33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Aberrant Auditory Evoked Responses in Schizophrenia: Evidence from Single-Trial Analysis

Darshan Iyer, *Member, IEEE*, Nash N Boutros, George Zouridakis, *Senior Member, IEEE*

***Abstract*— The average N100 (a negative response occurring around 100 ms poststimulus) component of the auditory evoked potential (EP) has been recently used in the study of schizophrenia. Averaging, however, eliminates all temporal variability of the recorded signals and, therefore, hampers the exploration of the temporal dynamics underlying the generation of the N100 component. In this study, we analyzed EPs on a single-trial basis using an iterative independent component analysis procedure that is capable of extracting individual components out of an entire EP waveform. This approach allowed estimation of an N100 in each single trial and measurement of its morphological features such as polarity, which could be either negative (most frequently) or positive (less frequently). In the latter case, the N100 component was termed aberrant. We analyzed responses from 23 normal controls (NC) and 15 schizophrenia (SZ) patients in a paired stimulus paradigm, where a first stimulus S_1 was followed by a second one S_2 0.5 s later.**

To compare N100 responses within and across the two subject groups, we defined a *negative polarity index NPI* as the percentage of single trials that had a negative polarity N100. Our results show significantly higher *NPI* values in NC compared to SZ, for both the S_1 and S_2 responses. Additionally, the difference in *NPI* values between the S_1 and S_2 responses was significant in NC but not in SZ. We conclude that both normal and schizophrenia subjects exhibit aberrant N100 responses, but these events are more frequent in the SZ patient group. The higher number of aberrant responses can explain the lower amplitude EPs typically observed in schizophrenia, and may be one of the factors contributing to sensory gating deficits consistently reported in these patients.

I. INTRODUCTION

The N100 (a negative response occurring around 100 ms poststimulus) is one of the largest components present in auditory evoked potentials (EPs) [3] and is typically associated with late sensory and/or early attentive information processing [2]. For these reasons, it has often been used to study sensory gating and inhibitory mechanisms in schizophrenia [2], [4], [10]. For example, the average N100 amplitude in response to simple auditory stimuli was found decreased in both medicated and unmedicated schizophrenia subjects [1] compared to normal controls. Several other studies have used a paired-stimulus paradigm (PSP), whereby pairs of clicks or tones are presented at 0.5 s intervals and average responses to the first ('conditioning' - S_1) and second ('testing' - S_2) stimuli are computed. In normal controls, the amplitude of the S_2 response is drastically decreased compared to the S_1, but in most schizophrenia subjects, no substantial S_2 reduction is seen [2], [4], [10]. This EP abnormality has been postulated to represent an inability of schizophrenia subjects to inhibit, or gate out, irrelevant sensory input, which leads to sensory overload as the amount of information reaching consciousness increases, possibly because of a defect in subcortical and cortical inhibitory pathways [13].

In our previous work [7], we used iterative independent component analysis (*i*ICA) to estimate the N100 component in single-trial EPs and showed that the amplitude and latency of the N100 estimated from single trials were more accurate and reliable measures than the ones obtained from classical ensemble averaging [8], [17]. Furthermore, such single-trial estimates allowed accurate separation of normal controls from schizophrenia subjects [9].

In this study, we again use *i*ICA to estimate the N100 component in single-trial responses, but this time we focus on the *morphological* characteristics of the N100 estimates. In particular, we analyze the *polarity* of the N100 component obtained from each single trial, and we compare its characteristics across two groups, one of normal controls and a second one of age- and sex-matched schizophrenia subjects.

Typically, individual components are not clearly visible in single-trial responses, and therefore it is not possible to measure a component polarity reliably. However, as we showed previously [7], the *i*ICA procedure can extract a particular component out of the entire EP waveform, and this component is made clearly visible in each single trial [17].

II. METHODS

A. Subjects and experimental set up

Auditory evoked potentials were recorded from nine scalp locations in 23 normal controls (NC) and 15 schizophrenia patients (SZ) using a PSP, where two identical stimuli of 1 kHz frequency were presented with an inter-stimulus interval between 400-600 ms and inter-trial interval of at least 8 s (with a computer-imposed jitter of 100 ms). Data were acquired with a hardware bandpass filter between 0.05 and 300 Hz and then digitized at a sampling rate of 1 kHz. Additional details on the subjects and the data collection procedure can be found elsewhere [10].

