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Altered auditory processing in frontal and left temporal cortex in 22q11.2 deletion syndrome: A group at high genetic risk for schizophrenia

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ABSTRACT

In order to investigate electroencephalographic (EEG) biomarkers of auditory processing for schizophrenia, we studied a group with a well known high-risk profile: patients with 22q11.2 deletion syndrome (22q11 DS) have a 30% risk of developing schizophrenia during adulthood. We performed high-density EEG source imaging to measure auditory gating of the P50 component of the evoked potential and middle to late latency auditory processing in 21 participants with the 22q11.2 deletion and 17 age-matched healthy controls. While we found no indication of altered P50 suppression in 22q11 DS, we observed marked differences for the first N1 component with increased amplitudes on central electrodes, corresponding to increased activations in dorsal anterior cingulate and medial frontal cortex. We also found a left lateralized reduction of activation of primary and secondary auditory cortex during the second N1 (120 ms) and the P2 component in 22q11 DS. Our results show that sensory gating and activations until 50 ms were preserved in 22q11 DS, while impairments appear at latencies that correspond to higher order auditory processing. While the increased activation of cingulate and medial frontal cortex could reflect developmental changes in 22q11 DS, the reduced activity seen in left auditory cortex might serve as a biomarker for the development of schizophrenia, if confirmed by longitudinal research protocols.

1. Introduction

The search for biological markers of schizophrenia is attracting renewed attention in view of its potential to allow for early treatment interventions and reduce its burden of disease (McGorry et al., 2002; McGlashan et al., 2007; Morrison et al., 2007).

Patients with the 22q11.2 microdeletion are well suited for the investigation of biomarkers that appear early in the pathogenesis of schizophrenia since these patients have an estimated 30% risk of developing schizophrenia during adulthood (Baker and Skuse, 2005; Schaer et al., 2009; Chow et al., 2011; Kates et al., 2011). The 22q11.2 deletion syndrome (22q11 DS), or velo-cardio-facial syndrome, is a developmental disorder due to a small deletion on chromosome 22 with a length of 1.5–3 megabases. Its clinical picture is defined by cardiac anomalies, cognitive deficits (Karayiorgou et al., 2010) and a well-defined psychiatric symptomatology with a high incidence of psychotic symptoms during childhood and adolescence (Debbané et al., 2006; Philip and Bassett, 2011).

Event-related potentials are promising potential biomarkers for the study of schizophrenia (Luck et al., 2011). Auditory evoked potentials in particular are repeatedly found to be deficient in schizophrenic patients and have been considered as endophenotypes or biomarkers for the disease (Calkins et al., 2007, Turetsky et al., 2007; Greenwood et al., 2011). Deficiencies are found for early pre-attentive components as well as for higher-order functions that mostly occur during later stages of processing (Javitt, 2009; Luck et al., 2011).

Concerning early effects, evidence of reduced auditory sensory gating of the P50 component was found in chronic schizophrenic patients. Auditory gating is expressed as a reduction of the P50 amplitude to the second click in a pair of clicks with fixed intervals. Schizophrenic patients do not show this reduction, indicating an impaired ability to inhibit intrinsic responses (Turetsky et al., 2007). The failure to inhibit the P50 response was also observed in unaffected siblings of schizophrenic patients (Myles-Worsley et al., 2004; Cadenhead et al., 2005; Preston and Weinberger, 2005; Olincy et al., 2010), thus strongly proposing the P50 suppression as a candidate endophenotype.

Concerning later cortical processing, a reduction of the amplitude of the auditory N1 component in schizophrenic patients has been described. The N1 component occurs at a latency of around 100 ms

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after the onset of an auditory stimulus. Schizophrenic patients show reduced amplitudes of the N1 component elicited by sinusoidal tones (Ogura et al., 1991; Potts et al., 1998; Ford et al., 2001; O'Donnell et al., 2004; Salisbury et al., 2010; Foxe et al., 2011) as well as click sounds (Boutros et al., 2004), in active as well as passive listening paradigms. Reduced N1 amplitudes were also found in patients with psychotic disorders (Hansen and Hillyard, 1980; Strik et al., 1992; Laurent et al., 1999, Hubl et al., 2007) and in their unaffected relatives (Foxe et al., 2011; Simons et al., 2011), thereby proposing the reduced N1 component as a potential endophenotype for schizophrenia.

Given the widely reported changes of the middle and late latency auditory evoked potentials in schizophrenia and their potential value as an endophenotype for schizophrenia, the investigation of these evoked potentials in patients with 22q11 deletion syndrome appears as an obvious choice. To our knowledge, such a study has not yet been performed with high-density electroencephalography (EEG) in this group.

In this article, we report on the auditory sensory gating of the P50 component as well as the amplitude of the auditory N1 component in adolescents with 22q11 deletion syndrome using high-density EEG recordings from 256 channels and topographic analysis. We expected to find indications of reduced sensory gating as well as reduced N1 amplitude in the 22q11 DS group, and predicted that the high-resolution recordings and subsequent source analysis would allow us to better understand the neuronal generators underlying these effects.

