Archival Report

Dopamine Synthesis Capacity and GABA and Glutamate Levels Separate Antipsychotic-Naïve Patients With First-Episode Psychosis From Healthy Control Subjects in a Multimodal Prediction Model

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ABSTRACT

BACKGROUND: Disturbances in presynaptic dopamine activity and levels of GABA (gamma-aminobutyric acid) and glutamate plus glutamine collectively may have a role in the pathophysiology of psychosis, although separately they are poor diagnostic markers. We tested whether these neurotransmitters in combination improve the distinction of antipsychotic-naïve patients with first-episode psychosis from healthy control subjects.

METHODS: We included 23 patients (mean age 22.3 years, 9 male) and 20 control subjects (mean age 22.4 years, 8 male). We determined dopamine metabolism in the nucleus accumbens and striatum from ^{18}F-fluorodopa (^{18}F-FDOPA) positron emission tomography. We measured GABA levels in the anterior cingulate cortex (ACC) and glutamate plus glutamine levels in the ACC and left thalamus with 3T proton magnetic resonance spectroscopy. We used binominal logistic regression for unimodal prediction when we modeled neurotransmitters individually and for multimodal prediction when we combined the 3 neurotransmitters. We selected the best combination based on Akaike information criterion.

RESULTS: Individual neurotransmitters failed to predict group. Three triple neurotransmitter combinations significantly predicted group after Benjamini-Hochberg correction. The best model (Akaike information criterion 48.5) carried 93.5% of the cumulative model weight. It reached a classification accuracy of 83.7% ($p = .003$) and included dopamine synthesis capacity (K_i^{4P}) in the nucleus accumbens ($p = .664$), GABA levels in the ACC ($p = .019$), glutamate plus glutamine levels in the thalamus ($p = .678$), and the interaction term $K_i^{4P} \times$ GABA ($p = .016$).

CONCLUSIONS: Our multimodal approach proved superior classification accuracy, implying that the pathophysiology of patients represents a combination of neurotransmitter disturbances rather than aberrations in a single neurotransmitter. Particularly aberrant interrelations between K_i^{4P} in the nucleus accumbens and GABA values in the ACC appeared to contribute diagnostic information.

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We consider dysregulated dopamine, GABA (gamma-aminobutyric acid), and glutamate transmitter systems to be key elements in the development of psychosis. The dopamine hypothesis has a long history (1), but alternative hypotheses of more complex disturbances of neurochemical circuits involving GABA and glutamate have been proposed (2). However, because of clinical and technical challenges, only limited empirical data have been available for testing whether disturbances of the neurotransmitter systems of dopamine, GABA, and glutamate interact in the early stages of psychosis, and joint measures of all 3 neurotransmitters have not previously been available for the purpose of testing this claim.

The effect size of the evidence of elevated dopamine synthesis capacity (DSC) in psychosis appears to have lessened over time (3–15), and neither of the 2 largest first-episode studies replicated elevated DSC (16,17). Using refined 4-parameter (4P) modeling of DSC in antipsychotic-naïve patients with first-episode psychosis, we previously found the 4P model to be superior to the conventional model. Particularly, we found the striatal decarboxylation rate of ^{18}F-fluorodopa (^{18}F-FDOPA) to ^{18}F-dopamine (k_3) to be associated with psychotic symptoms and treatment outcome (17). Yet, neither k_3 nor DSC estimates from the 4P or conventional model (K_i^{4P} and K_i^{cer}, respectively) discriminated patients from healthy control subjects (HCs), implying that disturbances of dopamine

metabolism may be rather discrete at early stages of illness. Another explanation may be that patients are better characterized by combinations of neurotransmitter events in the cortico-striato-thalamo-cortical networks, such as by striatal dopaminergic activity combined with glutamatergic and GABAergic activities in the thalamus and prefrontal cortex (PFC).

Knowledge of GABAergic involvement in psychosis largely is based on animal models and postmortem studies (18–21), and few clinical studies exist. Findings of GABA levels in frontal brain regions, typically the anterior cingulate cortex (ACC) and medial PFC, ranged from increased (22–26) to similar (27–29) or decreased (30–32) GABA levels in patients with psychosis compared with HCs. A recent positron emission tomography (PET) study found decreased GABA$_A$ receptor levels in the hippocampus in antipsychotic-free patients but not in medicated patients (33).

