Striatal Reward Activity and Antipsychotic-Associated Weight Change in Patients With Schizophrenia Undergoing Initial Treatment

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IMPORTANCE Weight gain is a common and serious adverse effect of antipsychotic treatment. A variable individual predisposition to development of metabolic disturbances calls for predictive biological markers.

OBJECTIVES To investigate whether attenuated striatal activity during reward anticipation is associated with amisulpride-induced weight change in antipsychotic-naïve patients with schizophrenia undergoing initial treatment and to examine the association between weight change and changes in reward anticipation activity after treatment.

DESIGN, SETTING, AND PARTICIPANTS Sixty-nine antipsychotic-naïve inpatients and outpatients with schizophrenia were included in a multimodal longitudinal cohort study from December 16, 2008, to December 11, 2013. Fifty-eight patients underwent functional magnetic resonance imaging (fMRI) while performing a monetary reward task. After 6 weeks of treatment with amisulpride, a relatively selective dopamine D2 antagonist, 39 patients underwent a second fMRI scan and measurement of change in body weight. Final follow-up was completed on January 14, 2014, and data were analyzed from October 25, 2014, to June 15, 2015 and August 31 to September 19, 2015.

EXPOSURES Six weeks of individually dosed amisulpride treatment.

MAIN OUTCOMES AND MEASURES Reward-anticipation activity in the striatum before and after treatment and weight change.

RESULTS Of the 69 patients who consented to the study, 39 underwent the follow-up fMRI and weight measurement (age range, 18-45 years; 17 women and 22 men). The mean (SD) daily dose of amisulpride was 272 (168; range, 50-800) mg, and patients gained a mean (SD) of 2.3 (2.8; range, −4 to 8) kg in body weight. Improvement from baseline to follow-up was found on the mean (SD) positive (19.9 [4.1] to 14.3 [3.8]), general (39.7 [7.7] to 30.5 [7.7]), and total (78.5 [15.3] to 63.2 [13.9]) scores on the Positive and Negative Syndrome Scale (P < .001). Weight gain was predicted by low mean (SD) baseline reward-related activity in the right-sided putamen (0.20 [0.93]; F35,3 = 5.64; P = .003). After 6 weeks, weight gain was associated with an increase in mean (SD) reward activity in the same region during treatment (0.28 [0.74]; F71,7 = 4.48; P = .04).

CONCLUSIONS AND RELEVANCE Activity in striatal regions of the reward system appears to be associated with the individual variability in the predisposition for antipsychotic-associated weight gain. Moreover, pharmacologic modulation of the reward system may play a role in antipsychotic-associated weight gain.
Antipsychotic-associated weight gain predisposes to development of metabolic syndrome and type 2 diabetes mellitus and thereby contributes to a decreased life span by approximately 20 years in patients with schizophrenia. The weight gain is mediated through complex peripheral and central mechanisms involving various neurotransmitters and neuropeptides. Histamine H2 receptor blockade may be of importance in quetiapine fumarate-associated weight gain. However, antipsychotics with lower histaminergic or serotonergic affinity, such as chlorpromazine hydrochloride and the relatively selective dopamine D2 receptor antagonist amisulpride, are associated with weight gain. This association suggests that dopamine D2 receptor antagonism may play a critical role in antipsychotic-associated weight gain.

The dopaminergic cells projecting from the ventral tegmental area to the striatum are key players in the brain reward system, and the reward system is pivotal for appetite regulation. Central stimulants, which increase dopaminergic turnover in the striatum, decrease the appetite and lead to weight loss. Conversely, preclinical findings have indicated that antipsychotic compounds with high dopamine D2 receptor affinity in the striatum lead to increased appetite and overeating.

