71. ELEVATED DOPAMINE-INDUCED Gs PROTEIN MEASURES IN PATIENTS WITH SCHIZOPHRENIA

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Heterotrimeric G proteins play a pivotal role in post-receptor information transduction and were previously implicated in the pathophysiology and treatment of mood disorders. Changes previously detected in G protein levels in postmortem brains of patients with schizophrenia could reflect effects of antipsychotic medication. The present study aims at quantitatively and functionally evaluating receptor-coupled G proteins in mononuclear leukocytes obtained from 23 untreated patients with schizophrenia and 30 healthy subjects, in an attempt to unravel a pattern of G protein measures in schizophrenia distinct from patterns previously described in mood disorders. Dopamine-enhanced guanine nucleotide binding capacity to Gs protein through D1 receptor in mononuclear leukocytes of untreated patients with schizophrenia was significantly increased in comparison with healthy subjects. β-adrenergic and muscarinic receptor-coupled G protein functions, as well as Gso, Gia and Gβδ immunoreactivities were similar to healthy subjects. These findings, distinctive for schizophrenia, unrelated to drug treatment, and differential from previous findings in mania and depression, may potentially help to differentiate between the major psychoses: schizophrenia vs. manic-depressive illness after the first psychotic episode.

72. A GENETIC VARIANT OF CCK PROMOTER REGION MAY LINK TO NEGATIVE SYMPTOM OF SCHIZOPHRENIA

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The finding that neuropeptide cholecystokinin (CCK) co-localized with dopamine in central nervous system has made CCK an important candidate gene for schizophrenia research. Several previous studies have found reduced CCK level in cerebrospinal fluid of schizophrenia patients. A more recent study reported a marked decrease of CCK mRNA in the frontal and temporal cortex of schizophrenia. In present study, mutation screens were carried out on the CCK gene by means of polymerase chain reaction. A C to T substitution was found in transcription factor Sp1 binding site of CCK promoter region. Such variation can affect the gene expression by altering the strand conformational polymorphism (SSCP). A C to T substitution was found in transcription factor Sp1 binding site of CCK promoter region may related to the negative symptoms of schizophrenia.

73. BCL-2 PROTEIN REDUCED IN SCHIZOPHRENIC TEMPORAL CORTEX

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Schizophrenia is an illness in which both neurodevelopmental and neurodegenerative processes have been implicated, yet the underlying pathophysiology remains elusive. Active apoptosis (programmed cell death) and altered Bcl-2 proteins have been documented in neurodegenerative disorders including Alzheimer’s disease. Involvement of apoptosis has also been hypothesized in schizophrenia. Apoptosis is regulated by Bcl-2 family proteins. Bcl-2 is a neuroprotective protein that inhibits apoptosis and can regenerate damaged CNS neurons. We hypothesized that Bcl-2 protein levels are altered in schizophrenic brain. Using ELISA, Bcl-2 protein was measured in postmortem temporal cortex (Brodmann area 21) from the Stanley Foundation Neuropathology Consortium in control, schizophrenic, bipolar, and depressed patients, n = 15 per group (matched on age, gender, and post-mortem interval). A priori, the primary analysis was limited to control versus schizophrenic specimens, given our underlying hypothesis. Bcl-2 levels were 25% lower in schizophrenic temporal cortex (21.9 ± 2.8 U/mg protein, mean ± SEM) compared to control (29.3 ± 2.1 U/mg protein) by Student’s t test (p = 0.046). In a secondary analysis we compared all samples. While Bcl-2 levels in all diagnostic groups were decreased compared to controls (schizophrenia < bipolar < depressed), ANOVA analysis was not statistically significant. Individual levels did not correlate with cumulative neuroleptic exposure. Interestingly, by combining schizophrenic and bipolar groups and separating them on neuroleptic naïve (n = 4) vs neuroleptic treated (n = 26) status, Bcl-2 levels in the treated group were higher (p = 0.034), demonstrating a potential neuroprotective role for neuroleptics. In conclusion, reduced Bcl-2 protein suggests a vulnerability to neurodegeneration through pro-apoptotic insults and/or atrophy in schizophrenic temporal cortex.

74. INHIBITORY DEFICITS IN STATE HOSPITAL SCHIZOPHRENIA PATIENTS

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Negative priming measures have been used extensively to evaluate sequential attentional processes in patient populations. Negative priming is a normal slowed reaction time to select items that were previously ignored. We have previously reported that unmedicated schizophrenia outpatients fail to exhibit normal negative priming (NP), while at the same time exhibiting within-trial inhibition equivalent to controls (Salo, Robertson & Nordahl, 1996). Previous studies have also reported that neuroleptic medication normalizes NP in outpatients and increases NP effects in controls (Beech, 1990; Salo, 1997). Since all of these studies were conducted with high functioning outpatients, it was of interest to conduct the same experimental procedure with chronic state hospitalized patients. In this study we tested 12 outpatients, 12 hospitalized inpatients and matched controls on a computerized Stroop negative priming paradigm. Both patient groups were medicated and matched on age, education and parental level of education. The controls were matched
the patients on age and parental level of education. Our results showed NP deficits only in the state hospitalized patients. Within-trial inhibitory processes were intact in both groups. Because the groups differed in length of illness and age of onset (p < .03), the findings suggest that severity of illness may contribute to the absence of NP effects over and above medication. Although neuroleptic medication may have a normalizing effect on sequential attentional processing in less chronic schizophrenia patients, the cognitive benefit may be limited in the more severely ill state hospital patients.

