Increased Release of Dopamine in the Striata of Young Adults With Hearing Impairment and Its Relevance for the Social Defeat Hypothesis of Schizophrenia

Martin Gevonden, MSc; Jan Booij, PhD, MD; Wim van den Brink, PhD, MD; Dennis Heijtel, MSc; Jim van Os, PhD, MD; Jean-Paul Selten, PhD, MD

**IMPORTANCE** An increased risk for psychosis is observed in people with hearing impairment. According to the social defeat hypothesis, the long-term experience of exclusion leads to enhanced baseline activity and/or sensitization of the dopamine system and puts the individual at increased risk for psychosis.

**OBJECTIVE** To investigate whether young adults with severe hearing impairment (SHI) experience more feelings of social defeat, show greater dopamine release in response to dexamphetamine, and report a stronger subjective reaction to this substance than normal-hearing young adults and to examine whether dopamine release is associated with both self-reported social exclusion and dexamphetamine-induced psychotic experiences.

**DESIGN, SETTING, AND PARTICIPANTS** A sample of 19 participants with SHI and 19 smoking-, age-, and sex-matched healthy controls underwent single-photon emission computed tomography with iodine 123-labeled iodosobenzamide as a radiotracer before and after an amphetamine challenge at an academic hospital.

**EXPOSURES** Dexamphetamine sulfate (0.3 mg/kg) administered intravenously.

**MAIN OUTCOMES AND MEASURES** Baseline D_{2/3} receptor binding and endogenous dopamine release.

**RESULTS** The participants with SHI reported experiencing more feelings of social defeat (U = 109, z = −2.09, P = .04) and loneliness (U = 87.5, z = −2.72, P = <.001) than did healthy controls, but they did not differ from healthy controls with regard to baseline psychotic symptoms (U = 156.5, z = −0.70, P = .48). There were no significant group differences in baseline D_{2/3} receptor binding. However, repeated-measures multivariate analysis of covariance with age (in months) and tobacco smoking (in pack-years) as covariates showed that there was a greater amphetamine-induced striatal dopamine release among the participants with SHI than among the healthy controls (F_{1,34} = 4.55, P = .04). After amphetamine administration, the participants with SHI reported more changes in affect than the healthy controls, but not a greater increase in psychotic symptoms. Likewise, reports of social exclusion and an increase in psychotic symptoms were not associated with dopamine release.

**CONCLUSIONS AND RELEVANCE** Our study presents preliminary evidence of dopamine sensitization in a socially excluded group of people with hearing impairment. If replicated by future studies in other excluded groups, this finding may have major implications for our understanding of the underlying mechanism and for prevention of psychotic disorders.
According to the social defeat hypothesis, long-term exposure to the experience of being excluded from the majority group may lead to increased activity and/or sensitization of the mesolimbic dopaminergic system and thereby increase the risk for schizophrenia. The hypothesis posits that social defeat is the common denominator of 5 major schizophrenia risk factors: urban upbringing (which is associated with a higher level of competition), migration, childhood trauma, low IQ, and drug abuse. Animal studies provide evidence of this sensitization by showing that repeated episodes of social defeat lead to changes in mesolimbic dopamine release and in the behavioral reaction to amphetamine. Hearing impairment is another risk factor for psychotic experiences and psychotic disorders, of which social defeat could well be the underlying mechanism. However, other explanations for this association, such as brain abnormalities due to meningitis, a common cause of severe hearing impairment (SHI), are also possible.

Social position, psychotic symptoms, and dopamine function have not yet been jointly studied, although several studies have reported associations between 2 of the 3. For example, a positron emission tomography study of healthy volunteers found a positive association between striatal dopamine D$_{2/3}$ receptor availability and social status. In addition, 2 recent meta-analyses confirmed that patients with schizophrenia show both elevated presynaptic dopamine activity (dopamine synthesis)$^{14}$ and higher striatal dopamine D$_{2/3}$ receptor availability compared with healthy controls, although there is no convincing evidence for the latter in medication-naive patients. Furthermore, patients with schizophrenia show more dexamphetamine-induced dopamine release in the striatum. The same has been shown (to a lesser extent) in patients with schizotypal personality disorder and healthy individuals with schizotypal traits. Finally, a recent study reported elevated presynaptic striatal dopamine function in a population at ultra-high risk for the development of psychosis, and the dopamine synthesis capacity in that population was predictive for transition to a psychotic disorder.

