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Feedback-loop between psychotic symptoms and brain volume: A cross-lagged panel model study

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ABSTRACT

Brain structural changes are known to be associated with psychotic symptoms, with worse symptoms consistently associated with brain volume loss in some areas. It is not clear whether volume and symptoms interfere with each other over the course of psychosis. In this paper, we analyse the temporal relationships between psychosis symptom severity and total gray matter volume. We applied a cross-lagged panel model to a public dataset from the NUSDAST cohorts. The subjects were assessed at three-time points: baseline, 24 months, and 48 months. Psychosis symptoms were measured by SANS and SAPS scores. The cohort contained 673 subjects with schizophrenia, healthy subjects and their siblings. There were significant effects of symptom severity on total gray matter volume and vice-versa. The worse the psychotic symptoms, the smaller the total gray volume, and the smaller the volume, the worse the symptomatology. There is a bidirectional temporal relationship between symptoms of psychosis and brain volume.

1. Introduction

Several brain volume alterations have been reported in the course of schizophrenia. Both intracranial and total brain volume are significantly decreased in schizophrenic individuals (Haijma et al., 2013). More specifically, temporo-parietal and pre-frontal areas seem to be most affected (Castro-de-Araujo and Kanaan, 2017). Though reduced volumes in people with schizophrenia are also commonly reported in the insula, the superior temporal gyrus (STG), the gyrus rectus, and the anterior cingulate cortex (ACC) when compared with healthy controls (Kim et al., 2017). Gray matter volume alterations are less pronounced in antipsychotic naive patients (Haijma et al., 2013). These findings suggest that brain volume alterations may be part of neurodegenerative processes that result in worse clinical outcomes (Castro-de-Araujo et al., 2020).

Some of these changes are associated with symptom severity. It has been found that the left anterior STG was inversely correlated with psychotic symptoms, whereas the right posterior STG was positively correlated with negative symptoms (Kim et al., 2003). The same author later reported that gray matter volumes of the insula, STG, and ACC and white matter volumes of the STG were negatively correlated with the duration of the disorder (Kim et al., 2017). Studies on the effect of untreated psychosis on brain volume differences can potentially be informative for this discussion of the temporal relationship between symptoms and structural change. Longer duration of untreated psychosis (DUP) is related to worse clinical outcome, and worse treatment response. An association between DUP and structural change has been proposed, including purported mechanisms (Anderson et al., 2014), but the subject remains largely uncertain due to difficulties with methodological approaches and small numbers of subjects (Bora et al., 2018; Murru and Carpiniello, 2018; Rapp et al., 2017).

Causal relationships of symptom severity and brain volume are hard to demonstrate. In particular, the temporal direction of the relationship has not been well described to date, and may not be simple. Since schizophrenia is thought of as a syndrome resulting from abnormalities in several systems (neurotransmitter, genetic, and psychopathological) it may be expected that brain alterations will worsen over time and a feedback loop be formed with symptom severity.

We are used to inferring causality in psychiatry through methods

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such as randomized controlled trials (RCTs), or Mendelian randomization (MR) (Castro-de-Araujo et al., 2022). However, these methods are not always feasible, either for high costs and logistical reasons in RCTs, or because of the absence of genetic information in cohorts. A third line of methodology that allows for causal inference when RCTs and MRs are not available is cross-lagged panel models (CLPM). This method controls for autoregressive effects (Granger, 1969) and was later extended to include random intercepts (RI-CLPM, Hamaker et al., 2015). RI-CLPM is useful for causal inference in longitudinal designs, and rarely used in psychiatry. In this paper, we apply a RI-CLPM (Baribeau et al., 2022) implemented in structural equation modelling (SEM) to investigate the association between symptom severity and gray matter total volume over three time-points in a data set including people with schizophrenia, their siblings and healthy subjects. Since this method controls for autoregressive effects, or the effect of psychosis at one time-point on the next measurement occasion and the effect of the brain volume on the next occasion brain volume, it might help reveal smaller effects between these, that otherwise wouldn't be captured in case-control designs, for example.

