Can quantitative EEG measures predict clinical outcome in subjects at Clinical High Risk for psychosis? A prospective multicenter study

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Abstract

Background: Prediction studies in subjects at Clinical High Risk (CHR) for psychosis are hampered by a high proportion of uncertain outcomes. We therefore investigated whether quantitative EEG (QEEG) parameters can contribute to an improved identification of CHR subjects with a later conversion to psychosis.

Methods: This investigation was a project within the European Prediction of Psychosis Study (EPOS), a prospective multicenter, naturalistic field study with an 18-month follow-up period. QEEG spectral power and alpha peak frequencies (APF) were determined in 113 CHR subjects. The primary outcome measure was conversion to psychosis.

Results: Cox regression yielded a model including frontal theta (HR = 1.82; [95% CI 1.00–3.32]) and delta (HR = 2.60; [95% CI 1.30–5.20]) power, and occipital–parietal APF (HR = .52; [95% CI .35–.81]) as predictors of conversion to psychosis. The resulting equation enabled the development of a prognostic index with three risk classes (hazard rate 0.057 to 0.81).

Conclusions: Power in theta and delta ranges and APF contribute to the short-term prediction of psychosis and enable a further stratification of risk in CHR samples. Combined with (other) clinical ratings, EEG parameters may therefore be a useful tool for individualized risk estimation and, consequently, targeted prevention.

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1. Introduction

Useful clinical criteria have been developed for identification of subjects at Clinical High Risk (CHR) for a first psychotic episode (Yung et al., 2005; Schultze-Lutter, 2009; McGlashan et al., 2010; Ruhrmann et al., 2012). However, conversion rates vary across studies applying these criteria (Simon et al., 2011; Fusar-Poli et al., 2012a). Therefore, additional parameters have been investigated, including neuroimaging (Fusar-Poli et al., 2012b), neuropsychological (Becker et al., 2010; Fusar-Poli et al., 2012c; Pukrop and Ruhrmann, 2012), and neurophysiological measures (Shin et al., 2011). Particularly, event related potentials have been identified as potential biological predictors of psychosis, e.g. N100 (Brockhaus-Dumke et al., 2008), P300 (e.g. Bramon et al., 2008; Frommann et al., 2008; van Tricht et al., 2010) and mismatch negativity (Bodatsch et al., 2011; Higuchi et al., 2013).

Although the electroencephalogram (EEG) is a valuable method to investigate associations between functional brain abnormalities and cognitive deficits or psychopathology (Clementz et al., 1994; Alfinano and Uvarova, 2003; Uhlhaas et al., 2008; Leiser et al., 2011), to our knowledge, only two studies investigated background EEG measures as predictors of future psychosis (Gschwandtner et al., 2009; Zimmermann et al., 2010). In schizophrenia patients, resting-state EEG spectral abnormalities have been frequently reported (for a review: Boutros et al., 2008). Specifically, excess of quantitative EEG (QEEG) slow wave (delta and theta) was often observed (Boutros et al., 2008). A lower alpha power, predominantly on frontal scalp positions, has also been reported (Wuebben and Winterer, 2001). Additionally, decreased alpha peak frequency (APF), i.e. the dominant frequency of the EEG at rest with the largest power estimate, has been observed (Clementz et al., 1994). As the
most heritable feature (81%) of the EEG (van Beijsterveldt and van Baal, 2002; Smit et al., 2005), the APF is an ideal candidate endophenotype with prognostic utility.

The aim of our study was to investigate whether QEEG measures are helpful in predicting conversion to psychosis in a relatively large CHR sample established as part of the European Prediction of Psychosis Study (EPOS) (Ruhmann et al., 2010). We hypothesized that CHR subjects with conversion to psychosis (CHR-T) at follow-up will present higher beta, delta and theta and lower alpha power at baseline than CHR subjects without conversion (CHR-NT) and a group of healthy controls. Additionally, we hypothesized that baseline power in alpha, beta, theta and delta bands would predict clinical outcome at follow-up.