The present imaging study is the first experimental investigation of the social defeat hypothesis with regard to humans. Our study compares dexamphetamine-induced dopamine release in 2 groups that are assumed to differ substantially in terms of social exclusion: young adults with SHI and normal-hearing healthy controls. Dopamine release was measured by use of single-photon emission computed tomography (SPECT) with iodine 123-labeled iodoamphetamine ([I$^{123}$]iodobenzamide) as the dopamine D$_{2/3}$ radiotracer. The following 4 hypotheses were tested: (1) participants with SHI report having more feelings of exclusion than do healthy controls; (2) the reduction in striatal [I$^{123}$]iodobenzamide binding potential after the amphetamine challenge (representing endogenous dopamine release) is significantly larger in participants with SHI than in healthy controls; (3) participants with SHI show a stronger subjective (psychotic and affective) response to amphetamine than do healthy controls; and (4) dexamphetamine-induced dopamine release is positively associated with both self-reported social exclusion and dexamphetamine-induced psychotic experiences, regardless of group membership.

### Methods

#### Participants

The participants with SHI were recruited through local media advertising and from audiology services and patient organizations. Severe hearing impairment was diagnosed for participants having a Fletcher index (ie, a pure-tone audiometry threshold averaged over 500, 1000, 2000, and 4000 Hz in the best ear) of higher than 60 dB for at least 3 years. The participants with SHI were individually matched to normal-hearing healthy controls (with a Fletcher index of <20 dB) on sex, age (±2 years), and tobacco smoking (number of pack-years of <1 or ≥1) who were recruited via advertisements in the local media.

Inclusion criteria were (1) age between 18 and 30 years, (2) completion of primary school, and (3) white skin color and Dutch descent. Exclusion criteria were applied to ensure a healthy population that could be scanned safely, with minimal confounding influences on the dopamine system. The most important criterion for exclusion was a history of neurological problems, psychotic disorder, or substance abuse. For a complete list of exclusion criteria, and for a description of the scanning procedure before the scanning day, see the eAppendix in the Supplement. Our study was approved by the local medical ethics committee of the Academic Medical Center, Amsterdam, the Netherlands. All participants provided written informed consent and received a remuneration of €140.

#### Behavioral Assessments

Before the start of the SPECT session, all participants completed the Community Assessment of Psychic Experiences (CAPE), a questionnaire to assess the lifetime presence of positive, negative, and depressive symptoms associated with psychotic disorders. To measure the subjective experience of social exclusion, the participants completed the Social Comparison Scale, the Social Defeat Scale, and the UCLA Loneliness Scale.

#### Measurement of Baseline D$_{2/3}$ Receptor Availability and Dopamine Release

On a single day, participants underwent 2 SPECT scans measuring the nondisplaceable binding potential (BP$_{ND}$) of [I$^{123}$]iodobenzamide: the first scan was performed to quantify baseline D$_{2/3}$ receptor availability, and the second scan was performed to quantify dopamine release after intravenous administration of dexamphetamine sulfate. A schematic overview of the procedure during the scanning day is presented in Figure 1. For further details of the SPECT procedure, see the eAppendix in the Supplement.

#### Cortisol and Cardiovascular Response to Amphetamine

Saliva samples were requested for the measurement of dexamphetamine effects on cortisol. Blood pressure and heart rate were measured at baseline and every 2 minutes up to 22 minutes after the administration of dexamphetamine. See Figure 1 for a visual representation of the timing of measurements.
subjective response to amphetamine
The affective response to amphetamine (hypothesis 3) was monitored using a simplified 4-item version of the Amphetamine Interview Rating Scale. Participants rated how good (euphoric), energetic, restless, and anxious they felt using a 0- to 100-mm visual analog scale at −2, 2, 6, 10, 14, 18, 22, 35, 55, and 120 minutes after dexamphetamine administration.

