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Neurocognitive Deficits Mediate the Relationship Between Structural Abnormalities and Clinical Outcomes in Individuals With Ultrahigh Risk for Psychosis: A Multimodal Neuroimaging and Longitudinal Neurocognitive Study

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Background: **Cognitive deficits and improvements have been observed in individuals with ultrahigh risk for psychosis (UHR) over their clinical course, but the relationship between brain structural and functional characteristics, neurocognitive deficits and improvements, and clinical prognosis remains unclear.** ***Methods:*** **A total of 50 UHR individuals were assessed using 129 neurocognitive assessments to explore cognitive deficits and improvements over 3 years. Neurocognitive deficits (intercept) and improvements (slope) were investigated using a general linear mixed model, and their relationship with symptom severity was assessed using the Positive and Negative Syndrome Scale five factor scores. In addition, psychobiological measurements including brain structure, brain activity during a verbal fluency task, and mismatch negativity were also tested. Possible models including the paths from brain structure, brain function, neurocognitive function, and symptom severity outcomes were compared.** ***Results:*** **The intercept of verbal fluency was negatively associated with negative symptoms at baseline (corrected $P = .0001$) and at the 4-month follow-up (corrected $P = .0016$).A model including these relationships exhibited significant paths from the cortical surface area in the right banks of the superior temporal sulcus to verbal fluency ($P < .001$) and from verbal fluency to 4-month negative symptoms ($P < .001$), but not from brain activity to negative symptoms ($P = .072$).** ***Conclusion:*** **Structural and functional characteristics of the brain may not be directly associated with short-term symptom severity, and these relationships may be partly mediated by neurocognitive function.**

Key words: cognitive deficits/cognitive decline/prognosis/magnetic resonance imaging/brain activity/schizophrenia

Introduction

Cognitive impairments are a core feature of schizophrenia and manifest in various neurocognitive domains prior to the onset of psychosis.[1,2] Systematic reviews suggest that individuals with schizophrenia and ultrahigh risk for psychosis (UHR) generally present with cognitive deficits prior to onset, with no cognitive decline over the course of the illness.[1,3] Longitudinal investigations have highlighted three major patterns of cognitive deficits and decline in schizophrenia: no deficits prior to onset and no decline, no deficits but a subsequent decline, and both deficits and decline.[4,5] These patterns have also been reported in UHR individuals. A multicenter study demonstrated that neurocognitive profiles could be classified into four clusters: significantly impaired, mildly

impaired, normal, and high.[6] Of these, UHR individuals with subsequent transition to psychosis (UHR-P) exhibited similar neurocognitive deficits to those of individuals with schizophrenia, especially in verbal function domains. Conversely, UHR individuals without subsequent psychosis (UHR-NP) exhibited similar neurocognitive profiles to those of healthy controls.[1–3,7–10] In addition to psychosis onset, low baseline cognitive performance, especially in verbal function and processing speed, is associated with poor clinical outcomes in UHR individuals.[1,8–12] Longitudinal studies have indicated that cognitive performance in UHR individuals may recover in their clinical course, and changes in assessment scores are associated with social functioning.[8,9,13] Therefore, the pattern of neurocognitive alterations over the clinical course is heterogeneous and may predict prognosis.

The neural basis underpinning neurocognitive deficits and improvements in UHR individuals remains obscure. In schizophrenia, 3-year changes in IQ were negatively associated with volume changes in the lateral ventricle and positively associated with changes in cortical volume and thickness.[14] Patients with severe cognitive deterioration exhibited significantly reduced volume in the hippocampus, lingual gyrus, and superior temporal sulcus (STS) compared to putatively preserved patients.[15] Another study showed that cortical gray matter volume in the fusiform gyrus, inferior frontal gyrus (IFG), superior temporal gyrus (STG), and insula was decreased in the deteriorated group compared to the preserved group.[16] However, to the best of our knowledge, the relationship between neurocognitive deficits and improvements, psychobiological characteristics, and clinical outcomes in UHR individuals has not been reported to date. Multimodal investigations have been proposed to facilitate understanding of clinical prognosis and objective markers.[17–19] We thus assessed this relationship using multimodal characteristics including neurophysiology and structural neuroimaging.

