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Generators of the intracranial P50 response in auditory sensory gating

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Clarification of the cortical mechanisms underlying auditory sensory gating may advance our understanding of brain dysfunctions associated with schizophrenia. To this end, data from nine epilepsy patients who participated in an auditory paired-click paradigm during pre-surgical evaluation and had grids of electrodes covering temporal and frontal lobe were analyzed. A distributed source localization approach was applied to the intracranial P50 response and the Gating Difference Wave obtained by subtracting the response to the second stimuli from the response to the first stimuli.

Source reconstruction of the P50 showed that the main generators of the response were localized in the temporal lobes. The analysis also suggested that the maximum neuronal activity contributing to the amplitude reduction in the P50 time range (phenomenon of auditory sensory gating) is localized at the frontal lobe.

Present findings suggest that while the temporal lobe is the main generator of the P50 component, the frontal lobe seems to be a substantial contributor to the process of sensory gating as observed from scalp recordings.

Keywords: Auditory EP; P50 response; Gating; Neuronal generators

Introduction

The P50 component of auditory evoked potentials (EP) is elicited around 45–75 ms after the presentation of an auditory stimulus. This EP component is also known as the P1 component or the Pb complex (Yvert et al., 2001). In healthy subjects when paired click stimuli (interval about 500 ms) are presented, the second stimulus usually elicits a much smaller amplitude response for the P50 (Dolu et al., 2001; Waldo and Freedman, 1986). The current leading psychological interpretation of the P50 amplitude decrement in the normal population is that a continuous stream of incoming auditory information is gated or screened – that is, redundant or potentially irrelevant information is filtered out – in order to prevent overloading the limited capacities of higher-order stages of auditory information processing.

Specific interest in the P50 response was stimulated by a number of studies which demonstrated poor suppression of the P50 amplitude in a paired stimulus paradigm among schizophrenia patients. This finding has been proposed as a potential trait marker of brain dysfunctions associated with schizophrenia spectrum disorders (for a review: Bramon et al., 2004). In this view, along with other possible brain dysfunctions, the gating mechanism in schizophrenia patients is impaired, leading to unfiltered transmission of auditory sensory information from primary auditory areas to hierarchically higher-order brain structures presumably located in prefrontal and frontal brain regions (for a recent review on prefrontal and temporal lobe interactions see: Simons and Spiers, 2003).

The brain mechanisms subserving auditory sensory gating are not well understood. The P50 response is generated by the activity of neuronal populations, at which level there are several possible scenarios that may result in the phenomenon of gating:

(1) *Refractoriness of the P50 neural generators.* Neural generators of the P50 component may cease being active when physically identical information is retransmitted through the auditory sensory pathways and therefore activates the same neuronal populations. Although this interpretation of gating phenomena might appear plausible, based on well-known refractoriness properties of individual

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neurons, mechanisms underlying EP refractoriness have not been determined at the level of neuronal populations (Javitt et al., 2000). The refractoriness of individual neurons may contribute to auditory sensory gating, however this factor cannot by itself fully explain the decrement in activity of complex neuronal assembles in which neurons utilize sophisticated interneuronal relationships to open a gate for transmission of auditory information within the P50 time window. At the level of auditory cortex neurons, long-lasting suppression of neuronal firing after the first click (time intervals from 128 to 512 ms) was found only in 50% of recorded neurons. But even for these neurons suppression of the activity might be caused by a suppression of the synaptic inputs they receive from apparently intracortical synapses (Wehr and Zador, 2005). Moreover, there is no reliable evidence that faster or more efficient recovery after stimulation in schizophrenia patients compared with healthy subjects can be explained by membrane-based mechanisms of refractoriness at the level of individual neurons. If refractoriness were a significant factor in mediating sensory gating, it would be expected that the neural generators of the response to the initial stimulus would be the same as for the second identical stimulus, but with a much lower magnitude.

(2) Neuronal mechanisms of the phenomenon of gating (expressed in inhibition of P50 response) might be triggered by neuronal activity originating beyond the location of primary temporal lobe generators of P50 and occurring in the time period between first and second clicks. During the response to the second click an inhibitory signal might suppress activity of primary P50 generators resulting in the phenomenon of gating observable from the scalp recordings. In this hypothesis, an additional generator becomes (for some reason) less active in schizophrenia patients compared to healthy subjects.

Finally, it is possible that a *combination of the above mechanisms contributes to the function of sensory gating*.

Clarification regarding which scenarios contribute to the mechanisms of normal and pathological auditory sensory gating will further advance our understanding of brain dysfunctions associated with schizophrenia (Edgar et al., 2003).