2. Methods

2.1. Data source

Subjects from the NUSDAST data set (NU Schizophrenia Data and Software Tool Federation using BIRN Infrastructure, North-Western University) (Wang et al., 2013) were used for this analysis. These are made accessible through the online interface SchizConnect (http://schizconnect.org) (Ambite et al., 2015). This dataset comprises subjects recruited by advert from the community. Diagnosis was made according to DSM-IV criteria using a semi-structured interview, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997), in consensus between a psychiatrist and a research assistant. Exclusion criteria were: substance abuse/dependence diagnosis coded by DSM-IV, a clinically unstable mental state or other severe clinical condition, present or past head injury, or a diagnosis of mild (or greater) mental retardation by DSM-IV criteria (Harms et al., 2007). Furthermore, it comprised two cohorts with identical selection procedures, which were later anonymized and made available online in compliance with the Health Insurance Portability and Accountability Act (Csernansky et al., 2002; Harms et al., 2007). Data collection happened between 1998 and 2006, and complete explanation of the procedure is presented elsewhere (Wang et al., 2013). For this analysis we used all subjects, including participants with schizophrenia, controls, and their siblings who had completed both psychological assessment and neuroimaging. This resulted in a total of 673 subjects for this study, all from North America.

2.2. Neuroimaging and symptom severity

The NUSDAST data set includes MRI scans from a 1.5 T Vision scanner platform (Siemens Medical Systems) (Ambite et al., 2015). FreeSurfer version 3.0.4, (http://surfer.nmr.mgh.harvard.edu/), was used to obtain cortical parcellations, which automates neuroanatomical labelling of locations on a cortical surface model (Desikan et al., 2006; Wang et al., 2013). Volumetric information was provided in mm^3.

Psychotic symptomatology was assessed with the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983). Raw scores for SAPS and SANS were summed at each time point and included in the model.

2.3. Data analysis

We used R version 4.1.3 (https://cran.r-project.org/) in all further steps of our analyses. The volumetric data information and the symptom scores were provided in separate files, which were manually linked using a data dictionary also provided by the authors of the data set. Descriptive analysis of the variables was carried out, including statistical tests between groups (baseline, 24 months, and 48 months). Means and standard deviation (SD) are reported for continuous variables; frequencies and absolute counts are reported for categorical variables. For continuous variables an ANOVA was performed, and for categorical variables, chi-square contingency table tests were used (Table 1). Before SEM estimation, data was scaled.

All analyses were performed using R, with the *umx* package used for SEM (structural equation modelling) analysis (Bates et al., 2019). The estimation was based on full information maximum likelihood (FIML) with the NPSOL optimizer. We checked identification using an OpenMx utility (mxCheckIdentification) (Hunter et al., 2021). Missingness increased with time points, all together (including all variables and all waves) it reached 38.4%, mainly due to time point 48 months. Although higher at the last wave due to drop-outs, the use of FIML should reduce the impact of missing values as the likelihood is calculated row-wise incorporating information from previous study waves. Age was residualized on the observed variables, therefore results are controlled for age.

2.4. Model specification

The model specification can be seen in Fig. 1. It has three study time-points, each wave including information on the observed brain volumes and a latent variable reflective of the raw sum of SAPS and SANS scores for each wave, thus capturing the dimensional aspect of psychosis (Castro-de-Araujo et al., 2016). This model can be seen as a multilevel model, where individual measures are nested in each time-point. The latent variable and the observed brain volumes are allowed to correlate within waves. Between waves, there are the autoregressive paths or regressions between variables with themselves in the next wave; and causal paths (or cross-lagged paths), which are the paths from either the psychosis latent or brain volume in one wave to brain volume or psychosis in the next wave. The former are important to account for the invariance in psychosis or in volume that persists between study waves, the latter represents what we are interested the most, the causal effect of psychosis on volume between time points. Thus, we say, we are calculating the causal effects, controlling for autoregressive effects, and allowing variables to interfere in each other at each wave (the correlation paths, Fig. 1). The model was fitted to all the data in the dataset (including healthy controls and siblings). The rationale for this is that psychosis can be considered a dimensional construct, varying in degree from absent to severely psychotic. The autoregressive paths control for the invariance of the two variables of interest; all variance that is then passed on to the next wave is due to the changes in psychosis and in brain volume.

Finally, there are two random intercepts, with paths to the psychosis latent or to the measured brain volume. These intercepts are there to model across all waves stability. This approach reduces bias in the causal estimates according to Hamaker (2005) and improves on the original autoregressive model (Granger, 1969).

3. Results

There was a decrease in the mean of the total gray volume over time. On the first visit, the average volume was 622,496.23 mm^3 (SD 76,198.12); on the last, the average volume was 579,427.76 mm^3 (SD 579,427.76). Most of the individuals were African Americans (58.5%), single (75.6%), males (52.2%), and with age on average 32 years (SD 13.62) d (28.5%) (Table 1).