The reward deficiency hypothesis states that decreased dopaminergic turnover in the striatum may impair the reward circuitry and lead to abnormal craving behavior, overeating, and obesity. This hypothesis has been corroborated by functional magnetic resonance imaging (fMRI) studies of reduced reward-related activity in the dorsal striatum in obese individuals. Patients with schizophrenia who have received little or no antipsychotic treatment display similar deficiencies in the striatal parts of the reward system. Antipsychotic-associated weight gain is not explained directly by the medication dose, and considerable individual variability can be found in the degree of weight gain after antipsychotic exposure. Hypothetically, the variable predisposition to antipsychotic-induced weight gain may be related to reward disturbances.

The putative association between the effect of antipsychotics on body weight and the reward system has received little or no antipsychotic treatment display decreased life span by approximately 20 years in patients with schizophrenia. The weight gain is mediated through complex peripheral and central mechanisms involving various neurotransmitters and neuropeptides. Histamine H2 receptor blockade may be of importance in quetiapine fumarate-associated weight gain. However, antipsychotics with lower histaminergic or serotonergic affinity, such as chlorpromazine hydrochloride and the relatively selective dopamine D2 receptor antagonist amisulpride, are associated with weight gain. This association suggests that dopamine D2 receptor antagonism may play a critical role in antipsychotic-associated weight gain.

Methods
Participants
Patients with a first episode of schizophrenia aged 18 to 45 years were recruited from psychiatric hospitals and outpatient psychiatric centers in the Capital Region of Denmark from December 16, 2008, to December 11, 2013, as a part of a large multimodal study. None of the patients had ever received antipsychotics or methylphenidate hydrochloride. Patients met the diagnostic criteria of schizophrenia or schizoaffective psychoses from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), based on findings from a structured diagnostic interview (Schedule of Clinical Assessment in Neuropsychiatry, version 2.1). Patients were required to have normal physical and neurologic examination findings and no history of a major head injury. Previous diagnoses of drug dependency according to the ICD-10 or current occasional use of drugs were accepted. Patients with a current diagnosis of drug dependency were excluded, as were patients treated with antidepressants within the last month or during the study period. Benzodiazepines or sleep medication were allowed until 12 hours before fMRI scanning. Current drug status was measured by a urine test (Rapid Response; Jepsen HealthCare). The study was conducted in accordance with the Declaration of Helsinki and approved by the Danish National Committee on Biomedical Research Ethics. All patients provided written informed consent to participate.

Psychopathologic features were assessed with the Positive and Negative Syndrome Scale (PANSS), and the level of function was estimated using the Global Assessment Scale. Duration of untreated illness was defined as the period during which the patient had experienced continuous deterioration of functioning owing to disease-related symptoms. Weight was measured without shoes and jacket but with light clothes in the beginning of the day while fasting. The same digital apparatus was used throughout the study.

After the baseline examination, patients were treated for 6 weeks with individual doses of amisulpride. To minimize adverse effects and avoid anticholinergics, amisulpride dosages were adjusted according to the clinical impression of symptoms and adverse effects.

Reward data on a subgroup of the participants (22 patients) and data on other modalities have been presented elsewhere. A flowchart of patient recruitment is provided in Figure 1.

Experimental Design and Task
Striatal activation in response to cues indicating monetary gain and loss was evoked by a modified variant of the monetary incentive delay task. Details on the modified paradigm have
been described elsewhere\textsuperscript{29,40} and can be found in the eMethods and eFigure 1 in the Supplement.

**Imaging**

The fMRI scans were acquired on a 3.0-T whole-body scanner (Achieva; Philips Healthcare) using an 8-channel head coil (SENSE; Invivo). At baseline and after 6 weeks, 540 whole-brain functional echoplanar images per run were acquired (38 sections; voxel size, 2.9 × 2.9 × 2.4 mm; flip angle, 75°; repetition time, 2 seconds; and echo time, 25 milliseconds). For anatomic reference, whole-brain 3-dimensional, high-resolution, T1-weighted structural images were acquired (repetition time, 10 milliseconds; echo time, 4.6 milliseconds; flip angle, 8°; and voxel size, 0.79 × 0.79 × 0.80 mm).

