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Role of Serotonin in the Neurobiology of Schizophrenia and Association With Negative Symptoms

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IMPORTANCE The involvement of the serotonin system in the pathophysiology of schizophrenia has been proposed for over 60 years, but there has been no prior study to test if there is altered serotonin release in vivo in schizophrenia (to the authors' knowledge).

OBJECTIVE To investigate serotonin release in vivo in schizophrenia and its association with negative symptoms. It was hypothesized a priori that frontal cortex serotonin release capacity would be lower in schizophrenia compared with healthy controls and that this would be associated with more severe baseline negative symptoms.

DESIGN, SETTING, AND PARTICIPANTS This was a single-center case-control neuroimaging study conducted in London, UK. All participants had dynamic 90-minute [^{11}C]Cimbi-36 positron emission tomography (PET) scans at baseline and 3 hours after oral administration of D-amphetamine 0.5mg/kg. Data were collected between 2015 and 2024. Participants included stable adult outpatients with *DSM-5* schizophrenia (antipsychotic free or taking antipsychotics with negligible affinity for 5-hydroxytryptamine receptor 2A [5-HT2A] receptors) and healthy controls matched for age, sex, and body mass index.

MAIN OUTCOMES AND MEASURES The primary neuroimaging outcome was the group difference in serotonin release capacity, prespecified as the percentage change in frontal cortex [^{11}C]Cimbi-36 binding potential between the baseline and D-amphetamine scans.

RESULTS A total of 54 individuals were included, 26 with *DSM-5* schizophrenia (mean [SD] age, 33.3 [9.1] years, 16 male [62%]; 21 not taking antipsychotic medication [81%]) and 28 healthy controls (mean [SD] age, 32.0 [9.5] years, 19 male [68%]). Frontal cortex serotonin release was significantly greater in the group with schizophrenia compared with healthy controls (18.0%; 95% CI, 2.5%-33.6%; $P = .02$; Cohen $d = 0.69$). In schizophrenia, greater frontal cortex serotonin release was correlated with more severe baseline negative symptoms (Brief Negative Symptom Scale: Pearson $r = 0.42$; $P = .04$) and poorer functioning (Social Functioning Scale: Pearson $r = -0.42$; $P = .04$). Exploratory analyses showed significantly greater frontal cortex serotonin release in deficit schizophrenia, characterized by primary and enduring negative symptoms, compared with healthy controls (mean difference = 32.3%; FDR-corrected P value = 0.001; Cohen $d = 1.10$) and nondeficit schizophrenia (mean difference = 28.9%; FDR-corrected P value = 0.004; Cohen $d = 0.89$). These findings were all replicated in 21 individuals with schizophrenia not taking antipsychotic medication. Baseline cortical [^{11}C]Cimbi-36 binding (indexing baseline cortical 5-HT2A receptor levels) was unaltered in schizophrenia.

CONCLUSIONS AND RELEVANCE This case-control study found that serotonergic dysfunction in the pathophysiology of schizophrenia was associated with negative symptoms, suggesting the regulation of serotonin release as a target to treat negative symptoms. Results of the exploratory analysis suggest particularly marked serotonergic dysfunction in the subgroup with deficit schizophrenia.

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Supplemental content

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Schizophrenia is a severe mental disorder characterized by positive (psychotic) symptoms, negative symptoms (eg, social withdrawal, lack of motivation, anhedonia), and cognitive impairments.[1] The global prevalence of schizophrenia is approximately 0.5%, and it is the 20th leading cause of disability worldwide.[2,3] Negative symptoms are consistently associated with poor functional outcomes in schizophrenia and are, therefore, recognized as a great unmet need, as there are no licensed treatments.[4,5] Clarifying the underlying neurobiology of negative symptoms, and associated disability, is essential to address this.

Preclinical studies show associations between synaptic serotonin (5-hydroxytryptamine [5-HT]) levels and behaviors thought to underlie negative symptoms, including findings indicating serotonin release during reward processing in mice.[6,7] Additionally, mice lacking brain serotonin due to null variants in tryptophan hydroxylase 2, the rate-limiting enzyme in serotonin synthesis, show deficits in social interaction.[8,9] In healthy humans, a recent positron emission tomography (PET) study[10] found that reward processing increases serotonin synthesis, proposed to reflect replenishment after serotonin release. Moreover, in schizophrenia, acute depletion of tryptophan, a serotonin precursor, worsens negative symptoms, and meta-analytic evidence shows that antidepressants, which increase serotonergic neurotransmission, improve negative symptoms.[11,12]

These findings indicate that altered brain serotonin release could underlie the pathophysiology of schizophrenia, but there has been no prior study (to our knowledge) to test this directly in vivo in schizophrenia or whether alterations are related to negative symptoms and functional impairments. We, therefore, used the 5-HT2A receptor agonist radioligand, [^{11}C]Cimbi-36, which is sensitive to increases in extracellular serotonin induced by an acute D-amphetamine challenge, to conduct an in vivo imaging investigation of serotonin release and the high-affinity 5-HT2A subtype in schizophrenia.[13-17] Based on these experimental studies, we hypothesized a priori that schizophrenia would be associated with lower frontal cortex serotonin release capacity and that this would be correlated inversely with baseline negative symptoms.

