Cortical deficits in schizophrenia have been related to diverse psychophysiological, neurobiological, and genetic deficits. This chapter reviews specific psychophysiological deficits in sensory and motor gating, their neurobiological substrate in nicotinic acetylcholine-mediated neurotransmission, and their genetic basis. Detailed correlations between these several levels of observation are necessary to parse schizophrenia into discrete and hopefully more treatable elements.

5.1 Sensory Gating Dysfunction in Schizophrenia

The inability to filter out irrelevant information from the environment is a common feature of schizophrenia. (McGhie and Chapman 1961). Over the last two decades, investigators have developed experimental methods to reliably assess the brain’s ability to filter out irrelevant sensory stimuli, often termed “sensory gating” (Adler et al. 1982). One such measure is a conditioning-testing paradigm, in which evoked potentials are measured from repeated pairs of clicks, separated by 500 ms. This measure is often called the P50 auditory evoked potential because the most commonly measured component is a middle latency waveform that occurs approximately 50 ms post-stimulus. If inhibitory pathways are functioning properly, there is a response to the first (conditioning) stimulus, but a greatly diminished response to the second (test) stimulus of the same intensity because the first stimulus activates an inhibitory pathway which is still active at the time the second stimulus is presented (Eccles 1969). Only if the two stimuli are far apart temporally (6-10 sec), do they act as independent stimuli and the responses elicited by the conditioning and test stimuli become equal. As shown in Fig. 5.1, evoked responses to the second click in the click pairs are not diminished in
patients with schizophrenia, suggesting these patients have a defect in an inhibitory gating mechanism (Adler et al. 1998). Over the past two decades, this finding has been replicated by most (Adler et al. 1982; Freedman et al. 1983; Boutros et al. 1991; Judd et al. 1992; Adler et al. 1993; Freedman et al. 1996; Clementz et al. 1997; Erwin et al. 1998; Raux et al. 2002; Ghisolfi et al. 2002; Thoma et al. 2003) but not all studies (Kathmann and Engel 1990; Jin et al. 1998). Inhibitory failure during sensory gating has also been found in first degree relatives of schizophrenia patients (Waldo et al. 1988; Adler et al. 1992; Siegel et al. 1984; Clementz 1998; Myles-Worsley 2002; Wegrzyn and Wciorka 2004; Louchart-de la Chapelle et al. 2005). The fact that these gating abnormalities occur in approximately half of all first degree relatives in an apparent autosomal-dominant pattern suggests these deficits represent factors that increase vulnerability to schizophrenia (Freedman et al. 1997).

Fig. 5.1. Sensory gating deficits in schizophrenia. The P50 auditory evoked response to clicks 500 ms apart is indicated by the tick below the tracing. The ratio between the amplitude of the second or test response and the first or conditioning response is used as a measure for sensory gating. The control subject has a diminished response to the second stimulus. The subject with schizophrenia lacks inhibitory gating mechanisms. After Adler et al. 1998.