JAMA Psychiatry | Original Investigation

Multivariate Associations Among Behavioral, Clinical, and Multimodal Imaging Phenotypes in Patients With Psychosis

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IMPORTANCE Alterations in multiple neuroimaging phenotypes have been reported in psychotic disorders. However, neuroimaging measures can be influenced by factors that are not directly related to psychosis and may confound the interpretation of case-control differences. Therefore, a detailed characterization of the contribution of these factors to neuroimaging phenotypes in psychosis is warranted.

OBJECTIVE To quantify the association between neuroimaging measures and behavioral, health, and demographic variables in psychosis using an integrated multivariate approach.

DESIGN, SETTING, AND PARTICIPANTS This imaging study was conducted at a university research hospital from June 26, 2014, to March 9, 2017. High-resolution multimodal magnetic resonance imaging data were obtained from 100 patients with schizophrenia, 40 patients with bipolar disorder, and 50 healthy volunteers; computed were cortical thickness, subcortical volumes, white matter fractional anisotropy, task-related brain activation (during working memory and emotional recognition), and resting-state functional connectivity. Ascertained in all participants were nonimaging measures pertaining to clinical features, cognition, substance use, psychological trauma, physical activity, and body mass index. The association between imaging and nonimaging measures was modeled using sparse canonical correlation analysis with robust reliability testing.

MAIN OUTCOMES AND MEASURES Multivariate patterns of the association between nonimaging and neuroimaging measures in patients with psychosis and healthy volunteers.

RESULTS The analyses were performed in 92 patients with schizophrenia (23 female [25.0%]; mean [SD] age, 27.0 [7.6] years), 37 patients with bipolar disorder (12 female [32.4%]; mean [SD] age, 27.5 [8.1] years), and 48 healthy volunteers (20 female [41.7%]; mean [SD] age, 29.8 [8.5] years). The imaging and nonimaging data sets showed significant covariation (r = 0.63, P < .001), which was independent of diagnosis. Among the nonimaging variables examined, age (r = −0.53), IQ (r = 0.36), and body mass index (r = −0.25) were associated with multiple imaging phenotypes; cannabis use (r = 0.23) and other substance use (r = 0.33) were associated with subcortical volumes, and alcohol use was associated with white matter integrity (r = −0.15). Within the multivariate models, positive symptoms retained associations with the global neuroimaging (r = −0.13), the cortical thickness (r = −0.22), and the task-related activation variates (r = −0.18); negative symptoms were mostly associated with measures of subcortical volume (r = 0.23), and depression/anxiety was associated with measures of white matter integrity (r = 0.12).

CONCLUSIONS AND RELEVANCE Multivariate analyses provide a more accurate characterization of the association between brain alterations and psychosis because they enable the modeling of other key factors that influence neuroimaging phenotypes.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2017.4741
Published online March 7, 2018.

Supplemental content

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The main psychotic disorders, schizophrenia and bipolar disorder (BD), are genetically related,[1-3] have overlapping clinical phenomenology,[4-6] and rank among the leading causes of disability worldwide.[7] Current models of psychotic disorders are heavily influenced by brain magnetic resonance imaging (MRI) findings that collectively show that patients differ from healthy volunteers on multiple structural and functional measures.[8] The results of large-scale studies and meta-analyses suggest that schizophrenia and BD are associated with partially overlapping and distributed abnormalities in cortical thickness,[9,10] subcortical volumes,[11-13] and white matter integrity.[14,15] Patients also show altered patterns of brain activation, commonly involving inefficient engagement of regulatory cortical regions, across a wide range of experimental conditions.[16-21] Similarly, the intrinsic functional architecture of the brain is also altered in psychotic disorders, with hypoconnectivity within and between resting-state networks being the most prevalent observation.[20,22-25]

These neuroimaging findings have been associated with clinical variables of schizophrenia and BD, including illness severity and symptomatic burden, indicating a link between the anatomical and functional brain changes and disease expression.[8,20,26-30] However, the MRI signal can be influenced by lifestyle choices (eg, smoking, substance use, and physical activity),[31-33] general health (eg, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared]),[31-33] and antipsychotic exposure,[34-39] which are known to differ systematically between patients and healthy volunteers.[40-44] These findings have led to calls for caution in ascribing case-control differences in neuroimaging measures to psychosis-related mechanisms[45] and for integrated analyses of multimodal imaging as well as clinical and behavioral variables.[46] There is a notable paucity of multivariate approaches that address this issue despite increased interest in diagnostic classification and patient stratification based on neuroimaging data.[47,48]