The literature of glutamate and glutamate plus glutamine (Glx) levels in patients with psychosis compared with HCs likewise is at variance with data indicating increased (23,34–36), decreased (29,37–40), or similar (41–44) values. A recent meta-analysis yielded decreased Glx levels in medial PFC in patients compared with HCs at group levels (39).

A few studies combined measures of 2 of the 3 transmitters listed above. Treatment resistance has been suggested to be associated with elevated glutamate levels but normal DSC (45). An inverse relationship between striatal dopamine activity and glutamate levels in the ACC was reported for first-episode patients (16), while another study revealed a negative relationship between prefrontal glutamate levels and striatal DSC in healthy individuals (46). An association between striatal DSC and prefrontal GABA levels has not been reported.

In a large cohort of antipsychotic-naïve patients partly overlapping this study population, we previously reported reduced GABA levels in the dorsal ACC, but no alterations of glutamatergic metabolites (47,48). We also found increased glutamate levels in the thalamus in patients with a diagnosis of schizophrenia, the increase determined by subsequent non-responders after 6- or 26-week antipsychotic treatments (47,48).

So far, no single brain abnormality has allowed discrimination of patients with psychosis from HCs. In the past decades, some authors instead suggested more complex models of schizophrenia involving combined transmitter disturbances in linked brain networks (49,50). The models have support from the preclinical literature, but clinical data are missing. Examination of multiple key neurotransmitters believed to be involved in the development of psychosis must happen at the earliest stage of disease, and before patients are exposed to antipsychotic treatment to ensure undiluted assessments. Uncompromised data may provide novel insight into the identification of combined neurochemical profiles that characterize first-episode psychosis.

For this purpose, we argue that a multimodal rather than a unimodal approach may increase the accuracy of prediction of psychotic illness within the schizophrenia spectrum (51–55). As a completely agnostic approach may obscure signals and complicate interpretation because of inclusion of multiple variables (56,57), we applied domain knowledge and carefully selected the variables a priori, guided by other studies and findings in previous overlapping cohorts where we were not

able to identify group differences in DSC (17) or institutional unit–scaled proton magnetic resonance spectroscopy (^{1}H-MRS) measures (47).

We tested the hypothesis that a multivariable logistic regression model of 3 neurochemical measures, i.e., striatal dopamine synthesis rate (k_3) or DSC (K_i^{4p}) clearance, levels of GABA in the ACC, and levels of Glx in the thalamus or ACC, predicts group affiliation (antipsychotic-naïve patients with first-episode psychosis or HCs) more accurately than models of single neurochemical measures. We also evaluated the contribution of each of the neurotransmitters to the overall discriminatory power of the combinations applied.

METHODS AND MATERIALS

Participants

Participants were part of a large multimodal cohort study (PECANS II) approved by the Danish National Committee on Biomedical Research Ethics (H-3-2013-149). Detailed description of the cohort is provided in previous publications (17,47,48). Patients were referred from Mental Health Centers in the Capital Region of Denmark and could be included if they were lifetime naïve to antipsychotic compounds and central nervous system stimulants; legally competent; 18 to 45 years of age; and fulfilled the diagnostic criteria for schizophrenia, schizoaffective disorder, or nonorganic psychosis according to the ICD-10. The diagnosis was evaluated by certified interviewers with the Schedules for Clinical Assessment in Neuropsychiatry (58).

HCs matched on age, sex, and parental educational level were recruited via online advertisement. Exclusion criteria included lifetime psychiatric illness or ultrahigh risk of psychosis according to the Comprehensive Assessment of At-Risk Mental States (59) and having first-degree relatives with psychotic symptoms.

General exclusion criteria included head injury with more than 5 minutes' unconsciousness, metallic implants (incompatible with magnetic resonance imaging [MRI]), pregnancy, severe physical illness or previous substance abuse (ICD-10 criteria F1X.1), or use of antidepressant treatment within the past 30 days. Patients submitted to involuntary treatment or admission were excluded. Prescribed benzodiazepines were tolerated in patients prior to initiation of antipsychotic treatment. Two patients had a positive urine screening for benzodiazepines on the neuroimaging days and were excluded from this sample primarily because of the evidence of benzodiazepines' effect on the GABAergic system (60). Occasional substance use was accepted and self-reported and verified by a urine drug test (Rapid Response; Jepsen HealthCare) before neuroimaging.