2. Methods

2.1. Subjects

2.1.1. Clinical High Risk group

Subjects at CHR for psychosis who agreed to participate in the neurophysiological examination were included in this study between August 2002 and April 2008 at the Academic Medical Center (AMC) Amsterdam, the Netherlands (n = 61), and at the Department of Psychiatry and Psychotherapy of the University of Cologne, Germany (n = 52). CHR inclusion criteria were: age 16 to 35 years; meeting UHR criteria (i.e. attenuated psychotic symptoms and/or brief limited intermittent psychotic symptoms and/or genetic risk plus social decline) or the basic symptom criterion ‘cognitive disturbances’ (Ruhmann et al. 2010). Details on psychopathological inclusion criteria are presented in Supplement 1.

Exclusion criteria were: past or present psychotic episode for more than 1 week, i.e., fulfilling DSM-IV criteria of a brief psychotic episode not only for more than 1 day but for more than 7 days, as assessed with the Structured Clinical Interview for DSM-IV diagnoses (SCID; First et al., 1997); symptoms relevant for inclusion arising from a known general medical disorder or drugs or alcohol dependency and a low estimated verbal IQ (<85).

2.1.2. Control group

Fifty-four participants (Amsterdam: n = 29; Cologne: n = 25) served as a control group. Exclusion criteria were: visual disorders, a known general medical disorder potentially involving the brain, past or present psychiatric illness, familial history of psychiatric illness and estimated verbal IQ below 85. Healthy controls were matched on mean age and educational level to the CHR group.

The study was carried out in accordance with the Declaration of Helsinki and approved by the respective local Ethic Committees. Written informed consent was obtained from all participants and their parents if they were minors, after the nature of the procedures had been fully explained.

2.2. Materials

2.2.1. EEG – data acquisition

At both centers, Ag/AgCl electrodes were applied according to the international 10–20 system, with a ground electrode on the forehead, two electrodes attached at the outer canthi of the left and right eye to record horizontal eye movements and two electrodes above and below the left eye for the registration of vertical eye movements and eye blink artifacts. EEG eyes closed recordings lasted at least 5 min, with electrode resistances of less than 5 kΩ. In Amsterdam, the EEG was recorded with a band-pass filter of 0.04–300 Hz, a sampling rate of 1000 Hz, and a reference electrode on linked mastoids. In Cologne, EEG data were digitized with a sampling rate of 250 Hz, a band-pass filter of 0.1–50 Hz, and the vertex electrode (Cz) as reference electrode. Data were stored in a data base for off line analyses using Brainvision Analyzer 2.0 (BVA; Brainproducts; http://www.brainproducts.com).

2.2.2. Artifact correction

To enhance comparability between centers, the following processing steps were conducted: 1) after low pass filtering at 112.5 Hz to prevent aliasing, data from Amsterdam were down sampled to a sampling rate of 250 Hz; 2) data from Cologne were re-referenced to linked mastoids, and 3) a low-pass filter at 40 Hz and high-pass filter at 1 Hz was applied (48 dB/oct), using phase-shift free Butterworth filters. Vertical and horizontal eye-movements were removed using the Gratton, Coles and Donchin procedure (1982). Furthermore, data were segmented in 8 s epochs, and the EEG was further manually de-artifac ted by an experienced psychophysiol ogy subject’s group status to remove epochs containing excess EMG, residual EOG etc. The minimum allowed number of artifact free trials was set at 12 segments of 8 s to ensure adequate validity of frequency analyses.

2.2.3. Power calculation

Power across frequencies was calculated with Fast Fourier Transformation (FFT) in BVA software with a Hamming window of 20%. Fixed EEG frequency bands were set as follows: delta: 1.5–3.5 Hz; theta: 4–7.5 Hz; lower alpha: 8–10 Hz; upper alpha: 10–12 Hz; and beta: 14.5–30 Hz.

