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Ventral Striatal Activation during Reward Processing in Subjects with Ultra-High Risk for Schizophrenia

Georg Juckel[a, b] Eva Friedel[b] Michael Koslowski[b] Henning Witthaus[a, b] Seza Özgürdal[a, b] Yehonala Gudlowski[b] Brian Knutson[c] Jana Wrase[b] Martin Brüne[a] Andreas Heinz[b] Florian Schlagenhauf[b]

[a]Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, and
[b]Department of Psychiatry, Charité – University Medical Center, Campus Charité Mitte, Berlin, Germany;
[c]Department of Psychology, Stanford University, Stanford, Calif., USA

Key Words
Nucleus accumbens · Reward expectation · Functional magnetic resonance imaging · Prodrome · Schizophrenia

Abstract
Background: Early dysfunction of the brain reward system in schizophrenia might be already recognized in the prodromal phase of this illness. We used functional magnetic resonance imaging to assess the blood oxygen level-dependent response in the ventral striatum (VS) of subjects with ultra-high risk for psychosis during the presentation of reward-indicating and loss-indicating stimuli. ***Methods:*** Thirteen prodromal patients (mean age: 25.5 ± 4.6 years) and 13 age-matched healthy volunteers participated in an incentive monetary delay task, in which visual cues predicted that a rapid response to a subsequent target stimulus will gain money, avoid losing money or have no consequence. ***Results:*** Compared with the neutral condition, anticipation of reward loss-avoidance elicited significant activation of the VS in both healthy subjects and subjects with ultra-high risk for psychosis, but there was only a statistical tendency for less activation during loss-avoidance anticipation in prodromal compared to healthy subjects. ***Discussion:*** This study provides a first weak hint, as revealed by functional magnetic resonance imaging, for impaired activation of a central area of the mesolimbic dopaminergic brain reward system, the VS, already in subjects with ultra-high risk for psychosis, which is in line with results of patients with full-blown schizophrenic psychosis. This pilot study has, however, strong limitations, and its results need to be replicated first before they can be used e.g. for early recognition of patients in the schizophrenic prodrome.

Introduction

It has been shown that individuals with mild or temporary psychotic symptoms have a significantly higher risk of developing schizophrenia [1]. These so-called prodromal symptoms include positive and negative symptoms as well as cognitive deficits. Although the clinical assessment of prodromal symptoms helps to predict psy-

G.J. and E.F. contributed equally to this work.

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Prof. Georg Juckel, MD, PhD
Department of Psychiatry
Ruhr University, LWL University Hospital
Alexandrinenstrasse 1, DE–44791 Bochum (Germany)
Tel. +49 234 507 7201, E-Mail georg.juckel@wkp-lwl.org

chosis and may lead to antipsychotic treatment before the illness becomes manifest, little is known about the neural substrates of the schizophrenia prodrome. In a first functional magnetic resonance imaging (fMRI) study with prodromal patients, the individuals showed significantly smaller frontal activation during a continuous performance task [2]. The authors suggest that prefrontal circuits in prodromal patients become dysfunctional before the onset of the syndromally defined illness of schizophrenia. Individuals with at-risk mental state to develop psychosis showed elevated dopamine synthesis capacity in the associative subdivision of the striatum and a negative correlation between striatal dopamine synthesis capacity and middle frontal activation during working memory [3], which indicates that frontostriatal interactions play a critical role in the pathogenesis of schizophrenia.

Besides prefrontal dysfunction reflecting cognitive impairment, recent data suggest reduced neural activity of the brain reward system in unmedicated schizophrenics [4, 5]. This may be caused by a dysfunction of dopaminergic neurons in the ventral striatum (VS; including nucleus accumbens), the core region of the reward system [6, 7]. Ventral striatal activity has been associated with pleasant emotions of anticipation [8–10]. Reduced activation of this region could be a neural substrate for negative symptoms like apathy [10, 11], which can also be found in prodromal patients. So far, no brain imaging has been done on the reward system of individuals presumably being in the prodromal state for schizophrenia. We examined prodromal patients and healthy controls by measuring ventral striatal activation during the presentation of stimuli that predicted monetary gain or loss [12]. We hypothesized that prodromal patients would show a reduction of ventral striatal activation during reward anticipation compared to healthy controls.