2. Methods

2.1. Participants

Participants with 22q11 DS were recruited through announcements in patient association newsletters. We studied 21 participants with confirmed 22q11 DS (11 females; age 17.4 ± 4.7 years; mean $\pm$ S.D.) and 17 age-matched controls (6 females; age 16.6 ± 4.1 years) who reported normal auditory function. Healthy control participants were recruited through advertisements in local schools and by word of mouth. All of the participants in the control group were screened for neurological and psychiatric disorders. All participants are taking part in an ongoing longitudinal protocol and signed an informed consent approved by the Ethical Committee of the Geneva University School of Medicine in Switzerland. Parents signed the informed consent if participants were younger than 18 years old.

At the time of this evaluation, of the participants with 22q11 DS, two received antipsychotic treatment (age range 14.2–18.4 years), two received methylphenidate (age-range 13.2–19.5 years), four were prescribed antidepressant treatment (age-range 15.4–27 years) and one participant received antiepileptic treatment (15.4 years). None of the controls were taking psychotropic medication. Of the 12 participants that were not on psychotropic medications at the time of the EEG recording, none had a history of previously prescribed psychotropic medication. Seven participants with 22q11 DS had cardiac malformations and all seven underwent cardiac surgery during childhood. Within the 22q11 DS group, six participants had frequent psychotic symptoms as evidenced by clinical interview ratings and the subscales of the Brief Psychiatric Rating Scale (BPRS) as well as the Structured Interview for Psychotic Symptoms (SIPS). Amongst the six participants with frequent psychotic symptoms, two met diagnostic criteria for a brief psychotic disorder and one participant was diagnosed with schizophreniform disorder. None of the participants met DSM-IV-TR criteria for schizophrenia at the time of the study. The presence of a 22q11.2 microdeletion was confirmed in all participants by fluorescence in situ hybridization (FISH).

A full Wechsler Intelligence Scale for Children III-R (WISC-III-R) (or Wechsler Adult Intelligence Scale-III (WAIS-III) for participants >17 years old) was administered to every participant. The groups differed significantly on Full Scale IQ (FSIQ) as shown by an independent samples t-test on the FSIQ: [22Q11 DS: $70.6 \pm 10{,}1$; control group: 104.5 ± 13.7; mean $\pm$ S.D., t (df=36)=8.80, $p < 0.00001$].

2.2. Task

The auditory stimuli were 120 binaurally presented click-pairs (1.5-ms white noise bursts, 86-dB SPL) with a 500-ms fixed interval between each click. The interval between click pairs jittered between 10 and 12 s. Participants were watching a silent movie during the recording. Sounds were presented through ear insert earphones (Etymotic Research, Elk Grove Village, IL, USA).

2.3. EEG recording and data analysis

High-density EEG was recorded with a 256-channel hydrocelcap (Electrical Geodesics Inc., Eugene, OR, USA). Data were acquired with a sampling rate of 1000 Hz. Subsequently to the recording, electrodes located on the cheeks and on the nape were excluded and the remaining 204 channels were kept for further analysis. Data were re-referenced to the common average reference, band-pass filtered between 1 and 40 Hz and underwent ICA (independent component analysis) based correction (infomax) to remove eye-movement (eyeblinks, saccades) and ECG artefacts using the BrainVision Analyzer software (Brain Products, Germany). The data were then averaged from -200 ms before to 900 ms after the first click to the last 400 ms after the second click. During this step, a manual rejection of epochs contaminated by muscle artefacts was performed. The number of accepted epochs after artefact rejection did not differ between groups [22q11 DS: 60/120 epochs, S.D.=17.6; controls: 65/120 epochs, S.D.=17.99, t-test: df (36), $t=-0.98$; $p=0.33$]. For the waveform analysis of the P50 amplitude, data were filtered in the window between 10 Hz and 40 Hz as the identification of the P50 can be hindered by lower frequencies in the EEG signal (Jerger et al., 1992; Olincy et al., 2010). The analysis of P50 amplitude reduction at the Cz electrode was performed by computing the difference between the P50 peak identified between 40 and 75 ms post-stimulus and computing its difference from the preceding negativity. In addition to this identification of the Cz amplitude peak, the timing of P50 maxima was verified by manual inspection to show the characteristic P50 topography and to coincide with the Global Field Power peaks. To compute a measure of sensory gating at the Cz electrode, the P50 peak amplitude of the second click was subtracted from the amplitude of the first click (Lijffijt et al., 2009). A two-tailed independent sample t-test between the two groups was performed on this difference measure. Also, global parameters of field strength of the P50 were compared between the two groups (see below).