The model fit was assessed through typical indexes. It presented a Comparative Fit Index (CFI) = 0.955 (satisfactory) (Ben-Shachar et al., 2020), Tucker-Lewis Index (TLI) = 0.9 (satisfactory) (Schumacker and Lomax, 2015) and Root Mean Square Error of Approximation (RMSEA) = 0.068 (satisfactory) (Steiger, 2007). Fig. 1 and Table 2 show

Table 1
Demographics stratified by study wave.

n	Overall	Baseline	24 Months	48 Months	P-value
	673	426	190	57	
Total gray vol mm^3 (mean (SD))	612159.74 (76340.94)	622496.23 (76198.12)	605210.75 (77914.06)	579427.76 (61104.37)	0.002
SAPS (mean (SD))	11.78 (18.00)	11.53 (17.50)	11.82 (17.85)	12.68 (20.60)	0.926
SANS (mean (SD))	16.16 (19.24)	16.71 (19.83)	15.42 (18.72)	16.30 (18.92)	0.841
Condition (%)					0.007
No known disorder (healthy controls)	262 (38.9)	158 (37.1)	71 (37.4)	33 (57.9)	
Schizophrenia	265 (39.4)	166 (39.0)	76 (40.0)	23 (40.4)	
Sibling of no known disorder (healthy controls)	89 (13.2)	61 (14.3)	28 (14.7)	0 (0.0)	
Sibling of participant with schizophrenia	57 (8.5)	41 (9.6)	15 (7.9)	1 (1.8)	
Race (%)					0.054
Caucasian	248 (36.8)	160 (37.6)	61 (32.1)	27 (47.4)	
African American	394 (58.5)	240 (56.3)	125 (65.8)	29 (50.9)	
Hispanic	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	
Native American	6 (0.9)	3 (0.7)	2 (1.1)	1 (1.8)	
NA	24 (3.6)	22 (5.2)	2 (1.1)	0 (0.0)	
Ethnicity (%)					0.940
NA	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	
Hispanic	9 (1.4)	5 (1.2)	3 (1.6)	1 (1.8)	
Non-Hispanic	639 (98.5)	398 (98.5)	185 (98.4)	56 (98.2)	
Marital status (%)					0.078
Other	7 (1.0)	5 (1.2)	2 (1.1)	0 (0.0)	
Single	509 (75.6)	322 (75.6)	149 (78.4)	38 (66.7)	
Married	43 (6.4)	29 (6.8)	9 (4.7)	5 (8.8)	
Divorced	58 (8.6)	31 (7.3)	20 (10.5)	7 (12.3)	
Separated	11 (1.6)	7 (1.6)	2 (1.1)	2 (3.5)	
Widowed	6 (0.9)	2 (0.5)	2 (1.1)	2 (3.5)	
Unknown	9 (1.3)	4 (0.9)	3 (1.6)	2 (3.5)	
NA	30 (4.5)	26 (6.1)	3 (1.6)	1 (1.8)	
Sex (%)					0.062
Female	298 (44.3)	188 (44.1)	85 (44.7)	25 (43.9)	
Male	351 (52.2)	216 (50.7)	103 (54.2)	32 (56.1)	
NA	24 (3.6)	22 (5.2)	2 (1.1)	0 (0.0)	
Age (mean (SD))	31.89 (13.62)	30.40 (13.03)	32.01 (13.89)	42.05 (12.58)	<0.001
Years of schooling (mean (SD))	13.20 (2.75)	13.09 (2.76)	13.21 (2.73)	14.06 (2.60)	0.057

Main demographic characteristics of the sample, stratified by study wave. Group comparison was performed using chi-squared tests for the categorical variables and ANOVA for the continuous variables. n, number of observations; SD, standard deviation (SD).

standardised estimates in each path. Fig. 2 is a visualisation of the causal and autoregressive paths in a forest plot. First, we can see that the variances for the random intercepts varied, the random intercept for psychotic symptoms was lower (0.51), than the random intercept for gray volume (0.98). These represent the across all waves variances, and can be interpreted as showing that participants varied more in terms of brain volume across waves than in terms of psychotic symptomatology. It can be seen in Fig. 2 that the causal paths from the latent variable representing psychotic symptomatology at baseline to volume at 24-month follow-up was significant. The autoregressive paths from total gray volume at baseline to 24-month follow-up and psychosis at 24-month follow-up to psychosis at 48-month follow-up were significant. All causal paths are negative, the standardised path coefficient from psychotic symptoms at baseline to brain volume at 24 months was −0.203 and from psychosis at 24 months to brain volume at 48 months was −0.143, both large effects. The causal path from total gray volume at baseline to psychotic symptoms at 24 months was −0.002, the total gray volume at 24 months to psychotic symptomatology at 48 months was −0.04 (Fig. 2). These findings suggest that there is an effect of symptomatology on brain volume over time, and that this relationship is of a feedback type, where volume will in turn affect symptomatology on later waves.