Subjects and Materials

Subjects and Instruments

We compared 13 subjects in ultra-high risk state of schizophrenia (PANSS positive = 11.44 ± 3.85, PANSS negative = 10.56 ± 3.85; 7 drug-naïve and 6 medicated subjects (few days of atypical neuroleptic treatment); 2 females; age = 25.46 ± 4.61 years) with 13 healthy subjects (2 females; age = 25.69 ± 4.84 years) matched for age, gender, smoking habits and handedness. Inclusion criteria for prodromal patients were the following. Subjects had to show at least two basic symptoms according Klosterkötter et al. [13] of the category 'cognitive disturbances' or at least one attenuated positive symptom assessed on the Scale of Prodromal Symptoms [14]. Healthy controls had no axis I or II psychiatric disorder (SCID interview), no family history of psychiatric disorders in first-degree relatives, and no current drug abuse or a past history of drug dependence other than nicotine consumption (SCID interview and random urine drug testing). Handedness was assessed with the Edinburgh Handedness Inventory [15]. The local ethics committee approved the study, and written informed consent was obtained after complete description of the study.

Monetary Incentive Delay Task

We used a modified version of the monetary incentive delay (MID) task as described by Knutson et al. [16] as used before [17] to study the blood oxygen level-dependent response during anticipation of potential monetary reward (gain anticipation) and potential punishment (loss-avoidance anticipation) in prodromal patients and healthy volunteers. Subjects were scanned with fMRI during trials in which they could win or avoid losing money, depending on their performance on a simple reaction time task, which involved pressing a button during the brief presentation of a visual target. A visual cue at the beginning of each trial indicated reward, loss-avoidance, or neutral (no monetary consequences) trials. After target presentation, participants received feedback, whether they – depending on their reaction time – received or failed to receive money on reward trials or whether they lost or successfully avoided losing money on loss-avoidance trials. To minimize learning effects during the fMRI experiment, participants first completed a practice version of the task for which they did not receive monetary payment. Subjects were also informed about the amount of money that they could earn when the task was successfully performed in the scanner, and cash was shown to them. Once in the scanner, anatomical and functional scans were collected. A MID task session consisted of two runs including 72 trials each. The mean trial duration was 7.69 s, and the mean inter-trial interval was 3.53 s.

fMRI

fMRI was performed on a 1.5-tesla scanner (Magnetom VISION Siemens, Erlangen, Germany) equipped with a standard circularly polarized head coil with gradient-echo echo-planar imaging (repetition time = 1987 ms, echo time = 40 ms, flip = 90°, matrix = 64 × 64, voxel size = 4 × 4 × 3.3 mm^3, interslice gap = 0.3 mm). Eighteen slices approximately parallel to the bicommissural plane (anterior commissure–posterior commissure plane) were collected, covering the inferior part of the frontal lobe (superior border above the caudate nucleus) and large parts of the temporal and occipital lobe. For anatomical reference, a three-dimensional magnetization-prepared rapid gradient echo (repetition time = 9.7 ms, echo time = 4 ms, flip = 12°, matrix = 256 × 256, voxel size 1 × 1 × 1 mm^3) image data set was acquired. Head movement was minimized by using a vacuum pad.

fMRI Data Analysis

Functional MRI data were analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The first three volumes of each functional time series were discarded to remove non-steady-state effects caused by T_1 saturation. All volumes were corrected for differences in slice time acquisition, realigned to the mean volume, and spatially normalized to the standard echo-planar imaging template provided by the Montreal Neurological Institute (MNI template). Finally, the normalized images, with a voxel size of 3 × 3 × 3 mm^3, were smoothed with a Gaussian kernel of 8 mm FWHM