75. A PILOT TEST OF INTENSIVE COMPUTER-BASED COGNITIVE TRAINING IN SCHIZOPHRENIA

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Ten medicated subjects with schizophrenia, mean age of 36 years (range 18–64), illness severity ranging from mild to severe, and symptoms ranging from mainly positive to mainly negative or disorganized, were administered a detailed baseline clinical and neurocognitive assessment. Subjects then participated in an intensive computer-based cognitive training program (FastForward, Scientific Learning) originally designed for children with language-based learning disabilities. This program trains the spectro-temporal processing of sounds and phonemes as well as whole language sequencing and comprehension. The program continuously and incrementally adjusts the parameters requiring improved performance, while keeping tasks easy enough for patients to do well. As such this training experience requires sustained attention, auditory and verbal working memory and verbal short-term memory. Subjects trained for 100 minutes per day, 5 days per week, until training was completed (mean days of training = 50, range of 33–60). All subjects, including the most clinically impaired, were able to participate in the training program. Performance on the training exercises revealed consistent progress for all except two, who showed difficulty with the sound-based exercises. Analysis of data for the first 8 subjects shows statistically significant improvement in positive symptoms (p = .020), excited-agitated symptoms (p = .045), depressed-anxious symptoms (p = .033), and GAF (.024), as well as in neurocognitive tasks related to verbal/symbolic working memory and short-term verbal memory.

76. REACTION TIME SLOWING IN SCHIZOPHRENIA: DOMAIN-SPECIFIC FEATURES

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This study examines the relationship of lexical choice reaction time (CRT) to neurocognitive domains and symptom profiles, to address the issue of generalized cognitive inefficiency vs. domain-specific deficits. Sixty-five schizophrenic outpatients performed a lexical decision task and were assessed with a brief neuropsychological battery and an extended Positive and Negative Symptom Scale (PANSS-E). The schizophrenic group had a 25% slower CRT than a group of 20 normal controls (p < .001), and CRT was unrelated to age, illness duration or chlorpromazine equivalents, though correlated with verbal IQ and performance IQ (r = 0.29 and 0.50, respectively; p < .05 for both). CRT was correlated with positive symptoms (r = 0.38, p < .006), disorganized symptoms (r = 0.35, p = .004) and total symptoms (r = 0.27, p = .03). Among cognitive measures, CRT correlated with performance on Trails B (r = 0.41, p = .001) and visual memory span-backwards (VMS-B; r = 0.25, p = .05), but not with WCST, Stroop or sentence verification errors. To assess the contribution of non-lexical deficits, the above relationships were re-examined with partial correlations. Controlling for fullscale IQ preserved the CRT correlation with symptom scores; correlations with Trails B were reduced (r = 0.25, p = .06) and with VMS-B abolished. Controlling for fingertapping speed preserved all prior CRT correlations. Controlling for nonverbal (Ruff figural) fluency preserved the correlations with symptoms and Trails B but not with VMS-B. These findings suggest that slowing in this lexical task is related to impairments in the particular domain of attentional/working memory functions and not to a more generalized deficit. In addition, impaired semantic memory processing appears uniquely related to positive and disorganized symptoms.

77. NEUROCOGNITIVE FINDINGS IN SCHIZOPHRENIC SUBJECTS WITH ABOVE AVERAGE IQ

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Schizophrenia has been characterized as a disorder producing generalized deficits across multiple cognitive domains. We hypothesized that schizophrenic subjects with high IQ, while impaired in some domains, would show areas of preserved function. Using each WAIS-R subset and the full-scale test as sort criteria (VIQ, PIQ or FSIQ > 110) comparisons were performed between high-IQ (n = 10–18 depending on criterion) and average-IQ patients (n = 72–80), and high-IQ (n = 10–11), and average-IQ (n = 15–16) controls. Mean IQs for the groups created by these criteria were 118–120 (high) and 91–95 (low) for patients, and 120–123 and 97–101 for controls. Matching for IQ, comparison of patients to controls revealed different patterns of impairments in the high-IQ and average-IQ groups. Average-IQ patients were impaired on all tasks except Rey Copy and Recall (all criteria) and Stroop Color Naming (except PIQ). For high-IQ patients, Finger-Tapping (Dominant and Non-Dominant) and Stroop Color Naming were preserved regardless of sort criteria. However, in comparing the high-IQ groups, additional preserved functions were identified when the more specific scales were used. High- and average-IQ schizophrenic subjects performed differently from each other on Speed of Comprehension and Trails B regardless of sort method, on Rey Copy and Recall (sorted by PIQ), and on Stroop Color Naming (sorted by VIQ). These findings indicate that individuals with schizophrenia do not demonstrate generalized impairments in all cognitive domains, and that additional areas of preserved function are observed in “higher-functioning patients.”