**Data Analysis**

Data were analyzed from October 25, 2014, to June 15, 2015, and August 31 to September 19, 2015. The fMRI analyses were conducted using tools from the FMRIB Software Library (John Radcliffe Hospital, Oxford, England; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Images were corrected for section-timing effects (correction for 38 sections within each repetition time of 2 seconds) and 3-dimensional motion. Spatial smoothing was performed with a 5-mm full-width at half maximum gaussian kernel, and low-frequency noise was reduced using a high-pass filter with a cutoff at 200 seconds.

For the first-level analyses, the general linear model previously presented by Nielsen et al\textsuperscript{29} was used (details are given in the eMethods and eFigure 1 in the Supplement). The model consists of 15 predictors, and all explanatory variables were convolved with the hemodynamic response function. In addition, 6 motion parameters were included. Individual contrast images were computed to estimate the anticipation-evoked activity as the differential activation by uncertain gain and loss cues compared with neutral cues.\textsuperscript{29} First-level statistical maps of the anticipation contrast for each individual were transformed into Montreal Neurological Institute (MNI) space before second-level analyses.

**Regions of Interest**

Because we had a specific hypothesis regarding an association between attenuated reward activation in the dorsal part of the striatum and weight gain, and because previous analyses\textsuperscript{29,40} in patients with schizophrenia showed major impairment in the ventral striatum, we focused our analyses on these regions. Regions of interest (ROIs) were defined according to Zink et al\textsuperscript{44} as 6-mm-radius spherical regions centered in Montreal Neurological Institute (MNI) coordinates ±10, 14, and −6; those in the putamen (dark blue) are centered in MNI coordinates ±22, 4, and 4.

**Statistical Analysis**

All statistical analysis used SPSS software (version 19; SPSS, Inc). Unless otherwise indicated, data are expressed as mean (SD). Demographic and psychopathologic baseline differences between those who completed the study and those who dropped
**Results**

A total of 69 patients consented to participate. Baseline fMRI scans were obtained from 58 patients. At follow-up, fMRI scans were unavailable for 17 patients and weight data were missing for 2 patients. Thirty-nine patients had baseline and follow-up fMRI scans and weight data that were useable for the present analyses (Table). Reasons for discontinuing the study are provided in Figure 1.

**Clinical Variables and Weight Change**

The mean daily dosage of amisulpride was 272 (168; range 50-800) mg. During the treatment period, patients gained a mean of 2.3 (2.8; range -4 to 8) kg in body weight ($t_{50} = 5.2; P < .001$). The PANSS positive score ($t_{52} = 7.4; P < .001$), PANSS general score ($t_{51} = 7.5; P < .001$), PANSS total score ($t_{50} = 6.9; P < .001$), and Global Assessment Scale score improved ($t_{51} = 6.76; P < .001$), but the PANSS negative score was unchanged (Table). The 19 patients who were not examined at follow-up had higher PANSS negative and total scores at baseline but did not differ on age, baseline weight, or duration of untreated illness.

**Baseline Striatal Reward Signal and Weight Change**

The mean PE from each of the defined ROIs was included in a linear regression with weight change as the dependent variable and PE, age, and baseline weight as independent variables. For the right-sided putamen, the model was significant ($F_{35,3} = 5.64; P = .003$). We found no effect of age, but lower baseline contrast signal and lower baseline weight were both associated with more weight gain ($P = .001$ and $P = .04$, respectively) (Figure 3A). We found no significant associations between weight change and PE from the other ROIs ($P > .05$).

In explorative analyses, we tested whole-brain voxel-wise correlation analyses between baseline PE and weight change. We found a significant cluster in the right-sided putamen, which overlapped our predefined ROI, and a significant cluster in the left occipital lobe ($P < .001$, uncorrected) (Figure 4).

