ORIGINAL ARTICLE

Improvement of Brain Reward Abnormalities by Antipsychotic Monotherapy in Schizophrenia

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Context: Schizophrenic symptoms are linked to a dysfunction of dopamine neurotransmission and the brain reward system. However, it remains unclear whether antipsychotic treatment, which blocks dopamine transmission, improves, alters, or even worsens the reward-related abnormalities.

Objective: To investigate changes in reward-related brain activations in schizophrenia before and after antipsychotic monotherapy with a dopamine D_2/D_3 antagonist.

Design: Longitudinal cohort study.

Setting: Psychiatric inpatients and outpatients in the Capital Region of Denmark.

Participants: Twenty-three antipsychotic-naive patients with first-episode schizophrenia and 24 healthy controls initially matched on age, sex, and parental socioeconomic status were examined with functional magnetic resonance imaging while playing a variant of the monetary incentive delay task.

Interventions: Patients were treated for 6 weeks with the antipsychotic compound amisulpride. Controls were followed up without treatment.

Main Outcome Measures: Task-related blood oxygen level–dependent activations as measured by functional magnetic resonance imaging before and after antipsychotic treatment.

Results: At baseline, patients, as compared with controls, demonstrated an attenuation of brain activation during reward anticipation in the ventral striatum, bilaterally. After 6 weeks of treatment, patients showed an increase in the anticipation-related functional magnetic resonance imaging signal and were no longer statistically distinguishable from healthy controls. Among the patients, there was a correlation between the improvement of positive symptoms and normalization of reward-related activation. Those who showed the greatest clinical improvement in positive symptoms also showed the greatest increase in reward-related activation after treatment.

Conclusions: To our knowledge, this is the first controlled, longitudinal study of reward disturbances in schizophrenic patients before and after their first antipsychotic treatment. Our results demonstrate that alterations in reward processing are fundamental to the illness and are seen prior to any treatment. Antipsychotic treatment tends to normalize the response of the reward system; this was especially seen in the patients with the most pronounced treatment effect on the positive symptoms.

Trial Registration: clinicaltrials.gov Identifier: NCT01154829.

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DOPAMINE IS AN ESSENTIAL neurotransmitter in the brain reward system[1,2] and dopaminergic dysfunction has been suggested to be involved in the development of psychotic symptoms.[3] A dysregulated hyperdopaminergic state in the striatum might lead to development of psychoses through altered reward processing,[4,5] and antipsychotic medication is thought to relieve the psychotic symptoms by normalizing this altered transmission via D_2 antagonism.[6] As a result, studies of reward processing in schizophrenia are of considerable interest, and studies in unmedicated patients consistently find an attenuated signal in the ventral striatum (VS) during reward anticipation.[7,8] This has been suggested to be a result of an increased tonic dopaminergic tone that increases the noise, thereby decreasing the signal to noise ratio. Thus, the event-related blood oxygen level–dependent (BOLD) responses are often smaller, because phasic dopamine responses may not sufficiently differentiate from tonic dopamine levels.[9]

Most cross-sectional studies in patients medicated with second-generation antipsychotics (SGAs) do not find significant changes in the VS during reward anticipation,[10-12] while reduced activation is seen in patients medicated with first-generation an-

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tipsychotics (FGAs).[13,14] One longitudinal study examined the effect of switching schizophrenic patients from FGAs to SGAs and their results indicate that reward-related brain changes in schizophrenia improve as patients switch from FGAs to SGAs.[14] However, we are not aware of any prospective longitudinal studies correlating changes in the reward system to symptomatic improvement by examining reward dysfunction in unmedicated patients at baseline and after treatment with an antipsychotic compound. We present the results of the first such study, to our knowledge.

To investigate the effect of antipsychotic treatment, we designed a longitudinal study of initially antipsychotic-naive patients with first-episode schizophrenia. To meet national clinical guidelines of the first treatment choice being with an SGA, but still achieve a rather selective $D_{2/3}$ blockade, patients were treated with amisulpride. Amisulpride is a particularly useful choice in this study because it is relatively specific in its blockade of dopamine $D_{2/3}$ receptors and yet functions like an atypical antipsychotic because of the low occurrence of extrapyramidal adverse effects in low to moderate dosage,[15,16] which is explained by a limbic selectivity[17] or a fast dissociation from the D_2 receptor.[15] In animal studies, intermediate doses of amisulpride improve reward deficits induced by dopamine agonists,[18] whereas these deficits reoccur at high doses. Combining this observation with findings from human functional magnetic resonance imaging (fMRI) studies could suggest that a moderate blockade of the dopaminergic receptor (as with SGAs or moderate doses of FGAs) will increase the signal to noise ratio by decreasing the noise, whereas an extensive blockade of the D_2 receptor (as with high doses of FGAs) will decrease the signal to noise ratio by decreasing the signal.

In keeping with past studies, we expected patients to show an attenuated response in the VS during reward anticipation at baseline. We predicted that treatment with moderate doses of an SGA would lead to improvement in reward-related signaling, and we expected this improvement in the VS to correlate with symptomatic improvement.

METHODS

Conducted in accordance with the Declaration of Helsinki II, the project was approved by the Danish National Committee on Biomedical Research Ethics (H-D-2008-088). All participants approved participation by signed informed consent.

