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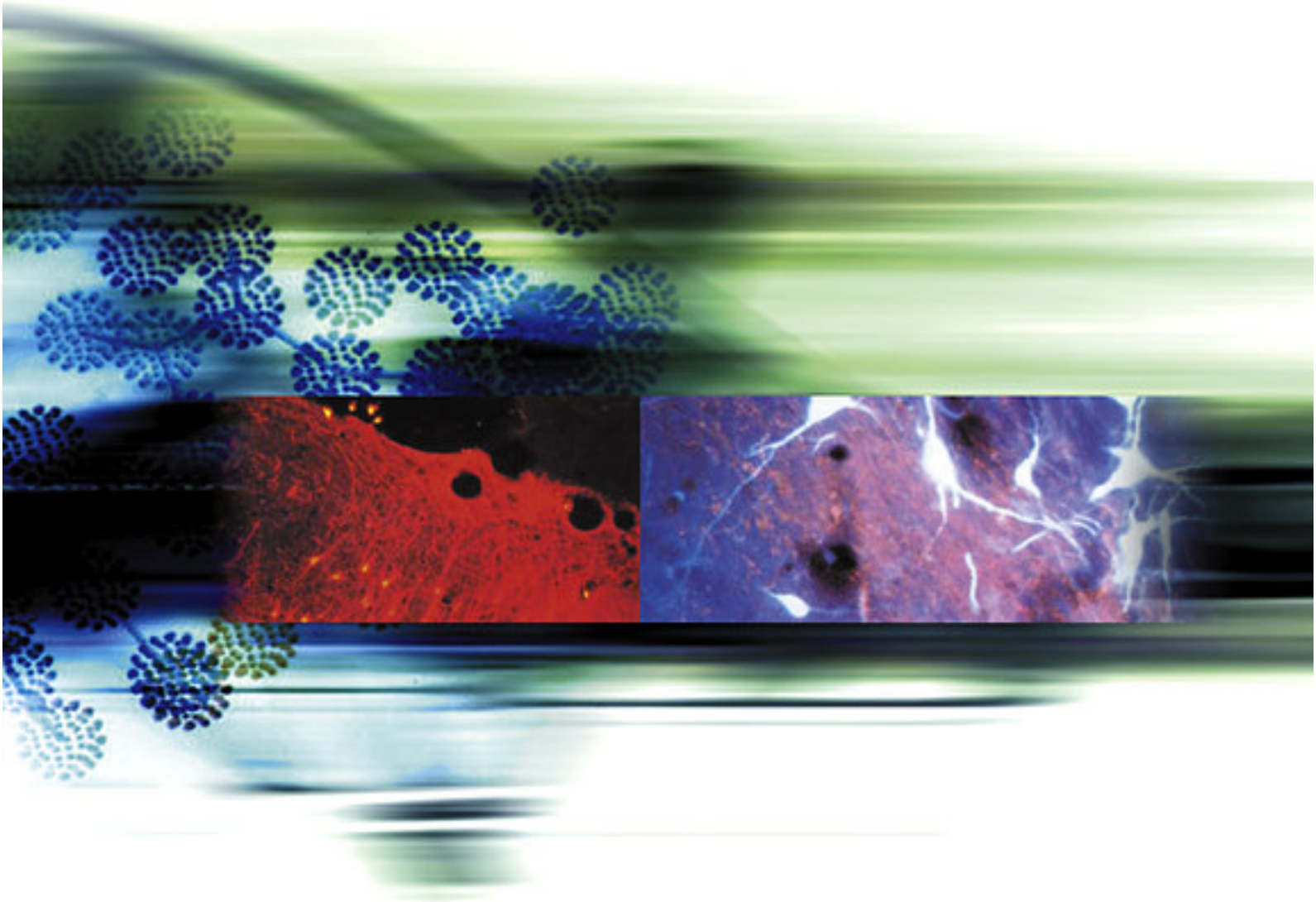

have not clearly or consistently documented associations between prefrontal cortex activation abnormality and presence of negative symptoms [for a review see 1]. The aims of the current study were to validate a new executive fMRI paradigm and to examine its association with negative symptoms in schizophrenia.