D. Iyer (Darshan_Iyer@neurometrix.com; phone: 781-301-1771; fax: 781-890-1556) was with the Department of Electrical and Computer Engineering, University of Houston, Houston, TX 77204 USA, and now he is with NEUROMetrix, Inc., Waltham, MA 02451, USA.

N. Boutros is with the Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, MI 48201, USA.

G. Zouridakis (zouridakis@uh.edu) is with the Departments of Engineering Technology, Computer Science, and Electrical and Computer Engineering, University of Houston, Houston, TX 77204-3058 USA.

Only data from the central channel Cz channel were used in this analysis since it reflects activity from both hemispheres. All data were inspected for artifacts, and trials were rejected when activity in any channel exceeded 75 μV. This resulted in each subject having a minimum of 60 single trials. Only epochs in which both the S_1 and S_2 responses were artifact free were analyzed. The original continuous recordings were segmented into separate sets of S_1 and S_2 responses by retaining 500 ms pre- and 500 ms poststimulus activity. The segmented data were detrended and bandpass-filtered between 1 and 20 Hz using a zero phase, bidirectional, third-order Butterworth filter.

B. Iterative ICA–iICA

The *i*ICA algorithm is an iterative implementation of the information maximization algorithm originally proposed by Makeig et al. [12]. A detailed description of the *i*ICA method can be found elsewhere [17]. Briefly, for a set of EP data obtained from N recording channels, each containing L single trials, the *i*ICA algorithm is applied to one channel at a time, in the following steps:

1) Compute an EP template by averaging all single trials in a set.
2) ICA-transform all single trials in blocks of 10.
3) Compute the absolute correlation between the current EP template and the ICs of all blocks, within a predefined window W_r.
4) Set to zero those ICs with correlation less than a predefined threshold r_{th}.
5) Inverse-transform the remaining ICs back to the time domain, separately in each block.
6) Shuffle the updated single trials in the entire set.
7) Repeat steps 1 to 6 until a convergence criterion is met.

The same procedure is then applied to the rest of the channels until all of them have been processed. Shuffling of the trials guarantees that each block will include different trials in the next iteration, and thus the resulting ICA system of equations will not be underdetermined.

The parameter values used in the study were W_r = 50-250 ms poststimulus, which was consistent with the occurrence of the N100-P200 complex, and r_{th} = 0.15.

C. Data Analysis

First, the single-trial responses of each subject were processed using *i*ICA, and the resulting signals were averaged together to obtain a processed average EP estimate, EP_{ICA}. The original unprocessed single trials were also averaged to obtain the classical ensemble average response, EP_{ave}.

Then, the absolute N100 peak was detected in each processed single trial within a search window of $\pm$15 ms centered around the average N100 peak latency. Subsequently, single-trial responses were separated into two groups, one in which the N100 peaks had the same polarity as the N100 of the average response EP_{ICA}, and a second in which the N100 peaks had the opposite polarity. Next, from these two groups two additional average responses were computed, indicated as EP_{pos} and EP_{neg}, respectively.

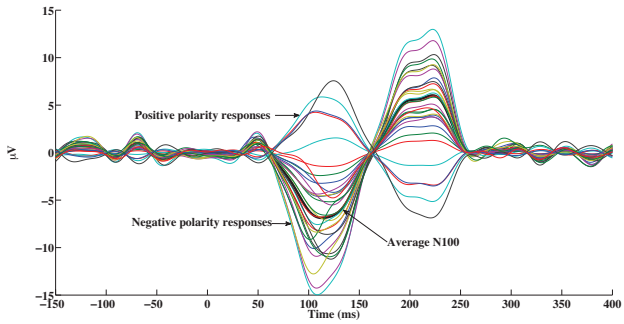

Fig. 1. *Typical average EP_{ICA} (thick line) and single-trial responses from the Cz channel of a normal control subject after iICA processing. The single-trial N100 components can have either a negative (expected) or positive (aberrant) polarity.*

Finally, to compare response characteristics within and across the two subject categories, we defined a *negative polarity index NPI* as the ratio

$$NPI = 100 \times \frac{\text{Number of single trials with negative N100}}{\text{Total number of single trials}},$$

which was computed separately for the S_1 and the S_2 response. These measures were computed for all the subjects. Statistical significance was assessed using the Wilcoxon rank sum test for equal medians.