In addition to the analysis of the auditory sensory gating of the P50 component, we performed a full analysis of the multichannel auditory evoked potential to the first click in order to test for differences in the later components (N1 and P2). We focused on the first click since it has been shown that the N1 amplitude reduction in schizophrenic patients is found after longer inter-stimulus-intervals (Roth et al., 1980; Shelley et al., 1999) and since differences between schizophrenic and control subjects are more pronounced for the analysis of the first click sound (Clementz and Blumenfeld, 2001). For the analysis of the evoked potentials we used comprehensive reference-independent spatiotemporal methods described in the literature (Michel et al., 2004; Murray et al., 2008; Michel and Murray, 2012). The analysis was performed using the Cartool software (brainmapping.unige.ch/cartool).

The first step consisted of an exploratory analysis of all time points and all electrodes using a randomization test for amplitude differences between the patient group and the controls. A significance level of $p < 0.01$ was fixed and a temporal criterion of at least 10 ms of significance was added, meaning that the threshold significance level has to be maintained for a minimal duration of 10 ms.

The second step consisted in the comparison of global measures of field strength and topography. Field strength was calculated as the Global Field Power (GFP), which is equal to the standard deviation of the average referenced potentials of all electrodes (Lehmann and Skrandies, 1980). The GFP was compared between the two groups for each time point with a randomization test using a significance level of $p < 0.05$ and a temporal criterion of at least 5 ms of significance.

The second parameter (field topography) was compared between the two groups using the so-called topographic analysis of variance: TANOVA (Murray et al., 2008). It is based on the computation of the Global Dissimilarity between maps at two successive time points. The Global Dissimilarity is an amplitude-independent measure of map difference and corresponds to the GFP of the difference of the normalized maps (Lehmann and Skrandies, 1980). The TANOVA is a randomization test based on the Dissimilarity values by randomly assigning the maps at a given time point to the two groups. Again a significance level of $p < 0.05$ and a time constraint of 5 ms of significance were fixed.

The third step consisted in calculating the source estimations of the event related potentials of each subject using the linear distributed inverse solution termed LAURA (Grave de Peralta Menendez et al., 2001) and comparing the estimated current density at each solution point and each time point between the two groups. Again, a randomization test was performed as well as an independent sample t-test with a significance level of $p < 0.01$ and a time constraint of 10 ms was fixed. The lead field for the inverse solution was calculated for a standard array of 204 electrode positions and the average brain of the Montreal Neurological Institute in a grey matter constrained head model using a modified version of the SMAC method with 4930 distributed solution points (Spinelli et al., 2000; Brunet et al., 2011).

In addition, and to investigate the influence of levels of psychosis on our results, steps 1–3 of the spatiotemporal analysis were also performed for the evoked potential of the first click sound comparing the 15 participants with 22q11 DS without frequent psychotic symptoms (7 females; age 17.6 ± 5.5 years; mean $\pm$ S.D.) using the same criterion for significance testing as for the whole group, namely $p < 0.01$ with a time constraint of 10 ms.

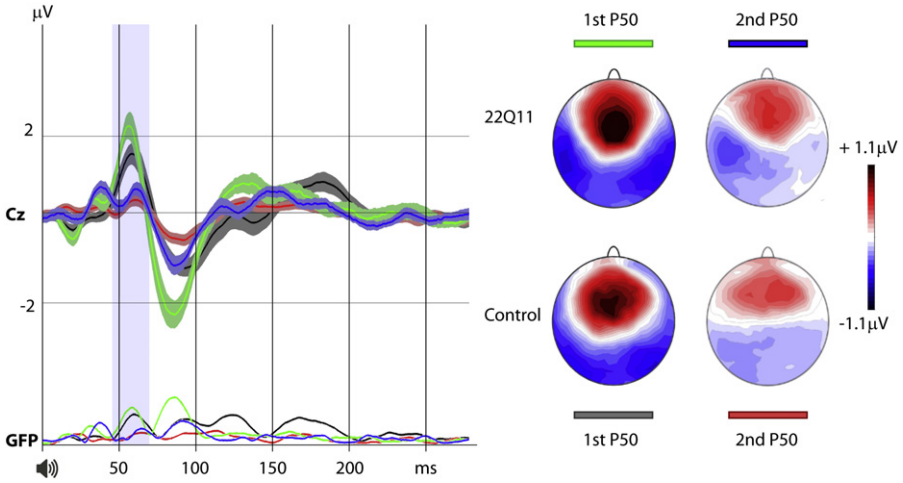

Fig. 1. Superimposed traces of the auditory evoked potential for the two clicks shown at the Cz electrode as well as the Global Field Power (GFP; measure of field strength) for the first 250 ms after each click (green and blue for the first and second click in the 22q11 DS group; grey and red for the first and second click in the control goup). Topographic maps show the P50 component for the first and second P50 (averaged over a window of 20 ms, shaded in blue). Data are filtered between 10 and 40 Hz.