^{18}F-FDOPA PET

We determined dopamine synthesis (k_3) and DSC (K_i^{4p}) with ^{18}F-FDOPA PET using integrated PET–computed tomography (Siemens Biograph m CT64, 2013). To minimize ^{18}F-FDOPA metabolic degradation before passage through the blood-brain barrier, we administered carbidopa (150 mg) and entacapone (400 mg) orally 1 hour prior to PET. We acquired an initial low-dose computed tomography scan before all PET sessions

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to enable attenuation correction. We injected ^{18}F-FDOPA as an intravenous bolus (mean dose: 330 MBq, SD: 33.0; range: 259–399 MBq) simultaneously with initiation of the first session.

Detailed information about settings, collection of arterial blood samples, equipment, and data processing including kinetic modeling was described previously for the same cohort (17) and in the associated Supplement.

MRI Data Acquisition

We acquired MRI scans at 3T (Achieva; Philips Healthcare) with a 32-channel head coil (Invivo). We instructed participants to not move during the scan and to keep the head in the same position. High-resolution, three-dimensional, structural T1-weighted images (response time 10 ms, echo time 4.6 ms, flip angle = 8°, voxel size = 0.79 × 0.79 × 0.80 mm) were obtained of the brain and used as reference for the tomography as well as for placement of the spectroscopic voxels and segmentation into cerebrospinal fluid and gray matter and white matter fractions.

We used FreeSurfer version 5.3.0 (61,62) for individual anatomical segmentation of participants' brains and to obtain regions of interest for the nucleus accumbens (NAcc), putamen, and nucleus caudatus. We selected the whole striatum (NAcc, putamen, and nucleus caudatus) and the NAcc as regions of interest. We included the NAcc on the basis of results from preclinical research (63). The NAcc has been tested as a potential therapeutic target of neurosurgical intervention for schizophrenia (64), and it was further found to be of interest to the understanding of psychosis and dopaminergic disturbances in clinical studies (7,65,66). We found this relationship also in an overlapping sample of subjects in whom we found that values of both k_3 and K_i^{4p} from the NAcc correlated with the severity of positive symptoms in the patients before the first treatment (17).

Proton MRS

We completed ^{1}H-MRS with the point-resolved spectroscopy (PRESS) sequence to determine Glx levels and with the Mescher-Garwood PRESS (MEGAPRESS) sequence to obtain GABA levels. We measured Glx using rectangular voxels in the dorsal ACC and left thalamus, while we measured GABA levels in the dorsal ACC only [see the Supplement; (48)]. We used the LCModel version 6.3-1L (67) for analysis of PRESS data and Gannet version 3.1 (68) for MEGAPRESS data, as described in the Supplement. The in vivo water-scaled values of metabolites were corrected for partial volume contamination by cerebrospinal fluid to obtain concentrations in institutional units, as previously described (48). There was significantly higher full width at half maximum values of patients for both dorsal ACC PRESS and MEGAPRESS acquisitions (Tables S1 and S3), but inclusion of full width at half maximum as covariate in the statistical analyses did not affect the results, as described in the Supplement.

Statistical Analysis

We used binomial logistic regression to know whether striatal dopamine synthesis (k_3) or DSC (K_i^{4p}), GABA levels in the ACC, or Glx levels in the thalamus or ACC would predict group. First,

we completed 7 simple logistic regressions with each of the 7 variables to predict group as independent variables. In the following, we denote these univariable models as individual neurotransmitter models. Second, we completed multiple logistic regressions combining either K_i^{4p} or k_3 (from the striatum/NAcc) with GABA levels (ACC) and Glx levels (thalamus/ACC) to predict group. The limited sample size required a priori selection of neurotransmitter combinations rather than combinations of all parameters in one model. With the following premises, all combinations represented all 3 neurotransmitters (dopamine, Glx, and GABA), and none of the included models could show multicollinearity. The latter premise was fulfilled when we constrained the neurotransmitter models to include either a K_i^{4p} or k_3 measure, resulting in a total of 8 different neurotransmitter models. In the following, we called these multivariable models neurotransmitter combinations, ordered 1–8. The a priori selection of regions of interest with regard to the dopamine measures was based on previous preclinical findings and our own results from an overlapping sample (17). See the Supplement for a discussion on the striatal locus of dopaminergic disturbances.

The interaction terms K_i^{4p} × GABA or k_3 × GABA were included in each of the neurotransmitter models because they contributed significantly to some of the models. Interaction terms combining the variables K_i^{4p} or k_3 with Glx levels, or with GABA and Glx levels combined, did not add significance and were excluded. We standardized all predictors (mean = 0, SD = 1) prior to fitting of the models to increase the comparability of predictors. HCs were used as reference population. Hence, negative β coefficients indicate a tendency toward lower values for patients than for HCs.

