adult age. The latter effect was apparent in post-mortem immunohistochemical analyses of the cell proliferation marker BrdU and the microtubule-associated protein DCX, a marker of newborn neuronal cells. Chronic CLZ treatment significantly improved the prenatal PolyI:C-induced working memory deficits, whist at the same time, it negatively affected working memory performance in adult offspring born to control mothers. These bidirectional cognitive effects of clozapine were not paralleled by concomitant effects on adult hippocampal neurogenesis.
Discussion: Our findings do not support the hypothesis that the atypical antipsychotic drug clozapine may influence cognitive functions by acting on adult neurogenesis in the hippocampus, regardless of whether the drug is administered to subjects with or without a neurodevelopmental predisposition to adult neuropathology.

doi:10.1016/j.schres.2010.02.709

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THE EFFECT OF NON-COMPETITIVE NMDA RECEPTOR ANTAGONIST MK801 ON HIPPOCAMPUS-PREFRONTAL CORTEX SYNAPTIC RESPONSES AND EXECUTIVE COGNITIVE FUNCTION IN RATS

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Background: Evidence suggests that the pathogenesis of schizophrenia cognitive symptom may involve abnormalities in glutamatergic transmission. Particularly, non-competitive antagonists of N-methyl-D-aspartate (NMDA) receptors such as phencyclidine and MK801 are known to cause cognitive states resembling schizophrenia in healthy humans and exacerbate preexisting symptoms in the patients. In rats, the administration of MK801 alters neuronal activity in the prefrontal cortex (PFC) as well as impairs executive cognitive function. In this study, we tested the effect of MK801 on synaptic responses of the cognitively important, hippocampus-PFC pathway and on executive cognitive function in rats.
Methods: Male Sprague-Dawley rats (350-400 g) were anesthetized by urethane (1.5 g/kg, i.p.) and placed in a stereotaxic frame (body temperature maintained at 37 ± 0.1 °C). A recording electrode was placed in the mid layer of the prelimbic area (rat PFC), and a stimulating electrode in ventral hippocampus. The electrode positions were adjusted to obtain the maximum amplitude of postsynaptic potential, whose peak appears with an 18.0-20.0 ms delay after stimulus artifact. The intensity of stimulation was set to evoke 60% of the maximum response (300-500 μA). The protocol for behavioral analysis followed Birrell and Brown (J Neurosci, 20, p4320, 2001).
Results: Single injection of MK801 (0.1 mg/kg i.p.) induced a gradual potentiation of the evoked responses which reached a significant level 2 hours after injection (63 ± 10 at 2 hours, $n = 12$) compared with saline control ($11 \pm 6.6\%$, $n = 10$, $p < 0.0005$). This MK801-induced potentiation does not require tetanic stimulation unlike the standard forms of long-term potentiation (LTP). Furthermore, significant MK801-induced LTP was induced even when single test stimuli (at 0.033 Hz) were stopped for 1 hour from the time of MK801 injection ($32 \pm 2.8\%$ at 2 hours, $n = 5$, $p < 0.001$ compared with saline control, $0.7 \pm 2.2\%$, $n = 7$), suggesting that the MK801-induced LTP occurs in the manner independent of synchronized synaptic stimuli. However, MK801-induced LTP appears to share the common mechanisms with the standard LTP, since a prior induction of LTP by tetani (50 pulses at 250 Hz, repeated 10 times at 0.1 Hz; such a train was applied twice with 6 min interval) severely occluded a subsequent MK801-induced LTP (19 ± 7.5, $n = 7$, $p < 0.005$). MK801-induced LTP was blocked also by prior injection of MAP kinase inhibitor SL-327 (10 mg/kg, i.p., $19.2 \pm 9.1\%$, $n = 5$, $p < 0.01$) and of mGluR2/3 agonist LY379268 (3 mg/kg, i.p.; $0.2 \pm 2.0\%$, $n = 5$, $p < 0.005$). Behavioral data showed that the injection of MK801 impairs PFC-dependent extra-dimensional set shifting ($p < 0.05$). In another series of experiments, we tested the effect of repeated injections of MK801 (7 or 14 daily injections) on a subsequent induction of LTP by tetani. We had verified that tetani delivered 24 h after single MK801 can induce clear LTP ($85 \pm 17\%$, $n = 5$). But tetani delivered 24 hours after a 7th daily injection of MK801 induced LTP only in 3 out of 6 animals, and tetani 24 hours after a 14th injection resulted in no LTP ($-11 \pm 4.1\%$, $n = 7$, $p < 0.001$). LTP was still absent 72 hours after the 14th daily injection ($-3.1 \pm 6.4\%$, $n = 4$, $p < 0.001$). Rats injected with the 14-daily MK801 showed severe impairments in the attentional set shifting task.
Discussion: These results suggest that MK801 induces an aberrant form of LTP in the hippocampus-PFC pathway. When injection is repeated, MK801 blocks a subsequent LTP induced by tetanic stimuli. We are currently testing the role of PFC dopamine receptors for the MK801-induced LTP.

doi:10.1016/j.schres.2010.02.710

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TARGETING PLANNING AND PROBLEM SOLVING VERSUS BASIC COGNITION IN COGNITIVE REMEDIATION FOR PATIENTS WITH SCHIZOPHRENIA