Approximately one-third of people with schizophrenia meet the criteria for deficit schizophrenia, a subtype characterized by primary and enduring negative symptoms and poorer prognosis.[4,5,18,19] It has been hypothesized that the neurobiology underlying deficit schizophrenia is different to nondeficit schizophrenia, but it has not been tested if this is the case for the serotonin system (to our knowledge).[4,5,19] We, therefore, aimed to conduct additional exploratory analyses to test this.

Key Points

Question Is serotonin release altered in vivo in schizophrenia, and is it associated with negative symptom severity?

Findings In this case-control neuroimaging study that included 54 adults, frontal cortex serotonin release was significantly greater in the 26 people with *DSM-5* schizophrenia compared with 28 matched healthy controls. In schizophrenia, greater frontal cortex serotonin release was associated with more severe baseline negative symptoms.

Meaning Findings suggest that serotonergic dysfunction in the pathophysiology of schizophrenia was associated with negative symptoms, identifying the regulation of serotonergic neurotransmission as a potential target to treat negative symptoms.

Methods

Study Design

This single-center case-control neuroimaging study was conducted in London, UK. This study was approved by local ethics committees. All individuals provided written, informed consent before participation. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[20]

Participants

We recruited people meeting *DSM-5* criteria for schizophrenia from community psychiatric services across London and by public advertisement and a sample of healthy controls matched for age, sex, and body mass index, as these factors may affect 5-HT2A availability.[21-24] Participant ethnicity data are available on request.

Evaluation against inclusion and exclusion criteria was performed at a screening appointment before enrolment. The main exclusion criteria for all individuals were age younger than 18 years, contraindications to D-amphetamine, magnetic resonance imaging (MRI) or PET scanning, recent (within 1 month or 5 half-lives if this was longer) use of antidepressants or drugs with affinity for 5-HT2A receptors (including antipsychotics other than haloperidol or amisulpride/sulpiride as these have negligible 5-HT2A affinity[25]), or a history of substance use disorder (excluding nicotine and caffeine). Additional exclusion criteria for healthy controls were a first-degree relative with a psychotic illness or a personal history of psychiatric illness. Additional exclusion criteria in schizophrenia were severe positive symptoms or significant mental health risk, in case D-amphetamine exacerbated this.[26]

Procedures

Neuroimaging and D-Amphetamine Administration

All individuals underwent structural MRI for the anatomical coregistration of PET data, on 3 similar Siemens 3-T scanners (Trio, Verio, and Prisma).

On the day of PET scanning, individuals received a single dose of oral D-amphetamine (0.5 mg/kg). Volunteers underwent 2 [^{11}C]Cimbi-36 PET scans, before and 3 hours after the acute D-amphetamine challenge, corresponding to the time when D-amphetamine levels were anticipated to be at maximum.[27-29] PET data were acquired over 90 minutes, with arterial blood sampling to provide an input function and a low-dose computed tomography (CT) scan performed immediately before each PET scan for attenuation correction. Data were acquired on 3 similar Siemens PET/CT scanners (Hi-Rez Biograph 6, Biograph 6 TruePoint with TrueV, and Biograph Horizon). All individuals had baseline and post-D-amphetamine scans performed on the same scanner.

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Clinical Measures

Baseline clinical symptoms and functioning were assessed in schizophrenia prior to the first PET scan using the Positive and Negative Syndrome Scale (PANSS), the Brief Negative Symptom Scale (BNSS), the Schedule for the Deficit Syndrome (SDS), and the Social Functioning Scale (SFS).[18,30-32]

Imaging Analysis

All imaging data were analyzed using MIAKAT, version 4.3.24 (MIAKAT Ltd). The frontal cortex (a region with high 5-HT2A receptor density) was defined a priori as the primary region of interest (ROI), based on meta-analysis of postmortem studies showing abnormalities in the 5-HT2A system in this region in schizophrenia with medium-large effect sizes.[16,24,33] The ventrolateral cerebellum was used as the reference region for calculation of [^{11}C]Cimbi-36 nondisplaceable binding, as it has negligible 5-HT2A receptor levels.[34,35] ROIs were delineated based on the Clinical Imaging Centre atlas, version 2, warped nonlinearly to the individual's MRI.[36] PET images were registered to each individual's MRI and motion corrected using frame to frame rigid-body registration. Regional total volumes of distribution (V_T) were derived from kinetic analysis using the 2-tissue compartment model (2TCM).[35,37] Sensitivity analyses are reported with the multilinear analysis-1 (MA1) method.[38]

Statistical Analysis

Our main neuroimaging hypothesis was that serotonin release capacity in the frontal cortex would be significantly lower in those with schizophrenia compared with healthy controls. This was tested using 2-sided analysis of covariance (ANCOVA) adjusting for MRI scanner,[39,40] PET scanner,[41] the interaction between PET scanner × group, and [^{11}C]Cimbi-36 injected mass at baseline and post-D-amphetamine,[39-42] due to group differences in injected mass. Consistent with previous studies,[16,24] our a priori primary outcome was the change in frontal cortex [^{11}C]Cimbi-36 nondisplaceable binding potential (BP_{ND}) between the baseline and D-amphetamine scans, delta BP_{ND}, expressed as a percentage: ΔBP_{ND} (%) = [1 − (BP_{ND} ROI postdose/BP_{ND} ROI baseline)] × 100. BP_{ND} ROI was calculated as (V_T ROI/V_T cerebellum) − 1.[37]

We conducted sensitivity analysis using delta V_T, expressed as a percentage: ΔV_T (%) = [1 − (V_T ROI postdose/V_T ROI baseline)] × 100. To address potential confounding, we performed additional sensitivity analyses including measures of potential confounds as covariates, comparisons of potential confounders between groups, and subgroup analyses of people with schizophrenia not currently taking antipsychotic medication and also those with no history of exposure to antidepressant medication.[43-45] Additionally, we investigated if time since prior exposure to antidepressants or 5-HT2A blocking antipsychotics influenced our findings.