(full width at half maximal) to create a locally weighted average of the surrounding voxels. The preprocessed fMRI data were then analyzed in the context of the general linear model approach as implemented in SPM5 at two levels. On the single subject level, the seven cues, the target, and the five feedback conditions were modeled separately as explanatory variables convolved with the canonical hemodynamic response function. Realignment parameters were included as additional regressors. The five feedback conditions were: successful reward feedback, failure to receive monetary reward, successful loss-avoidance, failure to avoid loss, and feedback of non-incentive trials. On the second level, our analysis focused on the anticipation phase and two-sample t tests were used to assess group differences during the anticipation phase for the contrasts 'gain cues – neutral cue' and 'loss-avoidance cues – neutral cue'. Given our strong a priori hypothesis of ventral striatal activation during anticipation of incentives in the MID task, a small volume correction approach was used for this structure. The ventral striatal volume of interest (VOI) was specified by a voxel mask from a publication-based probabilistic MNI atlas and used as a binary mask at the threshold of 0.90 probability (http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date August 1, 2006) with a VOI approach using a similar approach as before [17]. The significance level for the group contrasts was $p < 0.05$ familywise error rate (FWE) – corrected for multiple comparisons within the VOI. All other results are reported at $p < 0.001$ uncorrected.

Behavioral Data

Behavioral data (reaction time) were analyzed with SPSS (version 18.0, Chicago, Ill., USA) with a 2 (healthy controls vs. prodromal patients) × 3 (reward, loss-avoidance and neutral condition) analysis of variance design with repeated measures with valence as intrasubject factors and group as intersubject factor.

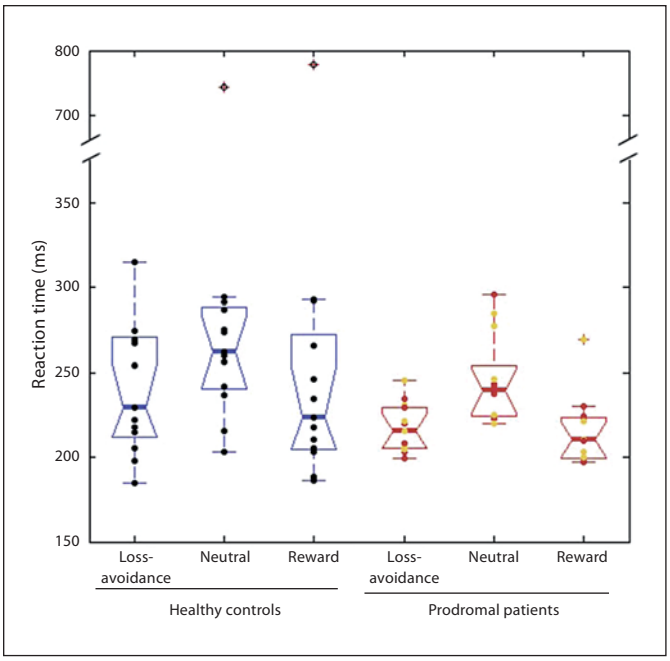


Fig. 1. Reaction times and standard error in response to loss-avoidance, reward, and neutral trials for healthy controls (blue) and prodromal subjects (red). The boxes have lines at the lower quartile, median, and upper quartile values. Whiskers mark the 1.5 times interquartile range, and outliers are data with values beyond the ends of the whiskers. Red circles show unmedicated subjects, and yellow circles denote prodromal patients with antipsychotic medication.

Results

Behavioral Performance

There was a significant effect of cue type (reward, loss-avoidance or neutral) on reaction times ($F = 8.802$, $p = 0.002$) but no significant main effect for group ($F = 1.797$, $p = 0.193$) nor a group × cue interaction ($F = 1.030$, $p = 0.373$). Post-hoc t tests revealed faster responses in reward vs. neutral for healthy control subjects ($T = 3.998$, $p = 0.002$) and prodromal patients ($T = 2.338$, $p = 0.038$). In loss-avoidance vs. neutral trials, only healthy subjects displayed significantly faster reaction times ($T = 4.11$, $p = 0.002$), while prodromal subjects did not differentiate between loss-avoidance and neutral ($T = 1.188$, $p = 0.258$).

There was one outlier in the healthy control group with reaction times around 750 ms (see fig. 1). Excluding this subject did not change the results of the behavioral analysis (main effect cue: $F = 17.29$, $p < 0.001$, main effect group: $F = 3.23$, $p = 0.086$; group × cue interaction: $F = 0.26$, $p = 0.77$).

