Reward-dependent modulation of working memory is associated with negative symptoms in schizophrenia

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Abstract

The negative symptoms of schizophrenia have been associated with altered neural activity during both reward processing and cognitive processing. Even though increasing evidence suggests a strong interaction between these two domains, it has not been studied in relation to negative symptoms. To elucidate neural mechanisms of the reward-cognition interaction, we applied a letter variant of the n-back working memory task and varied the financial incentives for performance. In the interaction contrast, we found a significantly activated cluster in the rostral anterior cingulate cortex (ACC), the middle frontal gyrus, and the bilateral superior frontal gyrus. The interaction did not differ significantly between the patient group and a healthy control group, suggesting that patients with schizophrenia are on average able to integrate reward information and utilize this information to maximize cognitive performance. However within the patient group, we found a significant inverse correlation of ACC activity with the factor diminished expression. This finding is consistent with the model that a lack of available cognitive [...]
Reward-dependent modulation of working memory is associated with negative symptoms in schizophrenia

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A B S T R A C T
The negative symptoms of schizophrenia have been associated with altered neural activity during both reward processing and cognitive processing. Even though increasing evidence suggests a strong interaction between these two domains, it has not been studied in relation to negative symptoms. To elucidate neural mechanisms of the reward–cognition interaction, we applied a letter variant of the n-back working memory task and varied the financial incentives for performance. In the interaction contrast, we found a significantly activated cluster in the rostral anterior cingulate cortex (ACC), the middle frontal gyrus, and the bilateral superior frontal gyrus. The interaction did not differ significantly between the patient group and a healthy control group, suggesting that patients with schizophrenia are on average able to integrate reward information and utilize this information to maximize cognitive performance. However within the patient group, we found a significant inverse correlation of ACC activity with the factor diminished expression. This finding is consistent with the model that a lack of available cognitive resources leads to diminished expression. We therefore argue that patients with diminished expression have difficulties in recruiting additional cognitive resources (as implemented in the ACC) in response to an anticipated reward. Due to this lack of cognitive resources, less processing capacity is available for effective expression, resulting in diminished expressive behavior.

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1. Introduction

Negative symptoms – comprising the domains of blunted affect, alogia, asociality, anhedonia, and avolition – are an integral component of schizophrenia. They are a strong predictor of poor prognosis and contribute to functional impairment (Azorin et al., 2014; Kirkpatrick et al., 2006; Milev et al., 2005; Rabinowitz et al., 2012). A recent consensus suggests that negative symptoms can be grouped into two factors. One factor is referred to as diminished expression, comprising blunted affect and alogia. The other factor is referred to as diminished motivation and pleasure, or apathy, and comprises asociality, anhedonia and avolition (Kring and Barch, 2014; Strauss et al., 2012). This distinction might allow a more differentiated approach in the search of underlying pathophysiological mechanisms (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Liemburg et al., 2013; Messinger et al., 2011).

Negative symptoms have been consistently associated with dysfunctional reward processing, in particular with diminished reward anticipation. On a neural level, this has been linked to a reduction in ventral striatal activity (Juckel et al., 2006; Nielsen et al., 2012; Schlagenhauf et al., 2008; Simon et al., 2010; Waltz et al., 2008). Negative symptoms have also been linked to neurocognitive deficits, although this association is rather modest (Lin et al., 2013; Milev et al., 2005; Ventura et al., 2009, 2013). The cognitive deficits, and to a lesser extent negative symptoms, have been associated with abnormal activity in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (dLPPC; Barch and Ceaser, 2012; Manoach, 2003).