The aim of the present study was to discover patterns of multivariate covariation between nonimaging and imaging variables and identify the most salient features that drive these associations. To achieve this aim, we obtained multimodal MRI data from patients with psychosis (n = 140) and healthy volunteers (n = 50) to derive measures of cortical thickness, subcortical volume, task-related brain activation, resting-state functional connectivity, and white matter fractional anisotropy (FA). In the same sample, we ascertained nonimaging factors known to be associated with the MRI signal that relate to psychopathology, cognition, lifestyle factors, and physical health. To go beyond simple correlations, we used sparse canonical correlation analyses (sCCAs), a powerful multivariate method. Sparse canonical correlation analysis is tailored to the analyses of high-dimensional data sets in which variables are expected to be correlated and does not require data reduction.

Key Points

Question What is the contribution of nonimaging clinical, behavioral, lifestyle, and cardiometabolic factors to multimodal neuroimaging phenotypes in psychosis?

Findings In this imaging study of 92 patients with schizophrenia, 37 patients with bipolar disorder, and 48 healthy volunteers, nonimaging and imaging data have substantial covariation. General intelligence, body mass index, positive psychotic symptoms, substance use, and antipsychotic medication were major contributors to variation in brain structure and function.

Meaning The results of this study underscore the importance of including these key factors in future research to derive a more accurate characterization of brain alterations associated with psychosis.

Methods

Participants

This imaging study was conducted at a university research hospital (Mount Sinai Health System, New York, New York) from June 26, 2014, to March 9, 2017. One hundred ninety participants were recruited at the Icahn School of Medicine at Mount Sinai (details of recruitment and assessment are provided in eMethods in the Supplement). The sample comprised 100 patients with schizophrenia, 40 patients with psychotic BD type 1, and 50 healthy volunteers (**Table**). The diagnostic status of all participants was ascertained via personal interview using the *Structured Clinical Interview for* DSM-5*, Research Version*,[49] supplemented by information from medical records in the case of patients. All participants provided written informed consent, and the study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai.

Nonimaging Data Set

The nonimaging data set comprised 18 variables and included demographic information (age and sex), personal and family psychopathology, IQ, substance use, psychological trauma, physical activity, BMI, and medication (detailed definitions are listed in eTable 1 in the Supplement). Duration of illness was not considered separately because it correlated highly with age (r = 0.74). In all participants, psychopathology was assessed using the 24-item Brief Psychiatric Rating Scale.[50] This scale was chosen because it is suitable for the assessment of nonclinical populations; provides reliable severity estimates for negative and positive symptoms, mania/disorganization, and depression/anxiety[51-53]; and is relevant to clinical practice because of its high interrater reliability even when administered by less experienced professionals.[54] Medication type and dosage were recorded in patients, and the daily antipsychotic dose was converted to chlorpromazine equivalents.[55] The Wechsler Abbreviated Scale of Intelligence II[56] was used to obtain an estimate of current IQ. We focused on IQ because it indexes the covariance between cognitive tests while accounting for most of the variance in cognitive ability.[57-59] We chose BMI as an index of cardiometabolic health because it is simple to measure in clinical practice and is widely used in determining public health policies. BMI is highly correlated with metabolic syndrome and insulin resistance[60,61] and is a reliable predictor of all-cause morbidity and mortality.[62,63]