The main clinical hypothesis, specified a priori, was that the magnitude of frontal cortex ΔBP_{ND} in schizophrenia would be related to the severity of baseline negative symptoms. We also investigated the correlation between frontal cortex ΔBP_{ND} and overall functioning, measured by the SFS full-scale score.[32] These analyses were corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) correction, with an FDR of 0.05.[46] We also conducted exploratory subgroup analysis to investigate whether frontal cortex ΔBP_{ND} differed between healthy controls, deficit schizophrenia and nondeficit schizophrenia, using a 1-way analysis of variance (ANOVA) with baseline [^{11}C]Cimbi-36 injected mass and post-D-amphetamine [^{11}C]Cimbi-36 injected mass as covariates and FDR-corrected post hoc group mean comparisons.[46] Effect sizes from ANCOVA and ANOVA analyses were converted to Cohen *d* using standard formulae.[47]

Our a priori secondary hypothesis was that baseline [^{11}C]Cimbi-36 frontal cortex BP_{ND} would be lower in people with schizophrenia compared with healthy controls. We also conducted uncorrected exploratory analyses of other ROIs and symptom subscales. All *P* values were 2-sided, and *P* value <.05 was considered statistically significant. Data were collected between 2015 and 2024 and analyzed using SPSS software, version 25 (IBM Corp), Matlab, version 9.13.0.2049777 (The MathWorks Inc), and plotted in GraphPad Prism, version 10.2.3 (GraphPad Software).

More details on inclusion and exclusion criteria, clinical assessments, statistical analysis, power calculation, image acquisition and imaging analysis including quality control, sensitivity analyses and exploratory analyses are available in the eMethods in Supplement 1.

Results

A total of 54 individuals were included in the analysis, 26 with *DSM-5* schizophrenia (mean [SD] age, 33.3 [9.1] years; 10 female [38%]; 16 male [62%]) and 28 healthy controls (mean [SD] age, 32.0 [9.5] years; 9 female [32%]; 19 male [68%]). Individuals with schizophrenia were well matched demographically to the healthy controls, although there was significantly higher injected radiotracer mass in both the baseline and post-D-amphetamine scans in schizophrenia (**Table** and eTable 1 in Supplement 1). A total of 21 individuals (81%) with schizophrenia were not taking antipsychotic medication, whereas 5 (19%) took haloperidol or amisulpride. A total of 22 individuals (85%) with schizophrenia had prior exposure to 5-HT2A-blocking antipsychotic medications (last exposure: median, 18 months prior; range, 2-132 months). Nine participants (35%) with schizophrenia had prior exposure to antidepressants (last exposure: median, 22 months prior; range, 3-164 months) (Table).

Frontal Cortex Serotonin Release

D-amphetamine led to robust reductions in frontal cortex BP_{ND} in both groups (healthy controls: baseline mean [SD] BP_{ND}, 1.22 [0.35] vs D-amphetamine: 1.08 [0.28]; paired *t* test *P* = .004; schizophrenia: 1.49 [0.54] vs D-amphetamine: 1.10 [0.27]; paired *t* test *P* < .001) (eFigure 1 and eTable 2 in Supplement 1).

Frontal cortex ΔBP_{ND} was significantly greater in those with schizophrenia compared with controls (ANCOVA mean difference, 18.0%; 95% CI, 2.5%-33.6%; *P* = .02; Cohen *d* = 0.69) (**Figure 1**, **Figure 2**, and eTable 2 in Supplement 1). Results were similar in sensitivity analysis with ΔV_T (ANCOVA mean

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Table. Demographics, Clinical, and Positron Emission Tomography (PET) Scan Characteristics[a]