The psychotic response to amphetamine (hypotheses 3 and 4) was operationalized as the increase in positive symptoms on the CAPE-state questionnaire. Participants completed this questionnaire twice, to assess the presence of these symptoms in the 2 hours before and the 2 hours after the administration of dexamphetamine (Figure 1). The total CAPE-state score, including positive, negative, and depressive symptoms, was used as a measure of general symptomatic response to amphetamine.

statistical analysis
Group comparisons were performed with χ² tests for categorical data and with Mann-Whitney U tests for continuous data because nonnormal distributions (right skewed) were observed for most questionnaires. Changes in BPND (ΔBPND [ie, dopamine release]) for all participants and differences between groups over time were tested using repeated-measures multivariate analysis of covariance. Between-group differences in BPND at baseline were tested with analysis of covariance. Non-parametric (Spearman rank) correlations were computed to explore the association between ΔBPND, percentage decrease from baseline) and measures of social defeat and psychotic symptoms. Repeated-measures analyses of variance, with the Greenhouse-Geisser correction for violation of sphericity, were used to assess possible differences in subjective responses to amphetamine.

Multivariate analysis of covariance and analysis of covariance included age (in months) and tobacco smoking (in pack-years) as continuous covariates because these factors were only approximately matched and are known to affect D2/3 receptor availability.26,27 Because an effect of inner-ear surgery on dopamine release cannot be excluded, a sensitivity analysis was conducted without the 3 participants with SHI who had a cochlear implant.

Repeated-measures analyses were performed using SPSS Statistics 21.0 for Windows (IBM Corp), and all other analyses were conducted with Stata 11.0 for Windows (StataCorp). The significance level for all analyses was set at 2-tailed α = .05.

results
Participants
Scans were acquired for 19 participants with SHI and 19 healthy controls with normal hearing, forming a total of 19 matched SHI-control pairs. The mean (SD) level of hearing loss was 87 (17) dB for the SHI group and 9 (3) dB for the control group. Participants with SHI considered themselves deaf (n = 11), severely hearing impaired (n = 6), or moderately hearing impaired (n = 2) when not wearing hearing aids. When wearing hearing aids, they reported severe (n = 4), moderate (n = 10), slight (n = 4), or no hearing impairment (n = 1). At the level of a loud conversation (55 dB) and with the use of hearing aids, the mean (SD) percentage of syllables heard by participants with SHI was 51% (20%). Participants with SHI and healthy controls did not differ in lifetime total CAPE scores (U = 156.5, z = −0.70, P = .48) or lifetime positive symptoms (U = 140, z = −1.21, P = .23). More healthy controls than participants with SHI had experimented with cannabis (χ² = 5.40, P = .02), but only 1 of the controls and none of the participants with SHI reported a frequency of use ever exceeding once per month. Additional characteristics of the participants are given in Table 1.

Indicators of social exclusion
As expected for a group selected for social exclusion, the participants with SHI scored higher on the UCLA Loneliness Scale (U = 87.5, z = −2.72, P < .001) and the Social Defeat Scale (U = 109, z = −2.09, P = .04) than did the healthy controls. In addition, the participants with SHI scored lower on the Social Comparison Scale, comparing themselves less favorably to others than did healthy controls, but the difference was not significant (U = 118, z = −1.83, P = .07) (Table 1).

Baseline D2/3 receptor availability
The participants with SHI and the healthy controls did not significantly differ in baseline BPND (F_{1,34} = 3.38, P = .08) (Table 2). Age (F_{1,34} = 3.78, P = .04) was significantly related to baseline BPND, whereas smoking (F_{1,34} = 1.55, P = .22) was not.

Dexamphetamine-induced effects on D2/3 receptor availability
Being a smoker was significantly related to ΔBPND (F_{1,34} = 5.05, P = .03), but age (F_{1,34} = 0.46, P = .50) was not. There was a significant effect of SHI on ΔBPND after adjusting for age and tobacco smoking (F_{1,34} = 4.55, P = .04,
η²_{partial} = 0.12). The mean (SD) percentage decrease in BP_{ND} was 18.7% (15.3%) for the SHI group and 10.5% (16.0%) for the control group, which indicates a higher release of dopamine in the SHI group than in the control group (Figure 2).