We assessed the assumption of linearity of the continuous variables with respect to the logit of the dependent variable via the Box-Tidwell procedure (69). Exploration of outliers, high leverage points, and high influential points led us to exclude 2 HCs as outliers with respect to k_3. These 2 outliers were excluded from all analyses.

We used the Akaike information criterion (AIC) to find the relative quality of the statistical models for given sets of data. Lower AIC reflects a better model that balanced goodness of fit and model complexity. Here, we used the model selection corrected for small sample sizes (AICc) to distinguish among the 8 neurotransmitter combinations based on evidence ratios for AICc weights for the best-fitted and the next best-fitted models (70).

As primary outcomes, accuracies represented the ability of a given individual neurotransmitter model to predict group. We used 10,000 permutations to test for significant differences from baseline accuracy. Baseline accuracy defines the accuracy of predicting the majority class of each observation (71), i.e., the more unequal the sample sizes of patients and HCs, the higher the baseline accuracy. We also provided the area under the curve (AUC) of the receiver operating characteristic curves. The receiver operating characteristic curve indicates the overall discriminatory ability of the neurotransmitter combination. For the interpretation of AUC, we used the following classifications: $0.7 \leq$ AUC < 0.8 indicates acceptable discrimination, and $0.8 \leq$ AUC < 0.9 indicates excellent discrimination (72). We applied the Benjamini-Hochberg procedure (BH) (73) to correct for multiple comparisons covering 7

univariable and 8 multivariable analyses. In the Results section, we denoted BH-corrected p values as p_{BH}.

We further ran cross-validation with 100 random splits stratified on group (70% training, 30% test) to estimate the generalizability of the models to an independent sample, and we tested significance with a test of 10,000 permutations.

We used Python 3.7 incorporating the statsmodels (74) and scikit-learn (75) modules for binominal logistic regression including cross-validation, and we completed demographic exploration and assumption testing using SPSS Statistics version 25 (IBM Corp.).

RESULTS

We obtained combined measures of the variables K_i^{4p}-estimates or k_3-variables, GABA levels in the ACC, and Glx levels in the thalamus of 23 patients and 20 HCs (Table 1) and included a few more members of the group of HCs in the samples of dopamine measures combined with Glx levels in the ACC (Table S4). The individual neurotransmitter models had larger sample sizes (see the Supplement and Table S4). The patients were moderately ill, with a mean Positive and Negative Syndrome Scale total score of 80. Fourteen patients (61%) were diagnosed with schizophrenia (Table 1).

None of the 7 individual neurotransmitter models had significant predictive performance (Table S5). Of the 8 combined neurotransmitter models, the best-fitted model included K_i^{4p} in the NAcc, GABA in the ACC, Glx in the thalamus, and the interaction term $K_i^{4p} \times$ GABA (combination 1). This model carried 93.5% of the cumulative model weight (AIC 48.475, AIC weight 0.935). In comparison, the next best combined model, combination 3, only carried 2.2% of the cumulative model weight. Hence, the evidence ratio shows that combination 1 is

42.5 times (0.935/0.022) more likely to be superior to the next best model. Table 2 displays the variables included in each of the 8 neurotransmitter models and their accuracies, AUC, AICc, and AICc weight.

Combination 1 predicted group with an accuracy of 83.7% (p_{BH} = .003) and an AUC of 83.8% (p_{BH} = .003) (Table 2 and Figure 1). In combination 1, the values of GABA in the ACC (p = .019) and of the interaction term $K_i^{4p} \times$ GABA (p = .016) were predictive, while K_i^{4p} in the NAcc (p = .664) and Glx in the thalamus (p = .678) were not. GABA levels tended to be lower in patients than in HCs (negative β coefficients). β Coefficients and contribution of each of the independent variables to the neurotransmitter models (combination 1–8) are provided in Table 3.

We list the estimated predictive performances of an independent sample of the 8 models after cross-validation in Table S6. Combination 1 significantly predicted group (accuracy 74.1%, p_{BH} = .021, AUC 82.8%, p_{BH} = .007). Combinations 2 and 3 were significant at trend level (p = .064 and .043, respectively).

