



Longer illness duration is associated with greater individual variability in functional brain activity in Schizophrenia, but not bipolar disorder

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ABSTRACT

Background: Individuals with schizophrenia exhibit greater inter-patient variability in functional brain activity during neurocognitive task performance. Some studies have shown associations of age and illness duration with brain function; however, the association of these variables with variability in brain function activity is not known. In order to better understand the progressive effects of age and illness duration across disorders, we examined the relationship with individual variability in brain activity.

Methods: Neuroimaging and behavioural data were extracted from harmonized datasets collectively including 212 control participants, 107 individuals with bipolar disorder, and 232 individuals with schizophrenia (total $n = 551$). Functional activity in response to an N -back working memory task (2-back vs 1-back) was examined. Individual variability was quantified via the correlational distance of fMRI activity between participants; mean correlational distance of one participant in relation to all others was defined as a ‘variability score’.

Results: Greater individual variability was found in the schizophrenia group compared to the bipolar disorder and control groups ($p = 1.52e-09$). Individual variability was significantly associated with aging ($p = 0.027$), however, this relationship was not different across diagnostic groups. In contrast, in the schizophrenia sample only, a longer illness duration was associated with increased variability ($p = 0.027$).

Conclusion: An increase in variability was observed in the schizophrenia group related to illness duration, beyond the effects of normal aging, implying illness-related deterioration of cognitive networks. This has clinical implications for considering long-term trajectories in schizophrenia and progressive neural and cognitive decline which may be amiable to novel treatments.

1. Introduction

Schizophrenia constitutes a multidimensional psychiatric condition, exhibiting pronounced variability between and within-subjects (Bosia et al., 2019). The understanding of cognitive and neurobiological heterogeneity in schizophrenia has been bound by experimental designs that contrast patients’ performance to healthy controls, failing to

consider within-group heterogeneity (Carruthers et al., 2019). Recent work has demonstrated that individual variability is a hallmark of functional task activity and connectivity (Gordon et al., 2017; Hawco et al., 2021; Miller et al., 2009), suggesting that applying a group-level map to individual subjects can dilute brain-behaviour associations that are crucial to understanding cognitive processes (Wang et al., 2020). Whereas there is an assumption that averaging mitigates the effects of

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signal variance in the data, within-person variability is not strictly noise, but an important by-product of meaningful individual differences in brain structure, function, and neuromodulation (MacDonald et al., 2006; Van Horn et al., 2008). Network variance found in fMRI studies are related to differences across individuals rather than transient factors like day-to-day fluctuations (Gratton et al., 2018; Poldrack et al., 2015), and a group description alone tends to fall short of adequately capturing functional brain activity at the level of precision needed to translate into a clinical impact (Gratton et al., 2018; Gratton et al., 2020). Differences between individual and group-average network descriptions carry important ramifications for analysis, as it is speculated that functional neuroimaging may not achieve its full potential until individual-level brain network estimates can be made (Michon et al., 2022; Gratton et al., 2022). Consequently, there is a need for a shift away from group aggregate averages and consider individual metrics that can better characterize variability.

Neural networks governing working memory (WM) may be vulnerable to the influence of aging (Elsabagh et al., 2009; Rajah and D'Esposito, 2005). Specifically, dysfunction in the prefrontal cortex, a central node within the WM network, has been well documented in individuals with schizophrenia (Jiang et al., 2015; Van Snellenberg et al., 2016; Koike et al., 2013; Schneider et al., 2007) and with increasing age (Kawakami et al., 2014; Schultz et al., 2002). Likewise, illness duration may also have an effect on WM-related functional brain activity in individuals with schizophrenia (Elsabagh et al., 2009). Illness duration is defined as the time after the onset of a psychiatric disorder (Breitborde et al., 2009). Understanding the neurobiological effects of illness duration has clinical implications, given its robust associations with poorer real-world outcomes and significant role in predicting cognitive performance (Altamura et al., 2015; Almeida et al., 2019; Bowie et al., 2014). However, despite the influence of illness duration on patients' functioning, this variable is often neglected in studies and rarely alluded to as a potential confounding factor (Altamura et al., 2015; Altamura et al., 2011). The majority of existing literature has investigated structural correlates of illness duration, relating volumetric loss in the frontal cortex to longer illness duration (Molina et al., 2004; Sapara et al., 2007; Premkumar et al., 2006; Premkumar et al., 2008). To our knowledge, no study to date has used age and illness duration as variables of interest while investigating idiosyncrasies of functional brain activity during WM performance in schizophrenia.

In our recent study, we quantified individual variability of WM-evoked brain activation using mean correlational distance (Hawco et al., 2020), a recently developed metric representing deviation from the common group pattern, and demonstrated that those with schizophrenia spectrum disorders exhibited greater overall individual variability than controls, indicating more idiosyncratic brain response patterns (Gallucci et al., n.d.). Variability was also found to increase with age in schizophrenia; however, information regarding illness onset or duration was not available, preventing us from disentangling the effects of aging as opposed illness duration. In this study, we used an existing large sample ($n = 609$) *N*-Back task fMRI dataset (Pomarol-Clotet et al., 2015; Fuentes-Claramonte et al., 2021) to investigate the separate impacts of age and illness duration on variability of functional brain activity in schizophrenia and determine whether findings were schizophrenia-specific, through the use of bipolar disorder as a psychiatric-control group. We hypothesized that a longer illness duration would be associated with greater variability uniquely in the schizophrenia group, due to the expected negative effects of psychosis-related morbidity on functional activity. Further, we anticipated the effects of aging on variability may be more pronounced in the schizophrenia group compared to the bipolar disorder and control groups. Our study is intended to provide strong evidence which may lead to a clinical impact by improving the ability to understand the effects of progressive changes in brain function within schizophrenia, separating the effects of age and illness duration. We aim to confirm whether these factors play a role in the functional activation deficits seen in patients; where targeting

such illness duration-related changes through personalized interventions may demonstrate therapeutic benefit.