The Integrative Neuroimaging Studies in Schizophrenia Targeting for Early Intervention and Prevention (IN-STEP) research project was designed as a prospective observational study to explore the pathophysiological features associated with the onset of psychosis and to investigate potential predictive biomarkers for clinical use since 2008.[20] In this project, we measured neurophysiological characteristics using electrophysiological responses during mismatch negativity (MMN), neuroimaging characteristics using structural MRI, and brain activity using functional near-infrared spectroscopy (fNIRS) in UHR individuals. Neurocognitive function was repeatedly assessed using the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J).[21,22] For the correlational analyses using clinical outcomes, we previously reported a relationship between attention/processing speed in UHR-NP with 12-month global function.[12] For biological features and symptom severity, the relationships between duration and frequency of MMN amplitude, and later symptomatic remission and cognitive function were found in UHR.[23] Furthermore, correlations between gray matter volume in the right triangular part of the IFG and positive symptom scores were also found in UHR.[24] However, these studies only explored the correlation between one measure and another, with the relationships between biological features, neurocognitive function trajectories, and symptom severity outcomes never previously investigated in a single model.

The present study aimed to find the model showing the relationships between demographic, clinical, neurophysiological, and neuroimaging characteristics, and neurocognitive deficits and improvements in UHR individuals using structural equation models (SEMs). For the model, we first explored whether cognitive deficits and improvements in UHR individuals were associated with baseline and follow-up symptom severity. According to previous studies of neurocognitive function trajectory and clinical outcomes in UHR,[1,8,9,11,12] cognitive deficits were associated with baseline and short-term severity, whereas cognitive improvements during the follow-up period would be correlated with long-term symptom severity. Subsequently, we also explored the associations between demographic, clinical, neurophysiological, and neuroimaging characteristics derived from multimodal measurements with neurocognitive deficits and improvements in UHR individuals. Finally, for the significant relationships, we compared the models including a neurocognitive character, which was associated with both biological features and symptom severity outcomes using SEMs. We hypothesized that a neurocognitive character, given a state factor, would mediate the relationship between baseline biological features and symptom severity in the follow-up period.

Materials and Methods

Participants

In the IN-STEP project, 129 BACS assessments of 50 UHR individuals (female: n = 23, mean age [SD] = 21.37 [3.90] years; supplementary table S1) were conducted for 3 years from registration (mean [SD] = 2.58 [1.51] assessments). Participants also received the measurements using one or more modalities within 90 days of registration (including MMN, structural MRI, and fNIRS brain activity). In all measurements of the BACS and other modalities, we assessed clinical symptom severity using the Positive and Negative Syndrome Scale (PANSS)[25] up to 18 months as clinical outcomes to provide sufficient sample sizes. The participants were recruited from the outpatient and inpatient units of the University of Tokyo Hospital, University of Tokyo Health Service Center, psychiatry clinics, and internet referrals.[20] The

inclusion criteria were: age between 12 to 30 years. All eligible participants were assessed using the Structured Interview for Prodromal Symptoms (SIPS)[26,27] and evaluated using the UHR criteria. The onset of psychosis, UHR-P condition, was defined according to the SIPS criteria during the 18-month follow-up period, else defined as UHR-NP.[23] The exclusion criteria were: (1) previous and/or current severe brain injury and/or neurological illness, (2) previous history of electroconvulsive therapy, (3) a premorbid IQ of 70 or less based on the 25-item version of the Japanese Adult Reading Test (JART25), [28,29] (4) previous and/or current alcohol addiction, (5) previous and/or current continuous substance use, and (6) clear comorbidity with autism spectrum disorders according to the DSM-IV criteria. The detailed inclusion and exclusion criteria of this study have been described in a previous protocol paper.[20]

This study was approved by the ethics committee of the Faculty of Medicine, University of Tokyo (Approval Nos. 397, 629, 630, and 2226). All participants provided written informed consent to participate in the project and to undergo the required measurements after receiving a complete explanation of the experimental protocol.

Neurocognitive Battery

The BACS-J[21,22] measures six neurocognitive subdomains thought to be affected by schizophrenia: (1) list-learning as verbal memory (VM), (2) digit-sequencing task as working memory (WM), (3) token motor task as motor speed (MOT), (4) category and letter fluency as verbal fluency (VF), (5) symbol-coding as attention and processing speed (PS), and (6) the Tower of London task as executive function (EXC). Trained psychologists conducted the examinations. *Z*-scores standardized according to healthy Japanese age-clustered participants were used for each category.[21]

Demographic and Clinical Assessments

Demographic, clinical, and psychobiological characteristics used in this study are listed in supplementary table S2. Handedness was evaluated using the Edinburgh Handedness Inventory.[30] Self and parental socioeconomic status was assessed using the Hollingshead scale.[31]