**Change in Striatal Reward Signal and Weight Change**

Linear regression with weight change as the dependent variable and change in fMRI contrast activity in the defined ROIs as the independent variable was significant for the right-sided putamen, showing that weight gain was associated with an increase in reward contrast signal ($F_{37,1} = 4.48; P = .04$) (Figure 3B). The model remained significant after adding medication dose and baseline PE as independent variables ($F_{32,3} = 3.41; P = .03$). However, this effect was then driven by a significant effect of baseline PE ($P = .02$), whereas we found no significant effect of change in PE or medication dose ($P > .1$ for both).

In addition, performing the regression analyses using change in body mass index instead of weight change as the dependent variable did not change the findings significantly for baseline signal ($F_{35,1} = 11.08; P = .002$) or change in signal ($F_{35,1} = 5.89; P = .02$). Furthermore, we found no effect of sex or smoking. The main effect of the anticipation contrast in the patients and the effect of time are presented in eFigures 2 and 3, respectively, in the Supplement.

**Weight Change and Psychopathologic Features**

Post hoc analyses did not reveal associations between weight change and psychopathologic measures at baseline. Further-
more, we found no association between weight change and change in psychopathologic features in PANSS total scores and subscale scores.

Discussion

This study is the first, to our knowledge, to examine striatal reward activity and weight change in initially antipsychotic-naive patients with schizophrenia before and after antipsychotic treatment. As hypothesized, we found a significant correlation between attenuated striatal activity during reward anticipation at baseline and the weight change after 6 weeks of selective dopamine D₂ receptor blockade. More specifically, lower baseline reward activity in the right-sided putamen was associated with the most pronounced weight gain. After 6 weeks of amisulpride treatment, an increased reward response in the same region of the right-sided putamen was positively correlated with weight gain.

Although amisulpride is often categorized as a compound with a relatively low risk for weight increase, we observed that 6 weeks of amisulpride treatment resulted in a moderate weight gain of 2.3 kg. This discrepancy is probably explained by the inclusion of patients with a first episode of schizophrenia, who are more sensitive to the adverse effects of antipsychotics. As such, our observed weight gain is comparable with findings in the European First Episode Schizophrenia Trial (EUFEST), which reported a mean weight gain of 9.7 kg after 1 year of amisulpride treatment. As clinically expected, our patients showed a high variability in weight gain, which ranged from an accelerated gain of 8 kg to a loss of 4 kg. Our results suggest that attenuated fMRI reward activation in the putamen before initiation of treatment may predispose individuals to weight gain if they are exposed to antipsychotics. This finding is in accordance with the reward deficiency hypothesis, which suggests that decreased reward activity results in a predisposition for abnormal craving behavior and obesity.

A decreased reward response has been observed in obese patients; however, to our knowledge, whether this response predates or is a result of the obesity has not been clarified. One strength of our longitudinal study is that it enables exploration of changes in the reward response during the period of weight change. According to the reward deficiency hypothesis, we would expect weight gain to be associated with a continuous attenuation or a further reduction in the striatal reward response. In our patients, the opposite was found: increases in reward activity in the putamen over time correlated positively with weight gain.

The correlation between weight gain and baseline fMRI signal (A) and between weight gain and change in fMRI signal (B) after 6 weeks of amisulpride treatment. Patients with the lowest contrast signal during reward anticipation at baseline gained the most weight during antipsychotic treatment. Patients who gained the most weight after amisulpride treatment had the highest signal increase (calculated using linear regression).

There was a partial overlap between voxels showing a significant correlation between baseline fMRI signal and weight change (red) and the predefined region of interest (blue) (P < .001, uncorrected). The figure is centered in Montreal Neurological Institute coordinates 22, 4, and 2.
although this association was modified by the baseline reward activity.