2. Methods

2.1. Participants

Participant data was collected from datasets originating from hospitals in Barcelona (Benito Menni CASM, Hospital Mare de Déu de la Mercé, Hospital Sagrat Cor de Martorell) (Fuentes-Claramonte et al., 2021). To consider diagnostic specificity of age and illness duration, we examined a group of adults meeting the DSM-IV criteria for schizophrenia, as well as a group with bipolar disorder as a 'psychiatric control group'. Datasets followed a common participant eligibility criteria. Patients were excluded if they were younger than 18 or older than 65, had a history of brain trauma or neurological disease, had alcohol or substance misuse in the previous 12 months, and/or had undergone electroconvulsive therapy in the previous 12 months (Fuentes-Claramonte et al., 2021). Patient symptom severity was evaluated using PANSS (Positive and Negative Syndrome Scale), YMRS (Young Mania Rating Scale), and HAM-D (Hamilton Depression Rating Scale). Healthy controls were recruited through local advertisement. In addition to the exclusion criteria above, control participants were excluded if they reported any history of mental illness and/or treatment of psychotropic medication, had a first-degree relative with a major psychiatric disorder, and/or had received any form of in- or out-patient psychiatric care (Pomarol-Clotet et al., 2015). All participants gave written informed consent prior to participating in the study in accordance with the Declaration of Helsinki. Study procedures were approved by the local Clinical Research Ethics Committee (Fuentes-Claramonte et al., 2021).

2.2. Illness duration

Age of illness onset was determined based on the first appearance of psychotic symptoms, established through clinical information derived from case notes as well as information provided by the patient and close relatives. Illness duration was then quantified as the patient's chronological age minus the age of onset, in accordance with previous studies (Elsabagh et al., 2009; Premkumar et al., 2008). It should be acknowledged that this reflects an estimate of illness duration, as prodromal stages and potential delays in diagnosis cannot be fully accounted for. Furthermore, different medications can have a moderating effect on illness-related biological processes (Almeida et al., 2019), and progressive changes in brain function may be related to the use of antipsychotic medication (Lesh et al., 2015) as well as the duration of untreated illness (Sarpal et al., 2017). As such, chronological considerations of illness duration cannot be fully separated from such processes, or other external social/personal factors (i.e., contact with clinical services and illness chronicity (Premkumar et al., 2008); potential changes in variability over time can be regarded as being related to a range of chronicity related determinants.

2.3. *N*-Back task

Individuals performed a letter-version of the *N*-Back task while in the scanner (Pomarol-Clotet et al., 2015). In an interleaved block design, two levels of WM load (1-Back and 2-Back) were presented for four blocks each. Each block consisted of 24 letters shown every-two seconds (one second on, one second off) with five targets occurring randomly within the blocks. A baseline stimulus was presented for 16 s in between blocks (an asterisk symbol shown at the same frequency as the letters). Participants were instructed to indicate targets by pressing a button. All participants underwent a training session prior to the scanner to familiarize themselves with the task and reduce novelty-induced brain activation. Task performance was measured by response accuracy ($D' = Z_{\text{Hits}} - Z_{\text{False alarms}}$), which computes the ability to discriminate targets

from non-targets (Green et al., 1966) and was considered our primary behavioural measurement.

2.4. MRI scan

Scanning was conducted using a 1.5 Tesla GE Signa scanner (General Electric Medical System) (Fuentes-Claramonte et al., 2021). An echoplanar imaging (EPI) sequence depicting the BOLD contrast was used with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle = 70°, section thickness 7 mm, in-plane resolution = 3x3mm² (Pomarol-Clotet et al., 2015). Prior to statistical analysis, functional data was smoothed using a 5 mm Gaussian kernel (FWHM), motion-corrected using MCFLIRT algorithm, and normalized to a common stereotactic space (Montreal Neurological Institute template) (Fuentes-Claramonte et al., 2021). Individual fMRI analysis was previously performed using the FEAT module in FSL (v4.19). General linear models were fit to generate individual activation *t*-maps for a contrast comparing the two regressors of interest (2-Back and 1-Back conditions) (Pomarol-Clotet et al., 2015). To reduce the potential effects of motion, movement parameters were included as confound regressors of non-interest in the model (six in total; three rotational, three translational) (Fuentes-Claramonte et al., 2021).

2.5. Individual variability in *N*-Back task activity via correlational distance:

To assess individual variability in functional brain activity pattern, each participant's unthresholded contrast *t*-map (2-Back – 1-Back) was used. A whole-brain approach was conducted in accordance with prior *N*-Back task activity variability literature (Hawco et al., 2020; Rieck et al., 2022). *T*-maps were parcellated using the Shen268 atlas to retain whole-brain findings while mitigating the effects of lower resolution during image acquisition. This parcellation was supported by a feasibility analysis performed on a separate dataset of 3 Tesla schizophrenia and control *t*-maps that demonstrated a near-perfect correlation between whole-brain and atlas based parcellated-brain individual variability scores, implying results would not be significantly influenced by inter-individual spatial differences in network topography. *T*-map values for each of the 268 ROIs were loaded into RStudio v1.3 as a numeric vector; creating a spatial series with each point in the vector representing the *t*-statistic at a specific ROI for that individual. All observations were combined into a single matrix (participants × *t*-statistic) and pairwise correlational distances were calculated between each pair of participants. Correlational distance can be expressed as 1 – correlation coefficient, in which increased distance is equivalent to a lower correlation; thus quantifying the similarity/difference of brain activity patterns between participants. Individual variability was defined as the mean correlational distance of a given participant in relation to all other participants, providing a unique value for each participant. Lower mean correlational distances represent individuals with patterns of *N*-Back task-evoked activation that are more similar to the overall group, and higher mean correlational distances represent individuals with more idiosyncratic brain response patterns (Hawco et al., 2020). This metric aimed to capture differences in which neural networks or systems are activated across individuals, as well as changes in the specific functional topography of individuals.