PARTICIPANTS

As part of a large first-episode project, antipsychotic-naive patients with schizophrenia aged 18 to 45 years were recruited from psychiatric hospitals and outpatient psychiatric centers in the Capital Region of Denmark. *International Statistical Classification of Diseases, 10th Revision* diagnoses of schizophrenia or schizoaffective psychoses were based on a structured diagnostic interview (Schedule of Clinical Assessment in Neuropsychiatry, version 2.1). Patients with a current diagnosis of drug dependency according to *International Statistical Classification of Diseases, 10th Revision* were excluded, but previous diagnoses of drug dependency or current occasional use of drugs were accepted. Current drug status was measured by urine test (Rapid Response; Jepsen HealthCare). None of the patients had ever received any antipsychotic medication or methylphenidate. Patients treated with antidepressants or mood stabilizers within the last month before inclusion or during the treatment period were also excluded. Patients were allowed to receive benzodiazepines or sleep medication but not later than 12 hours before scans (eTable, http://www.archgenpsychiatry.com). Healthy controls were recruited from the community and matched on age, sex, and parental socioeconomic status. They also underwent a Schedule of Clinical Assessment in Neuropsychiatry interview to ensure they had no former or present psychiatric illness, drug abuse, or any first-degree relatives with psychiatric diagnoses. Both patients and healthy controls were required to have a normal physical and neurological examination and no history of major head injury.

Initially, 31 antipsychotic-naive schizophrenic patients and 31 healthy controls were baseline examined between December 2008 and March 2011.[19] A total of 8 patients and 7 controls were not included in the follow-up analyses, which left 23 patients (16 male) and 24 controls (20 male) (**Table**). The patients who dropped out had a significantly lower Global Assessment of Functioning score at baseline ($t_{29}=3.4$; $P=.002$) and a higher Positive and Negative Syndrome Scale (PANSS) positive, negative, and total score at baseline ($t_{29}=2.1$; $P<.05$; $t_{29}=2.4$; $P=.02$; and $t_{29}=2.8$; $P=.008$). Further, there was a larger proportion of current or previous substance abuse among the patients leaving the study (eTable). Reasons for discontinuing the study or examinations were 5 patients refused to start or discontinued medical treatment; 2 patients had to change medication during the treatment period because of lack of effect or intolerable adverse effects; and 1 patient failed to complete the follow-up scan because of an anxiety surge inside the scanner.

MEDICATION

The patients' medicine was individually dosed according to the clinical impression of their symptoms and their report of adverse effects, particularly sedation and extrapyramidal symptoms. Generally, patients started with a daily dose of 50 to 100 mg, which was increased by 50 to 100 mg after 3 to 7 days. When reaching a dose of 300 mg, the dose increment was 100 to 200 mg per week. If patients complained about unpleasant or intolerable adverse effects, the dose was decreased by 50 to 100 mg. The follow-up examination was ideally planned for 6 weeks after medication start, but patients had to be receiving a stable dose of medication for the last 2 weeks before reexamination, which could postpone the time for follow-up examination.

CLINICAL MEASURES

Psychopathology of the patients was measured with the PANSS[20] and Global Assessment of Functioning. The Edinburg Handedness Inventory[21] was used to assess participant handedness and the Danish Adult Reading Test, which is a 45-word Danish version of the National Adult Reading Test, was used to estimate premorbid intelligence.[22] Adverse effects were measured with the Extrapyramidal Symptom Rating Scale,[23] and change in depressive symptoms was measured with the Calgary Depression Scale.[24] The change in the PANSS score over time was calculated as a percentage of change from baseline score subtracted from the theoretical minimum score, as recommended by Obermeier et al.[25]

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Table. Demographic Data and Psychopathology of the Final Cohort

	Mean (SD)		
	Healthy Controls (n = 24)	Schizophrenic Patients (n = 23)	
		Baseline	Follow-up
Age, y	25.7 (5.9)	26.0 (6.7)	
Male, No. (%)	20 (83)	16 (70)	
Smokers, No. (%)	8 (33)	18 (78)[a]	
Handedness, EHI score	63 (72)	60 (60)	
Parental socioeconomic status[b]	5/12/7	4/13/6	
Education, y	15.3 (2.6)	11.5 (2.3)[a]	
DART score[c]	17.7 (8.5)	24.6 (6.0)[a]	
Days between MRI 1 and MRI 2	46 (22)	51 (14)	
Days between medication start and MRI[c]		45 (12)	
Diagnoses, No. (%)			
Paranoid		13 (57)	
Undifferentiated		8 (35)	
Simplex		1 (4)	
Schizoaffective		1 (4)	
PANSS total score		82 (14)	65 (16.5)[d]
PANSS positive score		20 (4.2)	14 (4.3)[d]
PANSS negative score		20 (6.1)	19 (6.1)
PANSS general score		42 (7.4)	33 (9.2)[d]
Depression score (CDS)[e]		6.6 (3.7)	3.6 (3.0)[d]
GAF score		42 (9.8)	52 (11.3)[d]
Amisulpride dose, g/d, mean (range)			302 (100-800)

Abbreviations: CDS, Calgary Depression Scale; DART, Danish Adult Reading Test; EHI, Edinburg Handedness Inventory; GAF, Global Assessment of Functioning; MRI, magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale.
[a] Significant difference between patients and healthy controls ($P < .05$).
[b] High/moderate/low.
[c] Only available on 22 patients and 22 healthy controls.
[d] Significant improvement between baseline and follow-up ($P < .001$).
[e] Only available at both times for 20 patients.

