Drug induced dyskinesia (DID) is associated with cortical and subcortical D1 receptor hypersensitivity: a pharmacological MRI study.

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Background and Introduction: Repeated treatment with dopamine (DA) receptor agonists strongly potentiates contralateral turning behavior due to selective stimulation of D1 or D2-class receptors in 6-hydroxydopamine (6-OHDA)-lesioned rats (rat model of Parkinson Disease (PD)). This phenomenon, referred to as sensitization, is believed to be related to the motor response complications (dyskinesias, on-off states) that occur during chronic administration of levodopa in Parkinson's disease patients[2]. Pharmacologic fMRI studies (phMRI) in this model demonstrated an asymmetric increase in the blood oxygenation level dependent (BOLD) on the lesioned striatum (Str) after stimulation with apomorphine (APO) consistent with the concept of functional receptor supersensitivity[1]. Objective: To assess the role of BOLD signal changes as a measure of local receptor sensitivity for DID, striatal and cortical fMRI signal time courses in response to APO (D1/D2 agonist), quinpirole (D2 agonist, QP) and SKF 81297 (D1 agonist) was studied in a model of DID by repeated administration of the respective drugs[2]. **Methods:** The model involves a unilateral denervation of the middle forebrain bundle (MFB) with 6-OHDA and subsequent sensitization with APO (0.25 mg/kg), QP (0.1 mg/kg) and SKF (0.1 mg/kg) for three weeks. An Abnormal Involuntary Movements Test (AIMT) was performed to measure dyskinesias. Turning behavior was assessed too. phMRI was performed at the beginning of the sensitization experiment and after sensitization in separate groups resulting in six experimental groups. For BOLD fMRI studies, a multislice T2 weighted fast spin echo was used, before, during and up to 1 hour after i.p. drug administration in anaesthetized rats. The MRI was performed at 7T (Biospec Bruker, Germany) using a dedicated head coil. Blood pressure was controlled using titration of the rate of a continuous i.v. phenylephrine injection as described before[3]. Signal time courses were averaged over anatomically defined regions of interest in the motor cortex (MCx) and striatum (STR) ipsi- and contralateral to the lesion using a manufacturer's processing software (Fun tool). The maximum BOLD regional BOLD response and the mean response averaged over time were calculated and compared between the three classes of drugs using an multivariate analysis of variance (MANOVA). **Results:** In the STR, the maximum positive BOLD response was larger on the lesioned side compared to the non-lesioned side in all sensitized rats, in line with the expected effects of receptor hypersensitivity. In MCx we could find similar side differences in APO and SKF but no in QP sensitized rats. No significant differences of the BOLD response were present at the beginning of the sensitization in any group neither in STR or MCx (MANOVA, Wilks test $p>0.05$). At the end of the sensitization, there were significant differences between treatment groups ($p=0.02$) in the STR but no in MCx ($p>0.05$). Post hoc analysis revealed these differences to be significant between QP and APO treated animals ($p= 0.03$) and QP and SKF treated ones ($p=0.02$), whereas no difference was observed between APO and SKF sensitized rats ($p>0.05$). Conversely, only the APO and SKF treated animals developed significant dyskinesias compared with QP sensitized animals. **Discussion:** These results confirm that BOLD-based phMRI without contrast enhancement is a useful tool to map dopamine receptor-sensitivity. The study provides dynamic and behavioural evidence that the observed asymmetry in the BOLD response is associated with receptor supersensitivity and dyskinesias. The results furthermore suggest that dopaminergic hypersensitivity underlying drug-induced dyskinesia is related to the D1 receptor subtype and that cortical DA receptor hypersensitivity may play a crucial role in the development of DID.

1. Nguyen TV, Brownell AL, *et al*. Synapse. 2000;36(1):57-65.
2. Delfino M, Stefano A, *et al*. Beh. Brain Res. 2004; 152(2):297-306.
3. Kalisch et al., submitted 2004.

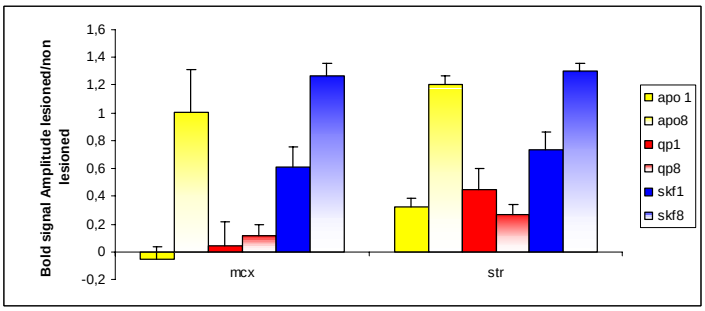

Fig 1: BOLD Amplitude (lesioned/non-lesioned) in MCx and STR.

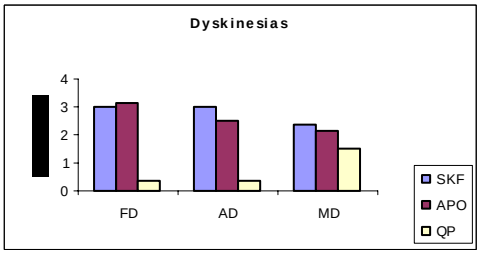

Fig 2: FD: Forelimb Dyskinesia, AD: Axial dystonia, MD: Masticatory Dyskinesia