2.6. Between-group variability analysis:

Individual variability was calculated for the total sample as described above; the variability score for each participant was relative to the entire sample. A linear model was then used for the analysis. The model assessed the relationship between mean correlational distance and all potential explanatory variables or covariates of non-interest (group, sex, age, motion; defined by mean framewise displacement (FD) (Power et al., 2014), and 2-Back D') as well as interactions of

group*sex, group*age, group*FD, group*2-Back D' and age*2-Back D'. Group*age was the interaction of interest, as we anticipated the effects of aging on variability to be more pronounced in the schizophrenia group compared to bipolar disorder and control groups. A hierarchical regression was performed to further evaluate the nonlinear effects (quadratic and cubic) of age on mean correlational distance.

2.7. Within-group variability analysis:

To assess within group effects, individual variability was recalculated separately within each diagnostic group; the variability score, is therefore relative to others within that diagnostic group rather than the sample as a whole. Following, a linear model was used for the analysis. For the control group, the model determined the relationship between mean correlational distance and sex, age, FD, and 2-Back D', as well as an interaction of age*2-Back D'. For the bipolar disorder and schizophrenia groups, the model assessed the relationship between mean correlational distance and sex, age, illness duration, FD, and 2-Back D' as well as interactions of age*2-Back D' and illness duration*2-Back D'. Both age and illness duration were included as variables of interest, as we attempted to disentangle their effects; variance inflation factors (VIF) were calculated to identify potential multicollinearity (VIF > 5) (Chatterjee and Simonoff, 2013; O'Brien RM, 2007). A hierarchical regression was performed to further evaluate the nonlinear effects (quadratic and cubic) of age and illness duration on mean correlational distance. In the schizophrenia group, the addition of Positive and Negative Syndrome Scale (PANSS) subscale scores, as well as interactions of PANSS General*illness duration, PANSS Negative*illness duration and PANSS Positive*illness duration were included in the hierarchical regression. To identify differences in functional brain activity between higher and lower mean correlational distances, individuals were separated into equal groups by median split based on mean correlational distance; schizophrenia ($n_{high} = 116$, $n_{low} = 116$), bipolar disorder ($n_{high} = 53$, $n_{low} = 54$), and control ($n_{high} = 106$, $n_{low} = 106$). A median split was justified through the use of univariate clustering by mean correlational distance of the schizophrenia group with 2 clusters estimated, equal in size, replicating the median split. Such binning of the data was extended to other diagnostic groups for comparison. For descriptive purposes, group comparisons were conducted by averaging the parcellated contrast *t*-maps of individuals belonging to specific subgroups. Averages were then projected onto surface space for improved visualization.

2.8. Code sharing

Code used in the analysis of this dataset has been made available (https://github.com/juliagallucci/illness_duration_individual_variability_SCZ).

3. Results

3.1. Participants

Data was included for analysis based on a quality-control criteria. 212 control participants, 107 individuals with bipolar disorder, and 232 individuals with schizophrenia were included for analysis after removing 15 participants that did not have accompanying demographic information, 2 participants for excessive motion (FD > 0.5 mm representing well above the norm) (Power et al., 2012) and 41 participants that did not possess behavioural scores or had negative D' values (reflecting subject did not perform the task) (Pomarol-Clotet et al., 2015) (consort flow diagram shown in Fig. 1). Participant demographics, clinical and behavioural scores are shown in Table 1.

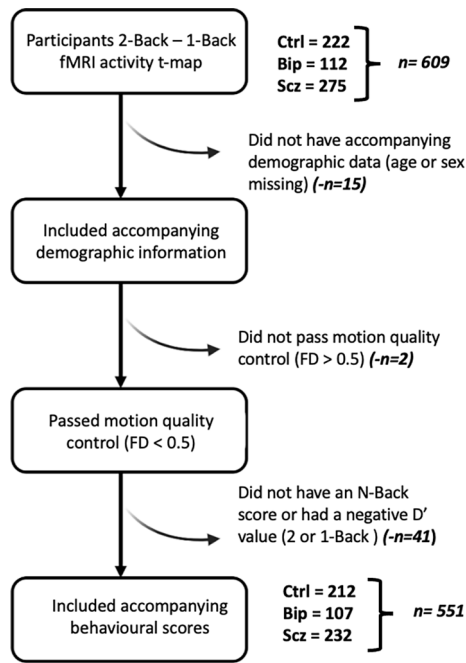


Fig. 1. Consort Flow Diagram. Participant data was evaluated for eligibility based on a quality-control criteria. The initial data from 222 control (Ctrl), 112 bipolar disorder (Bip), and 275 schizophrenia (Scz) participants were assessed for demographics availability; 15 participants were excluded. Following, data was controlled for excessive motion; 2 participants were excluded. Lastly, data was controlled for task performance; 41 participants were excluded. The resulting data from 212 Ctrl, 107 individuals with Bip, and 232 individuals with Scz were included for analysis.

Table 1
Participant’s Demographics, Clinical and Behavioural Scores.