EXPERIMENTAL DESIGN AND TASK

We used a modified variant of the monetary incentive delay task described by Knutson et al[26,27] and modified by Cooper and Knutson[28] to elicit VS activation in response to cues indicating monetary gain and loss (**Figure 1**).

In each trial, participants were presented initially with a cue indicating trial condition. After a short delay, a visual target appeared briefly on the screen, and participants were instructed to press a button while the target was on-screen. After another delay, participants received feedback on the outcome of the trial and how much money they had earned in total. Initial target duration for all participants and trial conditions was 300 milliseconds, but an automated adaptive timing algorithm adjusted target time to maintain a hit rate of approximately 66% over the experiment. After the scan, participants were paid the amount of money they won, typically €45 to €85 (US $57-US $108) for each session.

There were 6 different trial conditions representing 2 levels of uncertainty (certain and uncertain), crossed with 3 levels of value expectation (gain, neutral, and loss). In uncertain gain and loss conditions, the outcome depended on whether the button was pressed in time. In uncertain-gain trials, a participant could make €7 (US $9) on a hit but earn nothing on a miss. In uncertain-loss trials, a participant could make €0 on a hit but would lose €7 (US $9) on a miss. In the 2 certain conditions, outcome was predetermined and noncontingent on the response, and a participant would gain or lose €7 (US $9) regardless of pressing the button in time. In the 2 neutral trials, participants knew the outcome would be €0. After each trial, the recent and total amount won or lost was displayed on the screen. Participants were instructed to respond rapidly on all trials, regardless of whether they involved uncertain, certain, or neutral outcomes. Before scans, participants were instructed about the meaning of each cue. They performed a 10-minute training

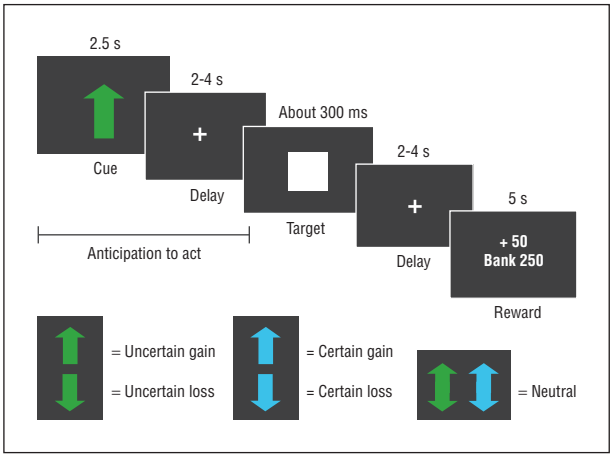

Figure 1. The modified monetary incentive delay task. A cue indicating the trial condition initiates each trial (1). After a short delay (2), a target appears briefly on the screen (3). For each condition, the goal is to press a button while the target is on the screen. After another delay (4), subjects receive feedback (5) on whether they lost or won money and how much money they have won so far. One of the 6 cues is presented in each trial. The color indicates if it is a certain (blue) or uncertain (green) condition; the direction of the arrow indicates if it is a gain (up), loss (down), or neutral (both) trial.

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version of the task. Participants were not told about the adaptive timing algorithm.

Duration of 1 trial was 15 seconds. Each of the 6 trial conditions was presented in a blockwise, randomized order 12 times in each of the 2 runs. Total task time was 36 minutes (18 minutes/run). Presentation of the task and recording of the behavioral data were done using Presentation software (Neurobehavioral Systems).

IMAGING

Functional and structural magnetic resonance imaging (MRI) were performed with a Philips Achieva 3.0-T whole-body MRI scanner (Philips Healthcare) using an 8-channel SENSE head coil (Invivo). In each scanning session, whole-brain 3-dimensional high-resolution T1-weighted structural images were acquired for anatomical reference (repetition time = 10 milliseconds, echo time = 4.6 milliseconds, flip angle = 8°, and voxel size = 0.79 × 0.79 × 0.80 mm). For each participant, we acquired 1080 (540 per run) whole-brain functional echo planar imaging images (38 slices, thickness = 2.4 mm, voxel size = 2.4 × 2.9 × 2.9 mm, flip angle = 75°, repetition time = 2 seconds, and echo time = 25 milliseconds). Smoking was stopped 1 hour preceding the MRI session.

DATA ANALYSES

Analyses were performed using BrainVoyager version 2.20 (Brain Innovation B.V.). Images were corrected for slice-timing effects and 3-dimensional motion correction was performed using trilinear interpolation. Spatial smoothing was performed with a 4-mm full-width-at-half-maximum gaussian kernel, and a high-pass filter (200 seconds) was applied to reduce low-frequency noise. The functional images were then coregistered to the 3-dimensional anatomical images and transformed into Talairach space.