We residualized age on the observed variables, hence controlling for age. Estimates obtained for causal paths were consistent with what we found before controlling for age. However, some autoregressive paths turned negative (Supplemental Material). We also performed model fit comparisons between the full model described above, and the model fitted to the dataset comprising only each gender, of the participants with schizophrenia separately (Table 3). There was no significant difference between the full model and the smaller sets. However, all the other models had worse resolution, with the optimizer not reaching a reasonable solution, resulting in missing standard errors or confidence intervals. We therefore report the full model here.

4. Discussion

This is a longitudinal study using structural equation model to assess the effect of brain volume on symptom severity using a sample that included individuals with schizophrenia, their siblings and healthy subjects. This model was specified to detect the effect of each of these variables on each other in a panel structure using random intercepts. This method is known to produce unbiased results within the CLPM methods (Hamaker et al., 2015). We found reciprocal associations between symptom severity and gray volume over time. Symptoms had a mild effect on volume, which decreased over time. Similarly, total gray volume had a small negative effect on symptom severity, counteracting the effect. One of four causal paths was significant, and two of four autoregressive paths were significant.

The RI-CLPM model is underutilized in psychiatry. We are much more focused in exploring possible causal links through RCTs and MRs. However, RCTs are not always feasible due to logistics (e.g. marshalling homogeneous enough participants) and classical MR cannot evaluate bidirectional associations, among other limitations. This paper uses RI-CLPM to examine the relationship between symptom severity and brain volume in participants with schizophrenia and their siblings. RI-CLPM has been recently used in obsessive compulsive disorder symptoms and depression (Simkin et al., 2022), brain trauma and depression (Juengst et al., 2017), and in the causal investigation of the effect of N-Acetylcysteine in depressive symptom reduction (Tomko et al., 2020).