3. Results

3.1. P50 amplitude reduction

As can be seen in Fig. 1, the healthy controls as well as the 22q11 DS participants showed the known reduction of the P50 amplitude to the second click as compared to the first click, indicating that sensory gating was present in both groups. The amplitude reduction did not differ between groups (22q11 DS vs. controls; 1.81 ± 1.42 μV vs. 1.23 ± 1.04 μV; mean ± S.D.; *t*-test: *df* (36), $t = 1.39$; $p = 0.17$). No differences were found for the latencies of the P50 component between the two groups (mean P50 latency 22q11 DS vs. controls for the first click (S1): 56.3 ± 6.6 vs. 58.1 ± 6.7 ms, and second click (S2): 57.6 ± 14.1 vs. 61.0 ± 12.1 ms). Repeated measures ANOVA for the factors group (22q11 DS vs. controls) and latency (S1 vs. S2) showed no significant main effect for group or latency, or interaction between group and latency.

Randomised tests comparing the field topography (TANOVA) showed no significant differences between groups for the first and second P50 component at a fixed *p*-level of 0.01. Highly significant amplitude differences were shown in a *t*-test comparing all electrodes in each group between the first and second P50 (S1 vs. S2) over fronto-central leads at a significance level of 0.01 with a time constraint of 5 ms for the window between 50 and 70 ms. Intact sensory gating was also revealed by significant GFP differences between the first and second P50 in both groups [22q11 DS: S1 vs. S2; 0.93 ± 0.09 vs. 0.52 ± 0.03 μV, mean ± S.D., *t*-test: *df*(20), $t = 6.12$, $p < 0.001$, controls: S1 vs. S2; 0.84 ± 0.07 vs. 0.48 ± 0.05 μV, *t*-test: *df*(16), $t = 6.38$, $p < 0.001$].

3.2. Spatiotemporal analysis of the auditory evoked potential after the first click

Fig. 2 shows the mean auditory evoked potential (AEP) waveforms after the first click at selected electrodes for the two groups. It shows the typical long-latency components expected for these channels: a positive–negative–positive deflection for the central electrode known as components P1 (or P50 around 50 ms), N1 (around 100 ms), and P2 (around 180 ms), and a negative component at around 120 ms for the lateral temporal electrodes, sometimes called N1c (Picton et al., 1999). A striking difference between the two groups is seen on the left lateral electrodes (C5, 56) where a strong N1c is observed in the controls, while this component is nearly absent in the 22q11 DS participants. This difference is not observed on the electrodes over the right hemisphere where both groups show similar peaks at comparable latencies.

Fig. 3A shows the first click AEP of the two groups as overlaid traces in a butterfly plot and as GFP curves. It clearly illustrates that the groups differ considerably in the latency range between 80 and 200 ms. While the 22q11 participants show enhanced amplitudes of the central N1 component on nearly all channels, the controls show an enhanced N1c and P2 amplitude. In fact, the controls show a strong GFP peak during the N1c latency, while it is virtually absent in the 22q11 DS group.

The first level of analysis consisted of a randomization test of the amplitude differences between the groups for each time point and each electrode. Fig. 3B shows the result of this statistical analysis. As expected from the butterfly plots, the major effects were found during the two N1's and the P2 component with increased amplitude in the 22q11 participants during the central N1 and increased amplitude in the controls during the N1c and the P2 component. Fig. 3C shows the mean maps during these three time periods for the two groups. While the increased central N1 in 22q11 DS is seen on many frontal and also occipital electrodes, the N1c difference is mainly due to increased negative amplitudes in left temporal electrodes in the controls compared to the 22q11 DS participants. The difference for the P2 component is mainly seen on central and posterior electrodes with larger amplitudes for the controls.

The second level of analysis concerned the global measures Dissimilarity (TANOVA) (Fig. 3D) and GFP (Fig. 3E). Both measures were significantly different between the two groups for the central N1 as well as the P2 windows described above, while the GFP comparison did not reach significance during the time of the N1c. This indicates that the differences were due to both global field strength and topography for the N1 and P2 components whereas the N1c only showed significant differences in the topography.

The third level of analysis was performed in the inverse space by comparing the estimated current density of each solution point across time (Fig. 4). This analysis revealed differences in the same time periods as for the scalp measures. In terms of localization, the increased potential during the central N1 in the 22q11 DS participants was explained by significantly stronger activation of the anterior cingulate cortex as well as the dorsal part of the medial frontal gyrus. The second and third time periods (during the N1c and