GENERAL LINEAR MODEL

A general linear model was constructed for statistical analysis. For the anticipation to act, the 6 different cues were modeled as separate predictors: uncertain gain (ug); certain gain (cg); uncertain loss (ul); certain loss (cl); uncertain neutral (un); and certain neutral (cn). The anticipation to outcome was modeled with 2 different predictors, 1 for uncertain events and 1 for certain and neutral events. The outcome period was modeled with 7 predictors, 1 for each of the possible outcomes. All the explanatory variables were convolved with the hemodynamic response function, and 6 realignment parameters were included.

CONTRASTS

Based on the results of the baseline changes in 31 patients,[19] the analyses focused on the contrast showing the most pronounced alterations in patients during reward anticipation. This was the salience contrast modeled by uncertain cues vs neutral cues [ug + ul > cn + un].

STATISTICS

The fMRI data were analyzed using a random-effects model. The individual contrast images from both groups and times were included in second-level voxelwise repeated-measures analysis of variance (ANOVA) with time as the within factor and group as the between factor. To confirm our previous baseline findings in the larger cohort of 31 patients,[19] we looked at the group difference in the salience contrast [ug + ul > cn + un] at baseline. Further, group differences at follow-up voxelwise were examined with an independent-samples *t* test. For all voxelwise analyses, the results are presented for a false discovery rate of $q < 0.05$. Because of a large difference between the 2 groups in overall brain activation, analyses were repeated with an uncorrected *P* value $< .001$.

At the region of interest (ROI) level, the contrast average β values were extracted and analyzed with a repeated-measures ANOVA. Analyses were done with and without sex, Danish Adult Reading Test score, and smoking status (smoking or nonsmoking) as covariates.

The behavioral data of the monetary incentive delay task, the statistical comparison of the demographic data, and the statistics of the psychopathological ratings were analyzed using SPSS version 11.0 (IBM SPSS). The total amount of money participants won during the task was analyzed with a repeated-measures ANOVA with group as the between factor and time as the within factor. Reaction time and hit rate during the task were analyzed using a 2 × 6 × 2 repeated-measures ANOVA with group as the between factor and trial type and time as the within factors.

Demographic and psychopathological baseline differences between patients dropping out and patients staying in the study were analyzed with an independent-samples *t* test and Pearson χ^2 test. Improvement in psychopathology was analyzed with a paired *t* test. Correlation analyses between medication dose, changes in PANSS score, and change in fMRI signal were performed using Spearman rank correlation.

REGIONS OF INTEREST

Along with the whole-brain analyses, a repeated-measures ANOVA of the average response magnitude (β value) in ROIs was performed. The right and left VS were chosen, since the VS is known to be active during reward anticipation in healthy controls,[26,27] and this activation is attenuated in medication-free patients.[7,14] Further, the VS is expected to be the target region for the amisulpride treatment.[17] The regions were defined as cubes measuring 10 × 10 × 10 mm centered in the Talairach coordinates 10, 5, −1 and −10, 5, −1.[29]

To assure that a possible change in the VS activation was not due to a nonspecific effect, eg, a pharmacological effect on blood flow, we analyzed a control region in the right occipital cortex, defined as a 10 × 10 × 10-mm cube centered in the Talairach coordinates 11, −97, −3.

RESULTS

SYMPTOMS AND TREATMENT

Medical treatment was given to the patients using individual, flexible doses of amisulpride. There was on average 45 days between medication start and the follow-up fMRI examination. One patient stopped medication after 3 weeks of treatment but completed a follow-up fMRI 3 weeks later without any other medical treatment. Since the patient's symptoms did improve during the short treatment period, the patient's data were kept in the analyses.

During the time between the examinations, there was a significant improvement in total PANSS score ($t_{22} = 5.8$; $P < .001$); PANSS positive score ($t_{22} = 5.3$; $P < .001$); and PANSS general score ($t_{22} = 6.8$; $P < .001$). The patients also improved in function ($t_{22} = -5.21$; $P < .001$) and depres-