Table. Study Sample Characteristics

Variable	HV (n = 48)	BD (n = 37)	SCZ (n = 92)
Age, mean (SD), y	29.8 (8.5)	27.5 (8.1)	27.0 (7.6)
Female sex, No. (%)	20 (41.7)	12 (32.4)	23 (25.0)
IQ, mean (SD)[a]	115.2 (16.6)	105.2 (18.1)	93.5 (15.2)
BMI, mean (SD)[b]	24.7 (4.4)	26.1 (6.7)	27.2 (6.4)
Overweight (BMI>25), No. (%)	18 (37.5)	20 (54.1)	51 (55.4)
Physical activity per week, mean (SD), d	1.7 (2.2)	2.8 (2.5)	2.3 (2.7)
Sedentary time, mean (SD)[c]	2.8 (0.5)	2.9 (0.2)	2.6 (0.7)
Lifetime cannabis use, No. (%)[d]	10 (20.8)	22 (59.5)	40 (43.5)
Lifetime substance use, No. (%)[d]	10 (20.8)	24 (64.9)	46 (50.0)
Current alcohol use, mean (SD)[e]	5.3 (2.2)	6.0 (2.9)	7.4 (2.2)
Currently smoking, mean[d]	1.3	1.6	1.6
Family history of depression, No. (%)[d]	10 (20.8)	24 (64.9)	46 (50.0)
Family history of psychosis, No. (%)[e]	0	5 (13.5)	53 (57.6)
Experience of trauma, No. (%)[e]	6 (12.5)	18 (48.6)	36 (39.1)
Age at onset of BD or SCZ, mean (SD), y	NA	20.9 (5.0)	21.5 (5.3)
BPRS score, mean (SD)[f]			
Positive symptoms[g]	4.2 (1.4)	9.6 (5.5)	12.4 (6.2)
Negative symptoms[g]	3.4 (2.3)	4.0 (1.8)	6.8 (3.8)
Depression/anxiety[d]	4.1 (0.6)	8.4 (4.3)	9.0 (5.3)
Mania/disorganization[d]	6.1 (0.3)	12.3 (8.5)	9.5 (5.2)
Antipsychotic dosage, mean (SD), chlorpromazine equivalents[h]	NA	267.5 (326.3)	264.5 (251.1)
Any antipsychotic, No. (%)	NA	30 (81.1)	86 (93.5)
First-generation antipsychotic, No. (%)[i]	NA	13 (35.1)	31 (33.7)
Second-generation antipsychotic, No. (%)[i]	NA	26 (70.3)	77 (83.7)
Antidepressant, No. (%)[h]	NA	7 (18.9)	12 (13.0)
Lithium, No. (%)[c]	NA	15 (40.5)	9 (9.8)
Mood stabilizers (various), No. (%)[h]	NA	5 (13.5)	15 (16.3)
>2 Medication classes, No. (%)[h]	NA	28 (75.7)	51 (55.4)

Abbreviations: BD, patients with bipolar disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BPRS, Brief Psychiatric Rating Scale; HV, healthy volunteers; NA, not applicable; SCZ, patients with schizophrenia.

[a] HV>BD>SCZ based on appropriate tests at $P < .05$, false discovery rate corrected.

[b] SCZ>HV based on appropriate tests at $P < .05$, false discovery rate corrected.

[c] BD>SCZ based on appropriate tests at $P < .05$, false discovery rate corrected.

[d] SCZ = BD>HV based on appropriate tests at $P < .05$, false discovery rate corrected.

[e] SCZ>BD = HV based on appropriate tests at $P < .05$, false discovery rate corrected.

[f] In the BPRS, symptoms are coded as 1 (absent) to 7 (extremely severe). The BPRS Positive symptoms are the sum of scores for hallucination, unusual thought content, and bizarre behavior subscales. The BPRS Negative symptoms are the sum of scores for blunted affect, emotional withdrawal, and motor retardation subscales. The BPRS Depression/anxiety scores are the sum of scores for anxiety, depression, suicidality, and guilt subscales. The BPRS Mania/disorganization scores are the sum of scores for motor hyperactivity, elevated mood, excitement, distractibility, and grandiosity subscales. For detailed definitions of other measures, see eTable 1 in the Supplement.

[g] SCZ>BD>HV based on appropriate tests at $P < .05$, false discovery rate corrected.

[h] SCZ = BD based on appropriate tests at $P < .05$, false discovery rate corrected.

[i] Some patients were taking both first-generation and second-generation antipsychotics.

MRI Modalities and Neuroimaging Data Set

We acquired structural, diffusion-weighted imaging (DWI) as well as task-related and resting-state functional MRI (fMRI) data on a 3-T scanner (Skyra; Siemens) in all participants (eMethods in the Supplement). After the analyses described below in the "Structural and DWI Analyses" and "Functional Imaging Analyses" subsections, we defined 167 variables that comprised regional brain measures from each modality, including measures of head motion (defined in eTable 2 in the Supplement).[64] Univariate case-control differences in these neuroimaging phenotypes are reported in the eResults in the Supplement (subsidiary analyses, including eTable 3, eTable 4, and eFigures 1, 2, 3, and 4 in the Supplement).