We completed post hoc analyses, excluding the consistently insignificant independent variable Glx (in the thalamus/ACC) to reduce model complexity and to explore whether combined dopamine measures and GABA levels in the ACC (double neurotransmitter models) would be comparable to triple neurotransmitter models. However, the double transmitter models were inferior to triple neurotransmitter models (Supplement and Table S7).

DISCUSSION

In this study, we found that a combination of striatal dopaminergic metabolism and levels of GABA and glutamatergic metabolites discriminated antipsychotic-naïve patients from

Table 1. Demographics and Clinical Characteristics of Participants With ^{18}F-FDOPA PET and Spectroscopy Including GABA Spectra in the ACC and Glx in the Thalamus, n = 43

Characteristics	Patients, n = 23	HCs, n = 20	Statistics
Age, Years, Mean ± SD	22.30 ± 3.9	22.35 ± 4.3	$t_{38.535}$ = −0.036, p = .971
Sex, Female/Male, n	14/9	12/8	Fisher's p = 1.000
Educational Level, Years, Mean/Median	12.5	13[a]	Mann-Whitney p = .233
Parental Educational Level, High/Moderate/Low, n	6/12/5	8/11/1	χ^2 = 0.003, p = .954
Race, Caucasian/Other, n	19/4	19/1	Fisher's p = .351
Current Substance Use			
Smoking, yes/no, n	8/15	2/18	Fisher's p = .076
Cannabis, positive urine screening, yes/no, n	0/23	1/19	Fisher's p = .465
Diagnosis ICD-10, n (%)			
Schizophrenia	14 (61%)	–	–
Nonorganic psychosis	9 (39%)	–	–
PANSS Score, Baseline, Mean			
Total	79.87	–	–
Positive	19.65	–	–
Negative	21.83	–	–
General	38.39	–	–

^{18}F-FDOPA, ^{18}F-fluorodopa; ACC, anterior cingulate cortex; GABA, gamma-aminobutyric acid; Glx, glutamate plus glutamine; HCs, healthy control subjects; PANSS, Positive and Negative Syndrome Scale; PET, positron emission tomography.
[a]Normal distribution violated; median reported instead of mean. The significance level is set to .05.

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Table 2. Predictive Values for the 8 Neurotransmitter Combinations

Neurotransmitter Combination		Accuracy	Accuracy p Value	Accuracy p Value BH	AUC	AUC p Value	AUC p Value BH	AICc	AICc Weight
K_i^{4p} $_{NAcc}$ Combined With									
1	GABA$_{ACC}$ and Glx$_{Thalamus}$	0.837	.000[a]	.003[a]	0.838	.000[a]	.003[a]	48.475	0.935
2	GABA$_{ACC}$ and Glx$_{ACC}$	0.778	.002[a]	.012[a]	0.778	.003[a]	.015[a]	55.968	0.022
K_i^{4p} $_{whole\ str}$ Combined With									
3	GABA$_{ACC}$ and Glx$_{Thalamus}$	0.791	.001[a]	.010[a]	0.791	.001[a]	.010[a]	55.947	0.022
4	GABA$_{ACC}$ and Glx$_{ACC}$	0.711	.038[a]	.115	0.709	.068	.203	61.844	0.001
k_3 $_{NAcc}$ Combined With									
5	GABA$_{ACC}$ and Glx$_{Thalamus}$	0.721	.031[a]	.115	0.713	.054	.203	56.565	0.016
6	GABA$_{ACC}$ and Glx$_{ACC}$	0.667	.140	.300	0.666	.174	.343	59.966	0.003
k_3 $_{whole\ str}$ Combined With									
7	GABA$_{ACC}$ and Glx$_{Thalamus}$	0.651	.222	.345	0.648	.259	.389	64.280	<0.001
8	GABA$_{ACC}$ and Glx$_{ACC}$	0.644	.230	.345	0.644	.260	.389	67.634	<0.001

k_3 is the enzymatic activity of DOPA-decarboxylase, converting DOPA to dopamine. K_i^{4p} is the dopamine synthesis capacity estimate from the 4-parameter model. The whole striatum is composed of putamen, caudate, and nucleus accumbens. AICc weight is the proportion of the total amount of predictive power provided by the full set of models contained in the model being assessed. The BH procedure was used to correct for 15 comparisons (7 univariable and 8 multivariable).

