Prepulse inhibition (PPI) refers to the attenuation of the amplitude of the startle reflex in response to sudden intense stimuli (pulse) if preceded by a weaker sensory stimulus (prepulse). PPI reflects sensorimotor gating i.e. the ability to filter out irrelevant information in the early stages of processing so that attention can be directed to more salient environmental features. Recent neuropsychological studies show greater PPI in healthy individuals with superior performance on tasks that rely on the integrity and efficiency of prefrontal cortical (PFC) function. The PFC is an important node in the cortico-striato-pallido-thalamic circuitry, which modulates PPI. PFC function has been examined in relation to the COMT Val158Met polymorphism, which determines basal PFC dopamine (DA) neurotransmission levels and consequently, performance on PFC DA-dependent cognitive tasks. Met/Met individuals have the best PFC performance or greater ''efficiency'' and the highest PPI, Val/Val the worst performance and the lowest PPI, and Val/Met intermediate performance and PPI. Consistent with the increasingly accepted model of an inverted U-shape relationship between PFC DA levels and PFC function, the COMT inhibitor tolcapone as well as attention-to-prepulse, increase PPI in Val/Val individuals, while Met/Met individuals are unaffected or get worse. These findings strongly suggest that inhibition at the early stage of information processing is modulated by the PFC DA activity in a ''top-down'' fashion and this may account for the normal inter-individual variability in PPI and in cognitive performance.

S57.04

Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia

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Schizophrenia patients exhibit impairments in prepulse inhibition (PPI) of the acoustic startle response (ASR). PPI is commonly used as an index of sensorimotor gating. Results of animal studies and some human data suggest that PPI deficits are in part genetically determined, such that PPI could be an endophenotypic indicator of risk for schizophrenia, Thus, PPI deficits should already be present prior to onset of psychosis. To test this assumption, we investigated PPI in individuals with prodromal symptoms of schizophrenia and patients with first-episode schizophrenia.

Startle reactivity, habituation, and PPI of ASR were assessed in 54 subjects with prodromal symptoms of schizophrenia (35 at an early prodromal stage, 19 at a late prodromal stage), 31 first episode schizophrenic patients (14 unmedicated, 17 medicated), and 28 healthy controls. Patients were also examined with the Positive and Negative Symptom Scale and the Global Assessment of Functioning Scale.

Prodromal subjects and unmedicated patients with first episode schizophrenia showed significant PPI deficits, whereas schizophrenic patients treated with risperidone had almost normal PPI. In contrast, startle reactivity decreased with severity of symptoms but was relatively unimpaired in the medicated patients. With respect to habituation, prodromal subjects and schizophrenic patients did not differ from healthy controls.

PPI disruption is present in subjects in a prodromal state likely to proceed to schizophrenia, supporting the hypothesis that PPI disruption is an endophenotype of schizophrenia. In contrast, startle reactivity and habituation deficits were not evident in the prodromal subjects, but only in unmedicated patients with diagnosis of schizophrenia.

S57.05

Imaging and pharmacological studies of prepulse inhibition in schizophrenia

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A key feature of schizophrenia is the inability to screen out irrelevant sensory input. Prepulse inhibition (PPI) of the startle response, a cross-species measure of sensorimotor gating, provides a valuable opportunity to study this feature. Patients with schizophrenia, first-degree relatives of patients with schizophrenia, patients with schizotypal personality disorder and healthy individuals scoring high on psychometric measures of psychosis-proneness display reduced PPI. Animal models of disrupted PPI have proved valuable for the evaluation of existing and potential new treatments for schizophrenia. Animal studies have also shown that PPI is modulated by the cortico-striatal-pallido-thalamic circuitry involving the prefrontal cortex, thalamus, hippocampus, amygdala, nucleus accumbens, striatum, ventral pallidum, globus pallidus, and subpallidal efferents to the pedunculopontine nucleus. Recent neuroimaging data from our and other laboratories confirm the involvement of this circuitry in (a) normal PPI in healthy people, (b) deficient PPI in patients with schizophrenia and related conditions, and (c) the effects of pharmacological agents relevant to the treatment of schizophrenic illness.

Symposium: The cognitive abnormalities as markers of abnormal brain activation

S61.01

Cognitive assessment using cog-test battery of abnormal brain activation

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Cognitive impairment is a core deficits in schizophrenia and in bipolar disorders. The cognitive dysfunctions are related to the abnormal brain activation in these illnesses. Working memory and executive dysfunctions associated with prefrontal cortex abnormalities in these illnesses are known as an neuropsychological marker of vulnerability to the diseases.

The most important methods used in assessment of abnormal brain activation are neuroimaging methods and neuropsychologial tests. Current data show high coincidence between the level of performance on cognitive tests and activation of the brain. The data obtained in patients with schizophrenia and bipolar disorder show the significant association between level of hypofrontality (decrease of blood flow and intensity of glucose metabolism) and the level of impairment of the performance of prefrontal tests.

The Cogtest Battery it the novel computerized neuropsychological battery used for cognitive screening in different mental and neurological diseases. This battery consisted with tests for evaluation different domains of cognition, such as frontal functions (working memory and executive functions), verbal abilities (connected mostly with left hemisphere activation), attention, psychomotor speed, spatial and motor performance, memory and learning (associated with temporal lobe activation). Based

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