Recent work suggests that there is a strong interaction of reward anticipation with cognitive performance. Knowing that a certain cognitive effort might result in the receipt of a reward leads to the prioritization of the respective process and influences the assignment of limited cognitive resources (Beck et al., 2010; Braver et al., 2014; Kennerley and Wallis, 2009; Krawczyk et al., 2007; Locke and Braver, 2008; Rowe et al., 2008). On the neural level, the anterior cingulate cortex (ACC) has been suggested to play an essential role in this interaction and to act as a hub linking reward and cognition (Krebs et al., 2012; Pessoa, 2006).
2008, 2009; Vassena et al., 2014). It is presumed that the ACC receives reward information from the ventral striatum (VS), thereby enhancing cognitive performance (Holroyd and Yeung, 2012; Pessoa, 2009; van Steenbergen et al., 2014). It remains unknown how negative symptoms in schizophrenia relate to the reward–cognition interaction at the neural level.

In the current study, we measured cognitive performance with a letter variant of the n-back working memory (WM) task and varied the financial incentives for the performance. We hypothesized that patients with schizophrenia would show impairments in the modulation of cognitive performance by reward and that these impairments are correlated with the severity of negative symptoms. On a neural level, we expected that the prospect of a future reward leads to the activation of the ACC as well as to a stronger activation in WM related regions in the lateral PFC. We expected that these effects are diminished in the patient group and show an inverse correlation with the severity of negative symptoms.

2. Methods

2.1. Participants

We studied 29 individuals meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) criteria for schizophrenia (n = 23) or schizoaffective disorder (n = 6) and 27 healthy control subjects with no personal history of a DSM-IV axis 1 disorder. All participants provided written informed consent to participate in the study, which was approved by the local Ethics committee. Patients were recruited either as inpatients (n = 16) or outpatient (n = 13) from the Psychiatric Hospital, University of Zurich, or from affiliated institutions. All inpatients were at the end of their hospitalization and they participated in a multimodal treatment program that encouraged them to engage in daily activities outside the hospital. All patients were clinically stable and received constant doses of medication for at least two weeks prior to testing, with the exception of one patient receiving a small increase of clozapine dose seven days before testing. Exclusion criteria included a daily lorazepam dosage greater than 1 mg, florid positive symptoms, i.e. any positive subscale item score of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) > 4, extrapyramidal side effects, measured with the Modified Simpson-Angus Scale (MSAS; Simpson et al., 1970), > 3, or any other DSM-IV axis 1 diagnosis. For confirmation, all participants were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1997).

2.2. Clinical and neuropsychological assessment

All patients were further assessed using the Brief Negative Symptom Scale (BNSS; Strauss et al., 2012), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen NC, 1982), the PANSS, the Global Assessment of Functioning scale (GAF; Frances et al., 1994), the Personal and Social Performance Scale (PSP; Schaub and Juckel, 2011) and the Calgary Depression Scale for Schizophrenia (CDS; Addington et al., 1993). We used the BNSS as our main measurement for negative symptoms since it was designed to facilitate a clear distinction of the factors apathy and diminished expression. For the total BNSS score, the assessment of the inter-rater reliability showed an intra-class correlation coefficient (ICC) of 0.97. The subscales reached ICCs from 0.87 to 0.97.

To characterize the sample and to disentangle the effects of neuropsychological functioning, the following cognitive domains were tested: verbal learning (Auditory Verbal Learning Memory Test, VLMT; Helmslaeder and Durwen, 1990), verbal and visual short-term working memory (Digit Span, DS; Stelzig, 2000) and Corsi block-tapping test (CBT; Kessels et al., 2000), processing speed (Digit–Symbol Coding, DSC; Von Aster et al., 2006), planning (Tower of London, ToL; Shallice, 1982), and semantic and phonetic fluency (animal naming, AN; s-words, SW; Delis et al., 2001).

2.3. Functional magnetic resonance imaging

2.3.1. Imaging acquisition

Two runs containing 185 whole brain T2* weighted echo-planar images (EPI) were acquired in ascending order using a Philips Achieva 3.0 T magnetic resonance scanner with a 32 channel SENSE head coil (Philips, Best, The Netherlands). Further specifications were: 3 × 3 × 3 × mm³ in-plane resolution, 0.5 mm gap width, 240 × 240 mm field of view, 2000 ms TR, 25 ms TE, flip angle 82°. Slices were aligned with the anterior–posterior commissure. The first five scans were discarded to eliminate the influence of T1 saturation effects. A T1-weighted high-resolution anatomical scan was obtained for registration: 160 sagittal plane slices, 1 × 1 × 1 mm³.