Structural and DWI Analyses

Structural and DWI data analyses, including quality assessment, are fully described in the eMethods in the Supplement. Detailed definitions of all the variables derived from these analyses are listed in eTable 2 in the Supplement. Briefly, 64 cortical thickness measures and 18 subcortical volumetric measures were derived from each data set using standard procedures and tools from an image analysis suite (FreeSurfer;

http://surfer.nmr.mgh.harvard.edu/). The DWI data were preprocessed using standard tools from FSL.[65] We used tract-based spatial statistics[66] to compute 38 measures of regional FA based on The John Hopkins University white matter atlas.[67]

Functional Imaging Analyses

Task and resting-state fMRI data were processed using the Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Data Processing & Analysis for (Resting-State) Brain Imaging toolbox[68] to extract measures of task-related activation and resting-state connectivity as detailed in eMethods in the Supplement. For the task fMRI, we focused on working memory (WM) and emotion recognition (ER) based on prior evidence that dysfunction in these processes is a core dimension of psychosis.[69-72] We used the 2-back WM task and the emotional face-matching ER task utilized by the Human Connectome Project (HCP) (humanconnectomeproject.org) to facilitate reproducibility and because the HCP tasks are similar to versions widely used in neuroimaging studies in psychosis.[16-19,21] We identified 12 WM task-related and 14 ER task-related activation peaks (eTable 5, eTable 6, and eFigure 5 in the Supplement). Separately for each task, we defined spherical, 5-mm-radius volumes of interest centered on the coordinates of each activation peak from which we extracted average β values from each participant (see eMethods and eTable 2 in the Supplement for alternative analyses). For the resting-state fMRI, we identified 6 major networks in each data set.[73,74] Specifically, we defined the default mode, central executive, salience, sensorimotor, visual, and auditory networks using validated masks available through the Functional Imaging in Neuropsychiatric Disorders Laboratory at Stanford University (http://findlab.stanford.edu/functional_ROIs.html) (eFigure 6 in the Supplement) and calculated within-network and between-network functional connectivity using Fisher *z*-transformed Pearson correlation (eTable 2 in the Supplement).

Sparse Canonical Correlation Analyses

We used an sCCA with an L1 penalty function that does not assume that the variables in the 2 data sets are uncorrelated[75] (more details are provided in eMethods in the Supplement). Before data entry, we explored the univariate correlations between imaging and nonimaging variables (eFigure 7 in the Supplement) and tested for linearity (details are provided in eMethods in the Supplement). Nonimaging and imaging variables were standardized to a mean (SD) of 0 (1) and entered into sCCAs implemented in a computer program (MATLAB, version R2015b; MathWorks) using an in-house script.[75] We performed a global sCCA that included all nonimaging variables (n = 18) (eTable 1 in the Supplement) and all imaging variables (n = 167) (eTable 2 in the Supplement). To increase granularity, we also conducted modular sCCAs to ascertain whether the nonimaging data set showed distinct patterns of covariation with each imaging subset (cortical thickness, subcortical volumes, FA, task-related activation, and resting-state connectivity). For each sCCA, (1) we computed the sparse parameters for a range of candidate values from $0.1x\sqrt{p}$ (high sparsity) to $1x\sqrt{p}$ (low sparsity at increments of 0.1, where p is the number of features in each data set) and fitted the resulting models; (2) we selected the optimal sparse criteria combination based on the parameters that corresponded to the values of the model that maximized the sCCA correlation value; and (3) we determined the optimal sCCA model and established its significance using permutations (n = 5000). The *P* value was defined as the number of permutations that resulted in a higher correlation than the original data divided by the total number of permutations. Therefore, the *P* value is explicitly corrected for multiple testing because it is compared against the null distribution of maximal correlation values across all estimated sCCAs. Only significant and reliable sCCA modes were reported based on the reliability analyses as detailed in the eMethods in the Supplement. In statistically significant modes, we calculated correlations between the individual variables and the opposite variate (ie, variable-to-variate correlations). We then ranked the variable-to-variate correlations based on their strength and reliability.