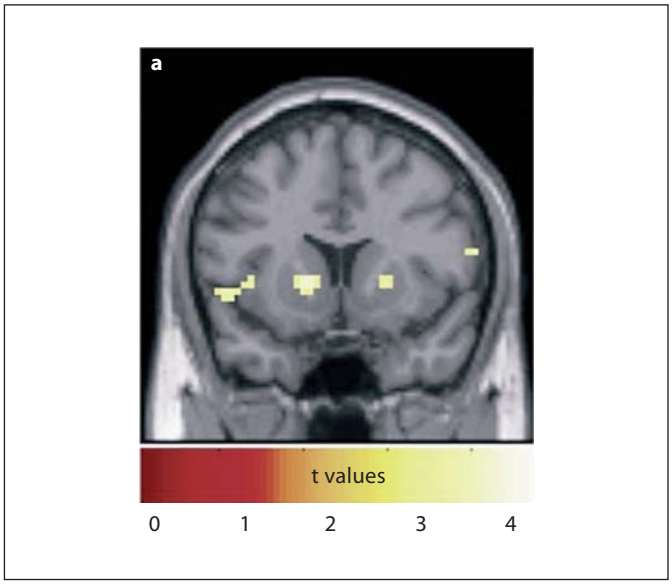
Regional fMRI Response during Anticipation Phase

Reward vs. Neutral Anticipation

During the anticipation phase, both groups displayed significant activation of the VS (healthy controls: right: x/y/z = 15/12/19, $T = 3.44$, $p_{FWE\text{-corrected for VS VOI}} = 0.001$; left: x/y/z = –15/9/–9, $T = 2.3$, $p_{FWE\text{-corrected for VS VOI}} = 0.015$, and prodromal patients: right: x/y/z = 12/9/–9, $T = 2.38$, $p_{FWE\text{-corrected for VS VOI}} = 0.04$). There were no significant group differences during reward anticipation within the VS using small volume correction. Furthermore, no group differences were observed outside the VS at an uncorrected threshold of $p < 0.001$.

Loss-Avoidance vs. Neutral Anticipation

Healthy controls displayed significant ventral striatal activation (right: x/y/z = 15/12/–3, $T = 3.11$, $p_{FWE\text{-corrected for VS VOI}} = 0.01$; left: x/y/z = –15/12/–3, $T = 3.69$, $p_{FWE\text{-corrected for VS VOI}} = 0.003$, fig. 2), while prodromal subjects did not display significant ventral striatal activation. There was a trend towards stronger ventral striatal acti-



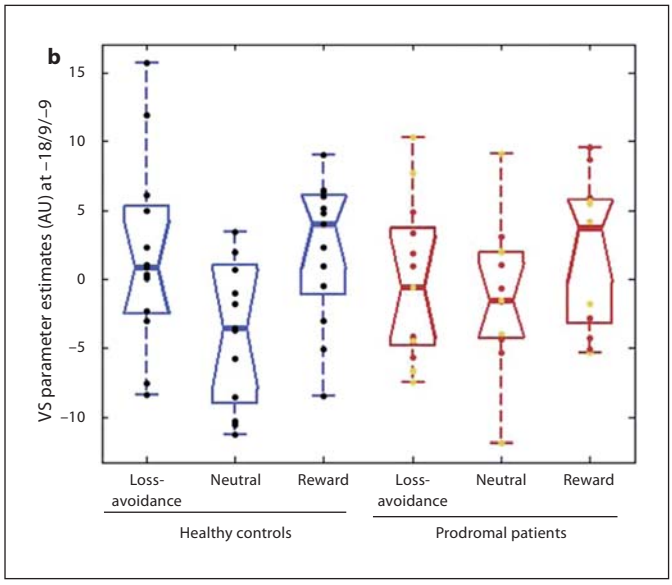
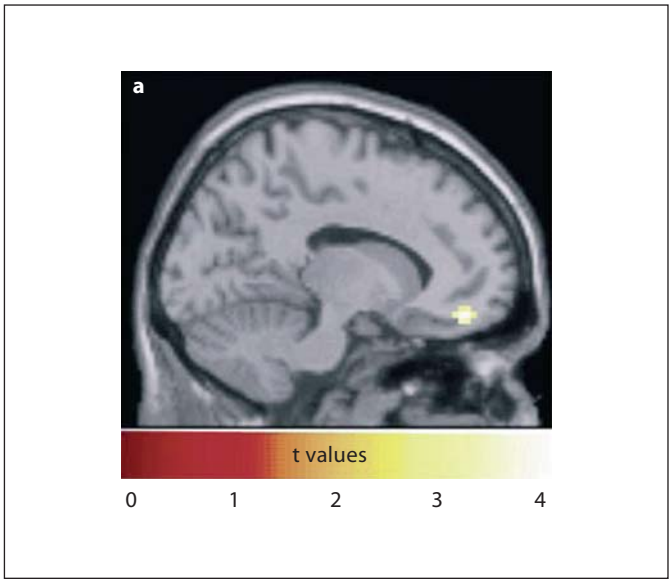