III. RESULTS

Figure 1 shows the responses obtained from the Cz channel of a typical normal control subject after processing the single trials with *i*ICA. The polarity of the N100 component in most single trials is *negative*, as expected. However, a few trials show an N100 component with an unexpected *positive* polarity, and for this reason we call these components *aberrant*. The classical ensemble average response EP_{ave} with the typical negative polarity for the N100 component is also shown on the same plot with a thick black line.

The indices of the trials identified as expected and those identified as aberrant after *i*ICA processing were used to separate the original unprocessed single trials into two groups to assess whether the patterns observed in the processed data actually existed in the original data as well. The top panel of Fig. 2 shows examples of expected trials (blue) superimposed onto the corresponding unprocessed trials (black), while the bottom panel provides similar information for aberrant responses. These single trials correspond to the butterfly plot of Fig. 1.

The box plots of Fig. 4 depict the average value and variation of the *NPI* index in each group for the S_1 and S_2 responses. In the group of normal controls, the S_1 *NPI* was significantly higher than the S_2 *NPI* (p <0.01), whereas in

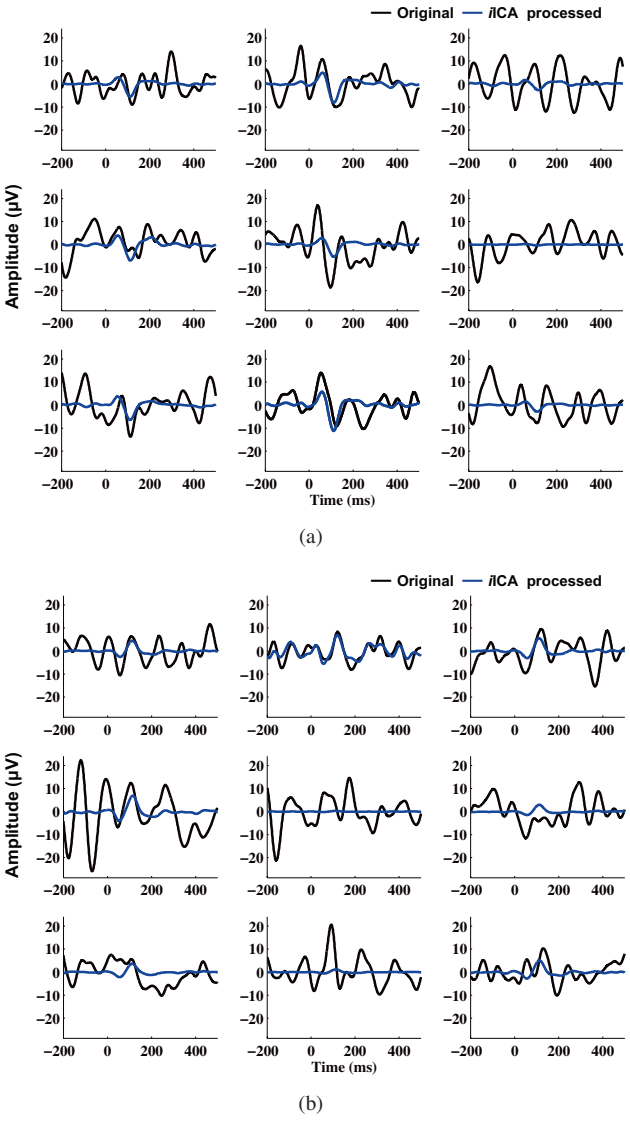

Fig. 2. *Single-trial responses before (black) and after iICA processing (blue), showing clear expected (a) and aberrant (b) N100 components.*

