantic control deficits in early psychosis and their potential association with dorsal stream pathways. Future research should explore the functional dynamics of these pathways using multimodal neuroimaging approaches, such as combining functional MRI with DTI, to better understand the interplay between structural and functional alterations in language networks. Additionally, the temporal dynamics of white matter changes across different stages of psychosis and their relationship with excitotoxic and neuroinflammatory processes require further exploration.

CONCLUSION

This study advances the field by splitting semantic processing into distinct components and linking these components to specific white matter pathways. Our findings extend traditional models of semantic organization in psychosis, suggesting that semantic control may be organized not only in ventral but also in dorsal language stream components.

DATA AVAILABILITY

The datasets used and analyzed are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

W.S. and P.H. conceived and supervised the study. N. Da., A.S., P.S., G.C., and W.O. performed the experiments. R.S. performed the statistical analysis. F.S., N. Da., and P.B. contributed to the conception of the study. N. Da., W.O., D.F., A.G., R.Hü., R.Ho., N.K., P.S. contributed to the analysis of the study. N.D. and T.B. performed the DTI analyses. W.S. and W.O. wrote the first version of the manuscript and revised the manuscript. All authors contributed to the writing of the final manuscript.

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COMPETING INTERESTS

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