Veijola et al. (2014) possibly has the most comprehensive

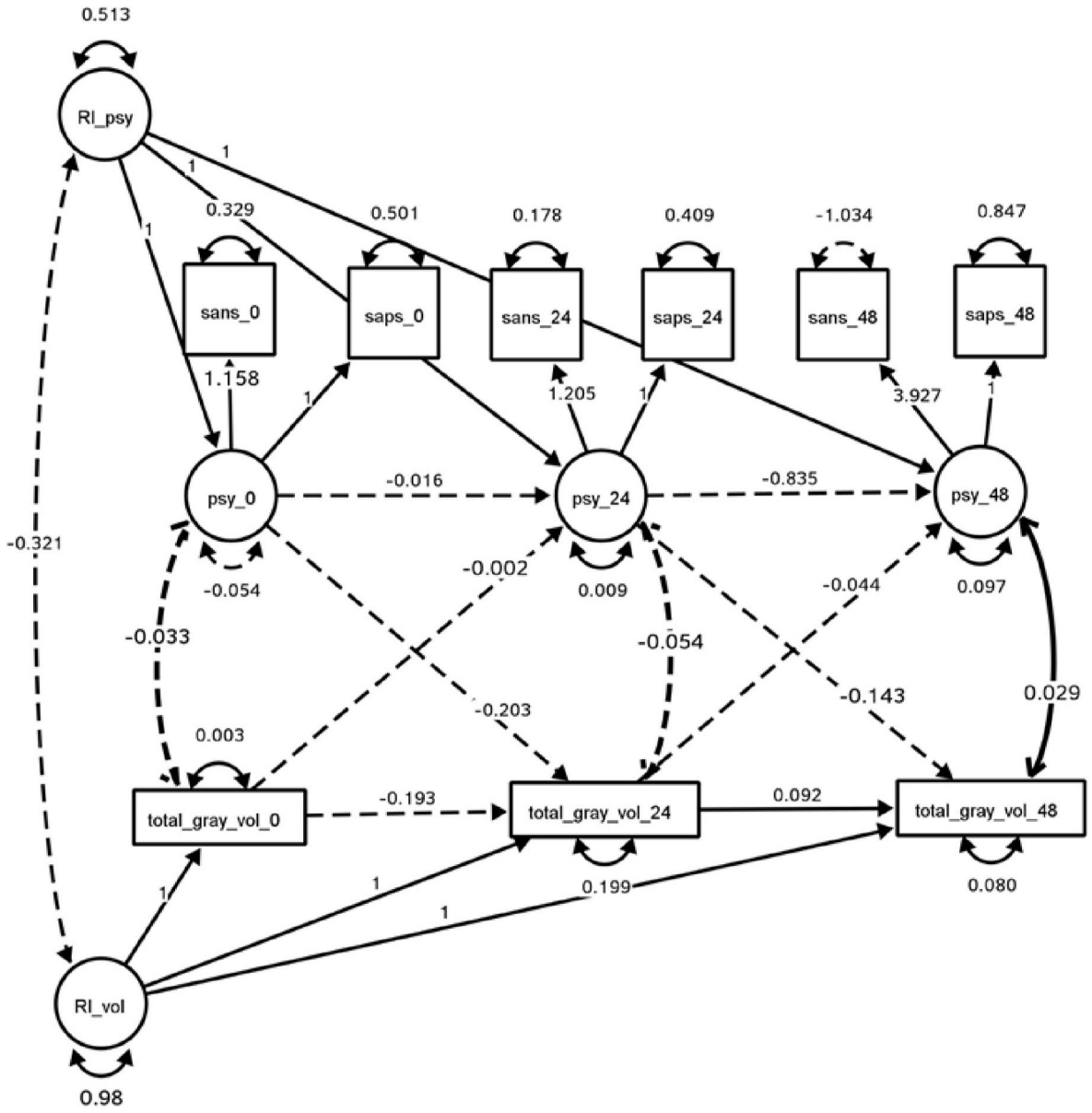

Fig. 1. Cross-lagged panel model specification with standardized coefficient estimates. Psy, psychotic symptoms: total_gray_vol, total gray matter volume. RI_psy, RI_vol: random intercepts. Saps: Scale for the Assessment of Positive Symptoms, sans: the Scale for the Assessment of Negative Symptoms. Raw scores for SAPS and SANS were summed at each time. Dashed lines: negative coefficients. Mean structure not shown. Of interest are the cross-paths, these represent potential causal effects between variables. The outer part of the model has two random intercepts, which play two roles: they reduce bias in the estimation of the causal path, and allow us to calculate the rate of change in symptoms or in volume over study waves.

investigation of the temporal effect of brain volume reduction on symptomatology (Veijola et al., 2014). They found no association between symptom severity, functional level, and decline in cognition with brain volume reduction in schizophrenia, in a study that followed 33 participants. Furthermore, they found that the volume reduction was better explained by medication use. Unfortunately, our studies cannot be directly compared due to differences in data sets, such as the absence of treatment information and the number of observations. But it is possible that they were not able to detect the effect due to the number of participants in their study.

The causal paths reported here are summaries of the more circumscribed (regional) volumetric changes' effect on symptom severity and vice-versa. A more fine-grained study could potentially reveal the specific regions which carry the most effects, perhaps using functional neuroimaging. Our design does not allow specific conclusions regarding positive or negative symptomatology on brain volume change to be drawn, however it reveals an overall symptom severity association with such volume changes.

Our study results need to be interpreted in the context of some limitations. This model does not allow for inclusion of other sociodemographic controls, like SES. The addition of these variables would have rendered the model unidentified. Additionally, the number of individuals was relatively small and mostly African American, which limits the generalizability of our findings. Medication information was not available for analysis, and medication with anti-psychotics is known to reduce brain volume over the course of treatment (Veijola et al., 2014). It should be stated that the psychotic symptom assessment is a snapshot in time and does not capture the full variance of symptom severity between time points. If a participant had an episode between measurements and had improved in the follow-up, this variation would not be captured in the model tested and would impact conclusions about the association between symptoms and brain volume. Finally, the

Table 2
Demographics stratified by condition.

n	No Disorder	Schizophrenia	Sibling of healthy	Sibling of participant with schizophrenia	p-value
	262	265	89	57	
Visit (%)					0.007
Baseline	158 (60.3)	166 (62.6)	61 (68.5)	41 (71.9)	
24-month follow-up	71 (27.1)	76 (28.7)	28 (31.5)	15 (26.3)	
48-month follow-up	33 (12.6)	23 (8.7)	0 (0.0)	1 (1.8)	
Total gray vol mm^3 (mean (SD))	623597.08 (65518.54)	577218.64 (82473.33)	660048.93 (48159.85)	637187.99 (66603.40)	<0.001
SAPS (mean (SD))	0.31 (1.01)	24.31 (19.42)	0.20 (0.74)	0.67 (1.78)	<0.001
SANS (mean (SD))	2.94 (5.20)	30.57 (18.93)	2.08 (3.49)	10.85 (13.62)	<0.001
Sex (%)					<0.001
Female	120 (45.8)	87 (32.8)	62 (69.7)	29 (50.9)	
Male	135 (51.5)	167 (63.0)	24 (27.0)	25 (43.9)	
NA	7 (2.7)	11 (4.2)	3 (3.4)	3 (5.3)	
Age (mean (SD))	34.62 (14.71)	35.33 (12.71)	20.33 (3.39)	21.19 (3.81)	<0.001
Years of schooling (mean (SD))	14.42 (2.65)	12.21 (2.43)	12.97 (2.56)	12.46 (2.70)	<0.001

Main demographic characteristics of the sample, now stratified by condition. Group comparison was performed using chi-squared tests for the categorical variables and ANOVA for the continuous variables. n, number of observations; SD, standard deviation (SD).

