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N2 event-related potential in schizophrenia – diffusion in time and space

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Background

Recent theories of schizophrenia have proposed a fundamental instability of information processing on a neurophysiological level (Andreasen et al, 1999; Winterer and Weinberger, 2004). It has been suggested that this instability can be measured as an increase in EEG noise or an increase in latency variability of event-related potentials (ERPs). Another common observation is a more diffuse activation of the prefrontal cortex on cognitive tasks, which is thought to reflect compensatory processes required due to inefficient processing (Kim et al, 2010).

Goals and Hypotheses

The main goal was to adress temporal and spatial diffusion of brain activation patterns conjointly. We selected the N2 event-related potential component, because it has been shown to be abnormal in patients with schizophrenia and is modulated by demands on executive control (Umbricht et al, 2006). The study hypotheses were:

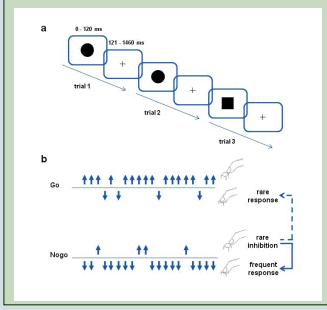
(1)The N2 component shows increased single trial latency variability in patients with schizophrenia.

(2)The N2 component shows a more diffuse spatial distribution in patients with schizophrenia.

Methods

Subjects: 28 patients with schizophrenia and 28 control particpants matched for gender, age and education participated in the study. Patients were stable patients recruited from a rehabilitation setting with relatively preserved cognitive performance.

	Healthy controls	Patients with schizophrenia	t-value	Degrees of freedom	p
Age	25.50 (9.40)	26.07 (6.90)	-0.26	54	0.80
Years of education	14.40 (2.60)	14.32 (2.70)	0.03	54	0.98
Male/female	20/8	20/8			
PANSS positive		12.79 (2.96)			
PANSS negative		18.43 (4.69)			
PANSS global		32.50 (5.67)			
MWT-B estimated IQ	103.25 (12.18)	103.61 (10.20)	-0.11	54	0.91
Letter number sequencing	11.36 (2.83)	10.67 (2.54)	0.95	54	0.35



Task: Subjects performed a visual Go/Nogo task, while event-related potentials were obtained.

EEG recordings: Scalp voltages were collected using a 35-channel Easy Cap (Falk Minow Systems, Germany). Electrode impedance was maintained below 5 kΩ for all recordings. Electrical signals were recorded with Brainamp amplifier (bandwidth DC-250 Hz, no notch filter) and digitized (sampling rate 500 Hz).

EEG analysis: The EEG data were preprocessed using the BrainVision Analyzer Software. Single-trial analysis was performed with custom MATLAB code using the EEG Lab data structure. Trial-to-trial latency variability was calculated with a Wavelet-based method developed by our group (Roth et al, 2007). In short, we used multiresolution analysis in order to decompose the single trial data into different scales or frequency bands. Since delta and theta frequencies play a major role in the generation of the N2 component, peak latency of single trials was determined subsequently by selecting the local maximum in the sum of the delta and theta band in the selected time window (190-400ms). Spatial distribution was assessed using repeated measures ANOVA across frontal electrodes.

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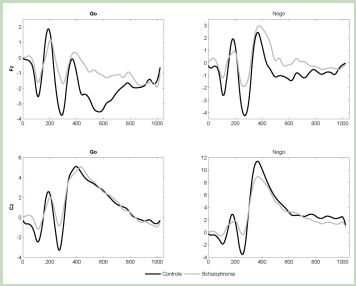
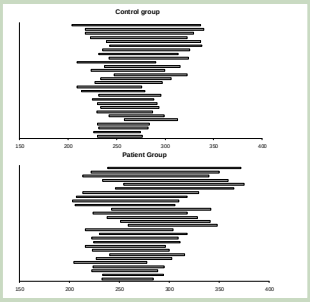
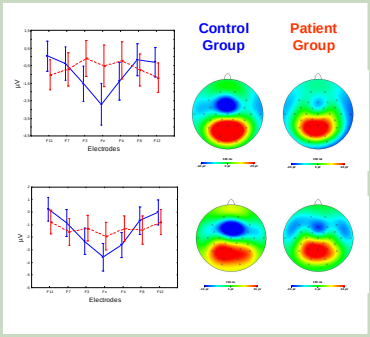
Results



Average N2 Event Related-Potential: A repeated measures ANOVA revealed that the latency of the N2 peak did not differ between patients and controls at either Fz or Cz. In contrast patients with schizophrenia showed a reduced N2 amplitude at midline electrodes (Fz: $F(1, 54)=9.95$, $p=0.003$), Cz: ($F(1, 54)=19.83$, $p<0.001$). There was no group x task interaction.



Single Trial Latency Variability: Percentage of excluded trials did not differ significantly among groups (patients: 4%, controls: 3%). Regarding latency variability there was a main effect of group indicating that patients with schizophrenia had increased N2 latency variability at electrodes Fz and Cz (Fz: $F(1, 54)= 5.40$, $p=0.02$; Cz: $F(1, 54)= 14.34$; $p=0.004$). There was no group x task interaction, i.e. the effect occurred in both Go and Nogo conditions. (Figure shows Nogo condition.)



Spatial Distribution of N2 component: On visual inspection of the scalp ERPs healthy participants showed a focused fronto-central N2 peak in both conditions. In contrast, patients with schizophrenia showed a more diffuse pattern with additional negative peaks over lateral electrodes. This was analyzed statistically by a mixed ANOVA with the factors group x electrode (frontal electrodes) separately for the Go and Nogo conditions. For both conditions a highly significant interaction emerged (Go: F(1, 54)=10.87; p<0.001, Nogo: (F(1, 54)=14.31; p<0.001) indicating a more focussed N2 peak in healthy subjects.

Relationship between N2 Latency Variability and Spatial Distribution: To address the relationship between latency variability and spatial diffusion, we first calculated an index of spatial diffusion by subtracting lateral from midline frontal electrodes. This index was consistently decreased in patients with schizophrenia. We then correlated the spatial diffusion index with latency variability. In the Go condition this correlation was not significant. In the Nogo condition there was a significant correlation at electrodes Fz and Cz (r=0.47, p=0.01 and r=0.56, p<0.01).

Discussion

These results clearly show that schizophrenia is associated with higher temporal variability of ERPs as well as a more diffuse scalp distribution.

The present findings confirm previous observations of increased latency variability and suggest that they are observed within different task contexts (Ford et al, 1994; Roth et al, 2007). Therefore, we suggest that increased temporal variability might index a fundamental instability of information processing.

Since patients were not impaired on task performance, the more diffuse spatial distribution might reflect processes compensating for the fundamental temporal instability. A correlation between latency variability and spatial diffusion was only observed in the Nogo-condition, suggesting that the inhibitory task demand leads to more compensatory processes.

Overall, the results are consistent with fMRI data delineating compensatory activation patterns in response to cognitive tasks (Kim et al, 2010). In addition, single-trial analysis suggests temporal instability as a fundamental mechanism leading to inefficient processing, which requires compensation.