Characteristic	Healthy controls (n = 28)	Schizophrenia (n = 26)	Comparison *P* value (N = 54)
Demographic and clinical parameters			
Age, y	32.0 (9.5)	33.3 (9.1)	.61
Sex			
Female	9 (32)	10 (38)	.63
Male	19 (68)	16 (62)	
BMI[b]	24.3 (4.3)	25.2 (3.7)	.40
Duration of illness, mean (SD) [range], y	NA	5.7 (6.7) [0.2 to 23.8]	NA
Baseline Positive and Negative Syndrome Scale (PANSS)	NA	Total: 55.9 (13.8) • Positive: 12.9 (4.0) • Negative: 14.4 (4.7) • General: 28.0 (7.6)	NA
Brief Negative Symptom Scale (BNSS)	NA	13.1 (11.2)	NA
Social Functioning Scale (SFS)	NA	113.4 (9.3)	NA
Current antipsychotic medication	NA	• 21 Antipsychotic-free: 81% (3 antipsychotic-naive, 1 antipsychotic treated for <5 d) • 5 Antipsychotic-treated: 19% (3 haloperidol LAI 150 mg monthly, 2 amisulpride 200-400 mg daily)	NA
Deficit schizophrenia	NA	• 8 with Deficit schizophrenia: 31% • 18 with Nondeficit schizophrenia: 69%	NA
Scan parameters: baseline PET			
Injected dose, MBq	164.0 (53.6)	152.8 (52.5)	.44
Injected mass, μg	1.42 (0.40)	1.75 (0.43)	.006[c]
Plasma-free fraction, f_P (%)	2.78 (0.79)	2.90 (0.95)	.64
Scan parameters: post-D-amphetamine PET			
Injected dose, MBq	184.2 (63.4)	164.8 (56.9)	.24
Injected mass, μg	1.38 (0.39)	1.64 (0.45)	.03[c]
Plasma-free fraction, f_P (%)	2.58 (0.40)	2.82 (0.61)	.08
D-amphetamine dose, mg	36.4 (6.5)	36.7 (7.8)	.89
Mid-scan D-amphetamine levels, ng/mL	93.4 (12.2)	87.2 (10.5)	.19
Change between PET scan 1 and PET scan 2			
Injected dose, MBq	20.1 (54.0)	12.0 (57.5)	.59
P value	.06	.30	NA
Injected mass, μg	−0.04 (0.12)	−0.11 (0.28)	.27
P value	.07	.07	NA
Plasma-free fraction, f_P (%)	−0.22 (0.86)	−0.08 (1.31)	.64
P value	.19	.77	NA

Abbreviations:
BMI, body mass index;
LAI, long-acting injection;
NA, not applicable;
PET, positron emission tomography.

[a] Values are mean (SD) for continuous variables, and frequencies for categorical variables. *P* values for group comparisons are from 2-sided independent samples *t* tests for continuous variables, and χ^2 tests for categorical variables. *P* values for PET scan 1 vs PET scan 2 are from 2-sided paired-samples *t* tests conducted within each group.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Indicates significant difference at $P < .05$; n = 25 for free fraction in schizophrenia due to technical issues, n = 7 in healthy control amphetamine levels, and n = 25 for Brief Negative Symptom Scale.

difference, 11.1%; 95% CI, 1.0%-21.2%; *P* value = .03; Cohen *d* = 0.65) (eTable 2 and eFigure 2 in Supplement 1), with ΔBP_{ND} values derived from MA1 modeling (ANCOVA *P* value = .04; Cohen *d* = 0.62) (eTable 3 in Supplement 1), in subgroup analysis restricted to 21 individuals with schizophrenia not taking antipsychotic medication (frontal cortex ΔBP_{ND}: ANCOVA *P* value = .01; Cohen *d* = 0.82; frontal cortex ΔV_T: ANCOVA *P* value = .01; Cohen *d* = 0.85) (eTable 4 in Supplement 1), and 17 individuals with schizophrenia who had never taken antidepressant medication (eTable 5 in Supplement 1). ΔBP_{ND} results were also robust to further sensitivity analyses on tracer delivery, brain volumes, motion, scanner effects, recent cannabis use, and outliers (eTables 6-9 and eFigures 3 and 4 in Supplement 1).

Association Between Frontal Cortex Serotonin Release and Schizophrenia Symptoms

We found a significant positive association between frontal cortex ΔBP_{ND} and the severity of negative symptoms at baseline in schizophrenia (BNSS: n = 25; Pearson *r* = 0.42; FDR-corrected *P* = .04) (**Figure 3**A). We also found a significant association between frontal cortex ΔBP_{ND} and poorer overall functioning in schizophrenia (SFS: n = 26; Pearson *r* = −0.42; FDR-corrected *P* = .04) (Figure 3B). The significance of these results was unchanged in subgroup analysis restricted to those not taking antipsychotic medications (BNSS: n = 20; Pearson *r* = 0.47; FDR-corrected *P* = .04; SFS: n = 21; Pearson *r* = −0.48; FDR-corrected *P* = .04). In exploratory analyses, we found that frontal cortex ΔBP_{ND} was correlated with the severity of baseline

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motivational negative symptoms (n = 25; Pearson r = 0.49; P = .01) but not with expressive deficits or baseline positive symptoms (eTable 10 in Supplement 1). Poorer overall functioning was highly correlated with more severe baseline negative symptoms (Pearson r = −0.67; P < .001), specifically with motivational symptoms (eTable 10 in Supplement 1). Frontal cortex ΔBP_{ND} was not associated with duration of illness, plasma D-amphetamine levels, or time since last exposure to antidepressants or 5-HT2A-blocking antipsychotics (where individuals had taken them, noted in the eResults and eFigure 5 in Supplement 1).

Exploratory Subgroup Analysis: Deficit Schizophrenia

A total of 8 individuals (31%) with schizophrenia met criteria for deficit schizophrenia on the SDS. Compared with those with nondeficit schizophrenia, they had significantly poorer overall functioning (SFS: n = 26; mean difference = 9.5; 2-sample t test P = .01; Cohen d = 1.15) and more severe baseline negative symptoms (BNSS: n = 25; mean difference = 18.5; 2-sample t test P < .001; Cohen d = 2.47) (eTable 11 in Supplement 1).