Reliability Analyses

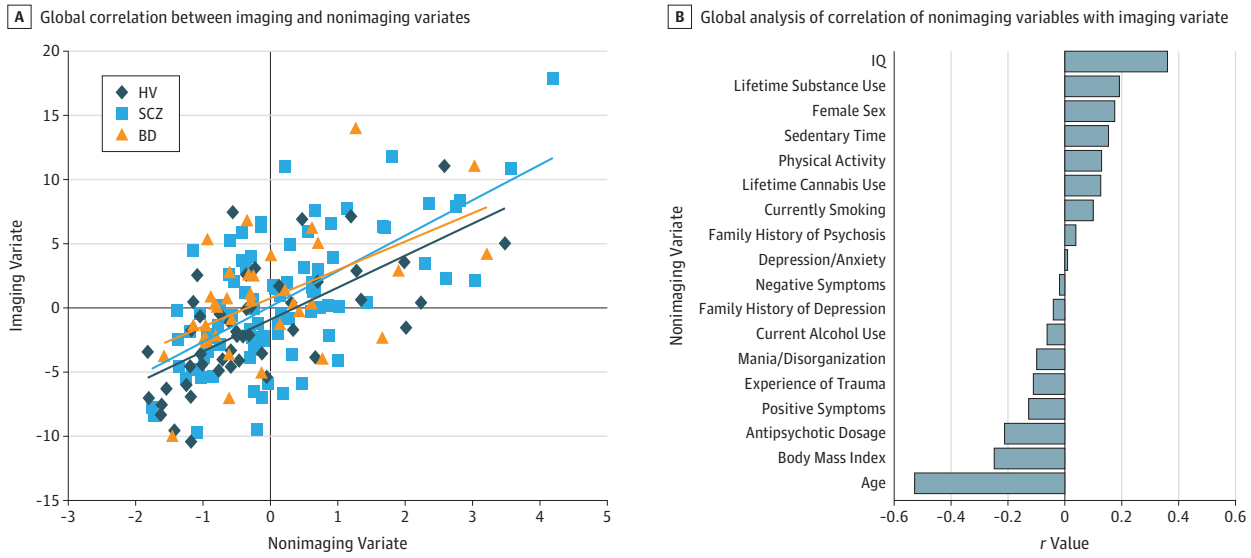
The results reported herein were shown to be reliable after comprehensive analyses detailed in the eMethods and the eResults in the Supplement. Briefly, we tested the stability of the overall sCCA correlations, the sCCA modes, and the variable-to-variate correlations by repeating the analyses after randomly splitting the sample into equal training and test sets 5000 times (eTables 7, 8, 9, and 10 and eFigures 8, 9, 10, 11, and 12 in the Supplement). We also tested the stability of the overall sCCA using the leave-one-out method (eResults in the Supplement). Furthermore, we examined the reliability of the overall sCCA correlation as a function of sample size and composition and showed that outcomes of the sCCA were stable for any sample larger than approximately 70% of the original (ie, from n >124) (eFigure 9 in the Supplement). Finally, we confirmed that the overall sCCA correlations (eFigure 10 in the Supplement) and the variable-to-variate correlations (eFigure 11 in the Supplement) were similar when each diagnostic group was considered separately. We used Fisher *r*-to-*z* transformation to assess the significance of the difference between pairs of correlation coefficients.

Results

Global sCCA

Only the first mode was both significant and reliable (eFigure 8 in the Supplement). The nonimaging (18 variables) and imaging (167 variables) data sets were significantly correlated ($r = 0.63$, $P < .001$) (**Figure 1**A). All groups contributed equally to the overall correlation ($r = 0.66$ for healthy volunteers, $r = 0.64$ for patients with schizophrenia, and $r = 0.54$ for patients with BD; $P > .40$ for all pairwise comparisons, with $z < 1$). Figure 1B shows the variable-to-variate correlations of the nonimaging measures; those with the highest correlations with the imaging variate were IQ ($r = 0.36$), age ($r = -0.53$), BMI ($r = -0.25$), antipsychotic dosage ($r = -0.21$), female sex ($r = 0.18$), and positive symptoms ($r = -0.13$) (eTable 7 and eFigure 12 in the Supplement). The imaging measures that were

Figure 1. Global Analysis of the Imaging and Nonimaging Data Sets



A, Scatterplot of the imaging and nonimaging variates. The overall correlation was $r = 0.63$ ($P < .001$). Correlations were similar across groups ($r = 0.54$ for BD, $r = 0.64$ for SCZ, and $r = 0.66$ for HV). B, Correlation of nonimaging variables with the imaging variate. The y-axis shows the r value of each imaging variable with the global imaging variate. BD indicates patients with bipolar disorder; HV, healthy volunteers; and SCZ, patients with schizophrenia.

highly associated with the nonimaging variate mainly involved frontal, superior and inferior temporal, parietal (including the posterior cingulate cortex and precuneus), and visual regional measures of cortical thickness (eTable 8 in the Supplement). Among the other imaging measures, notable correlations with the nonimaging variate were seen for the FA of the posterior thalamic radiation bilaterally and for the dorsolateral prefrontal and parietal activation during the WM task.

Modular sCCAs

The modular sCCAs were significant for cortical thickness ($r = 0.64$, $P < .001$), subcortical volumes ($r = 0.50$, $P < .001$), white matter FA ($r = 0.44$, $P = .009$), and task activation ($r = 0.44$, $P = .009$) but not for resting-state connectivity ($r = 0.39$, $P = .91$). Based on the reliability analyses, the sCCA for the resting-state connectivity module was not stable and appeared to be dependent on the size and composition of the sample (eFigure 5 and eDiscussion in the Supplement).