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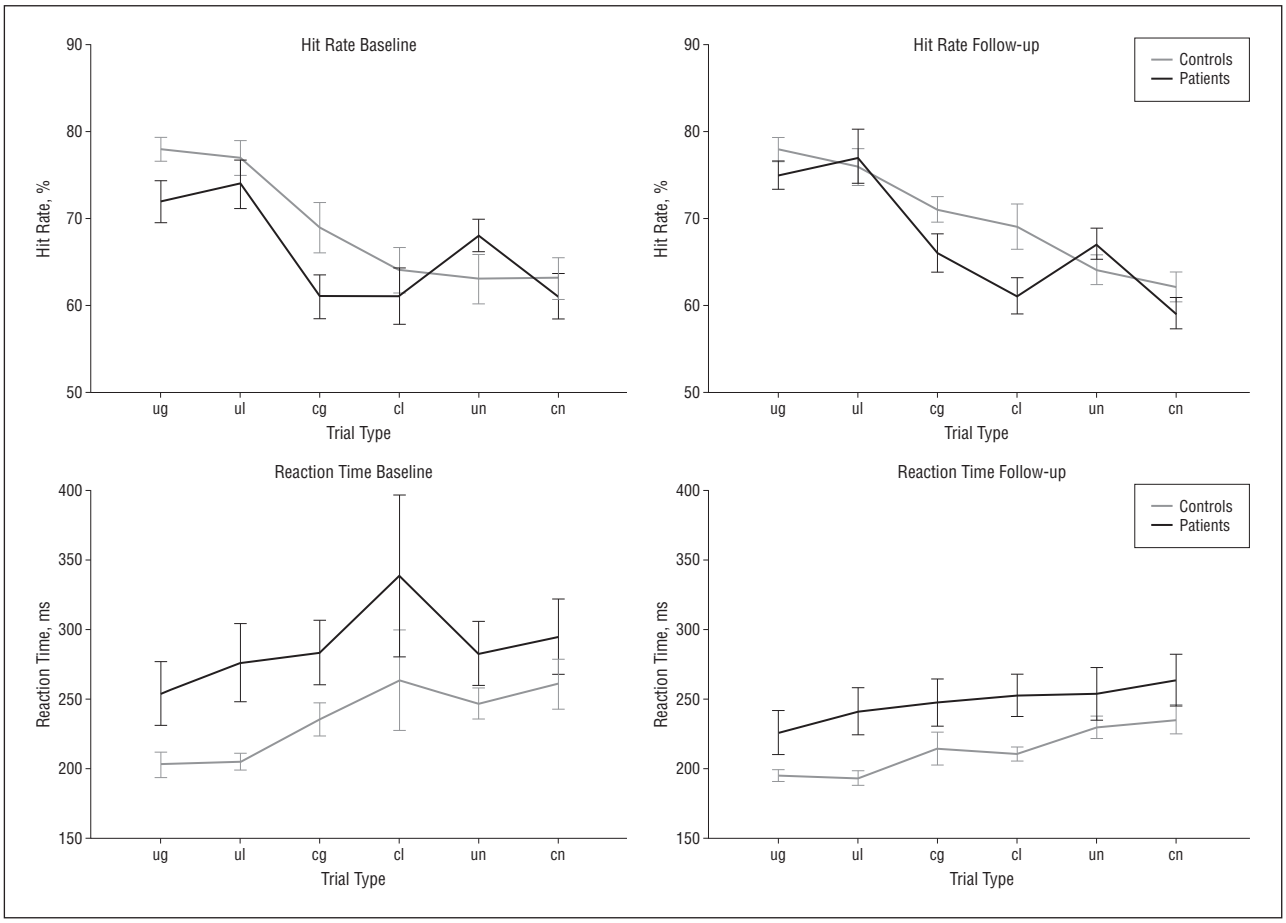

Figure 2. Behavioral data (see "Behavioral Data" subsection in the "Results" section for description). Error bars indicate standard error. cg Indicates certain gain; cl, certain loss; cn, certain neutral; ug, uncertain gain; ul, uncertain loss; and un, uncertain neutral.

sive symptoms (t_{19}=4.3; $P<.001$) (Table). The analyses were repeated without the patient who had stopped medication before follow-up, but this did not change the significance level.

At follow-up, the 22 patients who remained medicated had all been given a stable dose of amisulpride for at least 2 weeks, with an average daily dose of 302 mg (100-800 mg). Two patients experienced mild extrapyramidal symptoms in terms of muscular rigidity and mild tremors.

BEHAVIORAL DATA

The total monetary gain during the task was similar across groups and time, as there was no main effect of group, no effect of time, and no group × time interaction. There was a nonsignificant numeric increase in the amount of money participants won at follow-up, and this increase was larger in the patients.

In terms of reaction time, there was a main effect of group ($F_{1,45}$=4.3; P=.045), time ($F_{1,45}$=11.5; P=.001), and trial type ($F_{5,225}$=7; $P<.001$). There were no interactions. Patients were generally slower than healthy controls, but both groups improved in reaction time from baseline to follow-up, and both groups had the fastest reaction time in the uncertain gain and loss trials (**Figure 2**).

To account for the expected difference in reaction time, the paradigm was designed to aim at an overall hit rate of around 66% during the task. The actual hit rate showed no main effect of group or time, but there was a main effect of trial type ($F_{5,225}$=31; $P<.001$) and a trial type × group interaction ($F_{5,225}$=2.8; P=.02). In both groups, the highest hit rate was seen in the uncertain gain and loss trials. Generally, patients had an overall lower hit rate, except in the uncertain neutral trials, where their hit rate was higher than the controls. There were no time × group, time × trial type, or time × trial type × group interactions (Figure 2).

In summary, the patients were slower than the controls at baseline and follow-up. They missed a few more events, but because of the adaptive paradigm, they won on average the same amount of money. Both groups improved over time, with a decrease in reaction time and a numeric increase in the amount of money won.

fMRI DATA

To confirm our previous baseline findings in the larger cohort of 31 patients,[19] group difference in the salience contrast [ug + ul > cn + un] at baseline was examined. As expected, group differences were seen in several brain areas, with patients showing an attenuated activation in the contrast compared with healthy controls. At follow-up, there