Previous studies\(^{40, 45}\) have shown that second-generation antipsychotics increase reward-related activity in the striatum, whereas a decrease is usually found in healthy controls not receiving medication, which suggests a habituation effect. Recent findings\(^{32}\) from an fMRI study in healthy volunteers exposed to 1 week of antipsychotic treatment suggest that this increase could be one of the mechanisms leading to weight gain. That study showed that olanzapine induced an increase in reward activation in the dorsal striatum and that this increase was associated with increased food consumption and eating disinhibition.\(^{32}\) Our results extend these findings to be present in patients with schizophrenia who are naive to antipsychotics before treatment with a dopamine D\(_2\) antagonist and suggest that the increase in striatal activation appears particularly pronounced in patients who are characterized by having a decreased reward response in the putamen before treatment initiation.

Recent studies in obese people and patients with binge-eating disorder\(^{46, 47}\) have also reported increased reward response in the dorsal striatum and a positive correlation with binge eating habits. Although results from those studies are in conflict with observations of decreased activity supporting the reward deficiency hypotheses,\(^{15, 16}\) these inconsistencies may imply important effects of time and chronicity because different mechanisms may be involved in the development and maintenance of obesity.

Apart from a potential direct effect on appetite, reward-related activity in the putamen may be important during habit formation.\(^{48}\) Thus, increasing reward-related activity in the putamen during treatment may drive implementation of unhealthy eating habits and lead to weight gain. We found no association between reward activity alterations in the ventral parts of the striatum and weight gain. Consistent with previous findings,\(^{40}\) this result suggests that dopamine D\(_2\) receptor blockade in the ventral striatum may be correlated with symptom improvement rather than adverse effects.

In obese people, an association among dopamine receptor density in the striatum, body mass index, and opportunistic eating behavior have been reported.\(^{49}\) Given the putative association between dopamine D\(_2\) receptor occupancy and amisulpride dose, a linear relationship between amisulpride dosage and weight change would be expected. The absent dose-response relationship between medication dosage and weight change in this study is in line with previous observations\(^{33}\) and supports the common clinical observation of highly variable individual susceptibility to antipsychotic-induced weight gain. Ultimately, serum levels of amisulpride are required to resolve a dose-response relationship, but these data were not obtained systematically in the present study.

We found no association between symptom improvement and weight change. This association has been described previously,\(^{20}\) primarily in relation to clozapine and other second-generation antipsychotics. These antipsychotics affect a wide range of neurotransmitters, and only a few studies\(^{51, 52}\) have examined this relationship in dopamine receptor-selective compounds, with conflicting findings. An association between symptom change and weight change has been reported in patients treated with placebo,\(^{53}\) which could reflect an effect of clinical improvement on eating behavior resulting in weight gain. Because we did not find any association between weight change and symptom improvement, we consider the weight gain observed in the present study to be a direct effect of the medical treatment rather than an indirect effect of symptom improvement.

Some limitations should be considered. First, we used a reward paradigm, which was not food related but measured the reward function at a general level. However, based on recent findings, we can reasonably assume that a general effect in the reward system will also affect reward processing of food-related cues.\(^{54}\) Still, additional specific food-related alterations in the reward processing may not have been identified using a monetary paradigm. Second, outcome evaluation was not included in our analyses owing to differences in the evaluation of monetary and food rewards,\(^{54}\) and whether changes in outcome processing and antipsychotic-induced weight change are associated remains unknown. Furthermore, patients with schizophrenia already may be vulnerable to the development of metabolic syndrome before treatment starts.\(^{55}\) We did not assess appetite and eating habits, and we did not systematically measure blood markers suggestive of dysmetabolism (eg, triglyceride and gut hormone levels). Moreover, for ethical reasons, we did not include a control group of patients not treated with antipsychotics. Therefore, no definite causal inferences regarding the association between antipsychotics and weight gain should be drawn from this study.

Conclusions

Our findings suggest that reward activity in dorsal parts of the striatum appear to be associated with the individual variability in the predisposition for antipsychotic-associated weight gain. Moreover, pharmacologic modulation of the reward system may play a role in antipsychotic-associated weight gain.
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