Clinical assessments at baseline (n = 50), short-term follow-up (n = 31, mean [SD] = 116.9 [31.1] days from registration), and long-term follow-up (n = 33, mean [SD] = 391.1 [66.6] days from registration) were conducted using the PANSS.[25] The PANSS scores were categorized into five categories: positive, negative, disorganized, excitement, and emotional symptoms.[32] For patients receiving any antipsychotic, antiparkinsonian, anxiolytic, and/or antidepressant agents, we calculated the chlorpromazine, biperiden, diazepam, and imipramine equivalent doses, respectively,.[33]

Participants responded regarding their subjective depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CES-D).[34] The CES-D consists of 20 items with a 4-point Likert scale (0 [no symptoms] to 3 [severe]), and the total score reflects subjective depressive symptoms (range: 0–60). Subjective quality of life (QOL) was assessed using the 26-item brief version of the WHO Quality of Life Scale (WHOQOL-BREF).[35,36] The WHOQOL-BREF consists of 26 items with a 5-point Likert scale (1 [poor] to 5 [good]). Five factors were calculated based on the average score of the corresponding items in the physical domain, psychological domain, social relationships, environment, and general impression of QOL.

Psychobiological Measurements

Duration and frequency MMN, T1-weighted structural MRI, and brain activity in the fronto-temporal cortical area during a verbal fluency task measured using an fNIRS comprised the psychobiological measurements.

MMN. MMN is a negative component of the electrophysiological response elicited by infrequent deviant stimuli occurring within a series of frequent standard stimuli. MMN is considered a promising biomarker among other components.[37,38] As per previous studies,[23,39,40] electroencephalograms were recorded using a 64-channel Geodesic EEG System (Electrical Geodesics Inc., Eugene, OR). Two types of auditory oddball paradigms using duration and frequency-deviant stimuli were employed. Each paradigm comprised 2,000 stimuli consisting of 90% standard tones (1000 Hz, 50 ms) and 10% deviant tones (duration MMN: 1000 Hz, 100 ms; frequency MMN: 1200 Hz, 50 ms). Auditory stimuli were delivered at an 80-dB sound pressure level, 1-ms rise/fall time, and 500-ms stimulus-onset asynchrony. The duration and frequency of MMN amplitudes were calculated as the mean amplitudes from 135 to 205 ms and from 100 to 200 ms post-stimulus, respectively. Average amplitudes in seven electrodes around the frontocentral electrode (FCz) were employed as the MMN amplitude.[23,39,40]

T1-weighted Structural MRI. Two T1-weighted structural brain imaging scanning procedures were performed using 3.0-T MRI machines (supplementary materials). Abnormalities and anomalies were assessed by a trained neuroradiologist using T1- and T2-weighted images. Images with abnormalities and anomalies, substantial head motion, and/or poor quality were excluded from subsequent analyses. Following visual inspection, one participant was excluded due to the failure of preprocessing using FreeSurfer 6.0.[41] A final total of 33 images were used in this study. Cortical and subcortical structural information was extracted from preprocessed images, and 150 variables of the cortical surface area, cortical thickness, and subcortical volume were applied in the analyses (68, 68, and 14 variables, respectively). In

the preprocessing phase, outliers were assessed and segmented region-of-interest images were inspected using the ENIGMA quality control protocol.[42] Given that the effect size between scan procedures would affect the analysis, ComBat[43] was applied to the preprocessed dataset to harmonize the datasets (supplementary materials).

fNIRS. fNIRS is a portable functional neuroimaging instrument that enables convenient and noninvasive measurement of changes in hemoglobin over the cortical surface.[44] Near-infrared light (650–1000 nm) emitted from a source probe on the human scalp is partially absorbed by hemoglobin in small vessels (<1 mm) and the remaining light is scattered. A detector probe placed 3 cm from the source probe in adults detects scattered near-infrared light.[44]

Brain activity in the prefrontal and anterior temporal cortical surface areas during a 160-s block-designed version of the phonological VF task was measured using a 52-channel fNIRS instrument (ETG-4000; Hitachi Ltd., Tokyo, Japan).[44–47] The measured activity was assessed using automatic rejection software for visible artifacts derived from body and head movements.[46,48] Two measurements were excluded from further analyses. The location of fNIRS measurements for each channel was estimated using a probabilistic location by virtual registration from MRI measurements with an fNIRS probe attachment.[49,50] Relative brain activity according to the task was measured from 16 fronto-temporal regions considering the participant's head size (supplementary materials).[46] The total number of correct words during the task period was recorded as task performance. Following measurements, subjective sleepiness during the task was assessed using the Stanford Sleepiness Scale.[51]