In each significant modular sCCA, only the first mode was both statistically significant and reliable (eFigure 8 in the Supplement). All groups contributed equally to each modular correlation (eFigure 10.1, eFigure 10.2, and eDiscussion in the Supplement). **Figure 2** shows the variable-to-variate correlations for each significant modular sCCA.

Cortical Thickness Module

Figure 2A shows the variable-to-variate correlations of the nonimaging measures; those with the highest correlations with the cortical thickness variate were age ($r = -0.50$), IQ ($r = 0.39$), BMI ($r = -0.28$), antipsychotic dosage ($r = -0.29$), and positive symptoms ($r = -0.22$) (Figure 2A and eTable 7 and eFigure 12 in the Supplement). Cortical thickness measures most highly correlated with the nonimaging variate were widely distributed in the frontal, insular, temporal, parietal, and visual cortex (Figure 2A and eTable 9 in the Supplement).

Subcortical Volume Module

Figure 2B shows the variable-to-variate correlations of the nonimaging measures; those with the highest correlations with the subcortical volume variate were age ($r = -0.44$), female sex ($r = 0.37$), negative symptoms ($r = 0.23$), other substance use ($r = 0.33$), and cannabis use ($r = 0.23$) (Figure 2B and eTable 7 in the Supplement). The volume of the caudate, putamen, and pallidum was most highly correlated with the nonimaging variate (Figure 2B and eTable 10 in the Supplement).