Methods: Thirty-five patients meeting DSM-5 criteria for schizophrenia/schizoaffective disorder and 25 healthy controls, matched for age, sex and pre-morbid IQ, underwent fMRI scanning while performing a modified version of the computerized multiple elements test (CMET) [2]. This paradigm is designed to capture goal management and multitasking aspects of executive function in a more ecological way than conventional tasks. In the experimental condition (EXEC) subjects have to switch between four videogame-like tasks without prompts whilst in the control condition (CONT) task switching takes place automatically.

In the patients, negative symptoms severity was evaluated using the Clinical Assessment Interview for Negative Symptoms (CAINS), which has two expression (EXP) and motivation/pleasure (MAP) subscales. [3]

General linear models were used to obtain whole-brain maps of activation/deactivation for the contrast EXEC $>$ CONT, including age, sex and pre-morbid IQ as nuisance factors. Group comparison was performed using a mixed-effects GLM ($p < 0.05$, cluster corrected). In the patient group we performed a regression analysis to examine whether brain activations/deactivations were associated with negative symptom severity.

Results: In the contrast of interest (EXEC $>$ CONT), healthy controls showed activation in bilateral dorsolateral prefrontal cortex (DLPFC), insula, anterior cingulate cortex (ACC) and inferior parietal gyrus (IPG), and deactivation in the orbitofrontal cortex (OFC). Schizophrenic patients showed activation in the right DLPFC, the bilateral ACC, the left insula and the right IPG; deactivation was observed in the left middle temporal gyrus. Group comparison showed less activation in the patients in the bilateral DLPFC and ACC, mostly on the right, and the left precentral, postcentral and supramarginal gyri.

There were no clusters of significant correlation between the EXP-CAINS subscale scores and negative symptoms in the patients, but a significant negative correlation was seen between the MAP-CAINS subscale scores and activation in right IPG, the bilateral precuneus, the left cerebellum and the right occipital pole.

Conclusions: The CMET task shows sensitivity to executive function assessment in healthy controls and schizophrenic patients, the latter showing reduced activation in regions involved in executive functions, ie the PFC and ACC. We found no evidence of reduced prefrontal/anterior cingulate CMET-related activation in relation to negative symptoms, although there was evidence that reduced activation in inferior parietal and precuneus was related to the decreased motivation and inability to experience pleasure components of the syndrome [4].

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P.603 Agmatine attenuated sensorimotor gating deficit in schizophrenia model in rats: Combination of neonatal MK-801 and isolation rearing

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Background: Schizophrenia is one of the major psychiatric disorders with approximately 1% prevalance. It has been thought that neurodevelopmental deficits such as trauma and injury play critical role in schizophrenia etiopathogenesis. Besides glutamatergic N-methyl-D-aspartate (NMDA) receptors has been found hypoactive in schizophrenic patients. Recently, it has been proved that the combination of neonatal MK-801 administration and post weaning social isolation (SI) models (MK-801+SI) might be a valuable model to mimic schizophrenia like behavior in rats [1]. Agmatine is an endogenous amine synthesized from decarboxylation of arginine, which has been thought to play a role as a neurotransmitter/neuromodulator. It binds to imidazoline and alpha-adrenergic receptors, blocks nicotinic acethylcholine, serotonergic 5-HT3, glutamatergic NMDA receptors and inhibits nitric oxide synthase. Limited number of studies has conflicting results about effectiveness of agmatine on animal model of schizophrenia. Our recent study clearly showed that agmatine has beneficial effects on MK-801 model of schizophrenia in rats [2]. Herein, the aim of our study is to investigate the effect of agmatine treatment in neurodevelopmental model of schizophrenia in rats.

Methods: Sprague Dawley rat pups were used and grouped as vehicle (Dimethyl sulfoxide), MK-801+SI (0.2 mg/kg; ip.), MK-801+SI+Agmatine (40 mg/kg; ip.), MK-801+SI+Clozapine (5 mg/kg; ip.) ($n = 7$/each group). Rat pups received MK-801 (0.2 mg/kg) once a day in a volume of 0.1ml/100 g during postnatal day (PND) 7-10. All pups housed in groups until PND 21, which is accepted as mean weaning time. After PND 21, all pups except control group transferred to individual cages for isolation rearing. Agmatine and clozapine were injected once a day for 7 days after SI protocol for 8 weeks. Locomotor activity to a novel environment (two consequtive five min trials),