2.3.2. Task and stimuli

A modified version of a previously employed letter n-back task was used (Owen et al., 2005; Pochon et al., 2002). The task was presented as a two by two factorial design with the factors cognitive load (0-back vs. 2-back) and reward (reward vs. no reward), resulting in a total of four different conditions: 0-back/reward (0R), 0-back/no reward (0N), 2-back/reward (2R), 2-back/no reward (2N). Each condition was presented four times, resulting in a total of 16 blocks. The 16 blocks were split into 2 runs. The order of presentation was equal for all subjects and as follows: 0R, 2R, 0N, 2N, 0N, 2R, OR, OR, 0R, 2R, 2N, 2R, 0N, 0R (see Fig. 1).

2.3.3. Behavioral analyses

The sensitivity index d’ (Haatveit et al., 2010; Green and Swets, 1988) and reaction times were used to analyze the behavioral performance. D’ is calculated as the standardized probability of a hit minus the standardized probability of a false alarm: d’ = z(probability[hits]) – z(probability[false alarms]). To test for differences in behavioral performance, d’ and reaction times were entered into separate mixed-design ANOVAs with group (patient group, healthy control group) as between-subjects factor and cognition (0-back, 2-back) and reward (no reward, reward) as within-subject factors. To relate behavioral performance to psychopathological ratings of negative symptoms, we calculated Pearson’s r. All analyses were performed using IBM SPSS Statistics Version 21.

2.3.4. fMRI analyses

Functional MRI data were analyzed using SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). Differences in EPI slice acquisition timing were corrected using the central slice as reference. To reduce artifacts from head movements, functional images were realigned using a least squares approach and a six-parameter rigid body spatial transformation, using the first image as a reference. A voxel displacement map, calculated from double phase and magnitude field map data, was applied for a combined static and dynamic distortion correction. After co-registration, the “New Segment” toolbox was used for spatial normalization. Finally, images were smoothed using a Gaussian kernel of 6 mm width.

For our block design, we used a general linear model (GLM) with a two-stage approach. On the first stage of analysis, two levels of cognitive load (0-back/2-back) and two levels of reward (reward/no reward) were modeled. To study the cognition/reward interaction effect, i.e., the effect of reward-dependent modulation of working memory, the following contrast images were constructed: ((2-back/reward)–(0-back/reward))–((2-back/no reward)–(0-back/no reward)). These images were taken to the second stage of analysis for random-effects inference.

Due to our a priori hypothesis, we restricted our search volume to the PFC and ACC (Barch and Dowd, 2010; Cai and Padoa-Schioppa,
In the n-back task, the main effect of group on sensitivity was not significant, \( F(1,54) = .955, p = .333 \). Pooling over all subjects, we found a main effect of the factor cognition, \( F(1,54) = 43.789, p < .001 \), indicating that participants were significantly faster in the 0-back condition (\( x = 468.03, SD = 65.04 \)) relative to the 2-back condition (\( x = 546.64, SD = 110.63 \)). We also found a main effect of the factor reward, \( F(1,54) = 8.656, p = .005 \), showing that participants sped up in the rewarded trials (\( x = 499.09, SD = 81.38 \)) relative to the non-rewarded trials (\( x = 515.58, SD = 82.47 \)). The reward–cognition interaction, \( F(1,54) = .007, p = .935 \), as well as all other interactions were not significant. Furthermore, we found a significant positive correlation of BNSS apathy with the mean reaction time of the 2-back condition minus the 0-back condition (\( r = .38, p = .042 \)) and with the reward–cognition interaction term (\( r = .38, p = .041 \)). All other correlations between reaction time and negative symptom scores were non-significant.