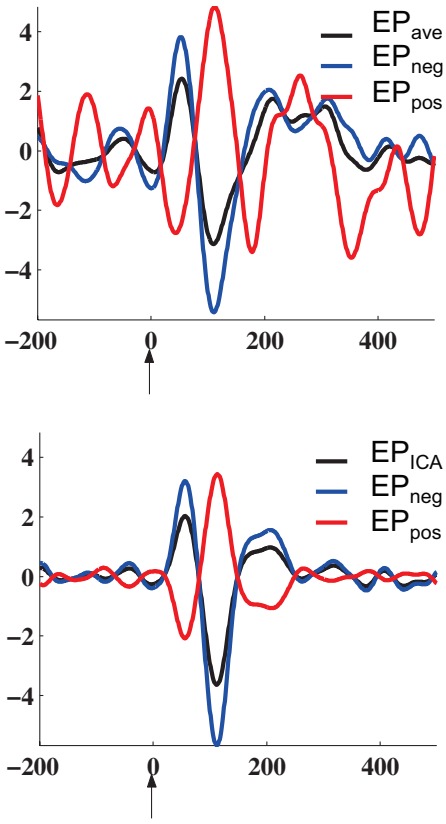

Fig. 3. *Comparison of responses before (top) and after (bottom) iICA processing: ensemble average (EP_{ave}), negative polarity (EP_{neg}), and positive polarity (EP_{pos}) average response. EP_{ICA} depicts the iICA-processed ensemble average.*

the schizophrenia group, the S_1–S_2 differences in *NPI* were not significant at 95% confidence level, but they only showed a trend (p =0.07).

In the group of normal controls, *NPI* was much higher for both the S_1 (89 $\pm$ 9 vs. 81 $\pm$ 12) and the S_2 responses (76 $\pm$ 9 vs. 74 $\pm$ 9) as compared to the schizophrenia patients, and these differences were statistically significant (p <0.01).

IV. DISCUSSION

In this study, we analyzed single-trial evoked potentials obtained in response to tone stimuli using an independent component analysis procedure that is capable of extracting individual components out of the entire response waveform [8], [17]. Apart from the typical negative polarity N100 components, our analysis showed the existence of positive polarity N100 responses, which we called atypical, or aberrant. Although fewer in number, aberrant responses were found in all subjects, both normal controls and schizophrenia patients. Previous studies have regarded these responses as noncontributing, nonresponsive, or inappropriate [6], [14]. However, we showed that they play a crucial role in determining the amplitude of the ensemble average response, which is the one most widely used feature in the EP clinical literature.

The N100 component has only been used recently in the study of the so-called gating mechanism in the context of a PSP. Overall, our findings agree with the existing studies in the literature which usually show abnormally decreased N100 amplitudes in schizophrenia patients compared to normal controls [10], [15].

In an earlier study, we used a combination of single-trial analysis and fuzzy clustering to show population differences [16] between normal controls and schizophrenia patients on the P50 (a positive response occurring around 50 ms poststimulus) component, and hypothesized that the amplitude of the evoked response was related to the phase of the electroencephalographic (EEG) activity at the time of stimulus arrival. In this study, we focused our attention on estimating reliable N100 components from single trials. The advantage of using the N100 instead of the P50 is that its

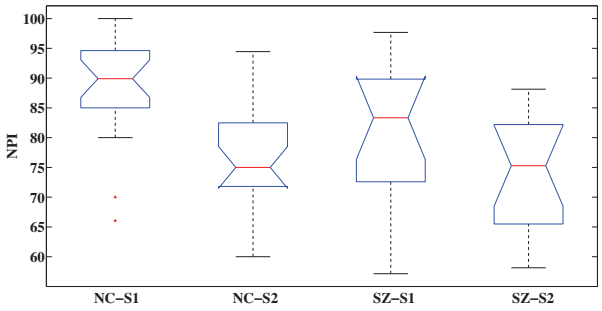

Fig. 4. *Box plots showing within and between-group differences in terms of NPI. Each box has lines at the lower quartile, median, and upper quartile values. The symbol '+' indicates outliers.*

amplitude is much larger than the P50, and it can therefore be measured in single trials with a greater degree of accuracy.

In our previous work [9], we studied the amplitude and latency of the N100 component estimated from single trial responses, and showed that these measures provided much better separation between normal controls and schizophrenia patients compared to classical ensemble averaging.

In the present study, we examined the *polarity* of the N100 component estimated from single trial responses, and showed that all subjects, both normal controls and schizophrenia patients generate a percentage of aberrant responses with a positive N100. In general, schizophrenics had a significantly higher number of aberrant responses ($p < 0.01$) compared to normal controls, both in response to stimuli S_1 and the S_2; also the differences between the populations were significantly higher in response to stimulus S_1 response ($p < 0.01$).

The increased number of aberrant responses seen in schizophrenics can explain both the lower average amplitude and the decreased attenuation ratio $\frac{S_2}{S_1}$ seen in these patients compared to normal controls [2], [4], [10].