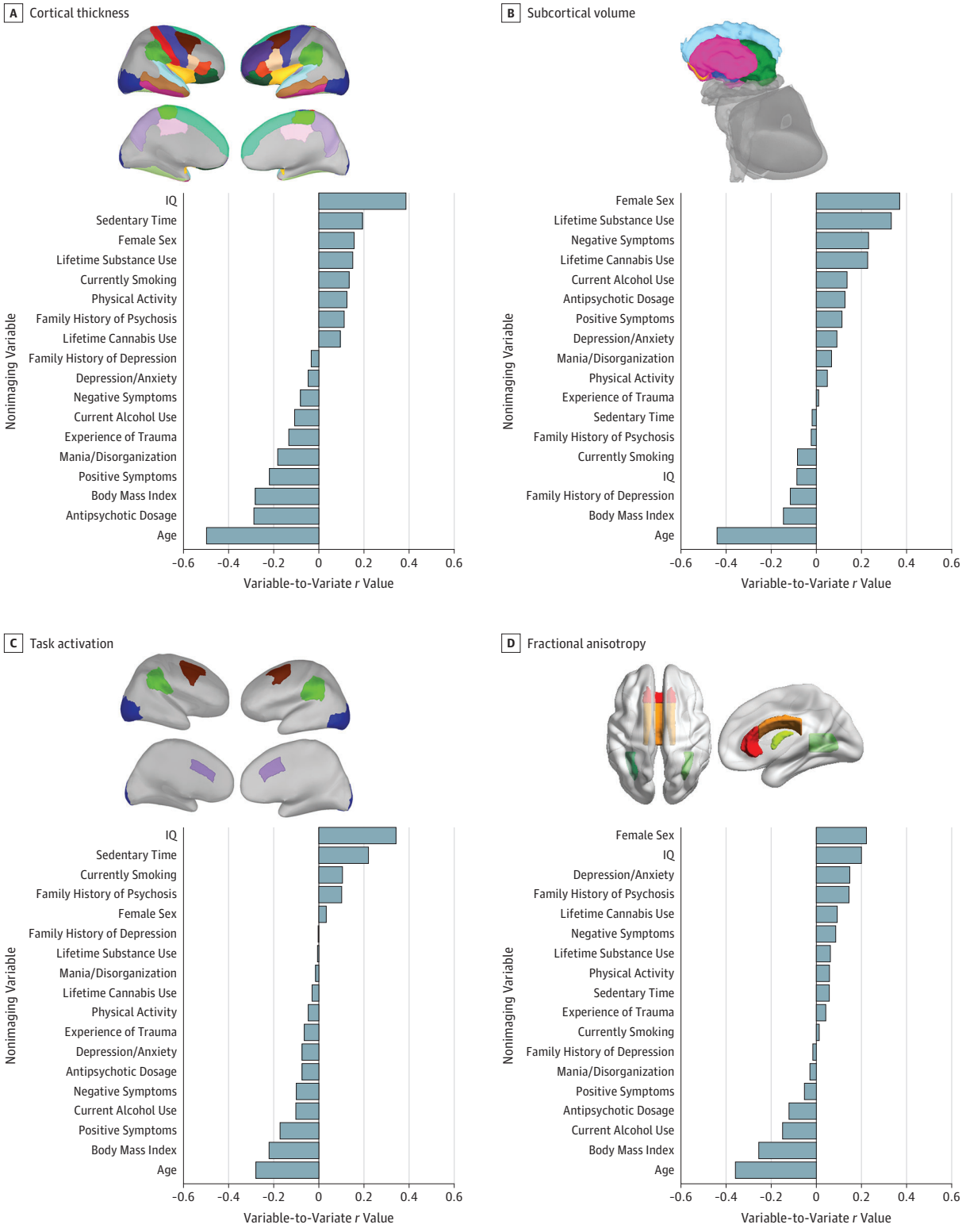
Task Activation Module

Figure 2C shows the variable-to-variate correlations of the nonimaging measures; those with the highest correlations with the task activation variate were age ($r = -0.28$), IQ ($r = 0.35$), BMI ($r = -0.22$), positive symptoms ($r = -0.18$), and sedentary time ($r = 0.23$) (Figure 2C and eTable 7 in the Supplement). The WM task activation in the dorsolateral prefrontal cortex, inferior parietal lobule, and dorsal anterior cingulate cortex were most highly correlated with the nonimaging variate (Figure 2C and eTable 11 in the Supplement).

White Matter FA Module

Figure 2D shows the variable-to-variate correlations of the nonimaging measures; those with the highest correlations with the white matter FA variate were age ($r = -0.36$), BMI ($r = -0.26$), female sex ($r = 0.22$), IQ ($r = 0.20$), and alcohol use ($r = -0.15$) (Figure 2D and eTable 7 in the Supplement). Depression/anxiety symptoms had the only psychopathology score that showed a correlation with the FA variate ($r = 0.12$). The regional FA of the posterior thalamic radiations, the fornix, and

Figure 2. Results of the Modular Sparse Canonical Correlation Analyses



A, Top: Regional cortical thickness measures correlated most highly with nonimaging variate. Bottom: Correlations between nonimaging variables and cortical thickness variate. B, Top: Subcortical volumetric measures correlated most highly with nonimaging variate. Bottom: Correlations between nonimaging variables and subcortical volumes variate. C, Top: Regional task-related brain activation correlated most highly with nonimaging variate. Bottom: Correlations between nonimaging variables and task-related brain activation variate. D, Top: Regional fractional anisotropy measures correlated most highly with nonimaging variate. Bottom: Correlations between nonimaging variables and fractional anisotropy variate.

the body and genu of the corpus callosum were the most highly correlated with the nonimaging variate (Figure 2D and eTable 12 in the Supplement).

Discussion

In this study, we demonstrate a substantial and significant covariation between multimodal imaging phenotypes relating to brain structure, white matter integrity, task-related activation, and intrinsic functional connectivity and nonimaging variables of psychopathology, cognition, BMI, substance use, psychological trauma, and medication. Diagnostic status did not appear to alter the association between imaging phenotypes and nonimaging factors known to influence MRI signals (eDiscussion in the Supplement).[31-33] Among the clinical dimensions of psychosis, positive symptoms were retained in the multivariate global, cortical thickness, and brain activation models while negative symptoms were mostly associated with measures of subcortical volume.

The present results reinforce the importance of age[31,76] and IQ[31-33] for multiple neuroimaging measures and highlight the association between BMI and neuroimaging phenotypes relating to cortical thickness, task-related brain activation, and white matter integrity. Higher BMI has been previously associated with lower cortical thickness and cortical gray matter volume in healthy volunteers.[31,77-80] Investigations into the mechanisms underlying the association between the brain, weight regulation, and cardiometabolic health should be considered a priority, particularly because they may lead to interventions that can mitigate potential risk.