3.3. Imaging data

In the whole group reward–cognition interaction contrast, we found significant activation within our volume of interest in the right superior frontal gyrus (rSFG: \( x = 17, y = 21, z = 58 \); \( k = 910, t = 6.13, \text{FWE}_p < .001 \)), the left superior frontal gyrus (lSFG: \( x = -18, y = 33, z = 42 \); \( k = 567, t = 5.33, \text{FWE}_p < .001 \)), the right rostral cingulate cortex (rACC: \( x = 9, y = 44, z = 1 \); \( k = 1018, t = 5.32 \text{FWE}_p < .001 \)), and the medial superior frontal gyrus (mSFG: \( x = 8, y = 68, z = 18 \); \( k = 267, t = 5.15, \text{FWE}_p < .001 \)), when working memory performance was rewarded compared to when it was not rewarded (see Fig. 2A). These regions could therefore be involved in integrating reward and cognition.

Next we looked at the groups separately and tested for activation differences. Within the healthy control group, we found a cluster in the right rostral anterior cingulate cortex (rACC: \( x = 9, y = 44, z = 1 \); \( k = 88; t = 5.91, \text{FWE}_p = .047 \)) that showed significantly more...
and categorical variables, 2-sample t tests and chi-square were applied to test for potential differences. Data are presented as means and standard deviations. For normally distributed continuous variables, Levene tests were applied.

*p values lower than .05 are in bold.

Schizophrenia: CBS, Corsi block span; DS, Digit span.

Duration of illness in months

<table>
<thead>
<tr>
<th></th>
<th>Patient group (n = 29)</th>
<th>Hc group (n = 27)</th>
<th>Test statistic (t/z²/u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>20/9</td>
<td>17/10</td>
<td>² = .225 .64</td>
</tr>
<tr>
<td>Formal education in years</td>
<td>12.03 (3.08)</td>
<td>12.35 (3.45)</td>
<td>U = 377.5 .82</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>5.07 (4.36)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalents (mg/day)</td>
<td>536.76 (409.96)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>
| Psychopathology
  BNSS apathya | 14.41 (7.22)           | –                 |                         |
  BNSS diminished expressiona | 9.45 (8.06)           | –                 |                         |
  SANS apathyb | 12.14 (5.13)           | –                 |                         |
  SANS diminished expressionb | 11.90 (10.78)         | –                 |                         |
  PANSS positive factorc | 6.52 (2.63)           | –                 |                         |
  PANSS negative factorc | 13.74 (5.38)           | –                 |                         |
  GAF | 57.41 (9.59)           | –                 |                         |
  PSP (total) | 56.97 (9.81)           | –                 |                         |
  CDSS (total) | 1.52 (2.18)            | –                 |                         |
| Cognition
  Composite cognitive abilityd | –45 (.78) | 0 (.49) | t = 2.583 .013          |
  CBS forward | 8.17 (1.81)           | 8.56 (2.04)       | t = .743 .46           |
  CBS backward | 7.66 (1.84)           | 7.96 (1.66)       | t = .653 .52           |
  DS forward | 7.31 (2.04)           | 7.59 (1.72)       | t = .559 .58           |
  DS backward | 6.55 (1.80)           | 6.22 (1.34)       | U = 359.5 .59          |

Data are presented as means and standard deviations. For normally distributed continuous variables, 2-sample t tests were applied to test for potential differences. If data were not normally distributed, Mann–Whitney U tests were applied.

All patients except one were receiving stable doses of atypical antipsychotic medication at the time of testing. Nine individuals were additionally receiving antidepressants, two were receiving mood-stabilizers, two patients were medicated against insomnia and one person was receiving a low dose of benzodiazepine.

BNSS, Brief Negative Symptom Scale; SANS, Scale for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; GAF, General Assessment of Functioning; PSP, Personal and Social Performance Scale; CDSS, Calgary Depression Scale for Schizophrenia; CBS, Corsi block span; DS, Digit span.

*p values lower than .05 are in bold.