These findings are also consistent with other N100 studies that looked at activity phase synchronization to show population differences [6], [10], [11].

Currently, we are investigating the relationship between prestimulus EEG characteristics at the time of stimulus arrival and the poststimulus polarity of the resulting N100 component [5].

V. ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support from Texas Learning and Computation Center and a training fellowship from the W.M. Keck Foundation to the Gulf Coast Consortia through the Keck Center for Computational and Structural Biology.

REFERENCES

[1] Boutros, N. N., Nasrallah, H., Leighty, R., Torello, M., Tueting, P., and Olson, S., "Auditory evoked potentials, clinical versus research applications," *Psychiatry Res*, 69(2-3): 183-195, 1997.

[2] Boutros, N. N., Korzyukov, O., Jansen, B., Feingold, A., and Bell, M., "Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients," *Psychiatry Res*, 126(3): 203-215, 2004.

[3] Buchsbaum, M. S., "The middle evoked response components and schizophrenia," *Schizophr Bull*, 3(1): 93-104, 1977.

[4] Clementz, B. A., Geyer, M. A., and Braff, D. L., "Poor P50 suppression among schizophrenia patients and their first-degree biological relatives," *Am J Psychiatry*, 155(12): 1691-1694, 1998.

[5] Diaz J., Iyer D. and Zouridakis G. Improved Estimation of Evoked Potentials Based on Inter-electrode Activity Synchronization, submitted, 2011.

[6] Hu, L., Boutros, N. N., Jansen, B. H., "Evoked potential variability," *J Neurosci Methods*, 178(1): 228-236, 2009.

[7] Iyer, D., "Improved Evoked Potential Estimation using Iterative Independent Component Analysis," *PhD Dissertation*, Dept. of Electrical and Computer Engineering, University of Houston, 2005.

[8] Iyer, D. and Zouridakis G. Single-trial evoked potential estimation: comparison between independent Component analysis and wavelet denoising, Clinical Neurophysiology, 118(3): 495-504, 2007.

[9] Iyer, D., and Zouridakis, G., "Single-trial Analysis of the Auditory N100 Improves Separation of Normal And Schizophrenia Subjects," *Conf Proc IEEE Eng Med Biol Soc.*, 3840-3843, 2008.

[10] Jansen, B. H., Hegde, A., and Boutros, N. N., "Contribution of different EEG frequencies to auditory evoked potential abnormalities in schizophrenia," *Clin Neurophysiol*, 115(3): 523-533, 2004.

[11] Jansen, B. H., Hu, L., Boutros, N. N., "Auditory evoked potential variability in healthy and schizophrenia subjects," *Clin Neurophysiol*, 2010.

[12] Makeig, S., Jung, T-P, Bell, A. J., Ghahremani, D., and Sejnowski, T. J., "Blind separation of event-related brain responses into independent components," *Proc Natl Acad Sci USA*, 94: 10979-84, 1997.

[13] Patterson, J. V., Jin, Y., Gierczak, M., Hetrick, W. P., Potkin, S., Bunney, W. E. Jr., and Sandman, C. A., "Effects of temporal variability on P50 and the gating ratio in schizophrenia: a frequency domain adaptive filter single-trial analysis," *Arch Gen Psychiatry*, 57(1): 57-64, 2000.

[14] Rodionov, V., Goodman, C., Fisher, L., Rosenstein, G. Z., and Sohmer, H., "A new technique for the analysis of background and evoked EEG activity: time and amplitude distributions of the EEG deflections," *Clin Neurophysiol*, 113(9): 1412-1422, 2002.

[15] Young, K. A., Smith, M., Rawls, T., Elliott, D. B., Russell, I. S., and Hicks, P. B., "N100 evoked potential latency variation and startle in schizophrenia," *Neuroreport*, 12(4): 767-773, 2001.

[16] Zouridakis, G., Jansen, B. H., and Boutros, N. N., "A Fuzzy clustering approach to EP estimation," *IEEE Trans Biomed Eng*, 44(8): 673-680, 1997.

[17] Zouridakis G., Iyer D., Diaz J., and Patidar U. "Estimation of individual evoked potential components using iterative independent component analysis," *Phys. Med. Biol.*, 52: 5353-5368, 2007.