When we repeated this analysis and excluded the participants with a cochlear implant, the effect of SHI on ΔBP_{ND} was very similar but no longer significant (F_1,31 = 2.01, P = .17), likely owing to reduced statistical power.

Physiological Response to Amphetamine

Table 2 shows that the administration of dexamphetamine led to increased salivary cortisol concentrations and an increase in blood pressure and heart rate in both groups. Repeated-measures analyses of variance showed that there were no significant time-by-group interactions (F_{1,31} = 1.55, P = .22; F_{1,36} ≤ 0.005, P = .99; F_{1,36} = 0.09, P = .76 for the outcomes of cortisol concentration, heart rate, and systolic blood pressure, respectively).

Subjective Response to Amphetamine

Changes in CAPE-state positive symptom scores after the administration of dexamphetamine did not differ between groups (U = 168.5, z = −0.42, P = .68). Total CAPE-state scores at baseline did not differ between groups (U = 164, z = −0.49, P = .62), but after amphetamine administration, total CAPE-state scores were higher in the SHI group than in the control group (U = 113.5, z = −1.96, P = .05). However, the changes in total CAPE-state scores following the administration of dexamphetamine were not significantly different between groups, probably owing to the large variation of change scores in the SHI group (Table 2).

The administration of dexamphetamine evoked a subjective response with significant time effects for all affective measures: euphoria (F_{4.45,142.32} = 9.34, P < .001), energy (F_{4.10,131.42} = 2.90, P = .02), restlessness (F_{4.70,150.43} = 15.17, P < .001), and anxiety (F_{3.85,123.14} = 14.82, P < .001). More importantly, there were significant group-by-time interactions for...
euphoria ($F_{4,45,142,32} = 2.93, P = .02$), energy ($F_{4,10,131,32} = 4.17, P = .003$), and anxiety ($F_{3,85,123,34} = 3.04, P = .02$), with a larger decrease in euphoria and energy and a greater increase in anxiety after administration of dexamphetamine in the SHI group compared with the control group (Figure 3).

### Associations Between Amphetamine-Induced Dopamine Release and Social Exclusion or Increase in Positive Symptoms

There were no significant correlations between dopamine release and baseline measures of social defeat ($p = −0.19, P = .27$), social comparison ($p = 0.15, P = .37$), or loneliness ($p = −0.20, P = .25$). Also, dopamine release was not correlated with an increase in CAPE-state positive symptom scores ($p = −0.13, P = .46$).

### Discussion

Single-photon emission computed tomography was used to test whether the participants with SHI displayed increased dopaminergic activity and whether this increase was associated with measures of social exclusion and with amphetamine-induced positive (psychotic) symptoms. In accordance with our first 3 hypotheses, participants with SHI reported higher levels of social exclusion, displayed higher amphetamine-induced striatal dopamine release, and reported stronger affective responses to amphetamine. However, in contrast to our third hypothesis, participants with SHI did not report more amphetamine-induced positive symptoms, although they did show higher general symptom levels than did healthy controls after amphetamine exposure. Also, in contrast to the fourth hypothesis, dopamine release was not associated with subjective reports of social exclusion or increases in positive symptoms. Together, these results suggest that SHI is associated with a hypersensitive dopamine system. We cannot conclude whether or not social exclusion plays a causal role in the observed difference in dopamine functioning or in the previously observed increased risk for psychosis in people with hearing impairment.

To our knowledge, the present study is the first to suggest that the dopamine system in a group of socially excluded humans is sensitized. The results are in line with studies of rats showing dopamine alterations after being subjected to social defeat by a dominant animal and a study of humans that showed a relation between socioeconomic status and D$_{2/3}$ receptor availability. Socioeconomic status, however, does not necessarily incorporate the experience of exclusion, which is central to the social defeat hypothesis. Positron emission tomography studies of humans using the Montreal Imaging Stress Task have shown that acute social stress causes a measurable release of dopamine and that people at high risk for psy-

### Table 2. Effects of Dexamphetamine Administration on Striatal D$_{2/3}$ Receptor Availability, and Physiological Measures and Subjective Experiences