Recreational cannabis and substance use showed a positive covariation with the subcortical volume variate. The available information about the pattern of the association between brain metrics and substance use is inconsistent, especially in the case of recreational and occasional users.[81-83] The present results align with reports of a modest increase in subcortical volumes in users, particularly in the basal ganglia.[84-86] Alcohol use was negatively correlated with the FA variate, adding to previous observations that even light and recreational use of alcohol may affect white matter microstructure.[87]

Positive and negative symptoms maintained substantial correlations with neuroimaging variates even when considered in the context of multiple other variables that influence the MRI signal. Specifically, we found negative correlations between positive symptoms and the multimodal, cortical thickness, and task-related brain activation variates. The neuroimaging literature to date has mainly supported an association between positive symptoms and cortical thinning.[30,88] The present study extends these findings to suggest that positive symptoms have multimodal associations with neuroimaging phenotypes that relate both to structure and function. The positive association between negative symptoms and the subcortical volume variate was unexpected because even large studies on psychosis have failed to identify symptomatic correlates of subcortical volumetric measures.[12,13] Conversely, the brain correlates of negative symptoms have not been reliably identified either; some studies have found that patients with chronic schizophrenia and persistent negative symptoms have reduced caudate volume,[89] although other reports have found otherwise.[90-92] However, the results of 2 previous studies[93,94] have suggested subtle but detectable increases in caudate volume in the early stages of psychosis in patients with persistent negative symptoms or apathy. This observation could also apply to the present study sample, which comprised mostly young patients with an approximate mean age of 27 years.

Depression/anxiety was correlated with the white matter FA variate. This finding conforms with the results of a large DWI study[95] on psychosis that reported a positive association between depressive symptoms and FA of the thalamic radiation and of the corpus callosum. Of note, FA measures in these regions had the highest correlation with the nonimaging variate in the present study.

Finally, antipsychotic dosage was negatively associated with the global and cortical thickness variates. Antipsychotic medication has been repeatedly linked to cortical thinning.[34-37] The functional consequences of this association are unclear[35]; however, the observational nature of most of the evidence precludes causal attributions.

Limitations

Our study has several limitations. Neuroimaging techniques include other modalities (eg, magnetic resonance spectroscopy), other analytic methods (eg, graph theory), and a multitude of other fMRI tasks that were not considered herein. Nevertheless, our study examined those modalities, analytic methods, and paradigms that are most commonly used in neuroimaging studies of psychosis. In future studies, the laboratory tests or other measures (eg, adiposity) of cardiometabolic health that were not included in the present study may provide more mechanistic insights about the association between BMI and imaging phenotypes. We did not use an extensive cognitive battery, which may have identified more detailed associations between cognition and imaging phenotypes. However, measures of general intelligence, such as IQ used herein, not only are correlated with individual task performance but also have been shown to have the most robust association with imaging phenotypes even when other cognitive measures are simultaneously considered.[31,32] Future work should replicate and extend these results by examining the association with nonimaging and imaging phenotypes in larger samples.

Conclusions

We found significant covariation between multimodal imaging phenotypes and behavioral, clinical, lifestyle, and general health-related measures that was comparable in healthy volunteers and patients with psychosis. The results suggest that the severity of positive symptoms, arguably the hallmark of psychosis, is likely to be meaningfully related to reductions in cortical thickness and brain activation even when other nonimaging factors are also modeled. In addition, IQ and BMI had significant contributions to neuroimaging findings; because both measures are easy to obtain, their routine inclusion in neuroimaging studies is both feasible and advisable.

ARTICLE INFORMATION

Accepted for Publication: December 27, 2017.

Published Online: March 7, 2018. doi:10.1001/jamapsychiatry.2017.4741

Author Contributions: Dr Frangou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Moser, Frangou.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Moser, Doucet, Lee, A. Rasgon, Krinsky, N. Rasgon, Frangou.
Critical revision of the manuscript for important intellectual content: Moser, Lee, Leibu, Ing, Schumann, Frangou.
Statistical analysis: Moser, Doucet, Ing, N. Rasgon, Frangou.
Obtained funding: Schumann.
Administrative, technical, or material support: Lee, A. Rasgon, Ing, Schumann.
Study supervision: Leibu, Frangou.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported in part through the computational resources and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount Sinai. Dr Moser reported receiving support from the Swiss National Science Foundation (P2GEP3_162104, P300PB_171584). Drs Ing and Schumann reported being partially supported by Imaging Genetics for Mental Disorders (IMAGEMEND) (602450), the National Institute for Health Research (Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King's College London), and the Bundesministerium für Bildung und Forschung (eMED SysAlc01ZX1311A). Dr Rasgon reported receiving support from the National Institute on Aging (R01 AG050345-01A1). Dr Frangou reported receiving support from the National Institutes of Health (R01 MH104284-01A1) and European Unit FP7 program (IMAGEMEND 602450) projects. No other disclosures were reported.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Daniel Weinberger, MD (The Lieber Institute for Brain Development, The Johns Hopkins University, Baltimore, Maryland), contributed to our presentation of the Results section in an early version of the manuscript.

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