Statistical Analysis

All analyses were performed using R version 3.6.2 (The R Foundation for Statistical Computing Platform, Vienna, Austria). To obtain the intercept and slope of neurocognitive scores, general linear mixed models (GLMMs) were employed, with six neurocognitive domains as dependent variables and the intercept (deficits) and slope (improvements) of days from registration as random effects using "lmer" package version 1.1.23.[52] Differences in demographics, intercepts and slopes of neurocognitive scores, and clinical assessments between UHR-P and UHR-NP were assessed using nonparametric statistics; if results were significant, UHR-P/NP was considered as a covariate.

For the first hypothesis, general linear models (GLMs) were employed, with the PANSS 5 factor scores as dependent variables and the intercepts of neurocognitive scores as independent variables. The slopes for participants who received BACS assessments at two or more time points were also assessed. Since these analyses were exploratory, statistical corrections were applied for the dependent variables using Bonferroni correction (corrected $P = .005 = .05/10$ [5 factor scores × 2 BACS variables per domain]).

Second, we explored the associations between the demographic, clinical, and psychobiological measurements listed in supplementary table S2 with the intercept and slope of neurocognitive scores using GLMs. For structural MRI variables, the models were controlled for intracranial volume. Statistical significance was adjusted using the Bonferroni correction for neurocognitive domains (corrected $P = .0083 = .05/6$).

Finally, we tested changes in psychobiological characteristics at baseline, cognitive function, and symptom severities using a model comparison of SEMs. SEM analysis was conducted using "lavaan" package version 0.6.5.[53] Estimation of the model was conducted using a robust maximum likelihood estimation. Missing values were handled using a full information maximum likelihood method. Indices of a good-fit model were *P*-values of 0.05 or greater based on a chi-square test, a confirmatory fit index (CFI) value of 0.90 or greater, or a root mean square error of approximation (RMSEA) value of 0.10 or smaller. The models were compared using the Akaike information criterion (AIC).

Results

Six UHR individuals had transitioned to psychosis during the follow-up period. No differences in demographic characteristics were observed between UHR-P and UHR-NP groups, with the exception of baseline PS score which was greater in the UHR-P group than in the UHR-NP group (0.58 [1.72] vs −0.49 [0.98], $P = .041$). The correlation matrix of intercepts and slopes of the cognitive domains are presented in table 1. The intercepts and slopes in most of the neurocognitive domains were correlated with each other, and the slopes were also correlated (table 1). The VM intercept was associated with the VM slope ($r = .31$, $P = .029$). A one-sample *t*-test revealed no difference from zero with the exception of the VM slope ($t = 3.30$, $P = .002$; figure 1). No differences were observed in any intercept or slope of the neurocognitive domains between UHR-P and UHR-NP groups. Regarding clinical assessments, the UHR-P group exhibited severe negative and disorganized symptoms at short-term follow-up when compared to the UHR-NP group (negative symptoms: 29.5 [7.6] vs 20.2 [5.9], $P = .008$; disorganized symptoms: 12.5 [2.4] vs 8.9 [3.0], $P = .029$; respectively).

Relationships Between Intercept and Slope of Cognitive Domains and Clinical Outcomes

The VF intercept was negatively associated with negative symptoms at baseline ($B = −5.27$, SE = 1.24, corrected

Table 1. Correlation Matrix of Intercepts and Slopes of Neurocognitive Domains

		VM		WM		MOT		VF		PS		EXC
		Int	Slp	Int	Slp	Int	Slp	Int	Slp	Int	Slp	Int
VM	**Intercept**	1										
	Slope	**0.31**	1									
WM	**Intercept**	0.28	−0.06	1								
	Slope	−0.10	−0.17	0.09	1							
MOT	**Intercept**	0.24	0.11	**0.45**	−0.04	1						
	Slope	0.27	**0.78**	−0.06	−0.20	0.10	1					
VF	**Intercept**	**0.54**	0.06	**0.46**	−0.03	**0.60**	0.05	1				
	Slope	0.20	**0.47**	−0.06	**−0.60**	0.08	**0.59**	0.07	1			
PS	**Intercept**	**0.66**	0.11	**0.43**	−0.01	**0.62**	0.09	**0.81**	0.07	1		
	Slope	0.23	**0.79**	−0.01	**0.35**	0.08	**0.67**	0.04	**0.31**	0.11	1	
EXC	**Intercept**	0.08	0.05	**0.36**	−0.01	0.09	0.05	0.12	0.02	0.17	0.04	1
	Slope	0.14	**0.40**	−0.02	0.00	0.05	**0.48**	0.01	−0.10	0.05	**0.32**	0.04