2.2.4. Individual alpha peak frequency (APF)

The dominant frequency, in which neural feedback loops generate oscillations during eyes-closed wakefulness, is estimated at 10 Hz, i.e. in the traditional alpha band. However, large individual differences exist in these peak frequencies (Posthuma et al., 2001). Therefore, several studies suggest abandoning the fixed frequency bands and instead to adjust the frequency windows of alpha and beta by using individual alpha peak (APF) frequency, i.e. the spectral component which shows the largest power estimate, as an anchor point (for a review: Klimesh, 1999). Our calculation of APF was identical to the procedure of Arns et al. (2012), except for using eyes closed data only. In short, the exact frequency was established, at which spectral power was maximum within 6–13 Hz for occipital-parietal (O1, Oz, O2, P3, Pz and P4) and frontal (F3, Fz and F4) scalp positions. Average scores for occipital–parietal and frontal scalp positions were calculated.

2.2.5. Psychopathology

UHR criteria were assessed by the Structured Interview for Prodromal Syndromes, version 3.0 (SIPS; McGlashan et al., 2001). The 4 SIPS subscales (Positive, Negative, Disorganization, and General Symptoms) include 4 to 6 items (in total 19) rated 0–6 on a 7-point severity scale. Cognitive disturbances were assessed by an abbreviated item list of the Schizophrenia Proneness Instrument (Schultze-Lutter et al., 2007) that includes 3 subscales, totaling 33 cognitive, perceptual, and motor disturbances assessed on a 7-point severity scale (score, 0–6), with maximum frequency of occurrence during the preceding 3 months as the guiding criterion.

2.3. Medication

CHR subjects were assigned to one of the following medication categories: I) antipsychotic medication (with or without any other medication); II) other medication, e.g. antidepressants or benzodiazepines, and III) no medication (Table 1). Possible medication effects on EEG were assessed by comparing spectral power between these three groups and between the categories ‘no medication’ and ‘medication’ (category I and II combined).

2.4. Procedure

Subjects were followed-up for 18 months with assessments at months 9 and 18. Subjects, their parents or caretakers and the referring instances were asked to contact us in case of increasing symptoms. Conversion to psychosis was operationalized as presence...
Psychotic Symptoms.

Abbreviations: CHR: Clinical High Risk; CHR + T: CHR subjects with transition to psychosis; CHR + NT: CHR subjects without transition to psychosis; BLIPS: Brief Limited Intermittent Psychotic Symptoms.

Socio-demographic characteristics of Clinical High Risk and control subjects.

<table>
<thead>
<tr>
<th>Age in yrs.: mean (SD)</th>
<th>CHR-T (n = 22)</th>
<th>CHR-NT (n = 91)</th>
<th>Controls (n = 54)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% males)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication prescription; n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychoticsa</td>
<td>64 (3.3)</td>
<td>64 (4.8)</td>
<td>44 (7.6)</td>
<td>F = .62, p = .54</td>
</tr>
<tr>
<td>Otherb</td>
<td>9 (41)</td>
<td>19 (21)</td>
<td>–</td>
<td>χ² = 5.55, p = .06</td>
</tr>
<tr>
<td>None</td>
<td>2 (9)</td>
<td>15 (16)</td>
<td>–</td>
<td>χ² = 35.3, p &lt; .001</td>
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<tr>
<td>Missing</td>
<td>10 (45)</td>
<td>47 (52)</td>
<td>54 (100)</td>
<td></td>
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<tr>
<td>Estimated verbal IQ score; mean (SD)</td>
<td>103.8 (10.3)</td>
<td>1063 (12.2)</td>
<td>106.7 (10.2)</td>
<td>F = .48, p = .62</td>
</tr>
<tr>
<td>Inclusion symptoms; n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenuated symptoms</td>
<td>8 (36)</td>
<td>34 (37)</td>
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<td></td>
</tr>
<tr>
<td>Attenuated and basic symptoms</td>
<td>8 (36)</td>
<td>28 (31)</td>
<td></td>
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<tr>
<td>Basic symptoms</td>
<td>0 (0)</td>
<td>13 (14)</td>
<td></td>
<td></td>
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<tr>
<td>BIPS</td>
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<td>1 (1)</td>
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<td></td>
</tr>
<tr>
<td>BIPS and attenuated symptoms</td>
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<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIPS and basic symptoms</td>
<td>1 (5)</td>
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</tr>
<tr>
<td>BIPS, attenuated and basic symptoms</td>
<td>4 (18)</td>
<td>4 (4)</td>
<td></td>
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<tr>
<td>Genetic risk reduced functioning</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td></td>
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</tr>
<tr>
<td>Genetic risk, reduced functioning and attenuated symptoms</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic risk, reduced functioning, attenuated and basic symptoms</td>
<td>1 (5)</td>
<td>4 (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHR: Clinical High Risk; CHR + T: CHR subjects with transition to psychosis; CHR + NT: CHR subjects without transition to psychosis; BLIPS: Brief Limited Intermittent Psychotic Symptoms.