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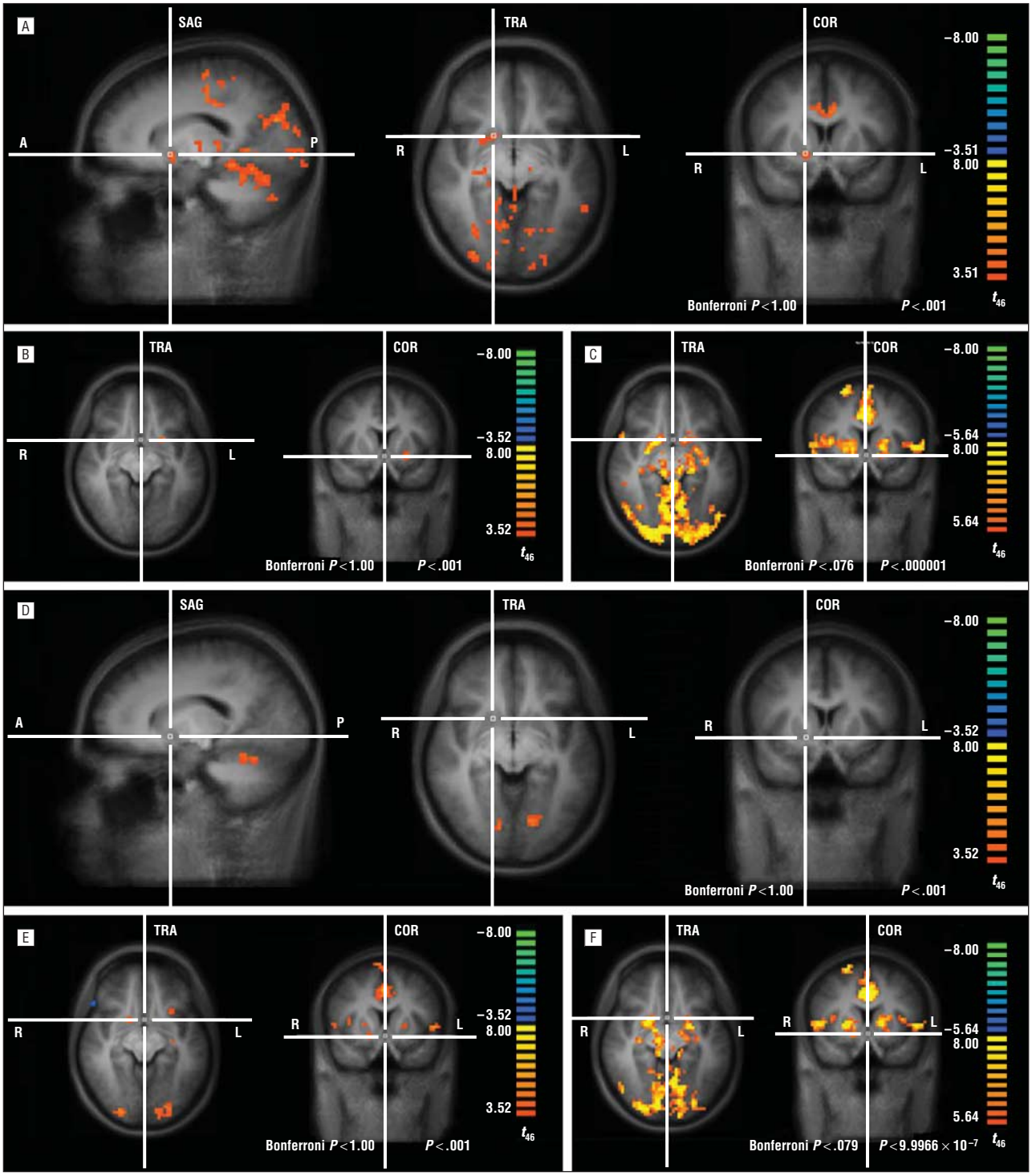

Figure 3. Activation map for the salience contrast at baseline and follow-up. A-C, Group differences in the voxelwise comparison at baseline (A) and activation map for the patients (B) and controls (C) at baseline. D-F, Group differences in the voxelwise comparison at follow-up (D) and activation map for the patients (E) and controls (F) at follow-up. The threshold is $P<.001$ uncorrected, except in the healthy controls, where the threshold is lowered to $P<.000001$ for illustrative purposes. A indicates anterior; COR, coronal; L, left; P, posterior; R, right; SAG, sagittal; and TRA, transverse.

were no group differences. The voxelwise analysis of covariance of the salience contrast showed a main effect of group, no effect of time, and no group × time interaction using the false discovery rate $q<0.05$. Repeating the analyses using an uncorrected P value $<.001$, there were still group differences at baseline. As with false discovery rate thresholding, the group differences at follow-up were smaller because of more activation in the patients as compared with baseline. The voxelwise analysis of covariance of the salience contrast showed a main effect of group. Further, there was a main effect of time in 2 temporal regions but no group × time interaction (**Figure 3**).

Patients and controls did not differ in their maximum, mean, or cumulative head movement (repeated-

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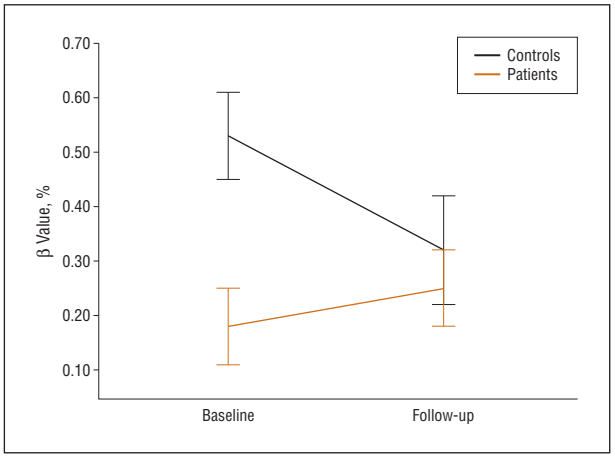

Figure 4. Interaction in the right ventral striatum region of interest. There was an overall signal increase in the patients, whereas a signal decrease was found in healthy controls.

measures ANOVA with time as the within and group as the between factor).