Brain generators of auditory P50

The neuronal sources of the scalp-recorded P50 are difficult to localize due to the low signal-to-noise ratio and also because the P50 brain response is preceded and followed in time (within 10–15 ms) by several EP components with brain localizations and biological significance that are distinct from the P50 neuronal sources.

Animal studies suggested that neuronal activity at the hippocampus might contribute to sensory gating (Freedman et al., 1996), however human hippocampus recordings did not find P50-like activity within the hippocampus (Grunwald et al., 2003).

Auditory EPs recorded intracerebrally in Heschl's gyrus have identified (within the limits dictated by the electrodes implantation locations) the following EP components: N30 (27–30 ms range latency), P50 (45–50 ms), N60 (55–65 ms), and N75 (at 70–80 ms Godey et al., 2001; Liegeois-Chauvel et al., 1994). Scalp-recorded EPs suggest that the P50 is preceded by a positive peak at 29 ms (Pa or P30) and a negative peak (inverting polarity at temporal electrodes) around 40 ms (TP41 or Nb; see: Cacace et al., 1990; Woods et al., 1995; Yvert et al., 2001). Two subsequent EP components – Pb1 (peaking about 52 ms) and Pb2 (peaking about 74 ms) – comprise what might be described as the P50 or Pb complex (Yvert et al., 2001). Magnetoencephalographic (MEG) studies of the magnetic counterpart of P50 (M50 or P50 m) support these findings by demonstrating peak responses at latencies 30, 40, 50 and 75 ms (Ackermann et al., 2001; Hertrich et al., 2000, 2004; Makela et al., 1994; Onitsuka et al., 2003).

Edgar et al. (2003) noted that in some studies identification of the P50 peak among preceding and following EP components was difficult since filters that remove high frequency noise may mask latency differences between relatively weak components surrounding the P50, thereby falsely producing a single peak. If two approximately equal amplitude peaks were present in the data around the P50 latency, researchers may pick up either the earlier (Hertrich et al., 2000) or the later (Edgar et al., 2003; Hertrich et al., 2004; Onitsuka et al., 2000) of these peaks for the P50/M50 analyses. This multiplicity of peaks might reflect distinct neurobiological processes having distinct anatomical locations. For instance, it was shown that components characterized by peaks at 46 ms and 76 ms will behave differently with respect to the stimulated ear (Ackermann et al., 2001).

The relatively dense chronology of activations associated with sound processing in the time window around the P50 suggests that information about neuronal sources may be obtained only with high temporal resolution techniques. Due to its unsurpassed time resolution, the majority of attempts to localize P50/M50 generators have used MEG (Edgar et al., 2003; Hanlon et al., 2005; Onitsuka et al., 2000; Reite et al., 1988) and scalp-recorded EP (Cardenas et al., 1993; Weisser et al., 2001).

From the methodological perspective, scalp-recorded EP is the most commonly used way of recording P50 and the phenomenon of gating. This approach allows the investigation of large clinical populations (Bramon et al., 2004; Heinrichs, 2004), the effect of medications (Freedman et al., 1983; Light et al., 2000; Nagamoto et al., 1996), and the genetic factors (Freedman et al., 2005; Myles-Worsley et al., 1996) associated with P50 gating. However, there are several limitations that reduce spatial resolution of P50 source localization methods using scalp EP data. One problem is that scalp-recorded EP is a result of summation of all possible simultaneously active neuronal generators in the given time period. This makes separation and localization of individual P50 generators more difficult. Another problem is that currents that determine the EEG potential differences are determined both by the topographies and electrical resistivities of the various kinds of tissue between the source and the head surface (Tepley, 2005). Some of these problems can be overcome with MEG. MEG studies of P50 gating provided valuable information about temporal lobe generators of P50 and a lateralized deficit in sensory gating for schizophrenia patients (Hanlon et al., 2005; Thoma et al., 2003). Since there is rapid attenuation of magnetic fields generated by neuronal sources, MEG offers a high spatial resolution for locating the position of reconstructed cortical sources. However MEG is less sensitive to brain generators that have radial orientations with respect to the magnetic sensors. Beginning with the first MEG attempts to localize P50/M50 sources (Huotilainen et al., 1998; Reite et al., 1988), it was suspected that, along with the conventionally observable pair of bilateral supratemporal sources, one or more additional generator(s) may contribute to the P50 response recorded by scalp EEG (Edgar et al., 2003). Indeed, studies suggested that the P50 is an overlapping potential