

53. A MULTIMODAL EXAMINATION OF ANTERIOR CINGULATE CORRELATES OF IMPAIRMENTS IN TRIAL-TO-TRIAL PERFORMANCE ADJUSTMENTS IN SCHIZOPHRENIA

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Background: Deficits in cognitive control contribute to impairments in the ability of schizophrenic patients to self-regulate their behavior. Our recent studies provide evidence for the neuroanatomic basis of two dissociable aspects of cognitive control: the involvement of the prefrontal cortex (PFC) in the implementation of control, and the anterior cingulate cortex (ACC) in the detection of response conflict which signals the PFC for increased control. Our aim was to evaluate the contribution of impairments in conflict monitoring and ACC activation to the disturbances in cognitive control observed in schizophrenia.

Methods: We compared performance of schizophrenic patients and controls on a visual discrimination (Eriksen flankers) task. We employed standard behavioral, ERP and fMRI methods (previously described in van Veen et al. 2001; van Veen et al., 2002), with analyses focusing on trial-to-trial adjustments and associated ACC correlates.

Results: We found that the normal slowing in reaction times after error trials, is significantly diminished in the schizophrenic group. ERP results show schizophrenic patients demonstrating diminished amplitudes of both the error-related negativity (ERN), a negative deflection associated with error trials, and the N2, a component related to high conflict associated with incompatible stimulus trials. Consistent with the ERP results, our fMRI studies show analogous decreases for schizophrenic patients in ACC (BA 24/32) activation for both high conflict and error trials. ERP and fMRI results show good co-localization to the ACC.

Conclusions: Our multimodal examination of disturbances in cognitive control in schizophrenia revealed deficits in trial-to-trial adjustments with associated ERP and fMRI evidence of impairments in ACC activation.

54. THE NEURAL CIRCUITRY OF PERSISTENT LATENT INHIBITION AS A MODEL OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Latent inhibition (LI) is the proactive interference of inconsequential stimulus preexposure with its ability to signal significant events, and disrupted LI is considered to model positive symptoms of schizophrenia. Lesions of Nucleus accumbens core (NACC), prefrontal cortex and basolateral amygdala (BLA) have been reported to spare LI. However, certain drug and lesion manipulations produce abnormally persistent LI and we have suggested this may model the impaired set shifting associated with negative symptoms of schizophrenia. The present study tested the possibility that lesion of NACC, BLA and orbitofrontal cortex (OFC), will induce LI perseveration. Since an animal model aspiring to predictive validity for negative symptoms is expected to be sensitive to atypical but not typical neuroleptics, we tested whether this lesion-induced perseveration would be reversed by clozapine but not by haloperidol.

Methods: LI was measured in a thirst motivated conditioned emotional response procedure by comparing suppression of drinking in

response to a tone in rats which received 0 (nonpreexposed) or 40 tone presentations (preexposed) followed by 2 or 5 tone-shock pairings.

Results: Control rats showed LI with 40 preexposures and 2 conditioning trials, but raising the number of conditioning trials to five disrupted LI. In contrast, lesioned rats persisted in exhibiting LI under the latter conditions, and this was reversed by clozapine but not by haloperidol.

Conclusions: Our finding that NACC- OFC- and BLA- lesion induced LI persistence was normalized by clozapine but not by haloperidol supports the relevance of lesion- induced LI perseveration to negative symptoms. Since these structures are reciprocally connected and produce similar pattern of results, the results may be relevant to the neural circuitry underlying negative symptoms in schizophrenia.

55. LONGITUDINAL NEUROPSYCHOLOGICAL FINDINGS 10 YEARS AFTER ILLNESS ONSET

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Background: It is now widely recognized that cognitive dysfunction in schizophrenia is a core deficit and may be more strongly related to clinical outcome than either positive or negative symptoms. Yet the longitudinal course of neuropsychological function in this disorder has not been fully delineated. Many studies have found that cognitive dysfunction is below average (1 to 2 sds) at the onset of illness and remains stable in the first five years of illness (Hoff et al., 1999). However, our data also suggested that some cognitive abilities may be more vulnerable to decline than others. We present data on a cohort of first episode patients who have been re-tested 10 years after the onset of illness to determine if cognitive abilities remain stable and if they are related to volumetric brain measurements or to clinical outcome.

Methods: Patients diagnosed with schizophrenia or schizoaffective illness received structured psychiatric interviews, symptom ratings, neuropsychological testing, and brain MRI measurements at the onset of illness and 10 years later. Controls were also evaluated.

Results: Similar to controls, patients improved on tests of visual memory, mental processing speed, cognitive flexibility, and pure motor speed, but did not improve on measures of verbal memory or showed mild decline. Improvements on neuropsychological testing were not associated with change in symptoms nor brain volume change. Female patients showed more cognitive improvement than male patients.

Conclusions: Consistent with our earlier findings, most cognitive domains are stable or mildly improved over the first 10 years of illness while verbal memory appears to decline. The lack of resilience in verbal memory functions may be related to preferential reductions in left temporal lobe structures found by some investigators.

56. NORMALIZATION OF WORKING MEMORY IN SCHIZOPHRENIA FOLLOWING COGNITIVE REMEDIATION: DURABILITY OF EFFECTS

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Background: Cognitive impairments in schizophrenia are widespread and have been proposed to mediate functional outcome. Neurocognitive