Fig. 2. a Bilateral VS activation in healthy controls during loss-anticipation, FWE corrected for SVC (right: x/y/z = 15/12/–3, T = 3.11, $p_{FWE\text{-corrected for VS VOI}} = 0.01$, left: x/y/z = –15/12/–3, T = 3.69, $p_{FWE\text{-corrected for VS VOI}} = 0.003$). **b** Parameter estimates for trend-wise group difference in healthy controls vs. prodromal subjects (x/y/z = –18/9/–9, T = 1.84; $p_{FWE\text{-corrected for VS VOI}} = 0.098$). The boxes have lines at the lower quartile, median, and upper quartile values. Whiskers mark the 1.5 times interquartile range, and outliers are data with values beyond the ends of the whiskers. Red circles show unmedicated subjects, and yellow circles denote prodromal patients with antipsychotic medication.



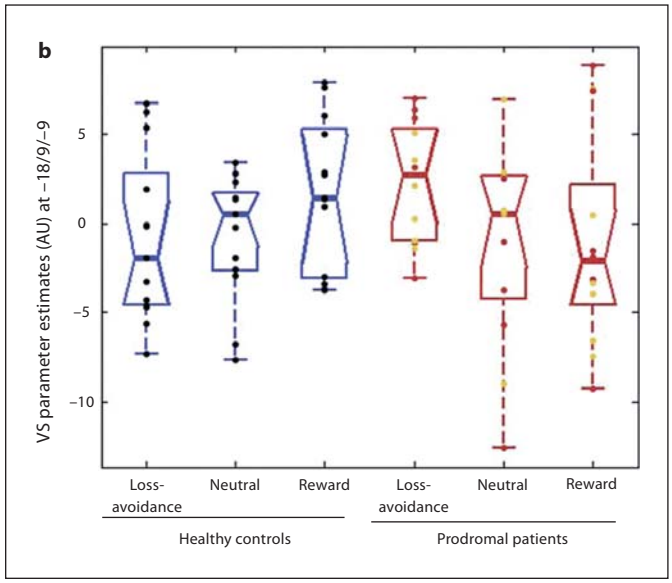


Fig. 3. a Prodromal subjects show stronger ventral medial PFC activation during loss-avoidance compared to healthy controls (x/y/z = –12/48/–15, p = 0.001 uncorrected, T = 4.02, displayed at $p < 0.005$ uncorrected). **b** Parameter estimates for the same voxel (x/y/z = –12/48/–15) for prodromal subjects and healthy controls during loss-avoidance. The boxes have lines at the lower quartile, median, and upper quartile values. Whiskers mark the 1.5 times interquartile range, and outliers are data with values beyond the ends of the whiskers. Red circles show unmedicated subjects, and yellow circles denote prodromal patients with antipsychotic medication.

Table 1. Regional activation outside the ventral striatum in healthy controls and prodromal patients