Group	1. Ctrl (n = 212)	2. Bip (n = 107)	3. Scz (n = 232)	P-value Unadjusted	P-value Adj Tukey Comparisons
Sex				2.53e-10 ^a	Ctrl-Bip 0.57 Scz-Bip 1e-07* Scz-Ctrl 1e-07*
Male	109 (51.4 %)	49 (45.8 %)	178 (76.7 %)		
Female	103 (48.6 %)	58 (54.2 %)	54 (23.3 %)		
Age (years)	37.1 ± 11.23 [18–64]	42.1 ± 10.01 [22–62]	37.9 ± 11.58 [18–65]	0.00066 ^a	Ctrl-Bip 0.00054* Scz-Bip 0.0049* Scz-Ctrl 0.69
Motion (FD)	0.055 ± 0.02	0.091 ± 0.06	0.108 ± 0.07	<2e-16 ^a	Ctrl-Bip 1e-07* Scz-Bip 0.024* Scz-Ctrl < 2e-16*
Illness Duration (n _{Bip} = 104 n _{Scz} = 213)	–	15.35 ± 9.54 [0 – 42]	15.14 ± 11.45 [0 – 43]	0.87 ^b	–
YMRS (n _{Bip} = 95)	–	1.00 ± 1.65	–	–	–
HAMD (n _{Bip} = 94)	–	2.52 ± 2.43	–	–	–
PANSS (n _{Scz} = 191)	–	–	–	–	–
Positive	–	–	16.69 ± 6.19	–	–
Negative	–	–	21.20 ± 7.52	–	–
General	–	–	34.09 ± 9.69	–	–
N-Back Task					
Response Accuracy (D’) 2-Back	3.42 ± 0.94	2.80 ± 0.81	2.22 ± 0.91	<2e-16 ^a	Ctrl-Bip 1.33e-08* Scz-Bip 5.82e-08* Scz-Ctrl < 2e-16*
Response Accuracy (D’) 1-Back	4.34 ± 0.73	3.99 ± 0.87	3.40 ± 1.07	<2e-16 ^a	Ctrl-Bip 0.0011* Scz-Bip 2e-07* Scz-Ctrl < 2e-16*

Note. Where appropriate variables are presented as Mean ± SD, square brackets demonstrate ranges. Ctrl = controls, Bip = bipolar disorder, Scz = schizophrenia, YMRS = Young Mania Rating Scale, HAMD = Hamilton Depression Scale, PANSS = Positive and Negative Syndrome Scale ^a = ANOVA performed, ^b = 2-sample T-test performed.

3.2. N-Back task activity via correlational distance between-groups

The addition of nonlinear effects of age did not significantly contribute to the model (age² ΔR² = 0.0035p = 0.087; age³ ΔR² = 0.0039p = 0.126) and thus was not included. Mean correlational distance of functional brain activity across schizophrenia (0.646 ± 0.049) was significantly higher than bipolar disorder (0.620 ± 0.050) and control (0.585 ± 0.036) (F(2,535) = 21.10, p = 1.52e-09) groups, indicating individuals with schizophrenia showed more idiosyncratic response to the N-Back task on average. Group differences in mean correlational distance are shown in Fig. 2A. Mean correlational distance was significantly associated with FD (F(1,535) = 26.71, p = 3.34e-07), however, a group by FD interaction was found non-significant (F(2,535) = 1.26, p = 0.28), indicating group differences in variability were not significantly influenced by differences in FD between groups. Additionally, older age was related to increased mean correlational distance (Fig. 2B; F(1,535) = 4.90, p = 0.027) and worse performance (lower 2-Back D’) was associated with increased mean correlational distance (F(1,535) = 100.32, p < 2.2e-16). A significant group by 2-Back D’ interaction was found (Fig. 2C; F(2,535) = 4.22, p = 0.015); mean correlational distance was significantly negatively correlated with 2-Back D’ in the schizophrenia (t = -7.19, p = 2.13e-12), bipolar disorder (t = -6.04, p = 2.89e-9) and control (t = -4.66, p = 3.97e-06) groups, however the strength of the relationship differed by group. Further, a significant age by 2-Back D’ interaction was found (Fig. 2D; F(1,535) = 4.05, p = 0.045) where the strength of the relationship between task performance and mean correlational distance increased with age (1 SD below mean age (t = -4.85, p = 1.65e-06), mean age (t = -6.04, p = 2.9e-09), 1 SD above mean age (t = -6.58, p = 1e-10).