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Background: The importance of cognitive impairment for functional outcome in patients with schizophrenia has led to the development of cognitive remediation programs designed to improve cognition. These interventions have targeted a wide range of cognitive functions. However, there are no direct comparisons between treatment programs addressing cognitive functions on different levels of complexity in a rehabilitation setting. The purpose of this study was to assess whether a planning and problem solving training is more effective in improving functional capacity in patients with schizophrenia than a traditional training program addressing basic cognitive functions.
Methods: Eighty-nine patients with schizophrenia or schizoaffective disorder were randomly assigned either to a training of planning and problem solving or a training of basic cognition. The dependent variables included functional capacity as a proxy measure for functional outcome, problem solving and planning ability. Assessment of the primary outcome was blind to group allocation. Participants received computer-assisted cognitive training three times a week over a three week period.
Results: A main effect of time indicated that both groups improved in functional capacity during the study. Calculation of the reliable change index suggests that this improvement is clinically significant. Contrary to our main hypothesis, no significant time x group interaction was

found for functional capacity suggesting that both types of training can improve functional capacity similarly. Measures of planning and problem-solving showed a similar pattern with an advantage for planning and problem solving training on one measure.
Discussion: Our results are in line with previous studies reporting an improvement of functional capacity when cognitive remediation is combined with other rehabilitation methods. However, a differential effect of targeting different cognitive functions on functional capacity remains to be established.

doi:10.1016/j.schres.2010.02.711

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FEASIBILITY STUDY OF MULTI-SITE COGNITIVE REMEDIATION IN THE SCHIZOPHRENIA TRIALS NETWORK (CRSTN)

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Background: The NIMH MATRICS Project and related efforts have stimulated the initiation of several studies of treatments for cognitive impairment in schizophrenia. Cognitive remediation may provide an excellent platform for the provision of new learning opportunities and the acquisition of new skills for patients who are engaged in pharmacologic trials to improve cognition. However, it is not clear whether cognitive remediation intervention would be feasible for large trials involving sites without specific cognitive remediation expertise. We sought to address the feasibility of a multi-site trial of cognitive remediation in schizophrenia, called the Cognitive Remediation in the Schizophrenia Trials Network (CRSTN) study.
Methods: Nine sites from the Schizophrenia Trials Network, formerly the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, were involved in the study. Each site was expected to enroll six patients with chronic DSM-IV schizophrenia over the course of approximately 3 months, estimating a reasonable rate of recruitment for a large-scale efficacy trial. Raters were certified on the MATRICS Consensus Cognitive Battery (MCCB) as the primary outcome measure, the 2nd edition of the UCSD Performance-based Skills Assessment (UPSA-2) as a co-primary measure, and key secondary measures including the Cognitive Assessment Interview (CAI) and trained on the Positive and Negative Syndrome Scale (PANSS). Patients met the following criteria: age 18-55; not fully satisfied with current level of functioning and able to identify functional goals; no hospitalization in last 8 weeks; no change in medication regimen in last 4 weeks; PANSS delusion and hallucination item scores ≤ 5, conceptual disorganization item score ≤ 4, and Calgary Depression Scale total score ≤ 10; WTAR > 5. Patients were randomized to one of two treatment conditions: 1. the PositScience Brain Fitness auditory training program with weekly 'bridging groups' adapted from the Neuropsychological Educational Approach to Remediation (NEAR), that help patients to learn how cognitive improvement can be applied to functional benefit in everyday life; or 2. a control condition that involved computer games and weekly healthy lifestyles groups. Patients were expected to complete the one-hour auditory training intervention or computer game activities 3-5 times per week until study end, which was 40 sessions or 12 weeks, whichever came first. Efficacy with the MCCB and UPSA-2 was assessed after 20 sessions and study end. The key indicator to evaluate the feasibility of this study was rate of enrollment, retention, and completion rate of primary outcome measures.
Results: Within the 3-month enrollment period, 67 patients signed consent, 60 patients were screened, and 53 were enrolled, one short of the maximum allowed. As of the date of abstract submission, 3 patients (1 receiving cognitive remediation) had terminated the study, and 32 patients had completed the trial. Of these, 26 completed the maximum 40 sessions and the other 6 patients completed an average of 30 sessions in 12 weeks. Weekly attendance in the bridging groups was excellent. Efficacy data will be available at the time of this presentation.
Discussion: In terms of training, enrollment and study completion, multi-site trials of cognitive remediation using the PositScience auditory training program with the NEAR method of weekly bridging groups appear to be feasible, supporting large-scale efficacy trials of cognitive remediation and the use of cognitive remediation as a potential platform for large-scale drug trials.

doi:10.1016/j.schres.2010.02.712

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CONCEPTUAL BACKGROUND OF IMAGING STUDIES IN PSYCHOTHERAPY RESEARCH: THE EXAMPLE OF CBT INTERVENTIONS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Cognitive behavioural therapy (CBT) is an important treatment in conjunction with psychopharmacotherapy in schizophrenia. However, there is only very little research on the effects of such interventions on brain function. Recent studies have suggested that jumping to conclusions and a specific attributional style is a predominant cognitive style in patients which might lead to the development of delusions.
Methods: In this multi-centre fMRI trial, we investigated the effect of CBT on neural correlates of "jumping to conclusions" and the "attributional style" in patients with schizophrenia. Eighty patients and 80 control subjects were recruited in six centres and measured with 3-Tesla functional magnetic imaging (fMRI) before and after 9 months of cognitive behavioural therapy.
Results: It could be shown that CBT ameliorates differences in brain activations between patients and controls after nine months.