Bold text indicates $P < .05$.
Abbreviations: VM, verbal memory; WM, working memory; MOT, motor speed; VF, verbal fluency; PS, processing speed; EXC, executive function.

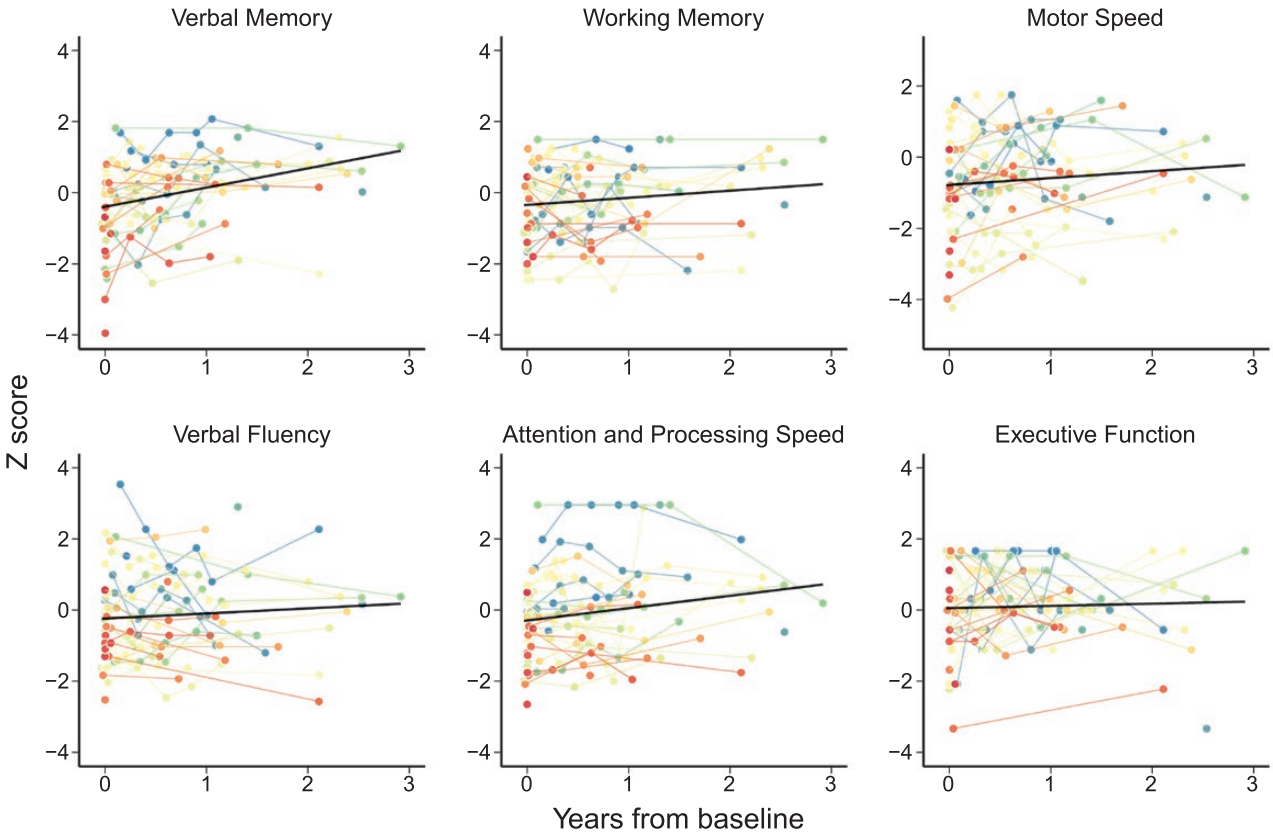

Fig. 1. Trajectory of cognitive scores in this study.