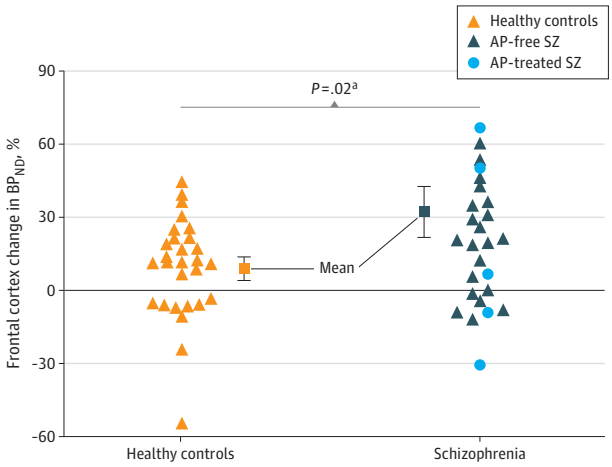
When comparing healthy controls with individuals with deficit and nondeficit schizophrenia, there was a significant difference in frontal cortex ΔBP_{ND} between the 3 groups (ANOVA: $F_{2, 49}$ = 7.64; P = .001). Post hoc tests demonstrated that this was due to significantly greater frontal cortex ΔBP_{ND} in deficit schizophrenia in comparison with both nondeficit schizophrenia (mean difference = 28.9%; FDR-corrected P value = .004; Cohen d = 0.89) and healthy controls (mean difference = 32.3%; FDR-corrected P value = .001; Cohen d = 1.10), with no significant differences between nondeficit schizophrenia and healthy controls (mean difference = 3.4%; FDR-corrected P value = .63) (**Figure 4**). The significance of the overall ANOVA and group comparisons were unchanged with ΔV_T as the outcome measure and in individuals not taking antipsychotic medication (eResults in Supplement 1).

Baseline [^{11}C]Cimbi-36 Binding and Exploratory ROI Analyses of Serotonin Release

In exploratory analyses, we found greater ΔBP_{ND} in the entire neocortex (ANCOVA P value = .04; Cohen d = 0.62) and the amygdala (ANCOVA P value = .04; Cohen d = 0.62) in those with schizophrenia compared with that of healthy controls (eTable 2 in Supplement 1 and Figure 2). Results were similar in those not taking antipsychotic medication (eTable 4 in Supplement 1).

We found no significant difference in baseline frontal cortex [^{11}C]Cimbi-36 binding between those with schizophrenia and healthy controls using BP_{ND} (ANCOVA P value = .06) or V_T (ANCOVA P value = .72), although exploratory analyses showed higher [^{11}C]Cimbi-36 BP_{ND} in schizophrenia at baseline in comparison with healthy volunteers in the amygdala (ANCOVA P value = .02) and hippocampus (ANCOVA P value = .049) (eTable 12 and eFigure 1 in Supplement 1). There were no differences in baseline [^{11}C]Cimbi-36 V_T between those with schizophrenia and healthy controls in any ROI, but we found lower [^{11}C]Cimbi-36 V_T in the cerebellum of those with schizophrenia in comparison with that of healthy controls (ANCOVA P value = .005) (eTable 12 in Supplement 1).

Figure 1. Group Comparison of Frontal Cortex Change in Nondisplaceable Binding Potential (ΔBP_{ND}) Between Healthy Controls and People With Schizophrenia



Individual values and adjusted mean (standard error of the mean) of frontal cortex change in BP_{ND} (%) in healthy controls vs people with schizophrenia (SZ). Individual values for those with SZ not taking antipsychotics (AP-free SZ) and those with SZ taking AP medication (AP-treated SZ) are represented with different symbols for visualization purposes. Group means were compared in an analysis of covariance with adjustment for differences in injected mass, magnetic resonance imaging scanner, and positron emission tomography scanner.

[a]Indicates statistical significance at P <.05.

Discussion

In this case-control study, we conducted the first direct assessment of serotonin release (to our knowledge) in people with schizophrenia, by quantifying in vivo brain binding of the serotonin 5-HT2A receptor PET radioligand [^{11}C]Cimbi-36 before and after an acute D-amphetamine challenge. Our main finding is that there was significantly greater D-amphetamine-induced displacement of [^{11}C]Cimbi-36 binding in the frontal cortex, expressed as ΔBP_{ND}, in those with schizophrenia relative to matched controls and that this was directly associated with both higher baseline negative symptom severity and poorer functioning.

D-Amphetamine leads to substantial serotonin release (>200% serotonin release in the prefrontal cortex of rats) and has negligible affinity for the 5-HT2A receptor (Ki >10 000nM).[16,24,48-50] Although D-amphetamine also releases dopamine and noradrenaline, [^{11}C]Cimbi-36 has greater than 1000-fold selectivity for the 5-HT2A receptor over dopaminergic and noradrenergic targets.[51] Furthermore, the change in [^{11}C]Cimbi-36 BP_{ND} is directly proportional to the magnitude of change in serotonin as measured by microdialysis.[52] Thus, our data were consistent with higher serotonin release in those with schizophrenia than in healthy controls.

