THE BROKEN P300 IN SCHIZOPHRENIA: CAN IT BE FIXED?

Ali Saffet Gönül

In patients diagnosed as schizophrenia, reduced amplitude of P300 ERP component is a robust finding that has been replicated with nearly uniform consistency even in the first episode patients and when patients are retested after an interval of 1 year (Duncan 1988, Ford et al. 1994, Salisbury et al. 1998, Turetsky et al. 1998). In a longitudinal study, Mathalon et al. (2000.) found that even when the patients are in their best clinical state, P300 amplitudes were smaller than those of controls. The stability of reduced P300 amplitude among schizophrenic patients suggests that it might be a neurological "trait" marker for enduring nature of the disease. In contrast, several longitudinal studies have found that the reduced P300 amplitude of among schizophrenic patients behaves as a clinical "state" marker, increasing toward normal range in parallel with improvements in clinical symptoms (Gallinat et al. 2001, Schall et al. 1998). A common though often necessary limitation of these studies is the use of medicated patients as subjects of the studies. Whether antipsychotic medication exerts a primary effect on P300 amplitude independent of changes in clinical state is a question. Some studies report that it does, while others find no independent effect (Ford et al. 1994, Coburn et al. 1998).

P300 latency also has been investigated in schizophrenia, with most authors reporting normal latencies but others finding P300 to be delayed (Blackwood et al. 1987, Duncan et al. 1987). Again, the common use of medicated patients is problematic, but a number of researchers found P300 delays among un medicated schizophrenic patients compared to controls, and Blackwood et al reported that delays remain stable during the subsequent antipsychotic treatment (Blackwood et al. 1987). St. Clair et al. (1989) found virtually identical P300 delays among medicated patents groups compared to controls. Although the evidence is not strong, a delayed P300, when it is found, appears in most studies behave more like a trait, rather than a state marker. However, Coburn et al. reported the P300 delays to be reversed by medication but to be independent of clinical symptoms, implying that a reversal of P300 delay might be a state marker for certain medications (Blackwood et al. 1987, Coburn et al. 1998).

Compared to typical antipsychotic medications, the new atypical antipsychotics have been shown to have advantages in terms of greater efficacy for negative symptoms, including beneficial effects on cognitive functioning, and fewer extrapyramidal side effects. Some researchers believed that new antipsychotics may have a capability to fix the broken P300.

Umbricht et al. (1998) reported that clozapine treatment was associated with increased P300 ampliude, which was not observed in patients treated with haloperidol. A later study found that risperidone had no significant effect on P300 amplitude but normalized the latency (Umbricht et al. 1999). Gallinat et al. (2001) could not find any significant change in P300 amplitude in patients treated with olanzapine or clozapine.

In a recently published paper, we have investigated the effects of olanzapine in a group of schizophrenic patients who were drug-free for at least 2 weeks (Gonul et al. 2003). Olanzapine has a similar receptor profile to clozapine and a positive effect on Brain Derived Neurotrophic Factor (BDNF) in schizophrenic patients (unpublished data from Pırıldar et al. from Ege University). It is interesting that we found normalized P300 amplitude in frontal region but no change in parietal region. In a very recent paper published in Archives of General Psychiatry, it is found that reduced temporoparietal P300 has a strong relative risk ratio for schizophrenia (Winterer et al. 2003). Although abnormal frontal P300 has some risk ratio, it is not as strong as temporoparietal P300.

Psychiatrist, Ege University School of Medicine Department of Psychiatry and Ege University Center for Brain Research, İzmir

As a conclusion, new atypical antipsychotics (olanzapine/clozapine) may be effective in fixing P300 in frontal regions but not in parietal regions. The generators of P300 in parietal region might be more related to genetic background of schizophrenia and is an enduring neurological "trait" marker for schizophrenia.

REFERENCES

Blackwood DH, Whalley LJ, Christie JE, Blackburn IM, St. Clair DM, McInnes A (1987) Changes in auditory P3 event-related potential in schizophrenia and depression. Br J Psychiatry; 150: 154-160.

Coburn KL, Shillcutt SD, Tucker KA, Estes KM, Brin FB, Merai P, Moore NC (1998) P300 delay and attenuation in schizophrenia: reversal by neuroleptic medication. Biol Psychiatry; 44: 466-474.

Duncan CC, Perlstein WM, Morihisa JM (1987) The P300 metric in schizophrenia: effects of probability and modality. Electroencephalogr Clin Neurophysiol, 40: 670-674 (Suppl.).

Duncan CC (1988) Event-related brain potentials: a window on information processing in schizophrenia. Schizophr Bull; 14: 199-203.

Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A (1994) ERPs in schizophrenia: effects of antipsychotic medication. Biol Psychiatry; 36: 153-170.

Gallinat J, Riedel M, Juckel G, Sokullu S, Frodl T, Moukhtieva R, Mavrogiorgou P, Nissle S, Muller N, Danker-Hopfe H, Hegerl U (2001) P300 and symptom improvement in schizophrenia. Psychopharmacology (Berl) 158: 55-65.

Gonul AS, Suer C, Coburn K, Ozesmi C, Oguz A, Yilmaz A (2003) Effects of olanzapine on auditory P300 in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry; 27: 173-177.

Mathalon DH, Ford JM, Pfefferbaum A (2000) Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. Biol Psychiatry; 47: 434-449.

Salisbury DF, Shenton ME, Sherwood AR, Fischer IA, Yurgelun-Todd DA, Tohen M, McCarley RW (1998) First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. Arch Gen Psychiatry; 55: 173-180.

Schall U, Catts SV, Chaturvedi S, Liebert B, Redenbach J, Karayanidis F, Ward PB (1998) The effect of clozapine therapy on frontal lobe dysfunction in schizophrenia: neuropsychology and event- potential measures. Int J Neuropsychopharmacol; 1: 19-29.

St Clair D, Blackwood D, Muir W (1989) P300 abnormality in schizophrenic subtypes. J Psychiatr Res; 23: 49-55.

Turetsky BI, Colbath EA, Gur RE (1998) P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. Biol Psychiatry; 43: 84-96.

Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, Kane J (1998) Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry; 44: 716-725.

Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, Kane J (1999) Effects of risperidone on auditory event-related potentials in schizophrenia. Int J Neuropsychopharmacol; 2: 299-304.

Winterer G, Coppola R, Egan MF, Goldberg TE, Weinberger DR (2003) Functional and effective frontotemporal connectivity and genetic risk for schizophrenia. Biol Psychiatry; 54: 1181-1192.