	BA	T value	X	Y	Z	Cluster
Gain – neutral anticipation						
Healthy controls > prodromal subjects						
No significance at p < 0.001 uncorrected						
Healthy controls < prodromal subjects						
No significance at p < 0.001 uncorrected						
Healthy controls						
Culmen		6.869	–6	–57	–6	29
Middle occipital gyrus	19	6.152	–51	–72	6	18
Middle occipital gyrus	18	6.015	27	–93	0	63
Inferior frontal gyrus	44	5.731	63	6	18	6
Thalamus		5.399	–15	–6	12	88
Insula	13	5.257	–36	12	9	
Insula	13	5.211	–45	–33	21	15
Middle temporal gyrus	21	5.055	63	–60	–3	11
Middle occipital gyrus	18	5.042	–27	–99	6	35
Middle occipital gyrus	19	4.779	–30	–90	9	
Lingual gyrus	18	5.025	6	–69	0	16
Midbrain		4.908	–3	–21	–15	32
Inferior temporal gyrus	37	4.801	–51	–69	–6	11
Parahippocampal gyrus/amygdala	28	4.587	15	–6	–15	39
Inferior frontal gyrus	46	4.517	54	30	18	4
Parahippocampal gyrus	28	4.481	–15	–9	–15	15
Prodromal subjects						
Cuneus	17	4.673	9	–81	3	22
Loss-avoidance – neutral anticipation						
Healthy controls > prodromal subjects						
No significance at p < 0.001 uncorrected						
Healthy controls < prodromal subjects						
Ventral medial prefrontal cortex	11	4.02	–12	48	–15	2
Healthy controls						
Cuneus	18	7.291	–12	–87	12	344
Parahippocampal gyrus/amygdala		6.308	18	–6	–12	76
Middle and inferior temporal gyrus	37	4.971	–48	–69	–6	29
Thalamus		4.538	–9	–3	6	22
Prodromal subjects						
Inferior frontal gyrus	11	5.015	21	33	–18	5
Superior frontal gyrus	11	4.556	–12	48	–15	2

All results are reported at p < 0.001 uncorrected.

vation in healthy controls compared to prodromal subjects (x/y/z = –18/9/–9, T = 1.84 $p_{FWE\text{-corrected for VS VOI}}$ = 0.098). Outside the VS, prodromal subjects displayed a significant activation of the superior frontal gyrus (BA 11; x/y/z = –12/48/–15, T = 4.56, $p_{uncorrected} < 0.001$, for whole brain activation, see table 1), which resulted in a significant group difference (prodromal subjects > healthy controls: x/y/z = –12/48/–15, T = 4.02, $p_{uncorrected} < 0.001$, fig. 3).

Discussion

Referring to our previous study with untreated first-episode schizophrenics [4], there was no difference during reward anticipation in ventral striatal activation between prodromal patients and healthy controls. During loss-avoidance anticipation, prodromal patients displayed only a trendwise reduced activation in the VS. Therefore, the deficit in the mesolimbic reward system

seems to be significantly less pronounced compared to patients with fully manifested schizophrenia. This absence of a significant group difference could be confounded by the possible influence of medication with second generation antipsychotics (SGAs) in the prodromal group. In previous studies, schizophrenia patients medicated with SGAs displayed no difference in ventral striatal activation during reward or loss-avoidance anticipation [5, 18, 19]. Furthermore, these studies have revealed that reward and loss-avoidance ('punishment') showed similar ventral striatal activation using fMRI. Thus, both contrasts appear to represent at least partially overlapping measures for motivational processes within the mesolimbic dopaminergic system.

Exploratory analysis outside the VS revealed that the ventral medial prefrontal cortex (BA 11), which is known to be involved in the processing of mood and affects [20], showed higher activation in the prodromal group during loss-avoidance anticipation. This could be due to an altered processing of cues that indicate potential negative rather than positive behavioral consequences, which could reflect the depressive states that are strongly and often present in patients on the road to schizophrenia.

Nevertheless, this pilot study exhibits several severe limitations. First of all, only a small sample was studied, which may have prevented us from detecting group differences due to power issues; secondly, there was a possible influence of medication since the administration of atypical neuroleptics had just started in 6 of the 13 subjects with ultra-high risk for psychosis. Furthermore, there are no longitudinal data yet available to show which of the participants developed schizophrenia. Finally, there was no significant group difference with regard to the VS even after a small volume correction, which indicates that prodromal patients still exhibit a near-normal mesolimbic reward function.

Taken together, this study showed that subjects suspected to be in a schizophrenic prodrome tended to respond with decreased ventral striatal activation during loss-indicating stimuli similar to that found in patients with fully developed schizophrenia. Due to the strong limitations of this pilot study, the results found here have to be treated with caution. In case of replication in a larger sample, a disturbance of the mesolimbic dopaminergic reward system could serve to identify such individuals as early as possible in order to treat them preventively.

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Disclosure Statement

None.

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