81. A COGNITIVE, PERCEPTUAL, AND MOTOR STUDY OF HEMISPHERIC ASYMMETRY IN THE MAJOR PSYCHOSES

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Studies have demonstrated asymmetric hemispheric dysfunction in patients with schizophrenia and bipolar disorder. However, few studies have compared directly the dysfunction in schizophrenia to that of bipolar disorder, and few have studied hemispheric asymmetries across modalities, which could address regional specificity of lateralized hemispheric dysfunction. We assembled a battery of assessments designed to measure lateralized hemispheric function of the following modalities: sensory information processing and arousal ( dichotic listening, chair identification, consonant-vowel-consonant test), memory (Warrington recognition memory test), and motor (hand force instability, velocity scaling, reaction time). To date, 19 right-handed male patients with schizophrenia (N = 11) and bipolar disorder (N = 8) have been assessed to determine whether differences in lateralized performance appear across multiple modalities. Effect sizes between diagnostic groups were large for L-R (left minus right) scores for chair identification and velocity scaling and medium for hand force instability. In measures purported to reflect dopaminergic tone (velocity scaling and hand force instability), schizophrenia patients showed diminished right hemispheric function relative to the left, whereas bipolar patients showed diminished left hemispheric function relative to the right. In a measure purported to reflect hemispheric arousal (chair identification), the reverse was true: schizophrenia patients showed diminished left hemispheric function relative to the right, whereas bipolar patients showed diminished right hemispheric function relative to the left. These findings support the literature demonstrating a hemispheric imbalance in schizophrenia and bipolar disorder. They also suggest that the hemispheric dysfunction in psychosis is complex and may be related to either increased activity in one hemisphere or decreased activity in the other hemisphere. They also indicate that there may exist different mechanisms of hemispheric control, one responsible for motor activity and another for arousal.

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82. NEUROPSYCHOLOGICAL EVALUATIONS OF HIGH RISK ADOLESCENTS FOR SCHIZOPHRENIA

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Early detection is critical to the treatment and understanding of schizophrenia. Children of one schizophrenic parent have a 10–15% risk of having schizophrenia themselves, compared to the risk of 1% for the general population. Through research with children and adolescents at high risk for schizophrenia, it may be possible to find vulnerability markers, which would allow for a greater understanding of this disorder. Schizophrenic adults have shown to have greater difficulties with executive functions and attention, which we are able to assess using neuropsychological testing. The Continuous Performance Test (CPT) and the Wisconsin Card Sorting Test (WCST) were administered to high-risk adolescents (n = 14, mean age 16.07 ± 2.02) and controls (n = 18, mean age 16.06 ± 1.63) between the ages of 13–19 in an on going study of neuropsychology and Magnetic Resonance Spectroscopy (MRS). Subjects were administered the Diagnostic Interview for Children and Adolescents or the Structured Clinical Interview for DSM IV (DC-CI) depending on age, to rule out any psychopathology. Statistical analysis using paired t-tests showed significant differences in the General Assessment of Functioning (GAF) between the high risk and controls between the ages of 16–19 years old (p = .05), but not for the subjects ages 13–15. Results of the CPT showed trend differences in the number of commissions (p = .09), and rates of attentiveness (p = .18) with controls performing at a higher level. Differences were not found in the WCST scores. These results must be considered preliminary given the small sample size.

83. PHARMACOLOGY OF PSYCHOTIC-LIKE ABNORMALITIES EXPRESSED BY REELER HETEROZYGOUS MOUSE

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Reelin is not only essential for the normal development of the telencephalon and cerebellum, but this protein also exerts a continued neurotrophic function in the adult. Reelin and its mRNA are decreased by approximately 50% in the postmortem brain of schizophrenic patients (PNAS 95: 15718–15723, 1998) and bipolar patients with psychosis. Glutamic acid decarboxylase 67 (GAD 67), an enzyme critical for GABAergic function in the brain, is also decreased. Parallel to these findings in postmortem psychotic brain, we recently found in reeler heterozygous mouse (rele+/−): a) a 50% decrease of reelin mRNA and protein compared with wild type (rele+/+); b) a maldistribution of NADPH-d neurons in medial prefrontal cortex vs underlying white matter; c) neophobia on the elevated plus-maze; d) a deficient prepulse inhibition of startle, or PPI (Neuroreport 10: 1999); and e) a decrease in GAD 67 mRNA of more than 50% in frontoparietal cortex. Imidazenil is an allosteric modulator of the benzodiazepine binding sites located on GABA A receptors and is devoid of sedation or of tolerance and dependence liability. In rele+/− mice, a single dose of imidazenil increases prepulse inhibition of startle in a dose-dependent manner without affecting the overall level of startle. The effects of acute and chronic treatment with imidazenil compared with diazepam or saline controls on behavior and GABA function will be presented using the rele−/+ mouse as a model for psychosis. Our experience with imidazenil suggests that it would be an ideal drug for future testing in psychiatric patients.