ROI ANALYSES OF THE SALIENCE CONTRAST

For the ROI analyses, we extracted the average β value of the salience contrast [ug + ul > cn + un] from the 2 VS ROIs. A repeated-measures ANOVA showed a significant effect of group in the right VS ($F_{1,45}$=5.6; P=.02) and left VS ($F_{1,45}$=7.7; P=.008). Patients showed an attenuated activation compared with healthy controls. There was no main effect of time. In the right VS, we found a significant group × time interaction ($F_{1,45}$=4.6; P=.04), where patients had an increase and healthy controls had a decrease in contrast activation over time (**Figure 4**). There was no interaction in the left VS. There was no significant effect of sex, Danish Adult Reading Test score, or smoking as covariates. In the occipital control ROI, there was an effect of group and time ($F_{1,45}$=15; $P \leq .001$; $F_{1,45}$=4; $P < .05$) but no interaction. Both groups showed a signal decrease over time.

RELATION TO PSYCHOPATHOLOGY

We found a correlation between the change in positive symptoms and signal change in the right VS (**Figure 5**). The most pronounced change in positive symptoms was seen in the patients with the largest signal increase. There was no correlation between daily dose of amisulpride and change in positive symptoms over time or change in signal over time. Further, there was no correlation between signal change and change in depressive symptoms as measured by the Calgary Depression Scale.

INDIVIDUAL PREDICTORS IN THE ROIs

To determine which elements of the contrast changed over time, the mean ROI parameter estimates and the time courses of the signals were extracted at baseline and follow-up for each of the 4 predictors included in the contrast. At baseline, the bilateral decrease of the contrast signal in patients was caused by attenuated activation in

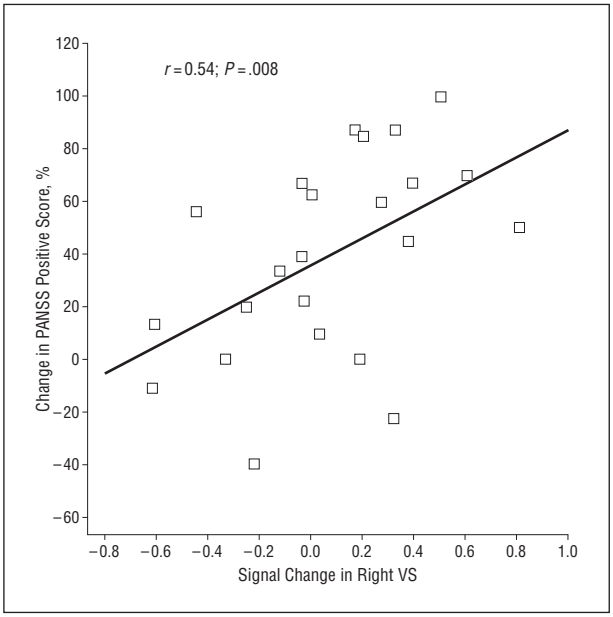

Figure 5. Improvement in Positive and Negative Syndrome Scale (PANSS) positive symptoms in patients correlated with the signal increase in the salience contrast. The most pronounced change in positive symptoms was in the patients with the largest signal increase. VS indicates ventral striatum.

relation to the uncertain cues. At follow-up, the BOLD response to the uncertain cues increased in the patients in the right VS, whereas this was not the case in the left VS (eFigure 1 and eFigure 2).

COMMENT

To our knowledge, this is the first longitudinal study of the effect of antipsychotic monotherapy on the reward system in initially antipsychotic-naive schizophrenic patients. At baseline, patients showed attenuated activation during reward anticipation compared with healthy controls. From baseline to follow-up, there was an increase of the signal over time in the right VS in patients, while the signal decreased in healthy controls. Further, the largest improvement in positive symptoms was seen in the patients with the highest signal increase in the VS, suggesting a link between the normalization during reward anticipation and the improvement of positive symptoms in schizophrenia.

The included patients were moderately ill, having an average PANSS total score of 82 at baseline. Because they were all medication naive, their medical treatment was initiated at a low dose and dosage increase was slow, individualized, and undertaken with awareness of not inducing unnecessary adverse effects. This naturalistic approach resulted in a mean dose of 302 mg and a dropout of only 2 patients (6%) owing to adverse effects, while 2 patients had mild, tolerable extrapyramidal symptoms. This is lower than the 450 mg and the dropout rate of 20% due to adverse effects in the EUFEST study,[30] where another 34% of the patients received anticholinergic medication. Nevertheless, the treatment was successful in having a notable impact on psychosis as there was a significant improvement in PANSS positive score (from 20 to 14) and additionally reflected by an improved Global As-

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sessment of Functioning score (from 42 to 52). Some of the patients might have had a further improvement in positive symptoms if the daily dosage had been higher, but then this would probably have been at the expense of inducing secondary negative symptoms or extrapyramidal symptoms.