In addition to this, our exploratory analysis provided preliminary evidence that deficit schizophrenia, a subtype characterized by primary and enduring negative symptoms, was associated with significantly greater frontal cortex serotonin release in comparison with both people with schizophrenia

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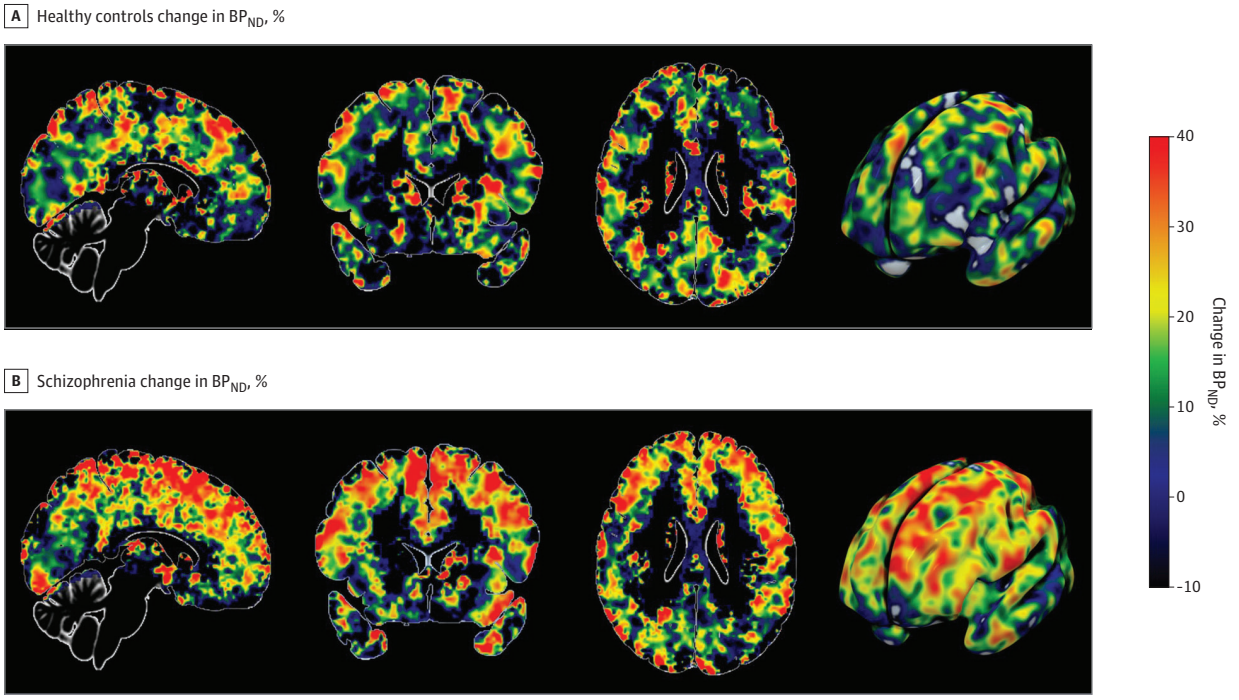
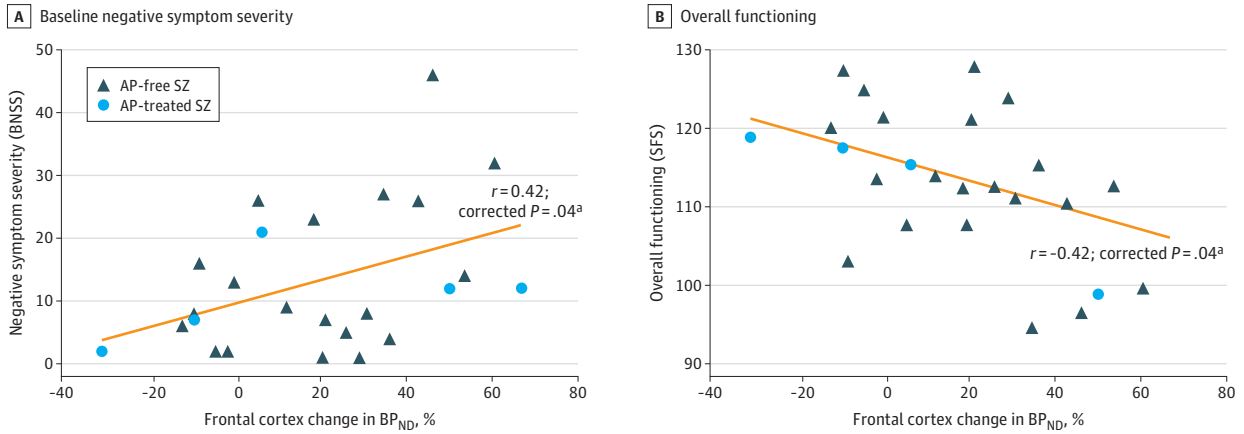
Figure 2. Group Average Representative Maps of Frontal Cortex Change in Nondisplaceable Binding Potential (ΔBP_{ND}) for Healthy Controls and People With Schizophrenia



Representative group average change in BP_{ND} maps are presented for healthy controls and people with schizophrenia. Coronal, sagittal, and axial slices are displayed at Montreal Neurological Institute coordinates (6, 19, 24), in addition to a surface rendering. The maps are masked; therefore, only change in BP_{ND} values from cortical and subcortical gray matter structures are displayed.