84. CLINICAL CORRELATES OF STRUCTURAL BRAIN ABNORMALITIES IN SCHIZOPHRENIA

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Although most longitudinal imaging studies suggest that structural brain abnormalities (SBA’s) in schizophrenics are not progressive, some
investigators have found evidence of progressive deterioration in SBA’s in patients who are treatment refractory. We will be examining the association of duration of illness, treatment response and positive and negative symptoms with structural brain abnormalities in 57 schizophrenic patients compared to healthy controls matched for age, SES, gender and handedness. The first patient group has less than 5 years duration of illness (n = 32) and the second patient group will be chronic patients who have more than 10 years duration of illness (n = 25). MR images will be processed using MRX software. This software can employ the contrasts from both images of a dual echo set (proton density and T2 weighted images) to segment tissue types. Volumetric assessments will be made for the whole brain volume, total brain white and gray matter, gray and white matter in the left and right hemispheres, total ventricles, and total ventricles, be made for the whole brain volume, total brain white and gray matter, weighted images) to segment tissue types. Volumetric assessments will be made for the whole brain volume, total brain white and gray matter, gray and white matter in the left and right hemispheres, total ventricles, left and right lateral ventricles, 3rd ventricle, hippocampal complex (hippocampus-amygdala), caudate nucleus, and putamen. We hypothesize that: (1) treatment refractory patients will have more SBA’s than treatment responsive patients and (2) within the treatment refractory group, longer duration of illness will be associated with more structural brain abnormalities, and this will provide evidence supporting the hypothesis of progressive deterioration in treatment refractory patients.

85. DISTURBANCES OF AUDITORY INFORMATION PROCESSING IN SCHIZOPHRENIA REFLECTED BY MMN

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Cognitive dysfunction in schizophrenia is associated with disturbances of working memory systems. The mismatch negativity (MMN), a short latency event-related potential, can be used as an objective measure of echoic memory. Reduction of MMN in schizophrenia patients has been shown in several studies. Effects of the antipsychotic medication are discussed controversially.

The mismatch negativity (MMN), elicited by an auditory odd-ball paradigm with rare (20%) deviant 1200 Hz stimuli and 1000 Hz standards, was recorded in frontal and central electrode sites. Fifty-seven schizophrenia patients and forty-four healthy controls were included. Schizophrenia subgroups consisted of 21 unmedicated patients (never medicated: n = 11) and 36 medicated patients (typical neuroleptics: n = 12, risperidone: n = 24). The MMN amplitude was measured as the first negative peak of the difference wave obtained by subtracting ERP’s for standard from those for deviants.

The MMN amplitude was significantly reduced in patients compared to controls. Furthermore, patients medicated with typical neuroleptics exhibited a significantly lower MMN amplitudes than did unmedicated patients. Never medicated patients exhibited lower MMN amplitudes in central electrode sites, whereas MMN amplitudes in frontal electrode sites were higher compared to controls.

The present findings support the hypothesis of an impairment in automatic processing of auditory stimuli in schizophrenia reflected by the MMN and indicate differential influences of antipsychotic medication on auditory echoic memory functions. Further research is necessary to elucidate, why never medicated patients exhibit higher MMN amplitudes in frontal sites. This might reflect an overexcitatory processing of auditory stimuli.

86. EFFECTS OF MEDICATION ON N100 TOPOGRAPHY IN SCHIZOPHRENIA

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N100 is an event related potential (ERP) component appearing about 100 ms after an auditory stimulus. In schizophrenia patients a deficit in auditory information processing is assumed, which has been shown for an earlier ERP component, the P50, as well as for later components, e.g., the mismatch negativity (MMN) or the P300.

Forty-nine schizophrenia patients (24 unmedicated, 25 treated with antipsychotic medication) and thirty-nine healthy controls were investigated. ERPs elicited by an auditory odd-ball paradigm were recorded according to the 10/20 system. Frequent stimuli (80%) consisted of 1000 Hz sounds (75 dB SPL), rare stimuli (20%) of 1200 Hz sounds (75 dB SPL). Mean amplitudes were normalized by a scaling procedure. Peak amplitudes as well as mean amplitudes were analysed with multifactorial ANOVAs.

The total group of schizophrenic patients showed significantly lower N100 amplitudes in central sites in comparison to the control group. This was also true for both, the medicated and the unmedicated subgroup. An effect of location was only observed in the medicated subgroup, having significantly lower mean amplitudes in frontal sites than controls.

In central, but not in frontal sites, the decrease of the N100 amplitude in schizophrenia patients was independent from medication. The topographic findings indicate differential effects of illness and medication on neural subsystems involved in auditory stimulus processing. Thus, it can be assumed that the N100 amplitude reduction in central sites has a very close association with the illness itself and is a robust parameter to discriminate between schizophrenia patients and healthy controls.

87. ATTENTION AND MEDICATION IN SCHIZOPHRENIA—AN ERP STUDY

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Attentional deficits are one of the main symptoms in schizophrenia. The “negative difference” (Nd) has been described as an electrophysiological correlate of attentional effects. The Nd is obtained by subtracting the event related potential (ERP) wave to unattended stimuli from the ERP wave to the same kind of stimuli when being attended. Therefore, the Nd has been interpreted as a correlate of an “attentional trace.” It is well known that attention may be impaired by antipsychotic medication. Controversial results have been published concerning the influence of antipsychotic medication on auditory ERPs.

In fifty-two schizophrenia patients (19 unmedicated, 36 medicated) and thirty-one healthy controls the negative difference (Nd), elicited by nonattended and attended sounds, was compared. For stimulation, an auditory odd-ball paradigm with rare (20%) deviant 1200 Hz stimuli and 1000 Hz standard stimuli was used. ERPs were recorded in frontal and central electrode sites. Data were acquired with an A/D rate of 500 Hz, 0.1 Hz high-pass, and 70 Hz low pass filter. Off line, a 30 Hz low pass filter, an ocular artifact correction, and a ± 50 µV artifact rejection criterion were applied.

Nd was significantly reduced in the total group of patients compared to controls (Cz, Fz). ANOVA with controls and schizophrenia subgroups