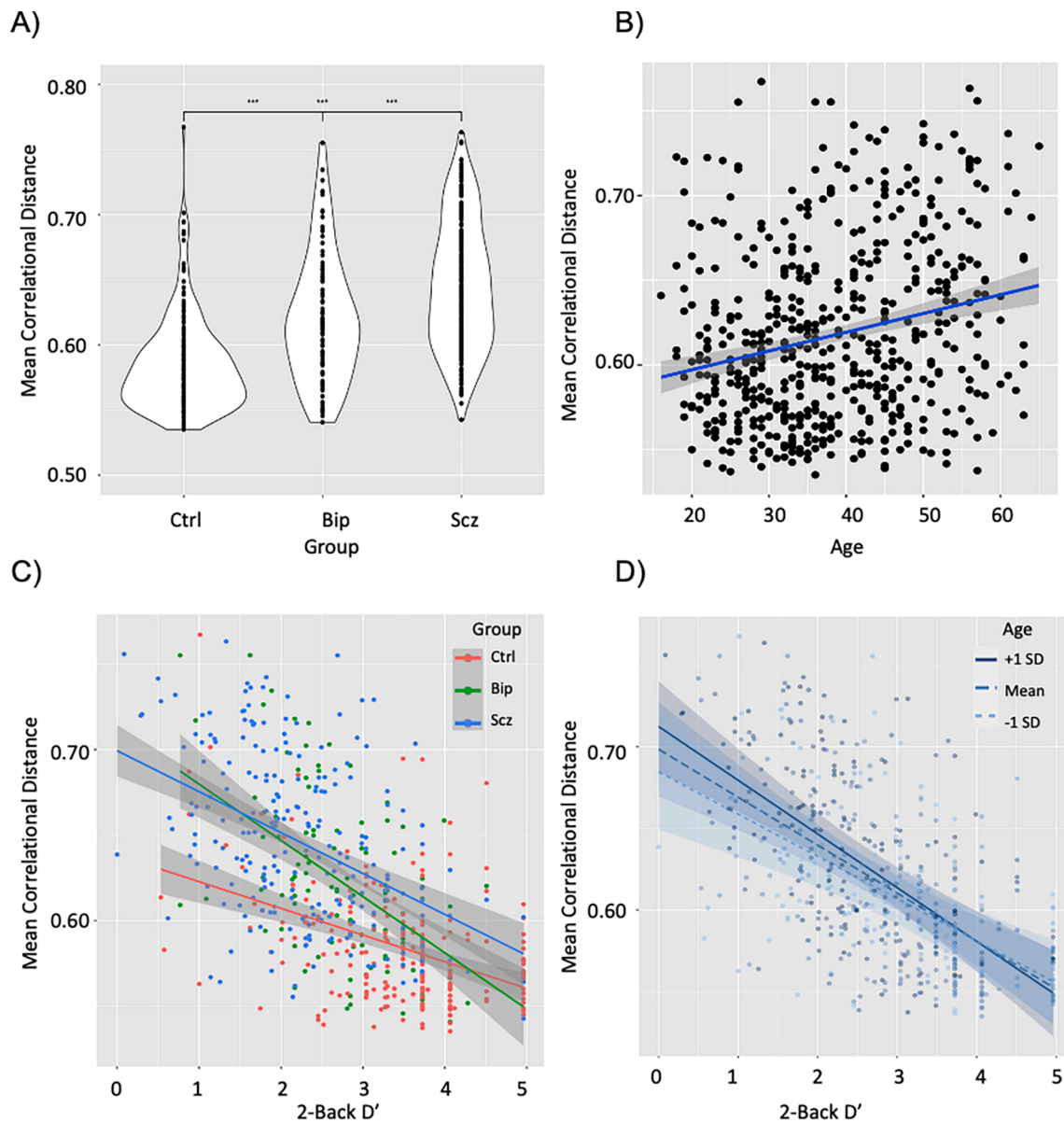


Fig. 2. Mean correlational distance across all participants. A) The schizophrenia (Scz) group had a significantly higher mean correlational distance than the bipolar disorder (Bip) and control (Ctrl) groups. Dots represent individual data points. B) Higher mean correlational distance was associated with older age. Dots represent individual data points. Ribbon surrounding the regression line indicates a 95% confidence interval. C) The strength of the negative association between mean correlational distance and 2-Back D' differed by group. Dots represent individual data points. Ribbons surrounding the regression lines indicates a 95% confidence interval. D) The strength of the negative association between mean correlational distance and 2-Back D' increased with age. Dots represent individual data points. Ribbons surrounding the regression lines indicates a 95% confidence interval.

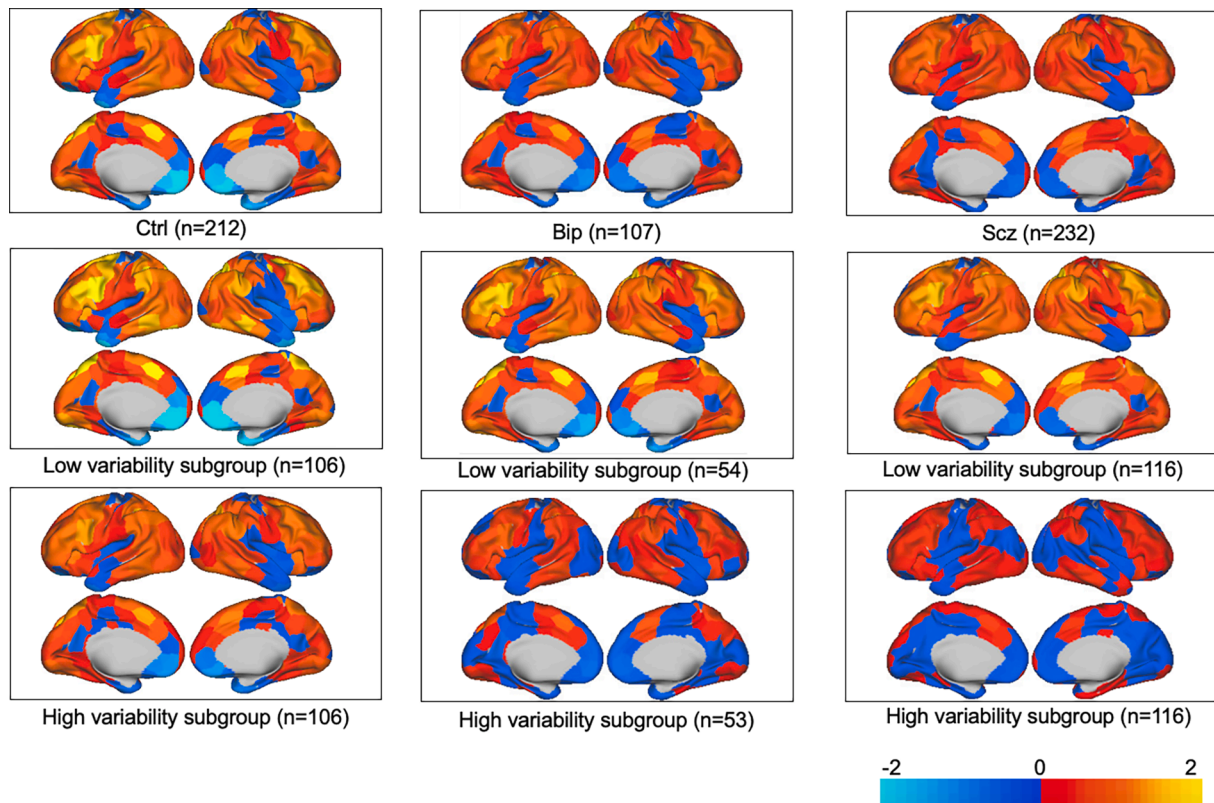


Fig. 3. Parcellated T -map activity during the N -Back task. Within-group averages for the parcellated contrast t -maps are presented for all control (Ctrl) participants, individuals with bipolar disorder (Bip), and individuals with schizophrenia (Scz) (top row left to right). Low variability (middle row) and high variability (bottom row) subgroups are also presented for each diagnostic category. Results are projected onto surface space and thresholded from $t = -2$ to 2 for improved visualization. Low variability patient subgroups did not appear to differ in their functional activity from the control subgroup. High variability patient subgroups showed substantially less activity.