Figure 3. Association Between [^{11}C]Cimbi-36 Frontal Cortex Change in Nondisplaceable Binding Potential (ΔBP_{ND}) and Baseline Negative Symptom Severity and Overall Functioning in People With Schizophrenia



A, Correlation between [^{11}C]Cimbi-36 frontal cortex change in BP_{ND} (%) and baseline negative symptom severity (BNSS) in people with schizophrenia (SZ). Positive change in BP_{ND} indicates greater serotonin release; higher BNSS indicates more severe negative symptoms. B, Correlation between [^{11}C]Cimbi-36 frontal cortex change in BP_{ND} (%) and overall functioning (Social Functioning Scale [SFS] full-scale score) in people with SZ. Positive change in BP_{ND} indicates greater serotonin release; lower SFS indicates poorer functioning. Values for individuals with SZ not taking antipsychotic medication (AP-free SZ) and those with SZ taking AP medication (AP-treated SZ) are represented with different symbols for visualization purposes.

[a]Indicates statistical significance at false discovery rate–corrected $P < .05$.

who did not fulfill criteria for the deficit syndrome and healthy controls. We further show that serotonin release was correlated with baseline negative but not positive symptoms, potentially suggesting specificity to negative symptoms although, as we excluded people with marked positive symptoms, this warrants testing in future studies.

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Methodological Considerations

We found lower [^{11}C]Cimbi-36 V_T at baseline in the cerebellum of those with schizophrenia compared with that in controls. This is unlikely to be explained by reductions in volume, as regional brain volumes were similar between the groups. We also found lower tracer delivery in schizophrenia, although as this was a global effect (with a similar degree in the frontal cortex and the cerebellum), it is unlikely to explain our findings in the cerebellum, as it would also affect the frontal cortex. Notwithstanding this, our findings remained significant after covarying for tracer delivery, indicating they are robust to this difference. A study[14] using the selective 5-HT2A antagonist radiotracer [18F]Altanserin previously reported lower cerebellar binding in schizophrenia. The explanation for these changes remains unclear, however, changes in the reference region cannot explain our main results on serotonin release, as they were consistent in both a reference region (ΔBP_{ND}) and blood-based (ΔV_T) approach.

Interpretation and Comparison With Previous Studies

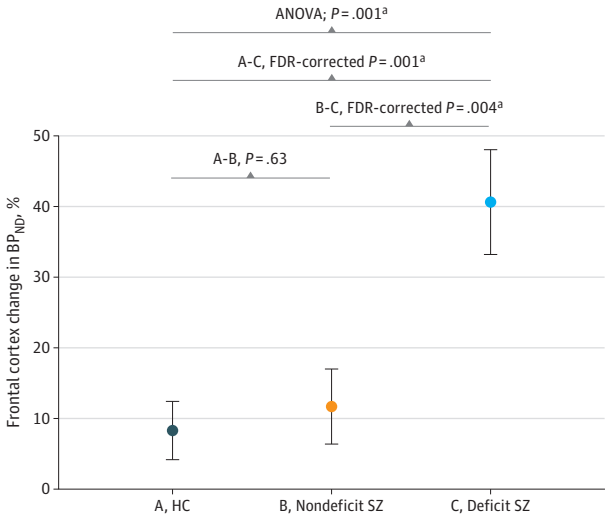
In contrast with our hypothesis, we found that schizophrenia was associated with increased frontal cortex serotonin release. Our a priori hypothesis was inferred from indirect data (as there were no prior in vivo studies) showing that antidepressants improve and tryptophan depletion exacerbates negative symptoms of schizophrenia.[11,12] However, the effect of antidepressants is weak (standardized mean difference = −0.35), could be confounded by an effect on depressive symptoms, and may not be mediated by increased serotonin levels.[4,11] Furthermore, tryptophan depletion studies may be confounded by alterations in other aspects of brain function following tryptophan depletion, such as reductions in melatonin.[53,54] Our findings suggest that assumptions of lower cortical serotonin release in schizophrenia based on indirect data are likely wrong.

There is prior evidence indicating that increased serotonergic signaling could lead to schizophreniform symptoms. This includes findings that potent 5-HT2A agonists such as lysergic acid diethylamide (LSD) can induce a schizophrenia-like state, including negative symptoms, in some healthy individuals and that this is attenuated by coadministration of the 5-HT2A antagonist ketanserin.[55-58] Our findings extend these by indicating that there is increased serotonergic signaling in schizophrenia and that this is linked to severity of symptoms.

We replicate previous findings that deficit schizophrenia is associated with greater disability than nondeficit schizophrenia and extend these to provide preliminary evidence that deficit schizophrenia is also associated with greater frontal cortex serotonin release, with a large effect size.[19]

We found no significant alteration in baseline frontal cortex 5-HT2A receptor availability in schizophrenia. Our study used an agonist radiotracer that binds to the high-affinity form of the 5-HT2A receptor, in contrast with the antagonist radiotracers previously used.[13-15,17] Our work, therefore, extends prior in vivo findings to indicate no major alteration in availability of high-affinity 5-HT2A receptors in schizophrenia, albeit it remains possible that increases are masked by higher synaptic serotonin levels (eDiscussion in Supplement 1).[59]

Figure 4. Comparison of [^{11}C]Cimbi-36 Frontal Cortex Change in Nondisplaceable Binding Potential (ΔBP_{ND}) Between Healthy Controls, Deficit Schizophrenia, and Nondeficit Schizophrenia



Adjusted mean (standard error of the mean) of frontal cortex ΔBP_{ND} (%) in healthy controls (HCs) (A), nondeficit schizophrenia (SZ) (B), and deficit SZ (C). Group means were compared in an analysis of variance (ANOVA) with adjustment for differences in injected mass.