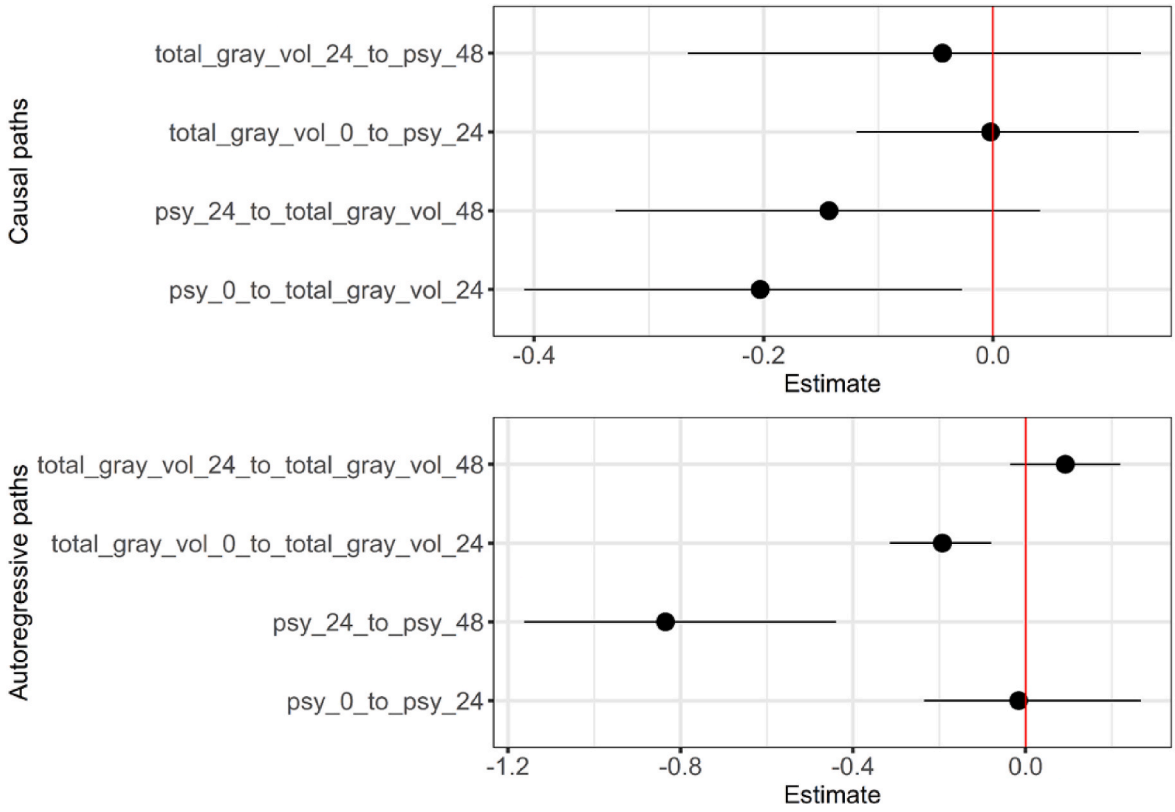

Fig. 2. Causal and autoregressive paths, standardized coefficient estimates with confidence intervals.

Table 3
Model comparisons.

Model	EP	Δ Fit	Δ df	p	AIC	Δ AIC	Compare with Model	Fit units
RIxCLPM_with_3_timepoints	38				2513	0		-2lnL
males	38	−1069.766	−506		1443	−1069.766	RIxCLPM_with_3_timepoints	-2lnL
females	38	−1546.509	−604		966	−1546.509	RIxCLPM_with_3_timepoints	-2lnL
Schizophrenia	38	−1185.547	−622		1327	−1185.547	RIxCLPM_with_3_timepoints	-2lnL

Model comparisons. The age controlled RI-CLPM was compared to the model fit only to males, females, and subjects with schizophrenia. There was no significant difference in fit (−2 log-likelihood) between models (p column).

inter-rater reliability scores on the SANS/SAPS ratings were not available.

