Quantitative Perfusion MRI detects Changes in Neural Activity in Rat Models of Schizophrenia

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Rationale - Schizophrenia is commonly seen as a chronic brain disorder, which affects the structure and functionality of several cortical and subcortical brain regions involved in cognitive, emotional and motivational aspects of human behaviour. Over the past years, MRI studies have identified morphological and functional anomalies in schizophrenic patients that have significantly helped in understanding the aetiology of the disease. In contrary, in animal models of schizophrenia very little is known about brain areas involved in the expression of psychotic-like symptoms. The objective of the present study was to investigate and compare the characteristic changes in neural activity in two well-established neurodevelopmental and pharmacological animal models of schizophrenia, which mimic specific aspects of the positive, negative and cognitive symptoms of schizophrenia [1,2].

Methods - ***Neonatal ventral hippocampal (NVH) lesion model:*** On postnatal day 7, male Sprague-Dawley rat pups received bilateral injections of ibotenic acid (n=9) or artificial cerebrospinal fluid (control, n=10) into the ventral hippocampal formations [1]. 14 weeks later, brain activity at rest was investigated using perfusion MRI. ***Acute pharmacological model:*** Brain activity in naive rats (350-400 g) was assessed using perfusion MRI after iv administration of saline, 0.1, 0.3 or 1 mg/kg phencyclidine (PCP) (n=5 per group), a non-competitive NMDA receptor antagonist [2]. ***Behavioural tests:*** Standard behavioural test were performed on all animals. In particular, reduced prepulse inhibition of the startle reflex to a strong acoustic stimulus was used as a measure of the severity of the psychotic symptoms [3]. ***MRI:*** For the MRI investigations, individual animals were anaesthetised with 2-2.5% isoflurane in O_2/air (1:5). Breathing rate and inhaled and exhaled O_2 and CO_2 were continuously monitored. Quantitative perfusion imaging was carried out using the continuous arterial spin labelling (CASL) technique with RARE readout (2 s labelling pulse, 400 ms post labelling delay, TR/TE=3 s/5.5 ms, RARE factor=32, 128x32 matrix, 2 averages) [4]. T1-maps (inversion recovery FLASH) and T_2-weighted anatomical images (RARE) were also acquired.

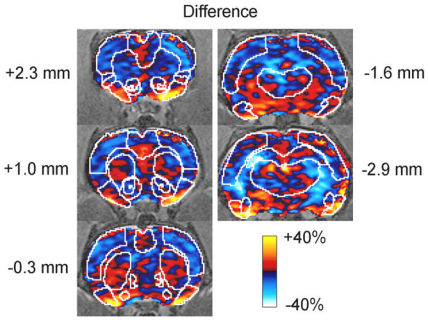

Figure 1: Brain activity measurements in NVH-lesioned rats versus controls. The images represent group data from 9 and 10 animals, respectively. Distances are given relative to the bregma [5].

Results - Figure 1 depicts the changes in normalised perfusion, i.e. regional perfusion normalised to the average perfusion within each brain slice, observed in NVH-lesioned rats versus corresponding control animals. Brain perfusion as a measure of neural activity increased significantly in the orbital prefrontal and entorhinal piriform cortices, the nucleus accumbens shell, amygdala, bed nucleus stria terminalis and ventral pallidum. A significant decrease in local activity was found in the temporal cortex. Analogous observations were made in PCP-treated animals. Figure 2 shows an excerpt of the dose-dependent changes in local neural activity. Significant increases were again found for the entorhinal piriform cortex, nucleus accumbens shell, ventral pallidum and, in addition, also in the thalamus. Significant and dose dependent decreases in activity were found in the temporal cortex, the lateral prefrontal cortex and the dorsal striatum.

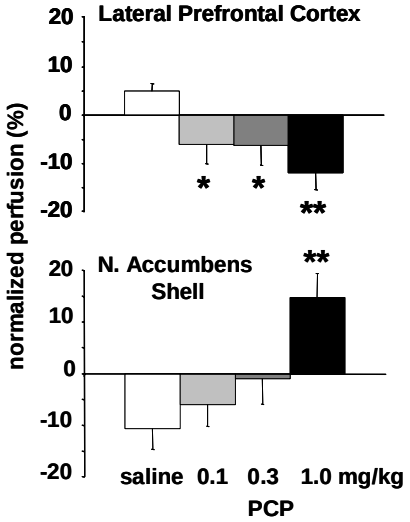

Figure 2: Dose-dependent changes of neural activity in representative cortical and subcortical brain areas of rats treated with increasing doses of PCP (* p<0.05; ** p<0.01).

Discussion - Quantitative perfusion MRI provided a robust readout of slowly developing and/or persistent changes in neural activity implicated in two different animal models of schizophrenia. In both NVH-lesioned and acutely PCP-treated rats similar patterns of changes in neural activity were detected in specific cortical and subcortical brain regions. These findings are in line with the hypo-frontality in temporal and lateral cortices and the involvement of basal ganglia reported in psychotic patients. Our data thus substantiate the notion of a disconnection in the frontal-subcortical brain circuitry in schizophrenia.

References

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