novel object recognition (one hour intertrial interval) and prepulse inhibition of acoustic startle response tests (70 dB background, 74, 78 and 86 dB prepulses and 120 dB pulse) were conducted on the 5th, 6th and 7th days of treatment, respectively. One-way analysis of variance followed by Dunnett's post hoc test was used for statistical analysis.
Results: MK-801+SI administered rats' locomotor activity were increased ($p<0.05$) in the second five minutes of test, decreased ($p<0.01$) discrimination index in novel object recognition test and disrupted ($p<0.05$) prepulse inhibition compared to control group. Agmatine treatment reversed the effect caused by MK-801+SI in the prepulse inhibition test ($p<0.05$). Clozapine treatment decreased locomotor activity ($p<0.05$), increased discrimination index ($p<0.05$) and increased prepulse inhibition ($p<0.01$) compared to MK-801+SI group.
Conclusions: This is the first report that examines effect of agmatine in neurodevelopmental model of schizophrenia in rats. Our results confirmed that combined model of neonatal MK-801 and isolation rearing has successfully mimics schizophrenia like behaviors and agmatine provides beneficial effect on sensorimotor gating deficit, which is one of the main indicators of schizophrenia in rats. It can be suggested that as an endogenous molecule agmatine might have a modulator role in regions which are important for negative and/or positive symptoms of schizophrenia and investigating of the underlying mechanism of this beneficial effects might be valuable for further studies.

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P.604 Exploring the brain correlates of ideas of reference with a virtual reality paradigm in fMRI

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Background and aim: The study of the brain correlates of delusions in psychotic disorders has been complicated due to the difficulty of implementing neuroimaging paradigms able to elicit these ideas. In this sense, virtual reality paradigms are promising since they can induce responses to events and situations as if they were real. One such task is the Metro task [1], a virtual reality paradigm that simulates a metro journey with other characters that look in different directions, sometimes to the subject, and smile if they meet their gaze. This task has been found to induce ideas of reference (IOR) in healthy subjects [1] and, at significantly higher frequency, in psychotic patients with delusions [2]. The aim of the present work is to study the brain correlates of IOR using an adaptation of the Metro task suitable for fMRI.
Methods: Participants were 37 patients with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder, and 24 healthy controls matched for sex, age, and pre-morbid IQ. In patients, IOR severity was assessed with the Ideas of Reference Interview Scale (IRIS) [3]. Participants underwent fMRI in a Philips 3T scanner while performing a version of the Metro task, which simulated a journey in a carriage from a first-person perspective. The task followed a block design, alternating periods of the condition of interest (Task) where the participant was accompanied by virtual characters that displayed various behaviors, with control periods where the train was empty (Control). After scanning, all participants completed a self-report questionnaire to assess IOR generated during the task.

For data analysis, whole-brain general linear models (GLMs) were fitted to generate individual activation maps for the Task>Control contrast. Group comparisons were performed with a mixed-effects GLM ($p<0.05$, cluster corrected). In patients, we performed a regression analysis to examine whether brain activity was associated with post-task self-reported IOR.
Results: Both groups activated similar regions during the task, including lateral prefrontal areas, hippocampus/amygdala, inferior parietal cortex, posterior cingulate and precuneus. Controls also activated the medial prefrontal cortex. Group comparison showed reduced activation in the patients in right angular gyrus (MNI 68, −56, 16; $z=4.93$; cluster size = 8320mm3), inferior frontal gyrus (MNI 40, 16, 22; $z=3.9$; cluster size = 4936mm3), precuneus (MNI 4, −64, 24; $z=3.47$; cluster size = 3312mm3), and cerebellum (MNI −18, −78, −30; $z=4.12$; cluster size = 5384mm3).

IRIS scores were significantly associated with the degree of IOR elicited by the task (Spearman $\rho=0.426$, $p=0.01$). In patients, those experiencing more IOR during the task showed a reduction in left angular gyrus activity (MNI −44, −78, 38; $z=4.22$; cluster size = 4264mm3), and an increase in occipital cortex activity (MNI −50, −86, −10; $z=3.91$; cluster size = 3768mm3).
Conclusions: Psychotic patients showed a pattern of reduced brain activity in attentional (frontal) and social cognition (right angular) [4] regions while performing the