3.3. High and low variability subgroups

To visualize the effects of individual variability on functional brain activity, participants were separated by median split based on mean correlational distance into equal groups of high and low variability (schizophrenia_{median} = 0.66, bipolar disorder_{median} = 0.61, control_{median} = 0.58). In line with our previous work, the low variability patient subgroups did not appear to differ from the control group in 2-Back – 1-Back activity, whereas the high variability patient subgroups, in contrast, seemed to show substantially less activity overall (particularly, less activation in WM networks, and less suppression within the default mode network)(see Fig. 3). This can further be interpreted as high variability patients having a shift in functional topography, aligning with recent literature surrounding greater individual variations in the spatial organization of brain networks and psychiatric disorders (Dickie et al., 2018; Nawaz et al., 2021).

3.4. N -Back task activity via correlational distance Within-Groups:

3.4.1. Control group:

The addition of nonlinear effects of age did not significantly contribute to the model (age² $\Delta R^2 = 0.0015$, $p = 0.241$; age³ $\Delta R^2 = 0.0017$, $p = 0.296$) and thus was not included. Mean correlational distance of functional brain activity across control participants was significantly associated with 2-Back D' ($F(1,206) = 28.54$, $p = 2.42e-07$) and FD ($F(1,206) = 10.59$, $p = 0.0013$).

3.4.2. Bipolar disorder group:

Multicollinearity was not present between age and illness duration ($VIF < 5$). The addition of nonlinear effects of age and illness duration

did not significantly contribute to the model (age² $\Delta R^2 = -0.0063$, $p = 0.740$; age³ $\Delta R^2 = -0.0078$, $p = 0.638$; illness duration² $\Delta R^2 = -0.0019$, $p = 0.393$; illness duration³ $\Delta R^2 = -0.0079$, $p = 0.643$) and thus were not included. Mean correlational distance of functional brain activity across individuals with bipolar disorder was significantly associated with 2-Back D' ($F(1,96) = 34.06$, $p = 7.23e-08$) and FD ($F(1,96) = 4.89$, $p = 0.029$).

3.4.3. Schizophrenia group:

Multicollinearity was not present between age and illness duration ($VIF < 5$). The addition of nonlinear illness duration effects as well as PANSS subscales did not significantly contribute to the model and thus were not included. However, cubic effects of age significantly improved the model and were included (see Table 2 for hierarchical regression). Mean correlational distance across individuals with schizophrenia was significantly associated with FD ($F(1,203) = 8.88$, $p = 0.0032$) and lower 2-Back D' ($F(1,203) = 39.97$, $p = 1.61e-09$). Additionally, a significant relationship between mean correlational distance and age³ was found ($F(1,203) = 4.85$, $p = 0.029$)(Fig. 4A); such finding was not present in bipolar disorder or control groups(Fig. 4B). Notably, mean correlational distance was significantly associated with illness duration ($F(1,203) = 4.93$, $p = 0.027$)(Fig. 4C) even when age was included in the model.

4. Discussion

The present study leveraged an existing large sample to examine the impact of age and illness duration on individual variability in functional brain activity during an N -back WM task, in controls and individuals with schizophrenia or bipolar disorder. Contrary to our first hypothesis,

Table 2
Hierarchical regression for schizophrenia model.

	F-Values	P-values	Adjusted R ²	ΔR ²	Model significance
<i>Step 1</i>			0.2947		
Age	5.40	0.021*			
Age:2-Back D'	1.76	0.186			
<i>Step 2</i>			0.3049	0.0102	Anova (Step1, Step2) p = 0.022*
Age	1.38	0.242			
Illness Duration	6.92	0.009*			
Age:2-Back D'	1.72	0.191			
Illness Duration:2-Back D'	0.83	0.363			
<i>Step 3</i>			0.3099	0.005	Anova(Step2, Step3) p = 0.117
Age	4.14	0.043*			
Age ²	2.48	0.117			
Illness Duration	6.91	0.009*			
Age:2-Back D'	1.72	0.191			
Illness Duration:2-Back D'	0.65	0.421			
** <i>Step 4</i>			0.3226	0.0177	Anova(Step2, Step4) p = 0.0267*
Age	6.27	0.013*			
Age ²	5.52	0.012*			
Age ³	4.85	0.029*			
Illness Duration	4.93	0.027*			
Age:2-Back D'	2.15	0.144			
Illness Duration:2-Back D'	0.90	0.344			
<i>Step 5</i>			0.3213	-0.0013	Anova(Step4, Step5) p = 0.436
Age	7.10	0.008*			
Age ²	5.94	0.016*			
Age ³	5.06	0.026*			
Illness Duration	3.51	0.062			
Illness Duration ²	0.61	0.436			
Age:2-Back D'	1.77	0.185			
Illness Duration:2-Back D'	0.57	0.451			
<i>Step 6</i>			0.3183	-0.0043	Anova(Step4, Step 6) p = 0.707
Age	5.13	0.025*			
Age ²	4.20	0.042*			
Age ³	3.58	0.060			
Illness Duration	0.62	0.431			
Illness Duration ²	0.01	0.911			
Illness Duration ³	0.09	0.766			
Age:2-Back D'	1.77	0.185			
Illness Duration:2-Back D'	0.58	0.445			
<i>Step 7</i>			0.3022	-0.0204	Anova(Step4, Step7) p = 0.868
Age	6.89	0.009*			
Age ²	6.44	0.012*			
Age ³	5.79	0.017*			
Illness Duration	3.26	0.073			
PANSS General	0.03	0.873			
PANSS Negative	1.42	0.235			
PANSS Positive	0.01	0.931			
Age:2-Back D'	2.60	0.109			
Illness Duration:2-Back D'	0.88	0.350			
PANSS General: Illness Duration	0.01	0.915			
PANSS Negative: Illness Duration	0.03	0.874			
PANSS Positive: Illness Duration	0.08	0.784			

Note. A hierarchical regression was performed to evaluate the linear and nonlinear effects (quadratic and cubic) of age (Step 1, 3 and 4) and illness duration (Step 2, 5 and 6) on mean correlational distance. Additionally, Positive and Negative Syndrome Scale (PANSS) subscale scores, as well as interactions with illness duration were included (Step 7) to determine the effect of symptom severity on mean correlational distance. Sex, 2-Back D', and FD are included as covariates in all models. ANOVA performed to compare models and determine the model that best represents the data (** =chosen model).

the relationship between age and variability in brain function did not differ between groups. This finding suggests a relationship between age and brain function variability that is not related to diagnosis. In support of our second hypothesis, increased variability in brain function was associated with illness duration in the schizophrenia group, but not the bipolar disorder group, even after age was accounted for in the model. This suggests alterations in brain function driven by a longer illness duration in schizophrenia beyond the effects of normal aging.

