Results: DTI followed by statistical parametric mapping revealed that radial diffusivity is increased (two-sample t-test, $p < 0.05$) and fractional anisotropy decreased (two-sample t-test, $p < 0.05$) in substantia nigra following dopaminergic neurodegeneration, in accordance with a loss of axons in the area. The connectometry analysis showed an increased isotropic diffusivity along the nigrostriatal tract of the medial forebrain bundle (MFB) in 6-OHDA animals (iso more than 40% higher in 6-OHDA lesioned animals along the tract) with a false discovery rate of 0.4% (evaluated using a permutation test with 1000 permutations). rs-fMRI studies showed that interstriatal functional connectivity is decreased while functional connectivity between CPu in the lesioned hemisphere and the sensorimotor cortices of both hemispheres is increased (two-sample t-test, $p < 0.05$). The latter change is reversed by L-DOPA (Paired t-test, $p < 0.05$), while this is not the case for the former.

Conclusions: Together, these results suggest that the loss of axons can be observed along the MFB and in substantia nigra as a result of dopaminergic neurodegeneration and that it results in a loss of functional synchrony between the CPu of both hemispheres and in the reinforcement of functional connectivity between the CPu of the lesioned hemisphere and its cortical afferents, in particular the sensorimotor cortex. We can also conclude that L-DOPA initially acts by reestablishing a normal functional connectivity between the CPu and its afferents rather than by synchronising the activity of the two CPu. Finally, these data demonstrate that rs-fMRI and dMRI are interesting methods for the development of new biomarkers and valuable tools in the search of new treatments for PD, already at the preclinical level.

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P.3.005 D-lysergic diethylamide modulates dopaminergic neurons of ventral tegmental area via 5-HT1A, D2 and TAAR1 receptors

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Background: D-lysergic diethylamide (LSD) is a hallucinogenic drug with potent psychotropic effects. LSD may produce psychotic-like symptoms such as visual, tactile, acoustic hallucinations, change in body perception, and synaesthesia [1]. Traditionally, the psychotropic properties of LSD have been attributed to its effects at the level of the serotonin (5-HT) system [2], but given the role of dopamine (DA) in the pathogenesis of psychosis, an interaction of LSD with the DA system cannot be excluded. Current knowledge regarding a possible in-vivo interaction of LSD with mesolimbic dopamine (DA) neurons of the Ventral Tegmental Area (VTA), the main source of DA innervation in the brain, is limited. In-vitro studies have demonstrated that LSD has affinity for DA receptors, in particular D2 receptors [3], and for trace-amine associated receptor 1 (TAAR1) [4], in addition to its affinity for 5-HT1A and 5-HT2A receptors [1]. Thus, we examined the in-vivo effects of cumulative doses of intra-venous (i.v.) injection of LSD on VTA DA neurons, and attempted to identify the underlying neurobiological mechanisms and we compared these effects with the interaction of LSD with 5-HT neurons in Dorsal Raphe Nucleus (DRN).

Methods: Using in-vivo electrophysiology, we first studied the effects of cumulative doses of LSD (5–120 ug/kg, i.v.) on VTA DA neurons and on DRN 5-HT neurons in Sprague-Dawley male adult rats. Secondly, we tested the contribution of 5-HT1A, D2, and TAAR1 receptors in the mechanism of action of LSD upon VTA DA neurons by using the D2 antagonist haloperidol (HALO, 50 μg/kg, i.v.), the 5-HT1A antagonist WAY-100,635 (WAY,500 μg/kg, i.v.), or the novel synthesized trace amine-associate receptor 1 (TAAR1) antagonist EPPTB (5 mg/kg, i.v.). Data were analyzed using S igmaPlot 13 (Systat Software, Inc.). Neuronal responses to cumulative administration of drugs were computed using Student t-test or one-way ANOVA or two-way ANOVA for repeated measures followed by Bonferroni post hoc comparisons where appropriate. Statistical values of $P \leq 0.05$ were considered significant.

Results: LSD dose-dependently decreased VTA DA firing activity at doses higher (30–120 μg/kg, i.v.) than those (5–20 μg/kg, i.v.) inhibiting DRN 5-HT neurons

(ED50: 71.8 vs. 13.1 μg/kg; $F(2,7) = 39.34$, $P < 0.0001$). The inhibitory effects of LSD on VTA DA firing activity were prevented by HALO, WAY and EPPTB, suggesting the involvement of D2, 5-HT1A and TAAR1 receptors in the mechanism of action of LSD. Interestingly, the single i.v. injection of 5 mg/kg EPPTB increased VTA DA firing activity compared to vehicle (2.89 ± 0.60 vs 2.15 ± 0.34 Hz, $P = 0.002$).

Discussion: These results demonstrate that LSD at low doses affects the 5-HT system while at high doses strongly modulates DA mesolimbic neuronal activity with a pleiotropic mechanism of action involving 5-HT1A, D2 and TAAR1 receptors. Moreover, for the first time, we demonstrated that EPPTB exerts a tonic enhancement of DA firing activity in vivo.

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P.3.006 The immune 8: impaired social cognition in schizophrenia related to genetic, environmental, and immune interactions

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Aims: The aim of this study is to characterise the effects of 8 already identified genetic risk variants on social cognitive deficits in schizophrenia. Although the aetiology of schizophrenia is largely unknown, it is increasingly clear that genetic and environmental interactions contribute to cognitive deficits associated with this disorder. The "Immune Hypothesis" suggests that schizophrenia is often predicted by early environmentally-driven immune challenges, and genetically driven sub-optimal immune responsiveness [1]. In the largest genetic study to date, recent genome wide association studies (GWAS) have established the strongest association with schizophrenia at a region of the genome that is synonymous with immune function [2]. Social cognitive deficits are core features of schizophrenia, which relate to genetic risk [3]. Furthermore, social cognitive deficit has been linked to early immune insults in a primate study [4]. The current study analyses the effects of immune challenge on social cognition, examining a set of genes related to immune function and schizophrenia risk in a human population. Environmental factors that may contribute to cognitive deficit are also examined, such as childhood trauma.

Methods: To test if genetic variants related to immune function impair cognition, 8 genes were selected by cross referencing "Immunology" Gene Ontology lists with the most recent list of genes implicated in schizophrenia from a psychiatric genetics consortium GWAS [2]. 1013 participants were genotyped and cognitively assessed in an Irish population of schizophrenia sufferers and healthy controls. A separate cohort with already collected genetic, cognitive and immune data was also examined from the Avon Longitudinal Study of Parents and Children (ALSPAC) for replication of results. Block regression analysis using SPSS statistical software was performed, testing a relationship between genetic risk levels and cognitive deficits. In a second element to the study, environmental factors were examined as possible mediators of the relationship between genetic risk variants for schizophrenia and cognitive impairment (PROCESS mediation, SPSS).

Results: Regression analysis suggests that 7 of 8 genetic variants selected contribute to impairments in cognition across an Irish sample, and these findings were replicated in the ALSPAC sample. Cognitive deficits overlapped for the majority of genes examined, across domains of social cognition, IQ, attention, and episodic memory. In examining ALSPAC as a replication sample, many of the same genetic variants also showed negative effects on social cognition. Environmental factors such as childhood trauma were also found to impact on this gene-cognition relationship using mediation analysis.

Conclusions: The 'Immune 8' may serve as significant risk markers for schizophrenia, and further elucidate aetiology of this disorder. Future studies on neurobiology