ACC, anterior cingulate cortex; AICc, Akaike information criterion controlled for small sample sizes; AUC, area under the receiver operating characteristic curve; BH, Benjamini-Hochberg; GABA, gamma-aminobutyric acid; Glx, glutamate plus glutamine; NAcc, nucleus accumbens; str, striatum.

[a]$p < .05$.

HCs, unlike the individual neurotransmitter measures that failed to do so. Specifically, we discovered that 3 neurotransmitter models (1, 2, and 3) resulted in satisfactory prediction of group. The combination of DSC in the NAcc, GABA levels in
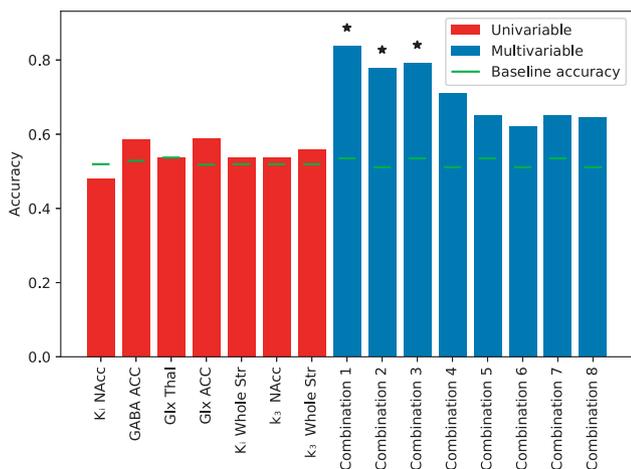

Figure 1. This graph shows the accuracies for prediction of group in univariable and multivariable models, illustrating the predictive accuracy of the tested models. None of the individual neurotransmitter models (red bars) could predict group. Among the multivariable models (blue bars), the best fit model, combination 1, carried out 93.5% of the cumulative model weight (Akaike information criterion controlled for small sample sizes [AICc] = 48.5 and AICc weight = 0.935) and differed from the rest of the models. The variables included in each of the 8 models are provided in Table 3. The dotted green lines indicate balanced accuracy. * indicates significant predictions ($p_{BH} < .05$). k_3 is the decarboxylation rate (conversion of ^{18}F-FDOPA to ^{18}F-dopamine). K_i is the estimate of the dopamine synthesis capacity from the 4-parameter model. ACC, anterior cingulate cortex; ^{18}F-FDOPA, ^{18}F-fluorodopa; GABA, gamma-aminobutyric acid; Glx, glutamate plus glutamine; NAcc, nucleus accumbens; Str, striatum; Thal, thalamus.

the ACC, and Glx levels in the thalamus was markedly superior to other combinations with respect to AIC weight and predicted the status of having a first-episode psychosis with an accuracy of 83.7%. In this model, GABA levels and the DSC-GABA interaction made significant contributions, unlike DSC and the Glx levels. However, all triple transmitter models, including Glx levels in the thalamus or ACC, had higher accuracy than the corresponding double transmitter models, excluding the Glx levels. Triple transmitter models additionally were a better fit in terms of AIC, although AIC penalize more complex models. Hence, overall, we found that all 3 neurotransmitters contributed to variable extents to the discrimination between patients and HCs.

DSC was not in itself a predictive factor. A large body of evidence suggests that disturbances in DSC are involved in the development of psychotic symptoms (3,5–7,10,12,65,66, 76–79), but the lack of predictive discriminative power of DSC in the present data is in agreement with the 2 so far largest first-episode studies (16,17) failing to confirm differences in DSC between patients and HCs.

The interaction between GABA levels in the ACC and K_i^{4p} values in the striatum added with the largest β coefficient to the prediction of subject group. This intriguing finding supports the claim that patients may have a disturbed relationship between the 2 transmitters. The so-called filter hypothesis for schizophrenia proposed that schizophrenia develops as a result of disturbances in interacting dopaminergic, glutamatergic, and GABAergic systems in the cortico-striato-thalamo-cortical loops, leading to disruption of the thalamic filter and an overload of information to the cortex (80). As an extension, Carlsson suggested that the balance between activation and inhibition in the direct and indirect pathways in the macrocircuits plays a key role for the level of subcortical dopamine and for the understanding of how psychotic symptoms evolve (2). The direct pathway results in activation of subcortical

Table 3. The Contribution of the Independent Variables in Each of the 8 Neurotransmitter Combinations