Recent work has shown that illness duration in schizophrenia may be related to cognitive deterioration (Altamura et al., 2015) and brain abnormalities (Altamura et al., 2011). The majority of the existing literature has investigated structural correlates of illness duration (Molina

et al., 2004; Sapara et al., 2007; Premkumar et al., 2006; Premkumar et al., 2008). However, as structural abnormalities do not have a clear relationship with functional deficits (Diwadkar et al., 2011; Fornito et al., 2012; Ikuta et al., 2014) and functional and structural changes may contribute independently to the neurobiology of schizophrenia (Diwadkar et al., 2011; Zhuo et al., 2017), the functional implications of structural brain changes are ambiguous. The effects of illness duration may be greater in regions associated with cognition (Antonova et al., 2004). The frontal lobes in particular have been shown to be vulnerable to the progressive effects of schizophrenia-related morbidity (Molina et al., 2004; Premkumar et al., 2006), with regional dysconnectivity (Woodruff et al., 1997) as well as a decline in structural integrity and

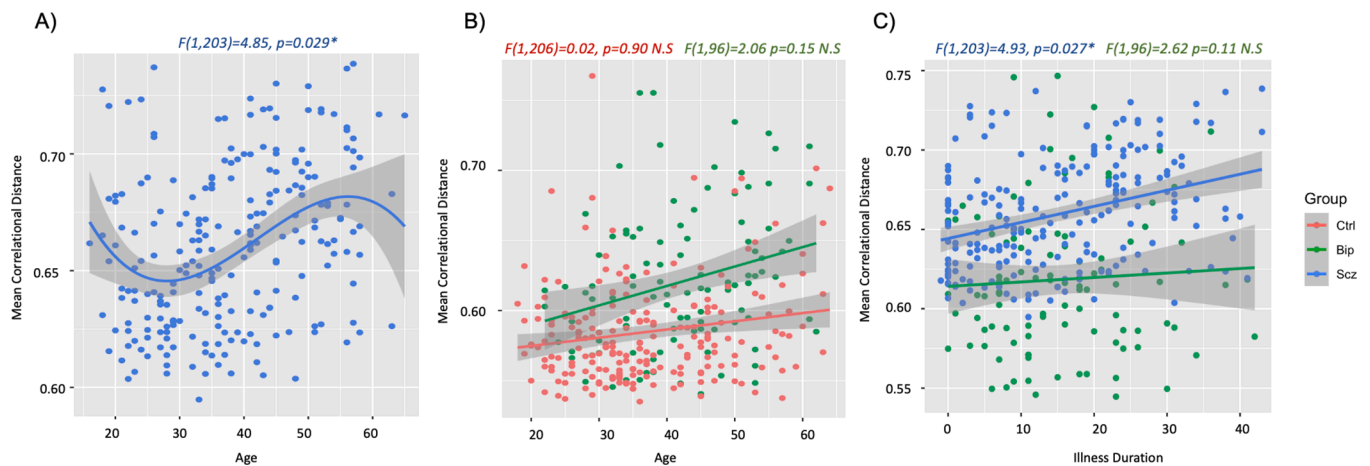


Fig. 4. Mean correlational distance associated with age and illness duration in schizophrenia. A) Cubic relationship between age and mean correlational distance in the schizophrenia (Scz) group. B) Such relationship was not found in bipolar disorder (Bip) or control (Ctrl) groups. Dots represent individual data points. The ribbon surrounding the regression line indicates a 95% confidence interval. C) Mean correlational distance was significantly associated with illness duration in the Scz group, but not in the Bip group. Dots represent individual data points. The ribbons surrounding the regression lines indicate a 95% confidence interval.

function as illness persists (Elsabagh et al., 2009; Premkumar et al., 2008). Consistently, illness duration is a significant predictor of cognitive deficits (Irani et al., 2011), with deterioration in cognitive abilities over the course of illness (Altamura et al., 2015; Almeida et al., 2019; Wood et al., 2002; Mathes et al., 2005). Our findings suggest illness duration-related changes in brain function that may lead to greater variability in patterns of brain activity. Such idiosyncratic activity could be a consequence of deterioration of core cognitive regions with concomitant compensation from other networks. This is further supported by our current and prior findings of high variability individuals demonstrating lower activation in task-relevant networks (Gallucci et al., n.d.).

Compensation for greater heterogeneity following decreased neural circuit function related to illness duration is supported by general aging literature. Healthy aging is associated with alterations in WM neural networks (Grady and Craik, 2000), in which the recruitment of additional brain regions may reflect a compensatory mechanism to counteract age-related neurocognitive decline (Vermeij et al., 2012). For instance, studies have found that older individuals demonstrate more bilateral patterns of activation in frontal regions of the WM circuit compared to younger individuals, where contralateral recruitment is needed during task performance (Vermeij et al., 2012; Reuter-Lorenz et al., 2000; Cabeza et al., 2004). Notably, despite normal aging and illness duration being closely related (Premkumar et al., 2008), there is only relatively small literature to date specifically examining the influence of both age and illness duration on neural activation during cognitive performance in individuals with schizophrenia (Elsabagh et al., 2009). A recent investigation regarding the influence of disease progression and aging on cognition in individuals with schizophrenia revealed that performance is more strongly affected by illness duration than aging (Kaneda et al., 2013). Our study was able to assess changes in variability related to age and illness duration, suggesting an additive consequence of illness duration beyond the normal effects of aging. In contrast to studies that solely examined age effects and suggested an ‘advanced aging’ mechanism (Hawco et al., 2017; Kochunov et al., 2013), our results imply the increased influence of age in schizophrenia may be further explained by illness-related determinants. The nonlinear relationship found between mean correlational distance and aging could perhaps reflect a normative phase or stabilization in early life prior to long-term functional disturbances, though this interpretation remains speculative as the available data was cross-sectional as opposed to longitudinal.