$P = .0001$, figure 2a) and short-term follow-up ($B = -5.22$, SE = 1.50, corrected $P = .0016$, figure 2b). The PS slope was negatively associated with excitement symptoms at long-term follow-up ($B = -712.7$, SE = 206.5, corrected $P = .0018$, figure 2c).

Relationships Between Demographic, Clinical, and Psychobiological Measurements and Cognitive Improvements

For neuroimaging characteristics, the intercepts of VM, MOT, VF, and PS were associated with fNIRS brain

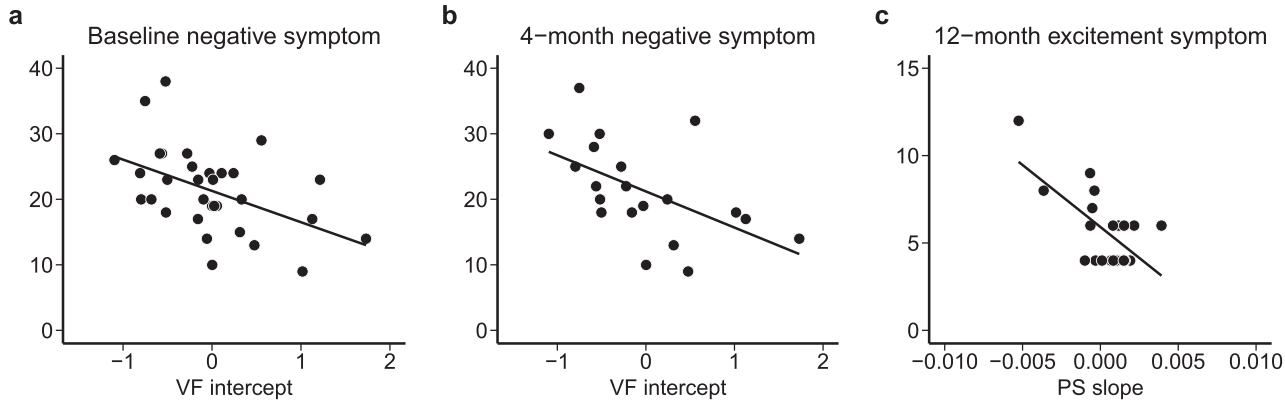

Fig. 2. Relationships between neurocognitive performance and clinical outcomes. Abbreviations: PS, processing speed; VF, verbal fluency.

Table 2. Relationships Between Neurocognitive Function and Demographic, Clinical, and Psychobiological Characteristics

Neurocognitive Score	Independent Variables	*B*	SE	*t*	*P*
Intercept					
VM	Diazepam dose	−0.0274	0.0096	−2.84	0.0066
	Activity in left IFG opercularis	1.64	0.54	3.05	0.0039
	Activity in left IFG triangularis	1.69	0.51	3.29	0.0020
	Activity in right middle frontal	1.56	0.56	2.80	0.0075
WM	Estimated premorbid IQ	0.0212	0.0075	2.81	0.0072
MOT	QOL social relationship	0.44	0.13	3.35	0.0017
	Left caudal ACC surf area	0.0033	0.0011	3.05	0.0047
	Right inferior temporal thickness	2.27	0.67	3.41	0.0019
	Right middle temporal thickness	2.68	0.71	3.80	0.0007
VF	Task performance during fNIRS	0.065	0.016	3.97	0.0003
	Activity in right IFG triangularis	1.35	0.43	3.12	0.0032
	Activity in left superior temporal gyrus	1.39	0.45	3.12	0.0033
	Right banks of the superior temporal Sulcus surf area	−0.00241	0.00082	−2.92	0.0065
PS	Activity in left IFG opercularis	2.04	0.64	3.17	0.0028
	Activity in left IFG triangularis	2.36	0.60	3.91	0.0003
	Activity in right IFG triangularis	1.42	0.46	3.06	0.0038
	Activity in right middle frontal	2.28	0.65	3.48	0.0011
	Activity in left superior temporal gyrus	1.62	0.48	3.39	0.0016
EXC	Female	−0.38	0.14	−2.77	0.0080
	Left superior parietal surf area	−0.00052	0.00017	−3.05	0.0047
Slope					
MOT	Right rostral ACC surf area	−0.0000305	0.0000044	−6.87	< 0.0001
EXC	Right Heschl's gyrus surf area	−0.000046	0.000013	−3.52	0.0020
	Left rostral ACC surf area	−0.0000136	0.0000047	−2.92	0.0082

Abbreviations: VM, verbal memory; WM, working memory; MOT, motor speed; VF, verbal fluency; PS, processing speed; EXC, executive function; IFG, inferior frontal gyrus; ACC, anterior cingulate gyrus.

activity, mainly in the IFG, middle frontal gyrus, and STG. The intercepts of MOT, VF, and EXC were associated with structural characteristics (table 2). Of these, the VF intercept was associated with VF task performance during fNIRS measurements, fNIRS brain activity in the right triangular part of the IFG and left STG, and cortical surface area in the right banks of the STS.