a risperidone 1 mg (n = 6), 2 mg (n = 8), 3 mg (n = 2) or dosage unknown (n = 4); ziprasidone 60 mg (n = 1); olanzapine 10 mg (n = 2); quetiapine 250 mg (n = 2), 150 mg (n = 1); pimozide 1 mg (n = 1) or 2 mg (n = 1).

b Antidepressants (paroxetine 20 mg (n = 5) or 30 mg (n = 1); venlafaxine extended release 75 mg (n = 1) or 150 mg (n = 1); nortriptyline 250 mg (n = 1); sertraline 150 mg (n = 1)); benzodiazepines (diazepam 5 mg (n = 1) or 3 mg (n = 2); oxazepam 30 mg (n = 1) or 40 mg (n = 2)); methylphenidate 30 mg (n = 1), and/or lithium carbonate 1200 mg (n = 1).

The Amsterdam sample included 26% (n = 16) CHR-T subjects, diagnoses were: schizophrenia (n = 12), schizoaffective disorder (n = 2), schizoaffective disorder (n = 1) and brief psychotic disorder (n = 1). The Cologne sample included 26% (n = 48) CHR-T subjects, diagnoses were: schizophrenia (n = 5) and schizoaffective disorder (n = 1).

Data were analyzed with the statistical package for social sciences (SPSS 18.0). If not described otherwise, p ≤ .05 was considered significant.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the three groups (i.e. CHR-T, CHR-NT and controls) are presented in Table 1. Distribution of gender or inclusion criteria, years of education and estimated verbal IQ scores did not differ between groups or centers. Mean age was higher in Cologne (mean = 25.16, SD = 4.4; Amsterdam mean = 19.74, SD = 3.6, t = 8.33, df = 165, p < .001). Medication prescription did not differ between CHR-T and CHR-NT (χ² = 3.42, df = 2, p = .18). Additionally, except for a median difference in posterior APF (p = .050), Kruskal–Wallis test yielded no differences in EEG parameters between the medication categories (Table 1).

The Amsterdam sample included 26% (n = 16) CHR-T subjects, diagnoses were: schizophrenia (n = 12), schizoaffective disorder (n = 2), schizoaffective disorder (n = 1) and brief psychotic disorder (n = 1). The Cologne sample included 12% (n = 6) CHR-T subjects, diagnoses were schizophrenia (n = 5) and schizoaffective disorder (n = 1).