In contrast to studies that found a greater decline in structural and functional correlates of aging in individuals with schizophrenia than

controls (Kawakami et al., 2014; Hawco et al., 2017; Wang et al., 2021), our findings suggest normal aging processes with regards to functional brain activity when illness duration effects are accounted for. Several aspects of cognitive processing become less efficient with increasing age (Salthouse, 1996), including an age-related decline in fluid cognition (Park et al., 2002) which is particularly prevalent in domains with high processing demands, such as WM (Salthouse, 1990). Evidence has suggested the decline in WM experienced in older individuals is related to the failure of core cognitive brain regions to modulate activity when faced with increased cognitive demand (Rieck et al., 2022). Age-related region recruitment may also reflect a difficulty in engaging specialized neural systems (Logan et al., 2002). Studies have demonstrated non-selective activation of frontal regions persists in older adults during memory tasks, in which additional recruitment is needed due to difficulties in engaging typically activated brain regions during the task (Grady and Craik, 2000; Park et al., 2001). Our results align with the existing literature, where greater individual variability may be due to older individuals relying on alternative regions and potentially simpler cognitive strategies due to age-related deficits in their task-relevant networks.

Illness duration effects were not found in the bipolar disorder group, indicating that findings were specific to schizophrenia. The inclusion of bipolar disorder as a ‘psychiatric control group’ with some similarities with regard to biological factors (Janssen et al., 2008), based on high rates of comorbidity (Laursen et al., 2009), overlapping etiology (Laursen et al., 2007), and clinical symptoms (Misiak et al., 2016) made it possible to disentangle effects that are specific to schizophrenia as opposed to non-specific effects of psychiatric illnesses. As previous studies examining brain age have found structural alterations most prominent in psychosis compared to bipolar disorder (Shahab et al., 2019; Nenadić et al., 2017; Hajek et al., 2019), our results align with such literature and support findings regarding schizophrenia-specific biological changes which may be related to poorer long-term functional outcomes (Altamura et al., 2015) and reduced lifespan (Moradi et al., 2018).

Several limitations of our study should be noted. Illness duration was quantified as an individual’s chronological age minus the age of onset. Despite improvements in diagnostic procedures, a recent meta-analysis revealed an estimated six-year delay in diagnosis of bipolar disorder (Dagani et al., 2017), in comparison to that of 8–48 weeks for psychosis (Dell’Osso et al., 2016). Diagnostic delays have been associated with factors such as absence of a family history (Tondo et al., 2014), lack of accessibility to mental health services (Murru and Carpinello, 2018), and misdiagnosis due to the presence of previous depressive episodes

(Fico et al., 2021). As such, illness duration is considered an estimate, where the time span from disorder onset to proper diagnosis cannot be accounted for. Additionally, as detailed medical history was not available, conclusions that can be drawn from this study are limited by potential effects of medication (Almeida et al., 2019) or other secondary effects such as sedentary lifestyle, social isolation, etc. that may play an important moderating role. Motion is also an ongoing challenge in many studies of brain structure and function (Savalia et al., 2017), where micro-movements of the head strongly affect neuroimaging outcomes (Parkes et al., 2018). Our study aimed to account for this confound by correcting for motion at several stages of the analysis (inclusion of movement regressors in the GLM, and FD as an explanatory variable in the linear models). Further, data was taken from a pre-existing larger sample that utilized a 1.5 Tesla scanner for image acquisition. Although 3 Tesla is more often used in research settings due to improvements in signal-to-noise ratio, the included sample size of 551 and robust N-Back task effects provided sufficient power to compensate for lower sensitivity. Lastly, as functional brain activity during WM performance was explored, findings cannot be extended to cognition in general. Future work utilizing datasets with many fMRI tasks across multiple cognitive domains may aid in determining whether variability in functional activity is generalizable across different cognitive facets.

To our knowledge, this was the first study that assessed the impact of illness duration on idiosyncratic functional brain activity during a neurocognitive task in schizophrenia. These findings attempt to disentangle the effects of aging as opposed to illness duration. Here, greater individual variability observed specifically within schizophrenia may be a result of adverse effects associated with longer illness duration, beyond aging. There is opportunity for future studies to solidify this tentative differentiation, as it may be beneficial to look at the neurobiological variability in age-matched individuals with schizophrenia that have different times of onset. If greater idiosyncrasy of functional brain activity in schizophrenia is indeed a negative implication of illness duration, one may expect separable neurobiological profiles between early vs late-onset, regardless of similarities in age. Additionally, subsequent research should investigate the role that antipsychotic medication plays, where the type of treatment and length of exposure may influence the relationship between individual variability and illness duration. Finally, new treatments could be tested in relation to effects on idiosyncratic brain function as a potential proxy that might serve to index illness effects over time.

CRedit authorship contribution statement

Julia Gallucci: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Edith Pomarol-Clotet:** Conceptualization, Writing – review & editing. **Aristotle N. Voineskos:** Writing – review & editing. **Amalia Guerrero-Pedraza:** Data collection. **Silvia Alonso-Lana:** Data collection. **Eduard Vieta:** Data collection. **Raymond Salvador:** Conceptualization, Writing – review & editing. **Colin Hawco:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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