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Striatal D$_{2/3}$ receptor availability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BP$_{ND}$</td>
<td>Healthy Controls (n = 19) 0.82 (0.19)</td>
<td>.12*</td>
</tr>
<tr>
<td>Baseline BP$_{ND}$</td>
<td>Participants With SHI (n = 19) 0.93 (0.25)</td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.64*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Healthy Controls (n = 19) 75 (14)</td>
<td>.67*</td>
</tr>
<tr>
<td>Baseline</td>
<td>Participants With SHI (n = 19) 72 (13)</td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.58*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Healthy Controls (n = 19) 69 (11)</td>
<td>.86*</td>
</tr>
<tr>
<td>Baseline</td>
<td>Participants With SHI (n = 19) 68 (18)</td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.58*</td>
</tr>
<tr>
<td>Cortisol concentration, μg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Healthy Controls (n = 19) 0.15 (0.07)</td>
<td>.07b</td>
</tr>
<tr>
<td>Baseline</td>
<td>Participants With SHI (n = 19) 0.10 (0.04)</td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.39b</td>
</tr>
<tr>
<td>Subjective experiences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CAPE-state scores, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Healthy Controls (n = 19) 4.60 (3.58)</td>
<td>.62b</td>
</tr>
<tr>
<td>Baseline</td>
<td>Participants With SHI (n = 19) 6.22 (6.75)</td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.64b</td>
</tr>
<tr>
<td>△Total CAPE-state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.64b</td>
</tr>
<tr>
<td>△Positive symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.64b</td>
</tr>
<tr>
<td>△Negative symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.64b</td>
</tr>
<tr>
<td>△Depressive symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP$_{ND}$ after amphetamine administration</td>
<td></td>
<td>.64b</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; BP$_{ND}$, nondisplaceable binding potential; CAPE-state, Community Assessment of Psychic Experiences–state version (refers to the preceding 2-hour interval); SHI, severe hearing impairment; △Max, maximum deviation from baseline across 9 measurements; △Total CAPE-state, change in CAPE scores after amphetamine administration (also listed for the 3 subscales separately).

SI conversion factor: To convert cortisol to nanomoles per liter, multiply by 27.588.

* Determined by use of the t test.

b Determined by use of the U test.
chotic disorders display an increased release of dopamine compared with healthy controls. The paradigm has not yet been applied to a socially excluded group such as people with SHI, yet Pruessner et al\textsuperscript{28} have reported that a low level of maternal care during childhood is associated with a greater release of dopamine in response to the Montreal Imaging Stress Task. Such findings suggest that a pharmacological challenge and an experimental social stressor can represent different ways to measure dopaminergic sensitization, and they can achieve similar results.

In contrast to earlier studies,\textsuperscript{16,30} we did not find any associations between dopamine release and changes in psychotic symptom scores. Previous studies using clinical interviews found such associations in patients, but importantly not in healthy controls. We selected the CAPE-state questionnaire because it is easy to use, and we expected it to be more sensitive to subtle symptomatic changes than a clinical interview.\textsuperscript{20} In retrospect, the short (2-hour) time window of structured activity, including 1 hour in a SPECT scanner, rendered a number of the CAPE-state positive symptom questions less relevant, for example: “In the past two hours, have you ever felt as if magazines or television programs contain messages that are directed especially at you?” The relatively low sensitivity to change of the CAPE-state positive symptom questions may be illustrated by the fact that 13 of the 19 healthy controls and 12 of the 19 participants with SHI had a positive symptom change score of 0. Moreover, it is known that responses to dexamphetamine among patients with schizophrenia are quite heterogeneous: for some patients, positive symptoms worsen, whereas for other patients, these symptoms improve.\textsuperscript{10} The large variation in CAPE-state change scores in the SHI group supports this observation.

Our study shows group differences in the amphetamine effects on affect. On average, the SHI group displayed a greater adverse reaction to amphetamine. In contrast to earlier studies\textsuperscript{16,31} showing mainly euphoric effects, we observed a decrease in positive affect and an increase in negative affect after amphetamine administration. Two explanations may be brought to bear on this finding. First, although a subgroup of participants may have experienced the pleasurable effects of amphetamine, we found that, by using mean Visual Analogue Scale scores, ceiling and floor effects reduced the weight of those observations. Second, the current sample was entirely naive to illicit drugs and did not know what to expect and may have been overwhelmed by the effects of amphetamine.