These findings suggest that controlling symptomatology might be important over the entire course of the disorder, as it is part of a feedback loop that results in reduced volume and worse clinical course. Future directions of this type of investigation should include more fine-

grained tests, evaluating brain regions effect on symptomatology and vice-versa. More generally, RI-CLPM could potentially be an important approach to complement RCTs in cases where the case-control design of the study is hampered by obvious effects in the intervention group, such as in the case of transcranial magnetic stimulation or in interventions with psychedelics.

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Ethics approval

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Code availability.

Code is available in a repository for replication.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by **LCdA**. The first draft of the manuscript was written by **LCdA**. **RAAK** contributed to later versions of the manuscript. All authors commented on versions of the manuscript, read and approved the final manuscript.

Declaration of competing interest

Authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.05.032.

References

Ambite, J.L., Tallis, M., Alpert, K., Keator, D.B., King, M., Landis, D., Konstantinidis, G., Calhoun, V.D., Potkin, S.G., Turner, J.A., Wang, L., 2015. SchizConnect: virtual data integration in neuroimaging. Data Integr. Life Sci. Int. Workshop DILS Proc. DILS Conf. 9162, 37–51. https://doi.org/10.1007/978-3-319-21843-4_4.

Anderson, K.K., Voineskos, A., Mulsant, B.H., George, T.P., Mckenzie, K.J., 2014. The role of untreated psychosis in neurodegeneration: a review of hypothesized mechanisms of neurotoxicity in first-episode psychosis. Can. J. Psychiatry Rev. Can. Psychiatr. 59, 513–517.

Andreasen, N.C., 1984. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa city, Iowa.

Andreasen, N.C., 1983. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa city, Iowa.

Baribeau, D.A., Vigod, S., Brittain, H., Vaillancourt, T., Szatmari, P., Pullenayegum, E., 2022. Application of transactional (Cross-lagged panel) models in mental Health research: an introduction and review of methodological considerations. J. Can. Acad. Child Adolesc. Psychiatr. 31, 124–134.

Bates, T.C., Maes, H., Neale, M.C., 2019. Umx: twin and path-based structural equation modeling in R. Twin Res. Hum. Genet. 22, 27–41. https://doi.org/10.1017/thg.2019.2.

Ben-Shachar, M.S., Lüdecke, D., Makowski, D., 2020. Effectsize: estimation of effect size indices and standardized parameters. J. Open Source Softw. 5, 2815. https://doi.org/10.21105/joss.02815.

Bora, E., Yalincetin, B., Akdede, B.B., Alptekin, K., 2018. Duration of untreated psychosis and neurocognition in first-episode psychosis: a meta-analysis. Schizophr. Res. 193, 3–10. https://doi.org/10.1016/j.schres.2017.06.021.

Castro-de-Araujo, L.F., Singh, M., Zhou, Y. (Daniel), Vinh, P., Verhulst, B., Dolan, C.V., Neale, M.C., 2022. MR-DoC2: Bidirectional Causal Modeling with Instrumental Variables and Data from Relatives. https://doi.org/10.1101/2022.03.14.484271.

Castro-de-Araujo, L.F.S., Kanaan, R.A., 2017. First episode psychosis moderates the effect of gray matter volume on cognition. Psychiatry Res. Neuroimaging. 266, 108–113. https://doi.org/10.1016/j.pscychresns.2017.06.007.

Castro-de-Araujo, L.F.S., Levy, N., Kanaan, R.A., 2016. RDoC and shift of reference. Australas. Psychiatr. 24, 470–472. https://doi.org/10.1177/1039856216646229.

Castro-de-Araujo, L.F.S., Machado, D.B., Barreto, M.L., Kannan, R.A., 2020. Subtyping schizophrenia based on symptomatology and cognition using a data driven approach. Psychiatry Res. Neuroimaging. 111136 https://doi.org/10.1016/j.pscychresns.2020.111136.

Csernansky, J.G., Wang, L., Jones, D., Rastogi-Cruz, D., Posener, J.A., Heydebrand, G., Miller, J.P., Miller, M.I., 2002. Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. Am. J. Psychiatr. 159, 2000–2006. https://doi.org/10.1176/appi.ajp.159.12.2000.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders. Clinician Version (SCID-CV).

Granger, C.W.J., 1969. Investigating causal relations by econometric models and cross-spectral methods. Econometrica 37, 424–438. https://doi.org/10.2307/1912791.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, P.C.M.P., Hulshoff Pol, H.E., Kahn, R. S., 2013. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr. Bull. 39, 1129–1138. https://doi.org/10.1093/schbul/sbs118.