[a]Indicates statistical significance at false discovery rate(FDR)–corrected $P < .05$.

Implications for Understanding Schizophrenia

Our results suggest an overactive serotonergic system in schizophrenia, reflected by higher frontal cortex serotonin release capacity, and that this could underlie greater severity of negative symptoms. This raises the question of how serotonergic dysfunction could underlie symptoms. Preclinical and human data show that serotonin signaling plays a key role in particular aspects of reinforcement learning.[60-63] Activity in serotonergic projections to the frontal cortex promotes waiting for future reward over acting immediately.[61] Thus, serotonin overactivity may impair motivated behavior through devaluation of immediate rewards. This is consistent with our finding that greater serotonin release was associated with more severe motivational impairments. Interestingly, the exploratory analyses indicate greater serotonin release in the amygdala, potentially implicating regions involved in emotional processing as well as the frontal cortex.

Our findings provide a potential explanation for why antipsychotic medications that are high-affinity 5-HT2A receptor antagonists have some efficacy against negative symptoms.[5,64] However, it should be noted that benefits of antipsychotic medications for negative symptoms are modest and could be largely driven by improvements in secondary negative symptoms.[4] Nevertheless, our exploratory finding that deficit schizophrenia was associated with significantly greater frontal cortex serotonin release in comparison with nondeficit schizophrenia and healthy controls provides preliminary evidence that increased serotonergic neurotransmission is involved in the pathophysiology of primary negative symptoms. Our findings are consistent with recent double-blind

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randomized clinical trials[65-67] that suggest that 5-HT2A antagonists/inverse agonists may be effective for negative symptoms when people with schizophrenia are selected for primary or predominant negative symptoms.

It is also interesting to note that serotonin release was less marked in the subgroup of individuals with nondeficit schizophrenia relative to controls. However, our subgroup analysis was exploratory, and the correlation between negative symptom severity and frontal serotonin release in the entire sample suggests that serotonergic alterations were associated with negative symptoms in schizophrenia in general, rather than the subgroup with deficit syndrome (who had more severe negative symptoms). The findings in the subgroup with deficit and nondeficit schizophrenia should, therefore, be considered preliminary and warrant further investigation in larger samples.

It is important to recognize that increased serotonin release could be acting at other serotonin receptors in addition to 5-HT2A receptors. Our data, therefore, suggest the regulation of serotonin release and serotonergic receptors as potential targets to treat negative symptoms. There is a need for further studies that directly assess the role of cortical serotonergic neurotransmission in regulating motivated behavior and to investigate the mechanisms underlying increased serotonin release in schizophrenia. This would aid in understanding whether serotonin release could be a biomarker for primary negative symptoms, as our findings on deficit schizophrenia suggest. Finally, if confirmed, our finding that serotonergic function was associated with negative symptoms adds to prior evidence that striatal dopaminergic function is particularly associated with psychotic symptoms and cortical dopamine associated with cognitive impairments, to indicate that different monoaminergic circuits may underlie distinct symptom domains.[43,45,68-71] It would be useful for future studies to determine the interactions between these circuits.[28]

Strengths and Limitations

Strengths of our study include the robustness of the primary neuroimaging outcome to variations in modeling approach and potential confounds such as head motion and differences between the PET scanners used (eDiscussion in Supplement 1). We quantified [^{11}C]Cimbi-36 binding using the 2TCM method, as it provides more robust description of tracer activity compared to the MA1 method.[35] Nevertheless, we found near perfect correlations between values from the MA1 and 2TCM methods and replicated the finding of increased frontal cortex ΔBP_{ND} in sensitivity analysis using the MA1 method. A further strength is that we demonstrated associations between serotonin release and poorer clinical outcomes using both the patient's own assessment of their real-world functioning, and the clinician-rated assessment of negative symptoms.[31,32]

Our findings are not confounded by current antipsychotic treatment, as most of our sample were not taking antipsychotic medications, and we replicated our main findings in a subgroup analysis of individuals not taking antipsychotic medications. Furthermore, the antipsychotic medications allowed have negligible 5-HT2A affinity.[25] In addition to this, most of the individuals had never taken antidepressant medication, the average time since last exposure to antidepressants/5-HT2A blocking antipsychotics was greater than 1.5 years in those who had received them, and there was no association between time since last antidepressant/5-HT2A blocking antipsychotic medications and frontal cortex ΔBP_{ND}, indicating that these factors are unlikely to contribute substantially to our findings. Although we did not find an association between duration of illness and frontal cortex ΔBP_{ND}, given the mean duration of illness was 5.7 years, it remains an open question when serotonergic alterations develop in the disorder. Future studies could test whether greater frontal cortex ΔBP_{ND} is also seen early in the course of schizophrenia.[72-74]

Conclusions

Results of this case-control study suggest that schizophrenia was associated with higher frontal cortex serotonin release and demonstrated that this is associated with greater severity of negative symptoms and poorer overall functioning. The exploratory analysis suggests that higher frontal cortex serotonin release was particularly marked in individuals with deficit schizophrenia, a subtype characterized by primary and enduring negative symptoms, when compared with both healthy volunteers and those with nondeficit schizophrenia. These findings suggest serotonergic dysfunction in the pathophysiology of schizophrenia and identify the regulation of serotonin release and serotonin receptors as promising therapeutic targets to treat negative symptoms.

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