Effects of EEG components on conversion rates were analyzed as described in the statistical literature (Hosmer and Lemeshow, 2000) and a previous report from EPOS (Ruhrmann et al., 2010). Subjects with survival times exceeding the 18-month follow-up were considered censored at the end of month 18. In a first step of the variable selection process, univariate Cox regression analyses were performed for the summed EEG scores and APF components. A liberal level of significance (p < .15) was chosen to avoid premature exclusion. Significant variables were entered into a multivariate backward regression analysis (p < .05), introducing domains blockwise. For the retained covariates, interactions were calculated and kept in the model if p < .05. Finally, the remaining covariates were analyzed together forward and backward, to exclude effects of blocking and selection procedure on the Cox model. Stability of the final model against potential confounding variables (i.e. medication status) was tested by entering the model variables into one block and adding the potentially confounding variables stepwise as a second block (Hosmer and Lemeshow, 2009). To control for center effects, the recruiting center was entered as a stratum variable throughout (Twisk, 2006). The final Cox model was used to calculate individual prognostic scores (Ruhrmann et al., 2010), which were stratified into three risk classes (RC). The respective survival curves were compared by Tarone–Ware tests.

Data were analyzed with the statistical package for social sciences (SPSS 18.0). If not described otherwise, p ≤ .05 was considered significant.
Values are mean (SD). Abbreviations: CHR-T: CHR subjects with transition to psychosis; CHR-NT: CHR subjects without transition to psychosis. iAPF = individual alpha peak frequency. Cox regression analysis (Table 3), which retained occipital-parietal APF recruiting centers. (Beta = −0.66, Wald = 7.23, p = .007, HR = 2.60, [95% CI 1.30–5.20]) and frontal theta power (Beta = .60, Wald = 3.84, p = .049, HR = 1.82, [95% CI 1.00–3.32]) in the model. Considering medication status as a potential confounding variable did not result in significant changes of our model.

3.3.1. Prognostic index

The Cox regression equation (−0.66 × APF) + [95% × frontal delta] + [40 × frontal theta] was applied to each patient. As the resulting individual prognostic scores followed a normal distribution (Kolmogorov–Smirnov, p = .94; mean = −6.16, SD = 1.13), a prognostic index (PI) was generated by stratification into three risk classes (RC): RC-I = −1 SD; RC-II between −1 SD and ≤+1 SD; RC-III ≥ +1 SD from the mean. Pairwise comparison yielded significant differences in conversion rates between RC-III and RC-I (Taron–Ware test $x^2 = 10.26, p = .001$) as well as RC-II ($x^2 = 17.90, p < .001$); RC-I and RC-II did not differ significantly. Hazard rate and mean survival times for the three classes are presented in Table 4, the corresponding survival curves in Fig. 1.

4. Discussion

We aimed to investigate whether QEEG measures are helpful for predicting later conversion in subjects at CHR for a first psychotic episode. Compared to CHR-NT subjects and healthy controls, CHR-T subjects showed higher theta and delta on frontal and central scalp locations and lower occipital-parietal APF. Furthermore, in CHR-NT, upper parietal delta (Beta = .95, Wald = 7.23, p = .007, HR = 2.60, [95% CI 1.30–5.20]) and frontal theta power (Beta = .60, Wald = 3.84, p = .049, HR = 1.82, [95% CI 1.00–3.32]) in the model. Considering medication status as a potential confounding variable did not result in significant changes of our model.

3.2. Quantitative EEG

Multivariate analyses of variance with the distinct EEG frequency bands, i.e. delta, theta, lower and upper alpha and beta, yielded a significant group effect (F = 2.10, df = 30, p = .002). Univariate tests revealed group differences in delta and theta on frontal scalp positions, central theta, parietal delta, and upper alpha (Table 2). Post-hoc Bonferroni tests showed significantly higher frontal delta in CHR-T compared to CHR-NT and controls and higher parietal delta in CHR-T compared to CHR-NT. In the theta range, CHR-T showed higher power on frontal and central scalp positions compared to CHR-NT and controls. Finally, parietal upper alpha power was lower in CHR-T than in controls. Regarding the APF, ANOVA revealed group differences in the occipital-parietal APF (Table 2). Post hoc test yielded lower occipital-parietal APF in CHR-T compared to CHR-NT subjects and controls.

3.2.1. Center effects

Besides a larger posterior APF in Cologne subjects (mean = 10.07, SD = 1.08; Amsterdam: mean = 9.52, SD = 1.18; p = .007) there were no significant differences in EEG measures between the two recruiting centers.