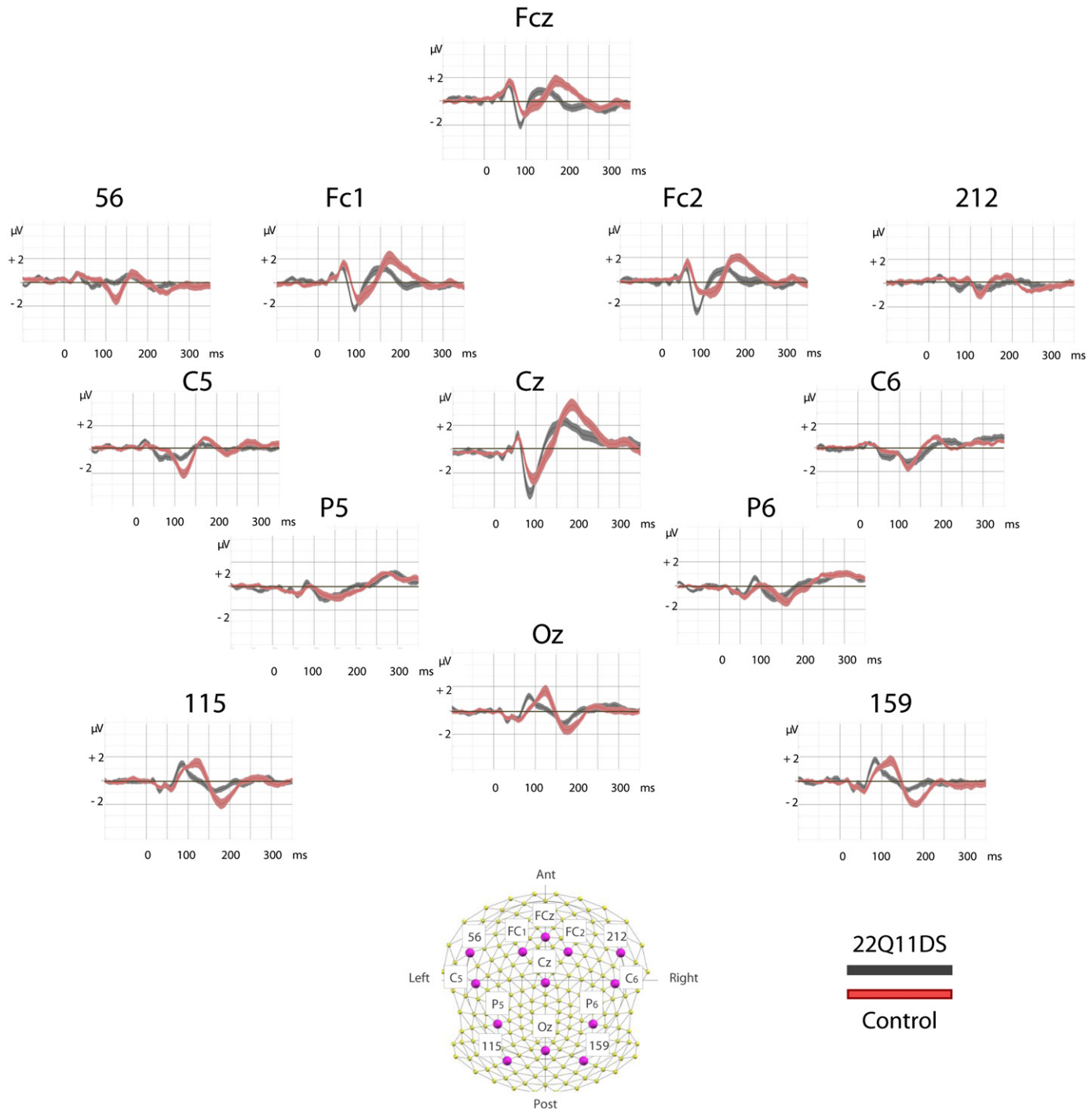

Fig. 2. Group averaged waveforms (mean ± SD) of the auditory evoked potential to the first click sound shown on selected electrodes for the control group (red traces) and the 22q11 DS group (black traces). The maximum peak of the N1 over Cz is at 90 ms for the 22Q11 DS group and at 100 ms for the control group, while the negative peaks over lateral electrodes (56, C5) of the N1c occur at 120 ms in the controls. The P2 component is observed at a latency of 160 ms in the 22q11 DS and 180 ms in the control group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

P2 components) were explained by decreased activation of the left auditory cortex in 22q11 DS relative to the controls.

The results of the multichannel comparison between the subgroup of 15 participants with 22q11 DS with a low level of psychotic symptoms and the controls revealed the same pattern as seen in the whole group for surface amplitudes, GFP, TANOVA and in the inverse space, namely significantly higher amplitudes during the central N1 for the 22q11 DS group and higher activation of anterior cingulate and the dorsal medial frontal gyrus followed by reduced activation of left auditory cortex for the lateral N1 and the P2.

4. Discussion

In this study we compared the cortical components of the (AEPs between participants with 22q11 DS and healthy age-matched controls. We particularly focused on two components

