Neurophysiological and neuropsychological assessment of recent-onset schizophrenia
Nieman, D.H.
A model of P300 event-related potential deficits in recent-onset schizophrenia

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Adaptation of an article that appeared in International Clinical Psychopharmacology 1998;13:S67-S73.
Chapter 4

Abstract

It is hypothesised that a defect in inhibition of incoming sensory information in the nucleus reticularis thalami may play a role in the P300 event-related potential abnormalities and in the pathogenesis of schizophrenia. Such a defect could result in a dysfunctional filter function of external stimuli and may therefore affect the social and psychological functioning of the patient.
A model of excitability dysfunctions in schizophrenia

Neurophysiological analysis of sensory information processing in schizophrenia has revealed a variety of abnormalities. Excitability changes, termed sensory gating (Coquery, 1979) could be dysfunctional in a subgroup of schizophrenic patients, representing an inability to filter out extraneous information, which in turn could lead to attentional deficits. Focusing attention and filtering out irrelevant information is one of the most pervasive problems of many schizophrenic patients (McGhie and Chapman, 1961; Neuchterlein et al, 1986; Cornblatt and Keilp, 1994). The anatomical origin of these deficits is, however, still basically unknown.

Event-Related Potentials (ERPs) are often used in research into attentional processes. An ERP is a derivative of the electroencephalogram (EEG) and it consists of voltage fluctuations measured on the skull. These voltage fluctuations represent neural activity in the brain in response to sensory input. An ERP is obtained by averaging EEG signals that have the same duration and that are recorded after application of the same stimulus. By this means, an ERP is profiled with a number of positive (P) and negative (N) components, which can be classified in early, intermediate and late. The early components have a latency shorter than 50 ms and are called evoked potentials (EPs). They represent the anatomically specific events in the relay of sensory information to the cortex (Grebb et al., 1986). The latency of the intermediate components ranges from 50 ms to 150 ms. The intermediate components are relatively sensitive to fluctuations in attention. The late components have a latency longer than 200 ms and include the P300 (P3) that occurs 300 ms after task-relevant, unexpected and infrequent stimuli. P3 latency and amplitude are strongly influenced by experimental manipulations that influence cognitive functions, such as attention.

ERP research in schizophrenia has yielded three relatively consistent findings (Grebb et al., 1986). Firstly, the early components tend to be increased in amplitude (Callaway and Naghdí, 1981; Kaplan et al., 1994). Secondly, the amplitude of the intermediate components is reduced by most stimulus patterns. Thirdly, the late components, notably the P3, are also reduced in amplitude (Grebb et al., 1986). Several studies (Pfefferbaum et al., 1984a; Blackwood et al., 1994; Souza et al., 1995) have also found the P3 latency to be prolonged.

In light of these observations, the model described by Skinner and Yingling (1977) may offer a better understanding of the underlying mechanisms. In this model, which
is partly based on animal research, the nucleus reticularis plays a pivotal role. The nucleus reticularis has been described extensively in neurological and neurophysiological journals (Crick, 1984; Mitrofanis and Guillery, 1993), but it has not yet received much attention in the psychiatric literature. However, a recent study supports the opinion that the nucleus reticularis may play an essential role in sensory gating processes (Leonard et al, 1996).

The relay of sensory information from the sensory nerves to the cortex involves a number of brain structures including the nucleus reticularis and the thalamus (Crick, 1984; Mitrofanis and Guillery, 1993). The nucleus reticularis is a thin layer of inhibitory (GABAergic) interneurons that is situated around the lateral part of the thalamus (Scheibel and Scheibel, 1966) and is influenced by two regulation systems - the frontocortical-mediolthalamic system (FC-MT) and the mesencephalic reticular formation (MRF). The FC-MT system consists of reciprocal pathways that connect the medial thalamus (MT) to the frontal cortex (FC), and has an excitatory effect upon inhibitory interneurons within the nucleus reticularis (Fig. 4.1).

Consequently, the ultimate effect is inhibition of transmission of information that travels from receptors through the sensory nerves to the primary sensory projection areas - the projection cortex. In contrast, the MRF has an inhibitory effect on the inhibitory neurons within the nucleus reticularis (Skinner and Yingling, 1977) and, therefore, MRF excitation leads to a total and diffuse inhibition of the nucleus reticularis. In turn, the diffuse inhibition of the nucleus reticularis facilitates
transmission of sensory information (through the lateral thalamus; Fig. 4.1) to the projection cortex. MRF excitation in animals leads to a state of over-arousal similar to that seen in some schizophrenic patients with positive symptoms (Kornetsky and Eliasson, 1969) and to an increase of primary sensory potentials.

In the model of Skinner and Yingling (1977), the effects of FC-MT and MRF differ in duration and specificity. The MRF has a tonic (long lasting), non-specific inhibitory effect, and its effect on the nucleus reticularis can last for 20-30 s after stimulation of the MRF (Skinner and Yingling, 1977). The FC-MT has a phasic (relatively shorter lasting), specific excitative effect, starting ± 100 ms after stimulation of the MRF. The neurons in the nucleus reticularis can be considered as a parallel series of gates that regulates the transmission of afferent sensory information. The pattern of input from the sensory receptors that reaches the cortical (projection) areas is determined by the combined actions of the MRF and FC-MT (Skinner and Yingling, 1977). Thus, the MRF opens gates immediately after sensory input and the FC-MT closes certain gates, as a function of time, in such a way that the gate that is associated with the stimulus upon which the attention is focused remains open. This process may be disturbed in schizophrenic patients.

If the model of Skinner and Yingling is also valid in man, it could explain the decrease in P3 amplitudes and prolonged P3 latencies and, in some cases, cortical activity to irrelevant stimuli seen in schizophrenic patients, as well as the ERP results reported by others over the past decades. Furthermore, this model may provide an insight into the anatomical origin of attentional deficits in schizophrenic patients. Given our findings and the model described above, it is possible that a subgroup of subjects with a vulnerability for schizophrenia, were born with an 'oversensitive', overexcitable nervous system. This 'oversensitivity' probably exists before the symptoms of schizophrenia appear. Sensory gating defects may thus be found only in a subgroup of schizophrenic patients. Heterogeneity of ERP results has been related to symptom dimensions of schizophrenia (John et al, 1994). When in our patient group symptom dimensions prove to be valid concepts, our future research effort will also be directed at identifying these dimensions.
Acknowledgements

This study was partly funded by a grant from the 'Praeventiefonds'. With special thanks to D Kropveld, A de Wilde, M Dekker and BPR Gersons for their contributions to this study.

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