Cortical surface area in the right rostral anterior cingulate cortex (ACC) was negatively associated with the MOT slope (B = −0.0000305, SE = 0.0000044, corrected P < .00001, table 2). Cortical surface area in the right Heschl's gyrus and left rostral ACC were both negatively associated with the EXC slope (B = −0.000046, SE = 0.000013, corrected P = .0020; B = −0.0000136, SE = 0.0000047, corrected P = .0082, respectively). Cortical surface area in the right middle temporal gyrus was negatively associated with the VM slope, and cortical thickness in the left frontal pole was positively associated with the PS slope;

however, these relationships became nonsignificant after excluding one outlier (P = .17 and .26, respectively). The MMN amplitudes showed no significant relationships with any cognitive deficits or improvements in any domains.

Model Comparison of the Relationships Between Brain Structural Characteristics, Brain Activity, Neurocognitive Function, and Clinical Outcomes

We compared three possible models to determine the relationships between cortical surface area in the right banks of the STS, brain activity in the right triangular part of the IFG and left STG during the VF task, neurocognitive function (VF intercept and VF task performance during fNIRS measurement), and short-term negative symptoms (supplementary figure S1). The model comparison revealed that the model including the path from cortical surface area, VF function, brain activity, and short-term negative symptoms had the best fit relative to that of the other models (supplementary table S3). The final optimized model (χ^2 = 9.1, df = 8, P = .33, CFI = 0.992, RMSEA = 0.047, AIC = 413.3; figure 3) exhibited significant paths from cortical surface area in the right banks of the STS to VF function (β = −.58, SE = 0.11, P < .001) and from VF function to negative symptoms at short-term follow-up (β = −.89, SE = 0.19, P < .001). A significant correlation between VF function and brain activity during the VF task was observed (β = .52, SE = 0.21, P = .011), and the path from brain activity to negative symptoms at short-term follow-up exhibited a trend for significance (β = .45, SE = 0.25, P = .072).

Discussion

The present study demonstrated that the VF intercept in UHR individuals was negatively associated with negative symptoms at baseline and short-term follow-up, whereas the PS slope was negatively associated with excitement symptoms at long-term follow-up. Neurocognitive deficits were associated with brain activity during the VF task, predominantly in the IFG, middle frontal gyrus, and STG, whereas neurocognitive deficits and improvements were associated with cortical structure in the fronto-temporal regions. Finally, SEM model comparison revealed significant paths among the cortical surface area in the right banks of STS, baseline VF function, and short-term negative symptoms. To the best of our knowledge, this is the first study to identify the relationships between fronto-temporal structural characteristics, cognitive deficits and improvements, and symptom severity outcomes in UHR individuals using a wide range of demographic, clinical, and psychobiological measurements.

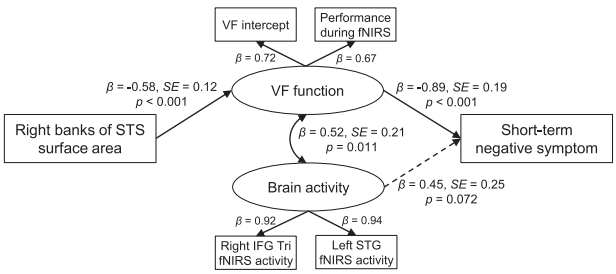

Fig. 3. A best-fitted path model between cortical surface area, cognitive function, brain activity, and clinical outcomes. The dashed line shows a nonsignificant path but remains in the best-fitted model. Abbreviations: STS, superior temporal sulcus; VF, verbal fluency; IFG Tri, triangular part of the inferior frontal gyrus; STG, superior temporal gyrus.