Neurotransmitter Combinations		β	SE	$p > \lvert z \rvert$	CI 0.025, 0.975
1	K_i^{4p} $_{NAcc}$	−0.301	0.693	.664	−1.658, 1.057
	GABA$_{ACC}$	−1.919	0.816	.019[a]	−3.519, −0.320
	Glx$_{Thalamus}$	−0.194	0.466	.678	−1.108, 0.720
	Interaction, $K_i \times$ GABA	3.570	1.479	.016[a]	0.672, 6.468
2	K_i^{4p} $_{NAcc}$	0.191	0.542	.725	−0.871, 1.252
	GABA$_{ACC}$	−1.343	0.636	.035[a]	−2.589, −0.097
	Glx$_{ACC}$	−0.131	0.342	.701	−0.801, 0.538
	Interaction, $K_i \times$ GABA	2.443	1.078	.024[a]	0.330, 4.556
3	K_i^{4p} $_{whole\ striatum}$	−0.099	0.457	.828	−0.994, 0.796
	GABA$_{ACC}$	−1.197	0.546	.028[a]	−2.267, −0.127
	Glx$_{Thalamus}$	−0.260	0.426	.542	−1.096, 0.575
	Interaction, $K_i \times$ GABA	1.619	0.717	.024[a]	0.214, 3.023
4	K_i^{4p} $_{whole\ striatum}$	0.113	0.402	.779	−0.674, 0.900
	GABA$_{ACC}$	−0.986	0.482	.041[a]	−1.931, −0.041
	Glx$_{ACC}$	−0.134	0.330	.685	−0.781, 0.513
	Interaction, $K_i \times$ GABA	1.259	0.607	.038[a]	0.069, 2.449
5	k_3 $_{NAcc}$	0.142	0.404	.726	−0.650, 0.933
	GABA$_{ACC}$	−1.343	0.558	.016[a]	−2.436, −0.251
	Glx$_{Thalamus}$	0.008	0.419	.985	−0.814, 0.829
	Interaction, $k_3 \times$ GABA	1.102	0.476	.021[a]	0.168, 2.035
6	k_3 $_{NAcc}$	0.089	0.373	.811	0.642, 0.820
	GABA$_{ACC}$	−1.203	0.531	.024[a]	−2.244, −0.162
	Glx$_{ACC}$	−0.340	0.359	.344	−1.044, 0.364
	Interaction, $k_3 \times$ GABA	1.047	0.448	.019[a]	0.169, 1.924
7	k_3 $_{whole\ striatum}$	0.029	0.357	.934	−0.670, 0.728
	GABA$_{ACC}$	−0.864	0.398	.030[a]	−1.643, −0.084
	Glx$_{Thalamus}$	−0.086	0.357	.809	−0.785, 0.613
	Interaction, $k_3 \times$ GABA	0.280	0.368	.446	−0.440, 1.001
8	k_3 $_{whole\ striatum}$	−0.059	0.346	.866	−0.737, 0.620
	GABA$_{ACC}$	−0.754	0.383	.049[a]	−1.504, −0.004
	Glx$_{ACC}$	−0.175	0.323	.588	−0.809, 0.459
	Interaction, $k_3 \times$ GABA	0.317	0.345	.357	−0.358, 0.993

The interaction terms $K_i^{4p} \times$ GABA or $k_3 \times$ GABA were included in models because the term $K_i^{4p} \times$ GABA added significantly to some models. Other interaction terms were insignificant and hence left out. k_3 is the enzymatic activity of DOPA-decarboxylase, converting DOPA to dopamine. K_i^{4p} is the dopamine synthesis capacity estimate from the 4-parameter model.

ACC, anterior cingulate cortex; GABA, gamma-aminobutyric acid; Glx, glutamate plus glutamine; NAcc, nucleus accumbens.

[a]$p < .05$.

structures via glutamatergic excitation from cortical neurons, whereas the indirect pathway, involving an odd number of GABAergic interneurons, counterbalances the activation. Hence, if the direct pathway dominates, the net result is disinhibition of the thalamic filter, whereas domination of the indirect pathway results in net inhibition of the cortico-striato-thalamo-cortical loop (1,2,81). Cortical GABAergic neurons have also been held to exert important effects on the balance between excitatory and inhibitory states by regulating the connectivity of GABA interneurons (20,21). The higher β coefficient for the interaction term between DSC and GABA levels than the β coefficients for the individual neurotransmitters indicates that the contribution of the interrelation exceeds the one from each neurotransmitter. See the Supplement for detailed discussion of the impact of the interaction term.