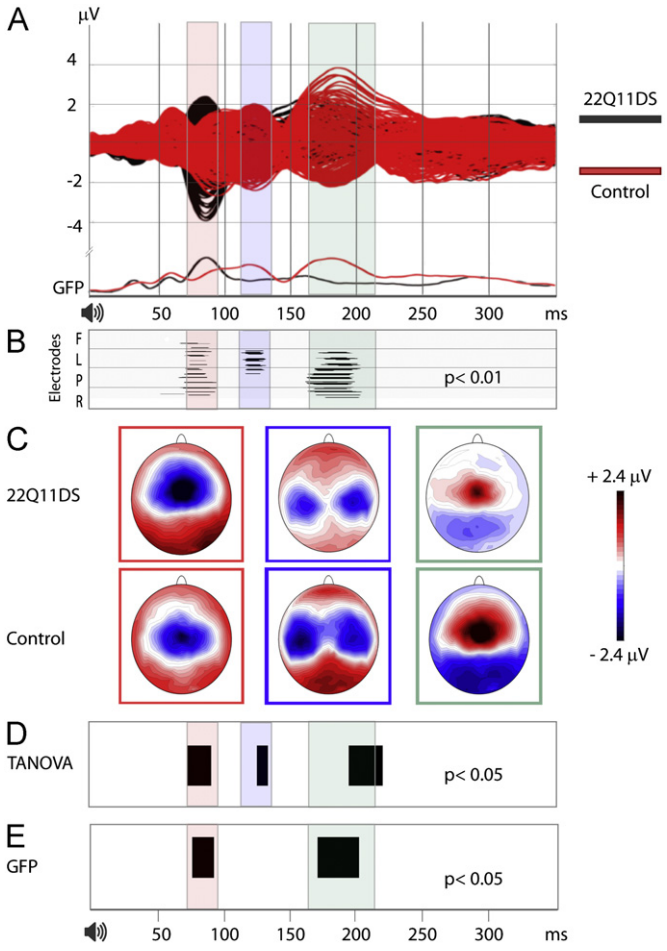

Fig. 3. (A) Overlaid traces for all 204 electrodes in the first 350 ms after the first click sound for the control group (red traces) and the 22q11 DS group (black traces). The time course of the global field power (GFP) is shown below in (B) followed by the results of the randomized test showing significant amplitude differences between groups ($p < 0.01$) on the 204 electrodes. Averaged topographic maps indicating the central N1 (red frame; 75–95 ms), the lateral N1 or N1c (blue frame; 110–130 ms) as well as the P2 (green frame; 160–210 ms) components are shown in the middle part of the graph (C). (D) and (E) indicate periods of significant differences for the randomised tests for topographical differences (TANOVA) as well as the GFP ($p < 0.05$) shown in (E).

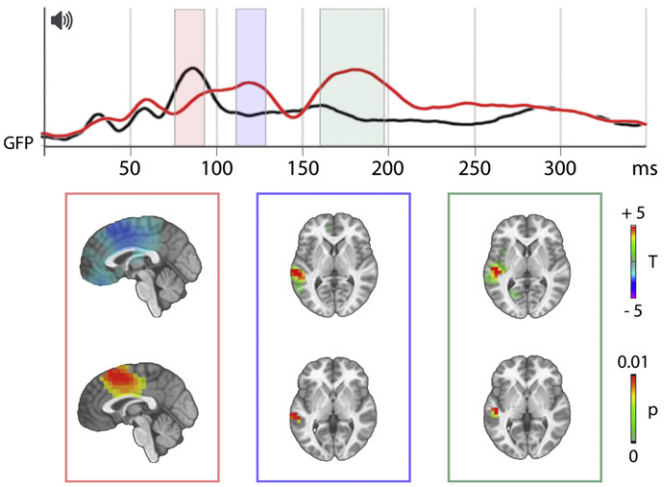

Fig. 4. Top: Overlaid traces for the GFP in the first 350 ms after the first click sound for the control group (red traces) and the 22q11DS group (black traces). The results of the independent samples t-test between source space activations are shown below indicating windows of significant differences between groups ($p < 0.01$) on the 4930 solution points. The t- and p-values shown for the contrast controls-22q11 DS indicate significant differences in the source activations for the time windows of the central N1 (red frame; 75–95 ms), the N1c (blue frame; 110–130 ms) and the P2 (green frame; 160–200 ms). Cold colors indicate negative values while hot colors indicate positive values.

that are known to be impaired in schizophrenic patients and that are considered good candidate endophenotypes for schizophrenia: the suppression of the 2nd click P50 amplitude in a double-click paradigm, and the reduced N1 component amplitude for auditory stimuli. We hypothesized that these two effects might be observed in adolescents with 22q11 DS as this group is at high risk for developing schizophrenia.

We did not find any signs of alteration of the P50 component of the 2nd click in the 22q11 DS group. The P50 amplitude suppression (the auditory sensory gating) was as strong as in the controls, and global measures of field strength and topography were similar for the two groups. This finding is in agreement with the study of Vorstman et al. (Vorstman et al., 2009) who did not find a deficit of P50 suppression in children with 22q11 DS. Thus we found no indication that P50 gating could be an early sign of developing schizophrenia or at least not in the 22q11 DS population.

On the other hand, we found clear alterations in the N1 and P2 components of the AEP in the 22q11 participants: while the first (central) subcomponent of the N1 was increased, the second (lateral) N1 as well as the P2 component were significantly reduced in 22q11 DS.