We did not observe extensive cognitive deficits in the UHR group, possibly due to the low transition rate of the participants in this study (6/50 = 12.0%). This observation agrees with previous findings that UHR-NP individuals exhibit similar neurocognitive deficits to those of healthy controls.[1–3,7–9] Further, we did not observe differences in cognitive deficits and improvements in any domain between UHR-P and UHR-NP individuals, possibly due to the small sample size of the UHR-P group. Our findings replicated previous reports that cognitive improvements were absent and VM scores recovered during the follow-up period.[8,9]

Similar to previous reports,[1,8,9,11,12] low baseline cognitive performance in VF and PS was associated with poor clinical outcomes in UHR. In particular, the VF intercept and PS slope were associated with short-term negative symptoms and long-term excitement symptoms, respectively. As per previous studies,[8,9] baseline cognitive function reflects short-term outcomes whereas the change over the course of the illness could be associated with long-term symptom severity.

Neurocognitive deficits were associated with brain activity during the VF task, predominantly in the IFG, middle frontal gyrus, and STG, whereas neurocognitive deficits and improvements were associated with cortical thickness and surface area in the fronto-temporal regions. Given that neurocognitive performance changes over the clinical course in UHR individuals,[8,9] neurocognitive deficits may be more strongly associated with state markers such as brain activity at baseline than with trait markers such as structural alterations. Conversely, neurocognitive improvements may be more strongly associated with trait markers. A 6-year follow-up study reported similar findings, whereby cortical thickness and surface area in the fronto-temporal regions at baseline were greater in UHR individuals with good functional outcomes than in those without.[54] Further, differences in cortical surface area in the left IFG pars triangularis, left precentral gyrus, and right frontal pole; and cortical thickness in the left STG and right posterior cingulate gyrus increased during the follow-up period.[54]

The comparison of the models which included baseline VF function and related features showed that the model comprising the paths from the cortical surface area in the right banks of STS, VF function, and short-term negative symptoms provided the best fit. This model suggests that brain structural and functional characteristics may not be directly associated with clinical outcomes, and neurocognitive function may mediate these relationships. Our findings replicate those of previous studies showing the relationship between VF function and later negative symptom outcomes.[10,13] One previous study also reported that this relationship was bi-directional in 12-month follow-up period.[13] Given that repeated measurements are more tractable for neurocognitive function than with other neuroimaging tools, assessing neurocognitive trajectories throughout the course of psychotic symptoms may provide a novel evaluation tool for the observation of long-term clinical outcomes in UHR individuals.

Longitudinal investigations in UHR individuals may provide a link with cohort studies of schizophrenia patients. The present findings are also in accordance with prospective birth cohort studies demonstrating that individuals who subsequently develop schizophrenia present with a developmental lag in processing speed[55] and deficits and a developmental lag in verbal ability during adolescence.[56,57] This trend is also observed in individuals with subjective psychotic experiences.[58] Therefore, long-term neurocognitive assessments in clinical investigations considering adolescent developmental trajectories may reveal factors underpinning cognitive changes and their relationships with symptom severity.[54,59]

There are several limitations to this study. First, we were unable to consider the onset of psychosis due to the small sample size in the UHR-P group. Consequently, the differences between UHR-P and -NP individuals were only observed in baseline PS scores and short-term negative and disorganized symptoms, and the results of the GLM analysis and SEM comparison may be limited. However, cognitive discrepancies and symptom severity outcomes have been reported, and these differences may predict subsequent onset of psychosis.[60] Future studies considering psychosis onset should clarify the mechanisms underpinning the relationship reported in this study. Second, although this is the first study to explore the relationship between neurocognitive trajectories and multimodal measurements, the sample size was small, and the results require confirmation in future multicenter investigations. Third, the VM intercept was negatively associated with diazepam dose for a proportion of UHR individuals who received medications. In a naturalistic design, individuals with severe symptoms are more likely to receive medications, and the dose would be higher. Those with severe symptoms were more likely to receive other treatment options such as psychological supports, which may affect clinical outcomes, as well as neurocognitive function and brain activity. To determine causal relationships between medications, cognitive function, and clinical symptoms, appropriately designed clinical trials are warranted.

In conclusion, the present study demonstrated the paths from the cortical surface area in the right banks of the STS, neurocognitive deficits in VF, and short-term negative symptoms in UHR individuals. These results suggest that multimodal brain measurements and repeated neurocognitive assessments over the clinical course of UHR may reveal the neural basis of clinical prognosis over a long period. Future studies with larger sample sizes involving multiple sites may reveal more robust relationships, ultimately providing therapeutic targets to improve clinical outcomes.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

Conflict of Interest

The authors have no conflict of interest to report.

Acknowledgments

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