Apathy = anhedonia, asociality, avolition; diminished expression = lack of normal distress, blunted affect, alogia.

b Apathy = avolition/apathy, anhedonia/asociality; diminished expression = affective flattening or blunting, alogia.

c Positive factor = P1, P3, P5, G9; negative factor = N1, N2, N3, N4, N6, G7.

d Cognition data have been standardized based on the HC group.

Activation in the interaction contrast (see Fig. 2B). This cluster was further used for our correlation analyses. The according parameter estimates are shown in supplementary Fig. 1. The patient group showed significant activation in the right superior frontal gyrus (rSFG: x = 23, y = 15, z = 55; k = 661; t = 7.21, FWEp = .002) within this interaction contrast (see Fig. 2C). However, we did not find any significant differences between the two groups, in line with the absence of a behavioral difference. In addition to the analysis in our a priori defined volume of interest, we also performed whole brain analyses using the same statistical thresholds (see Supplementary Table 1), which did not reveal any additional clusters.

3.4. Correlation analyses

Within the patient group, ACC activation in the reward–cognition interaction contrast correlated negatively with BNSS diminished expression (r(29) = −.393, p = .035). The correlation with SANS diminished expression reached trend-level significance (r(29) = −.365, p = .052). In contrast, the correlation between percent signal change in the ACC and BNSS apathy as well as SANS apathy did not reach significance (r(29) = −.015, p = .937, and r = −.001, p = .998, respectively; see Fig. 3). To test for a difference between these two dependent correlations, we performed a Steiger’s Z-test, which revealed that the correlation between BNSS diminished expression and percent signal change was significantly different from the correlation between BNSS apathy and percent signal change (Z = −2.04, p = .041). To confirm that other potentially confounding variables, i.e., depressive symptoms, chlorpromazine equivalents, and age, did not account for the correlation between BNSS diminished expression and activity in the ACC, we computed a partial correlation with the factors above included. The association between diminished expression and ACC activation remained significant (r(24) = −.402, p = .042).

Furthermore, we also found a significant correlation of ACC activation and BNSS diminished expression (r(29) = −.434, p = .019) when we defined the clusters based on the whole group (i.e. combined patients and controls) analysis, which underlines the robustness of this finding (see Supplementary Table 2). No other cluster from the whole group analysis showed a significant correlation with negative symptom dimensions.

We additionally performed an exploratory whole-brain ANCOVA with the standardized BNSS measures (diminished expression and apathy) as covariates in a whole brain analysis, but this analysis did not reveal any significant clusters.
4. Discussion

To our knowledge, this is the first study to investigate the neural effects of reward modulation on working memory in patients with schizophrenia and healthy controls. On the neural level, we found evidence that reward modulation influences working memory in both groups. In the patient group, we found a negative correlation of activity in the ACC with the negative symptom factor diminished expression, but not with the factor apathy.

Across all subjects, our behavioral data suggest that participants processed both cognitive and reward factors of the task. We further found that apathy was significantly correlated with the reaction time in the 2-back relative to the 0-back condition and in the in the reward–cognition interaction, indicating that cognitive load and the integration of complex information increases reaction time in apathetic patients. On the neural level, the reward–cognition interaction led, among others, to significant activation of the rostral ACC. This region has been suggested to play an important role in controlling current demands, which are influenced by the presence of a potential reward or punishment (Holroyd and Yeung, 2012; Pessoa, 2008, 2009; Pessoa and Engelmann, 2010; van Steenbergen et al., 2014). It is further assumed that the signal from the ACC is used to guide behavior via dense interconnections with cortical areas, such as the (pre-) motor cortex and the DLPFC (Haber and Knutson, 2009). In line with this hypothesis, we also observe three PFC clusters in the reward–cognition interaction contrast, which are part of the working memory network. Due to the reward at stake, the cognitive process leading to the harvest of the reward is prioritized, and cognitive resource capacities are allocated in order to maximize performance. Since we did not find any significant group differences, we believe that this process is generally functioning in patients with schizophrenia, at least at the relatively basic levels tested here.