Many studies demonstrated reduction of the central auditory N1 component in patients with schizophrenia, both for chronic and first-episode patients as well as in psychotic disorder and participants at ultra-high risk for psychosis (Hansen and Hillyard, 1980; Strik et al., 1992; Laurent et al., 1999; Turetsky et al., 2007; Brockhaus-Dumke et al., 2008; Salisbury et al., 2010; Foxe et al., 2011, Simons et al., 2011; Shin et al., 2012). Even unaffected first-degree relatives of individuals with a psychotic disorder showed an N1 deficit in some studies (Foxe et al., 2011, Simons et al., 2011), pointing to the N1 deficit as a candidate endophenotype (Turetsky et al., 2007; Salisbury et al., 2010; Foxe et al., 2011).

N1 deficiencies were also associated with clinical symptoms such as alogia and formal thought disorder (Turetsky et al., 2009), and N1 amplitudes were reduced during auditory hallucinations compared to periods without hallucinations in the same schizophrenic patients (Hubl et al., 2007).

However, several studies also failed to show reliable N1 reduction in schizophrenic patients, particularly when they were unmedicated (see Rosburg et al., 2008 for a review). Several factors might play a role in the detection of N1 effects, such as stimulus duration, stimulus type, inter-stimulus interval, type of paradigm (one sound, several sounds, pairs of sounds, active vs. passive) and medication.

But even more important for the inconsistency of the results across studies is, in our view, the fact that most studies did not take into account that the N1 component is generated by a complex combination of different sources in the brain (Naatanen and Picton, 1987). Schizophrenia might affect these generators differently, depending on the structural integrity of the cortex in which they are located. A reference-dependent measure of the amplitude peak at the central Cz electrode will not be able to differentiate between these sources and might thus fail to detect effects that are constrained to a subset of generators with different sensitivity to the stimulation parameters.

The present high-resolution AEP study in a paired click paradigm showed at least two very distinct topographies within the time window of the N1 component, one with a maximal negativity at central electrodes at around 90 ms and

another one with maximal negativity over bilateral temporal electrodes at around 120 ms. This distinction is not new and has been described repeatedly in many earlier multichannel EP studies that looked at the topography of the electric field (McCallum and Curry, 1980; Wood and Wolpaw, 1982; Naatanen and Picton, 1987; Scherg et al., 1989; Picton et al., 1999; Ponton et al., 2000; Gomes et al., 2001).

The first N1 map with the central negativity appears to be mainly generated by neuronal activity in the primary auditory cortex (Halgren et al., 1995). The resulting dipoles have a tangential orientation due to the convolution of Heschl's gyrus on the superior temporal plane (Morosan et al., 2001). Gallinat et al. (2002) performed one of the few topographical studies on the N1 effect in schizophrenia. Interestingly, they did not find a reduction of the amplitude of these tangential dipole sources, despite significantly reduced amplitude of the Cz potential. On the contrary, the amplitudes of the tangential dipoles were even slightly higher in the schizophrenic patients. The reduction of the Cz amplitude was attributed to a dipole source in the anterior cingulate cortex (ACC) oriented radially towards the vertex in the study by Gallinat et al. (2002). Several previous dipole analysis studies already showed that additional sources in the ACC are very quickly activated in the primary auditory cortex and that activity in the ACC strongly contributes to the N1 component (Giard et al., 1994, Baudena et al., 1995; Dien et al., 1997; Picton et al., 1999). This early ACC activation was also confirmed in a simultaneous EEG-fMRI study (Mayhew et al., 2010). In addition to the ACC activation, the contribution of sources in precentral, Broadmann area 6 and premotor areas to the generation of the N1 amplitude peak during passive listening paradigms was shown with dipole models (Giard et al.,1994), distributed inverse solutions (Gallinat et al., 2002), EEG-fMRI coregistration (Mayhew et al., 2010) and PET (Tzourio et al., 1997), as well as in intracranial recordings in monkeys (Steinschneider et al. 1980; Barbas et al., 1999) and epileptic patients (Kurthen et al., 2007).

Gallinat et al. (2002) showed that the activity of the ACC was reduced in the schizophrenic patients. The authors thus concluded that the reduced N1 amplitude usually observed at the Cz electrode in schizophrenia is rather due to an impaired activity of the ACC than of the primary auditory cortex. This hypothesis was supported by distributed linear inverse solution methods in this and in another study by the same group (Mulert et al., 2001).

The second N1 map with the bilateral temporal negative maxima has slightly later peak latency around 120 ms. It is generated by radial dipoles in the temporal lobe (Giard et al., 1994; Picton et al., 1999). Several studies indicate that these dipoles are located in the secondary auditory cortex in the planum temporale (see discussion in Gallinat et al., 2002). Both studies that used dipole localization methods found reduced amplitudes of the radial N1 dipoles in schizophrenia (Frodl et al., 1998; Gallinat et al., 2002). In Gallinat et al. (2002), this amplitude reduction was restricted to the left hemisphere.

