Background and aims: Deficits in response inhibition are considered as candidate endophenotypes of altered prefrontal brain function in Attention Deficit Hyperactivity Disorder (ADHD). Electrophysiological methods like Event-Related Potentials (ERPs) are adequate to measure abnormalities in brain functions underlying those deficits and to assess functionally relevant polymorphisms directly affecting neurotransmission systems and brain function. This principle of imaging genomics with ERPs has been demonstrated as early as 1999 for the serotonin transporter promoter polymorphism affecting prefrontal brain function (Fallgatter et al., International Journal of Neuropsychopharmacology, 1999).

Methods: We employed a multi-channel EEG during performance of a Go-NoGo task to assess the electrophysiological basis of response inhibition. The ERP-measure derived from this protocol was termed NoGo-Anteriorisation (NGA) and is characterized by a high interindividual stability, high short- and long-term test-retest reliability and, moreover, is independent from age- and gender.

Results: In patients with ADHD during childhood and adulthood the NGA was diminished as compared to age- and sexmatched healthy controls. Furthermore, a three-dimensional source location analysis with LORETA indicated an electrical dysfunction of the ACC in the patient groups. Moreover, the 158 val/val variants of the COMT gene were associated with an even worse prefrontal brain function.

Conclusions: These results exemplify the measurement of disease related disturbances in brain function in ADHD with ERPs. Future studies will show whether such electrophysiological endophenotypes may contribute to the diagnosis of subgroups of ADHD and whether they may serve as endophenotypes to further clarify genetic contributions to the disease.

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Paired associate learning in subjects at risk for psychosis: fMRI study

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Background: Executive and mnemonic impairments have been well documented in the high-risk states for development of psychosis and have been pinpointed as a possible core neuropsychological dysfunction. However, their neurofunctional correlates are still not clear.

Method: fMRI was used in 17 patients at risk for developing psychosis (ARMS, ''at risk mental state''), 10 patients with a first episode of psychosis (FEP) and 15 age-matched healthy comparison subjects to examine neural responses to increasing difficulty of mnemonic engagement in an object–location paired associate memory task. Groups were matched in terms of age, IQ, gender, and psychopathology ratings. Accuracy and reaction time were recorded during the scan.

Results: As the mnemonic load increased, response latency increased and response accuracy decreased in an approximately linear fashion. No main effect for group was observed. However, a trend towards decreased accuracy in FEP subjects, as compared with controls, was evident. As the task difficulty increased, increased brain activity was observed in the medial frontal cortex and in the medial posterior parietal cortex. Between-groups differences in activation were observed in a cluster spanning the MFG, SFG and SMA and in the right precuneus. However, these neurofunctional abnormalities were more evident in the most demanding level of the task than in the easy level, with the ARMS groups showing less activation than controls and higher activation than FEP.

Conclusion: Abnormal neural activity in medial frontal cortex and posterior parietal cortex during paired associate learning task may represent a neurofunctional substrates of vulnerability to psychosis.

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Age-related decline in 5-HT2A and 5-HTU sites in the rhesus monkey hypothalamus

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Serotonin 2A receptors (5-HT2A), and serotonin reuptake transporters (5-HTU) are involved in regulating some autonomic and cognitive processes. While the pre-synaptic and post-synaptic distribution of 5-HT2A receptors is unknown in the primate hypothalamus, in cortex, the majority of 5-HT2A receptors are located postsynaptically on pyramidal and glial cells. The density of 5-HT2A and 5-HTU sites declines with age in the primate and rodent hippocampus and frontal lobe but such changes have not been documented in the hypothalamus. To assess age-related changes in the density of 5-HT2A and 5-HTU binding sites in the rhesus monkey (Macaca mulatta) hypothalamus, autoradiographic ligand binding was utilized within the anterior, tuberal, and posterior hypothalamus, and the mammillary body (MMB) of 11-17 monkeys (4.4-31.8 yo). 5-HTU binding was assayed with tritiated citalopram and 5-HT2A with iodinated dimethoxyaminopropane (DOI). The density of 5-HTU binding was significantly reduced with age in the anterior (R= -0.57, N= 16, P=0.021), tuberal (R= -0.627, N= 17, P= 0.007), and posterior (R= -0.053, N= 15, P= 0.042) hypothalamus. Conversely, only the MMB displayed a significantly lower 5-HT2A density in aged animals (R=- 0.631, N= 11, P= 0.037). These results show a significant age-related decline in CIT binding throughout the hypothalamus, suggesting an age-related reduction in its serotonergic innervation. While we were unable to evaluate 5-HT U binding in the MMB, our results show a significant decline in DOI binding in this nucleus. Future studies are needed to determine the 5-HT2A receptor distribution in the monkey hypothalamus. (Supported by NIH Grant-P01-AG00001-29 and RR-00165).

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The WHO (Ten) well-being index as a screening instrument for major depression in a population-based sample

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Background: The present study evaluated the association between the WHO (Ten) Well-being index and major depression assessed by the Major Depression Inventory (MDI) and Schedules for Clinical Assessment in Neuropsychiatry (SCAN). The main aim was to examine how well the WHO (Ten) Well-being index worked as a screening instrument for depression in a population-based sample.

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