However, within the patient group, we found a significant inverse correlation of the negative symptom factor diminished expression with activity in the rostral ACC related to the reward–cognition interaction. This correlation was specific for the factor diminished expression, because it was significantly different from the correlation with the factor apathy. The correlation remained significant after controlling for confounding variables. Since the ACC has been proposed to play a crucial role in controlling resource distribution and behavioral adaptation, we hypothesize that patients with more severe negative symptoms, in particular diminished expression, have difficulties in regulating their limited available processing resources to meet the current demand (Holroyd and Yeung, 2012; Pessoa, 2009; van Steenbergen et al., 2014).

This idea is in line with the cognitive resource limitation model (Cohen et al., 2012, 2013, 2014a, 2014b). Cohen proposes that effective expression requires a range of mental resources. If these limited resources are engrossed in another task or process, they are not available for expressive behavior. Considering that patients with schizophrenia have lower cognitive abilities compared to healthy controls, the effects are magnified, since fewer resources are available in the first place. Our data suggest that patients with more pronounced diminished expression do not only have less cognitive resources available as proposed by Cohen et al. (2012, 2013, 2014a, 2014b), but that they have a specific problem in adjusting resources according to their priority. In other words, potential reward fails to recruit additional cognitive resources, which in turn leads to diminished expressive behavior.

There are several limitations to our study. Since this was the first study to investigate the neural correlates of reward–cognition interaction, the hypotheses were relatively broad. Thus, the study has to be considered exploratory and requires replication. Furthermore, although the antipsychotic medication did not have any statistical effects, further studies should elucidate whether these results can be generalized to unmedicated patients.

In conclusion, we found a specific inverse correlation of rostral ACC activation with the factor diminished expression. To our knowledge, this is the first study showing a specific correlation of neural activity with this factor, supporting the notion of separable neural bases for the two negative symptom dimensions. These findings highlight the need to further investigate the complex interaction of reward processing and cognition, with a particular focus on the adaptation of cognitive resources in schizophrenia and the relation to diminished expression.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Patient group (n = 29)</th>
<th>Hc group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-back reward</td>
<td>6.95 (.59)</td>
<td>7.13 (.80)</td>
</tr>
<tr>
<td>0-back no reward</td>
<td>7.15 (.48)</td>
<td>6.99 (.92)</td>
</tr>
<tr>
<td>2-back reward</td>
<td>6.48 (1.16)</td>
<td>6.90 (.68)</td>
</tr>
<tr>
<td>2-back no reward</td>
<td>6.54 (1.34)</td>
<td>6.70 (.98)</td>
</tr>
<tr>
<td><strong>Reaction time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-back reward</td>
<td>472.26 (72.88)</td>
<td>445.82 (52.49)</td>
</tr>
<tr>
<td>0-back no reward</td>
<td>495.57 (74.15)</td>
<td>456.14 (59.62)</td>
</tr>
<tr>
<td>2-back reward</td>
<td>564.43 (126.85)</td>
<td>511.02 (106.30)</td>
</tr>
<tr>
<td>2-back no reward</td>
<td>582.33 (109.68)</td>
<td>524.83 (114.86)</td>
</tr>
</tbody>
</table>

Data are presented as means and standard deviations. Accuracy is measured as the standardized probability of a hit minus the standardized probability of a false alarm. Reaction time is measured in ms.
Role of funding source
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Contributors
S. Kaiser, O. Hager, and P. Tohler designed the study. O. Hager, M. Kirschnier, M. Bischof, A. Kluge, and M.N. Hartmann conducted the study. O. Hager conducted the analyses and wrote the first draft of the manuscript. O. Hager, S. Kaiser, P. Tohler, and E. Seflisch revised the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
Stefan Kaiser has received speaker honoraria from Roche, Takeda, Janssen and Lundbeck. He receives royalties for cognitive test and training software from Schuhfried. Erich Seifritz has received grant support from H. Lundbeck and has served as a consultant for Lundbeck. He receives royalties for cognitive test and training software from Schuhfried.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.08.024.

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