Our study of the participants with 22q11 DS without diagnosis of schizophrenia showed increased activity during the first N1 component and a decreased activity during the second component. The increased amplitude in the initial N1 was explained by increased source strength in an area spanning the dorsal medial frontal gyrus including motor, premotor cortex and the dorsal anterior cingulate, whereas the decreased amplitude of the later N1 and of the P2 component was explained by decreased source strength in the left temporal lobe corresponding to secondary auditory cortex.

The ACC was repeatedly found to be a target area for abnormal structure and function in schizophrenia. Besides the AEP studies described above, several fMRI studies showed reduced activation of the ACC in schizophrenic patients, particularly during executive task performance and cognitive and attentional control in working memory tasks (Fletcher et al., 1999; Minzenberg et al., 2009). Also, anatomical studies have repeatedly demonstrated altered ACC grey matter with reduced cortical thickness and volume in schizophrenic patients and high-risk individuals (Fornito et al., 2008; Goldman et al., 2009; Goghari et al., 2010; for review, see Fornito et al., 2009). Correlations between functional and structural abnormalities of the anterior cingulate in schizophrenic patients have also been demonstrated (Schultz et al., 2012). It is therefore suggested that the disturbed cognitive process observed in schizophrenic patients is due to a failure of functional integration in the ACC. On the other hand, several studies found an overactivation of the ACC in healthy subjects prone to auditory verbal hallucinations as well as psychotic and schizophrenic participants when investigating state activity (during hallucinations) as well as trait markers of auditory verbal hallucinations (Cleghorn et al., 1990, Grossberg, 2000; Shergill et al., 2000; Woodruff, 2004; van Lutterveld et al., 2010; Lewis-Hanna et al., 2011).

This overactivation of the ACC was related to states of increased auditory attention in subjects prone to hallucinations (Lewis-Hanna et al., 2011) and was hypothesized to serve either as a compensatory mechanism or a risk factor for auditory hallucinations (van Lutterveld et al., 2010). In our study there is no direct link between psychotic symptoms and ACC activation since participants with and without high levels of auditory hallucinations showed the same pattern of results. In our passive task, the increased activation of the anterior cingulate might thus indicate that the patients were more distracted by the auditory stimuli and paid more attention to the stimuli than required. The fact that the increased activation was mainly found in the dorsal part of the anterior cingulate might speak in favor of an increased attention to the irrelevant stimuli (Orr and Weissman, 2009).

Another possible explanation is related to the findings reported by Schaer et al. (2009), which show that 22q11 DS patients have thicker cortex than controls during adolescence, particularly in frontal brain regions. The cortical thinning due to synaptic elimination that is observed in normal subjects seems to be delayed in 22q11 DS patients. Since, as described above, reduced ACC activity in schizophrenic patients is correlated with reduced cortical thickness, the increased thickness in 22q11 DS adolescents might lead to increased ACC activity. However, this interpretation remains speculative and would need direct correlation between the activity in the ACC and the measure of cortical thickness in this region.

The second clear effect shown by our study was a reduction of the activity in the left temporal lobe in the 22q11 DS patients at the N1c and P2 latencies. The only previous study on evoked potentials and source localization in 22q11 patients also described a reduced left temporal lobe activity while activity in the anterior cingulate was strong and not altered (Romanos et al., 2010). However, these findings concerned the P300 component in a visual Go-NoGo task and not the AEP in a passive listening task. More closely related to our finding is the study of Gallinat et al. (2002) on schizophrenic patients described above. In their auditory active oddball task they also found a selective reduction of the left temporal-radial dipole source (i.e. the source responsible of the generation of the second N1c component). As discussed above, these generators are supposed to be located in the secondary auditory cortex within the planum temporale.

Structural MRI studies of adult 22q11 DS patients demonstrated grey matter loss in the temporal lobe (Bearden et al., 2007; Chow et al., 2011). In the study of Chow et al. (2011) of 22q11 adults with schizophrenia, the reduced volume was particularly significant in

the left superior temporal gyrus. This is in line with many structural MRI studies in patients with schizophrenia who showed grey matter deficits in the superior temporal lobe and the planum temporale, particularly in the left hemisphere (Pearlson, 1997; Honea et al., 2005). As this area is important in language recognition, production and self-monitoring, structural abnormalities in schizophrenic patients are usually thought to lead to disorders in these functions and to auditory hallucinations (Pearlson, 1997), functions that might also be deficient in the 22q11 patients included in our study.

This study is limited by its small sample size as well as its cross-sectional nature, which reduces generalization of the findings. Moreover, it cannot be fully excluded that the heterogeneous use of psychotropic medication in some participants of the 22q11 DS group might affect the results (Rosburg et al. 2008).

In summary, our study indicates abnormal processing of auditory stimuli in a passive listening paradigm in 22q11 adolescents without schizophrenia while their auditory gating appears to be intact. The altered auditory processing is due to an increased activity in the anterior cingulate and dorsomedial frontal cortex followed by reduced activity of the left superior temporal gyrus. To establish whether one or both of these changes qualify as specific markers for the development of schizophrenia in this risk group will require longitudinal investigations with a larger sample size.

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