A recent study found a negative correlation between gray matter volume in the PFC and striatal DSC in treatment-responsive patients with first-episode psychosis (82). The authors suggested that lower PFC volume reflects fewer or disrupted inhibitory projections from the PFC (e.g., a disrupted indirect pathway), potentially leading to downstream disinhibition of striatal dopamine function and elevated DSC (82). Here, GABA levels in the ACC may represent a more direct measure of the prefrontal regulation of inhibitory projections to the striatum. The impact of the interaction between GABA levels in the ACC and striatal DSC in the present multimodal analyses suggests that the diagnosis of psychosis rather depends on disruption of the indirect pathway in the macrocircuits in the brain (2,83) than on dopaminergic or GABAergic abnormalities in themselves, although such a disruption, if present, did not lead to elevated DSC in this study.

We also showed GABA levels in the ACC to be an important predictor of group. A discrimination based on GABA levels agrees with a previous finding of lower baseline GABA levels in

antipsychotic-naïve patients (48). The lower baseline levels appeared to be driven by nonresponding patients compared with HCs in an overlapping sample of patients (47). The results also agree with the data from a recent 7T ^{1}H-MRI meta-analysis showing a tendency toward lower GABA levels in patients, although the summary effect size was nonsignificant (29). In agreement, we consistently found negative β coefficients, indicating lower GABA levels of patients.

The higher accuracies and lower AICc values of the triple transmitter models (Table 2) compared with the double transmitter models (Supplement and Table S7) suggest that Glx levels contributed to the significance of the overall models. Nevertheless, Glx measures did not serve as a predictor in any of the triple neurotransmitter models. The lack of predictive power implies that potential disturbances of Glx levels are minor in the thalamus and ACC in patients at this stage of psychosis. In agreement with this, a study of an overlapping sample (48) yielded no initial group difference of Glx levels in the thalamus or ACC. However, patients with a diagnosis of schizophrenia had higher glutamate levels in the thalamus than did the HCs (48), and as was the case for the abnormal GABA levels in the ACC, with the abnormality seemed to be driven by nonresponders to subsequent treatment (47).

Combinations 2 and 3 are discussed in the Supplement.

Taken together, these findings not only support the importance of dysfunction in specific neurotransmitters and regions in the aforementioned neural circuits for the development of psychosis, but also demonstrate that it is possible to predict patient status based on these. The consequent improvement in diagnostic validity might also, as argued by Tamminga (84), add to improvements in the precision and usefulness of (other) biomarker discoveries, particularly when the diagnostic validity is based on neurobiological findings.

To our knowledge, this study is the first to include both dopamine synthesis measures and GABA and glutamate levels in the same patients and HCs. The strengths of the findings are the presence of strictly antipsychotic-naïve patients in a relatively large sample free of substance abuse and antidepressant medication and further free from acute effects of benzodiazepines. Patients and HCs endured long neuroimaging sessions and completed an extensive examination program. This means that the participants may fail to be representative of the typical patient experiencing psychosis. However, the present patients were still moderately ill and, from that perspective, comparable to patients of other studies. It is a general issue that the most severely ill patients are hard to include in research.

The PET procedures were carried out with arterial input functions and steady-state kinetics that previously proved superior to the less comprehensive tissue reference method applied in most studies of this field. The 4P model procedure came with the price of a slightly decreased sample size, but relative to previous studies, the sample size is large. A priori knowledge-guided data selection and constraints in the number of combinations with requirements of information on all 3 neurotransmitters proved fruitful and superior for the purpose of identification of psychosis.

Cross-validation is an estimate of the out-of-sample generalizability. Combination 1, the best-fitted neurotransmitter model, reached significance with respect to both accuracy and AUC on the test set assessed with cross-validation

and therefore seems to be generalizable to an independent sample.

Conclusions

We found that a combination of 3 key biological markers of psychosis (striatal DSC, levels of GABA in the ACC, and levels of Glx in the thalamus or ACC) predicted patient status when single neurotransmitters failed to do so. The findings indicate that the diagnosis of psychosis rather depends on disruption of the indirect pathway in the macrocircuits in the brain than on isolated abnormalities in the involved neurotransmitters. The data add new perspectives to the stratification of patients according to a combination of neurotransmitter disturbances, particularly prefrontal GABAergic and striatal dopaminergic neurotransmission. Thus, future treatment strategies may benefit from focusing on the combined dopaminergic and GABAergic disturbances.

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