The present study has both strengths and limitations. The most important strengths are the objective measurements of hearing impairment and the attention paid to potentially confounding factors (age, educational level, medication, neurological disorders, and brain abnormalities).

The primary limitation is that we could not directly measure the risk of psychosis in this sample, but epidemiological studies,\textsuperscript{9–12} which generally also include milder forms of hearing impairment, show that this risk is moderately elevated for individuals with SHI. However, in contrast to our expectation, the participants with SHI did not report a greater lifetime prevalence of psychotic symptoms or a greater increase in psychotic symptoms following the dexamphetamine challenge than normal-hearing healthy controls. Two factors could explain these unexpected findings. First, selection bias may have occurred, because people with hearing impairment who volunteer to come to the hospital and to get injected with a radiotracer and amphetamine are generally high-functioning individuals and probably do not represent a more anxious and avoidant subpopulation that may present with more psychotic symptoms. The exclusion of people with first-degree family members with psychosis may have contributed to this selection bias. Second, the average age in our sample was 26 years, which made it unlikely that participants were still at a high risk for a first psychotic episode.

The second limitation is the relatively small sample size in our study. Although differences in dopamine release between the 2 nonpsychotic groups in our study were smaller than those found in studies comparing patients with schizophrenia and healthy controls, this sample size sufficed to detect them. Furthermore, the restrictiveness of our criteria eliminated a number of important confounders and allows the results to be interpreted with confidence. However, to detect associations between clinical measures and dopamine release, a larger sample size would be required.

The third limitation is that despite the relatively high spatial resolution of our SPECT scans, reliable differentiation of striatal subregions was not feasible. With positron...
emission tomography tracers, better topographical categoriza-
tor availability specific to the associative rather than the
limbic (ventral) or sensorimotor striatum. However, the
whole-striatum analysis in our study was fully automated

**Figure 3. Profile Plots of the Effects of Dexamphetamine on Affect**

Mean visual analog scale (VAS) scores for each of the 4 affect items (good, energetic, restless, and anxious) across the 10 time points. Separate lines represent the participants with severe hearing impairment (SHI) (n = 19) and the healthy controls (n = 19). Time is represented on the x-axis and relative to the start of dexamphetamine administration. Error bars represent SD. The first measurement was conducted before dexamphetamine administration, the second directly after. The 55-minute measurement was conducted immediately before the second single-photon emission computed tomography scan, and the 120-minute measurement at the end of the experiment.
and did not involve drawing individual regions of interest. Even while heterogeneous effects in different striatal subdivisions were averaged, a reliable and robust result was obtained, albeit with sizeable variability.

The fourth limitation is the possible effect of surgery on the 3 patients with a cochlear implant. When these patients were removed from the analysis, the difference in dopamine release between participants with SHI and healthy controls remained very similar, but it was no longer significant, possibly owing to a reduction in statistical power. This reduction may well be sizeable because the participants with a cochlear implant have greater hearing loss and reported higher levels of social exclusion than did the other participants in the SHI group.

The fifth and final limitation is that plasma concentrations of dexamphetamine were not measured in our study. We did, however, observe a consistent and strong cardiovascular response and a sharp increase in salivary cortisol concentrations, which implies that the administered dose was effective.

Conclusions

In conclusion, compared with normal-hearing healthy controls, the participants with SHI experienced a higher level of social exclusion and showed increased striatal dopamine release and a greater affective response to dexamphetamine administration. However, social exclusion scores and changes in psychotic symptoms were not associated with dopamine release. Overall, these findings suggest that individuals with SHI, a group at increased risk for psychosis, have a sensitized dopamine system. Replication of our study, using a larger sample and/or another socially excluded population at increased risk for psychotic disorders (eg, a stigmatized ethnic minority group), is needed to draw definitive conclusions.

REFERENCES

10. van der Werf M, van Winkel R, van Bokxel M, van Os J. Evidence that the impact of hearing impairment on psychosis risk is moderated by the level of complexity of the social environment. Schizophr Res. 2010;122(1-3):193-198.