Hamaker, E.L., 2005. Conditions for the equivalence of the autoregressive latent trajectory model and a latent growth curve model with autoregressive disturbances. Socio. Methods Res. 33, 404–416. https://doi.org/10.1177/0049124104270220.

Hamaker, E.L., Kuiper, R.M., Grasman, R.P.P.P., 2015. A critique of the cross-lagged panel model. Psychol. Methods 20, 102–116. https://doi.org/10.1037/a0038889.

Harms, M.P., Wang, L., Mamah, D., Barch, D.M., Thompson, P.A., Csernansky, J.G., 2007. Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. J. Neurosci. 27, 13835–13842. https://doi.org/10.1523/JNEUROSCI.2571-07.2007.

Hunter, M.D., Garrison, S.M., Burt, S.A., Rodgers, J.L., 2021. The analytic identification of variance component models common to behavior genetics. Behav. Genet. 51, 425–437. https://doi.org/10.1007/s10519-021-10055-x.

Juengst, S.B., Myrga, J.M., Fann, J.R., Wagner, A.K., 2017. Cross-lagged panel analysis of depression and behavioral dysfunction in the first year after moderate-to-severe traumatic brain injury. J. Neuropsychiatry Clin. Neurosci. 29, 260–266. https://doi.org/10.1176/appi.neuropsych.16100217.

Kim, G.-W., Kim, Y.-H., Jeong, G.-W., 2017. Whole brain volume changes and its correlation with clinical symptom severity in patients with schizophrenia: a DARTEL-based VBM study. PLoS One 12, e0177251. https://doi.org/10.1371/journal.pone.0177251.

Kim, J.-J., Crespo-Facorro, B., Andreasen, N.C., O'Leary, D.S., Magnotta, V., Nopoulos, P., 2003. Morphology of the lateral superior temporal gyrus in neuroleptic naïve patients with schizophrenia: relationship to symptoms. Schizophr. Res. 60, 173–181. https://doi.org/10.1016/S0920-9964(02)00299-2.

Murru, A., Carpiniello, B., 2018. Duration of untreated illness as a key to early intervention in schizophrenia: a review. Neurosci. Lett. 669, 59–67. https://doi.org/10.1016/j.neulet.2016.10.003.

Rapp, C., Canela, C., Studerus, E., Walter, A., Aston, J., Borgwardt, S., Riecher-Rössler, A., 2017. Duration of untreated psychosis/illness and brain volume changes in early psychosis. Psychiatr. Res. 255, 332–337. https://doi.org/10.1016/j.psychres.2017.06.004.

Schumacker, R.E., Lomax, R.G., 2015. A Beginner's Guide to Structural Equation Modeling, fourth ed., 0 ed. Routledge. https://doi.org/10.4324/9781315749105.

Simkin, V., Hodsoll, J., Veale, D., 2022. The relationship between symptoms of obsessive compulsive disorder and depression during therapy: a random intercept cross-lagged panel model. J. Behav. Ther. Exp. Psychiatr. 76, 101748 https://doi.org/10.1016/j.jbtep.2022.101748.

Steiger, J.H., 2007. Understanding the limitations of global fit assessment in structural equation modeling. Pers. Indiv. Differ. 42, 893–898. https://doi.org/10.1016/j.paid.2006.09.017.

Tomko, R.L., Baker, N.L., Hood, C.O., Gilmore, A.K., McClure, E.A., Squeglia, L.M., McRae-Clark, A.L., Sonne, S.C., Gray, K.M., 2020. Depressive symptoms and cannabis use in a placebo-controlled trial of N-acetylcysteine for adult cannabis use disorder. Psychopharmacology (Berl.) 237, 479–490. https://doi.org/10.1007/s00213-019-05384-z.

Veijola, J., Guo, J.Y., Moilanen, J.S., Jääskeläinen, E., Miettunen, J., Kyllönen, M., Haapea, M., Huhtaniska, S., Alaräisänen, A., Mäki, P., Kiviniemi, V., Nikkinen, J., Starck, T., Remes, J.J., Tanskanen, P., Tervonen, O., Wink, A.-M., Kehagia, A., Suckling, J., Kobayashi, H., Barnett, J.H., Barnes, A., Koponen, H.J., Jones, P.B., Isohanni, M., Murray, G.K., 2014. Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. PLoS One 9, e101689. https://doi.org/10.1371/journal.pone.0101689.

Wang, L., Kogan, A., Cobia, D., Alpert, K., Kolasny, A., Miller, M.I., Marcus, D., 2013. Northwestern university schizophrenia data and software Tool (NUSDAST). Front. Neuroinf. 7, 1–13. https://doi.org/10.3389/fninf.2013.00025.