3.3. QEEG as predictor of conversion to psychosis

Nine variables were selected for inclusion into the final multivariate Cox regression analysis (Table 3), which retained occipital-parietal APF (Beta = −.66, Wald = 8.72, p = .003, HR = .52 [95% CI .33–.80]), frontal delta (Beta = .95, Wald = 7.23, p = .007, HR = 2.60, [95% CI 1.30–5.20]) and frontal theta power (Beta = .60, Wald = 3.84, p = .049, HR = 1.82, [95% CI 1.00–3.32]) in the model. Considering medication status as a potential confounding variable did not result in significant changes of our model.

3.3.1. Prognostic index

The Cox regression equation (−0.66 × APF) + [95% × frontal delta] + [40 × frontal theta] was applied to each patient. As the resulting individual prognostic scores followed a normal distribution (Kolmogorov–Smirnov, p = .94; mean = −6.16, SD = 1.13), a prognostic index (PI) was generated by stratification into three risk classes (RC): RC-I = −1 SD; RC-II between −1 SD and ≤+1 SD; RC-III ≥ +1 SD from the mean. Pairwise comparison yielded significant differences in conversion rates between RC-III and RC-I (Taron–Ware test $x^2 = 10.26, p = .001$) as well as RC-II ($x^2 = 17.90, p < .001$); RC-I and RC-II did not differ significantly. Hazard rate and mean survival times for the three classes are presented in Table 4, the corresponding survival curves in Fig. 1.

4. Discussion

We aimed to investigate whether QEEG measures are helpful for predicting later conversion in subjects at CHR for a first psychotic episode. Compared to CHR-NT subjects and healthy controls, CHR-T subjects showed higher theta and delta on frontal and central scalp locations and lower occipital-parietal APF. Furthermore, in CHR-NT, upper parietal...
The speed of processing in thalamo-cortical networks (Steriade et al., 2001) controls. Additionally, the occipital parietal alpha was lower compared to controls. We developed a model for prediction of psychosis including frontal theta and delta as well as the APF as predictors of 18-month conversion rates.

The finding of higher frontal delta and theta in CHR-T subjects is in accordance with previous results (Gschwandtner et al., 2009; Zimmermann et al., 2010). However, to the best of our knowledge, our model demonstrates for the first time that excess theta and delta power are predictive of future conversion to psychosis; in the two previous models (Gschwandtner et al., 2009; Zimmermann et al., 2010), EEG parameters only became significant in combination with clinical scales. This difference might be attributed to the larger statistical power of our study. In contrast, we did not replicate group differences or predictive ability of variations in beta ranges as reported by Gschwandtner et al. (2009).

The Cox regression equation enabled the calculation of individual prognostic scores, which were stratified into three risk classes (RC). The prognostic index (PI) was generated by stratification into three risk classes (RC): RC I: \( \theta < -1 \) SD; RC II: \( -1 \) SD \( \leq \) \( \theta \) \( \leq +1 \) SD and RC III: \( \theta > +1 \) SD.

We conclude that power in theta and delta ranges and APF can contribute to the short-term prediction of a first psychotic episode. As recording the resting state EEG is a relatively simple procedure compared to other experimental EEG/ERP or MRI parameters, combined with (other) clinical ratings, the EEG might provide the clinician with a practical and useful tool for risk classification.

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Contributors
Authors MvT and SR wrote the first draft of the manuscript and undertook the statistical analyses. Author MA analyzed the EEG data and critically revised the manuscript. Authors RM, MR, EV and KZ were involved in the data collection and analyses. Authors JHK and LB supervised the neurophysiological recordings and analyses and wrote the neurophysiological protocol. Authors FSL, JK, DHL, LH, ABK and DHN designed the study and wrote the protocol. All authors contributed to and have approved the final manuscript.

Conflict of interest
None of the authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, our work.

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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.2014.01.019.

References