At the behavioral level, the hit rate was highest in the uncertain gain and loss trials in both groups, indicating that both groups learned the task and focused their effort on the behaviorally most important events. Although patients generally reacted more slowly than the healthy controls, the adaptive algorithm ensured the same monetary reward and average hit rate over the session. An increased reaction time in patients is in line with previous results in unmedicated[8] and medicated patients.[14] We had expected that medication would slow the patients' reaction time[31] because antipsychotics are often implicated in producing this motor adverse effect. This was not the case in our study, likely because we used low, individually titrated doses of an atypical antipsychotic. Instead, we found that both patients and controls reacted faster at follow-up, which is consistent with previous findings in a longitudinal study.[14]

Since our primary interest was the treatment effect of D_2 blockade in the VS, we focused our analyses on this region. In the right VS, we found an average increase in the contrast signal in patients, while healthy controls showed a decrease over time. Though the change in the contrast signal between baseline and follow-up was not significant in any of the groups, the average signal increase in patients was in line with our hypothesis. The extraction of the β values for each of the predictors showed that the change in contrast signal in patients was caused by a "normalizing" increase in BOLD response during the uncertain events. This increase improves the ability of the reward system to discriminate between salient and nonsalient stimuli. The normalization in assignment of salience might be involved in the improvement of positive symptoms, as suggested in the salience hypotheses.[4,6] This is supported by the finding of the largest improvement in positive symptoms in the patients with a contrast signal increase.

To our knowledge, the effect of amisulpride on the fMRI signal has not been examined previously in patients, but in healthy controls, a short-term dose of 200 mg of amisulpride was found to increase reward learning and the related fMRI signal in the VS.[32] In higher doses, amisulpride exceeds a robust D_2 blockade and thereby resembles an FGA.[33] While, to our knowledge, there are no fMRI studies on healthy controls using higher doses of amisulpride, the effect of a short-term dose of haloperidol has been examined in healthy controls, and it was found to reduce event-related BOLD response in the VS.[34] This supports similar findings of a decreased activation in the VS in cross-sectional studies on patients medicated with an SGA.[13,14,35] In our study, amisulpride was expected to act more like an SGA because of the relatively low doses used. The normalization of the VS activation is in line with several cross-sectional studies reporting a normal activation during reward anticipation in the VS in patients treated with SGAs.[10-13,35,36]

In a recent study in healthy controls combining fMRI and positron emission tomography, an inverse correlation between dopamine synthesis capacity and event-related BOLD response in the right VS was found.[37] This supports a putative link between increased dopaminergic tone and decreased BOLD response. However, because this has not yet been examined in schizophrenic patients, the attenuated BOLD response can just as well be a result of a failure to activate the VS in relation to salient cues, maybe as a result of decreased or delayed reward learning.[38-40] If this is the case, the increase over time found in our and another longitudinal study[14] could reflect delayed learning in patients. The relation between the decrease in psychotic symptoms and the signal increase might then reflect an indirect effect of a reduction in psychotic symptoms on reward learning.

Reward disturbances have been found in patients with major depression, where symptom improvement after antidepressive treatment correlated with the normalization of VS signaling during reward anticipation.[41] Our patients also improved in depressive symptoms and amisulpride is suggested to have an antidepressant effect due to blockade of the 5HT-7 receptor.[42] Although we did not find a correlation between improvement in depressive symptoms and signal change, we cannot exclude that this mechanism might also be relevant in explaining our findings.

There are several limitations to our study. To collect a large group of patients and to increase the external validity of our findings, previous drug abuse and current occasional drug use in patients was allowed, even though drug abuse is known to affect reward-related activation.[43,44] We have previously examined this confounder and found a similar difference between the healthy controls and the 2 subgroups of patients with or without an abuse history.[19] Regarding smoking, there was no effect of the current smoking status as a covariate. However, smoking chronicity was not assessed; thus, we cannot exclude that there might be an effect of a possible difference in the degree of smoking chronicity, as described by Rose et al.[45] After all, the patients in our study did not change their drug or smoking status between baseline and follow-up; thus, the interaction effect is not likely to be caused by differences in drug or smoking habits.

Participating in this kind of study takes a certain degree of collaboration from the patients, and therefore, we cannot avoid a selection bias excluding the patients with the most acute severe illness. Further, there was a dropout of the sickest patients at follow-up as measured on baseline Global Assessment of Functioning and PANSS total, positive, and general scores. Though not surprising, this does decrease the external validity of the study. Nonetheless, the finding of significant alterations in reward processing at baseline confirms that the group that stayed in the study was still representative for schizophrenic patients and relevant for studying medication effect on reward alterations.

Finally, even though the patients were assigned to treatment in an open design and were rated by clinicians who were aware of the treatment, bias may have been introduced. However, this would not have been a systematic bias because the clinicians were not aware of the fMRI results when patients were rated.

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In conclusion, to our knowledge, this is the first systematic controlled study of prospectively treated antipsychotic-naive patients examining the relationship between treatment, response, and reward-related activations. The data suggest that appropriately and individually titrated treatment with an antipsychotic compound is associated with the normalization of the reward-related activation abnormalities and that this normalization is correlated with clinical improvement.

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