Further characterisation of the rat model of Tourette-related striatal disinhibition

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Striatal disinhibition model
- Abnormalities of the cortical-striatal-thalamic-cortical circuit have been suggested to play a central role in Tourette Syndrome (TS) (Albin & Mink, 2006). Specifically, it was suggested that motor tics arise from neural disinhibition, i.e. loss of GABAergic inhibition, in the striatum, which in turn leads to disinhibition of the thalamus and hyperexcitability of the motor cortex, leading to tics (Gilbert, 2006).
- The effects of neural disinhibition in the striatum have been investigated directly through the use of microinjections of GABA-A antagonists, including picrotoxin and bicuculline, in rodents (e.g. Israelashvili & Bar-Gad, 2015; Klaus & Plenz, 2016) and non-human primates (e.g. Worbe et al., 2009). Such striatal disinhibition produced tic-like movements on the contra-lateral side to the disinhibited area that manifested several minutes after injection and lasted up to two hours (Israelashvili et al., 2015).
- Depending on the somatotopic location of the striatal infusion, the tic-like behaviours involved forelimb or hindlimb movements (Bronfeld, Israelashvili, et al., 2013).

Aims
- To confirm and extend previous studies of the impact of striatal disinhibition in rats, we examined the impact of unilateral picrotoxin infusion (300 ng in 0.5 ul of saline) into the anterior dorsal striatum of young adult male Lister hooded rats.
- We measured tic-like movements (1) and took automated photo-beam measurements of open field locomotor activity and fine movements (2) following striatal disinhibition.
- We examined the impact of striatal disinhibition on prepulse inhibition (PPI) of the acoustic startle response (3). PPI has shown to depend on the striatum and to be disrupt in TS (Koch, 1999; Swardlow et al., 2001).
- We examined the effects of striatal disinhibition on neural activity in the vicinity of the infusion site, using multi-unit and local field potential (LFP) recordings under isoflurane anaesthesia (methods adapted from Pezze et al., 2014) (4 and 5).

1: Robust induction of tic-like behaviour

Drug: Picrotoxin (300ng/0.5ul) and Control: Saline (0.5ul)

15/16 picrotoxin infusions led to tic-like behaviour in the left forelimb.

2: Increased locomotor activity and fine motor counts

Within-subjects design: n=13

Striatal disinhibition increased locomotor activity (F(1,1)=7.01, p<0.002). Locomotor activity reduced across 5 min blocks, reflecting locomotor habituation (F(1,1)=31.50, p<0.001), regardless of infusion condition (infusion X 5 min block interaction: F(1,1)=1.69, p<0.08).

Striatal disinhibition markedly increased fine motor counts, mainly during 5 min block 2 to 8 after infusion (main effect of infusion: F(1,1)=20.04, p<0.001; main effect of time: F(1,1)=8.34, p<0.001; infusion X 5 min block interaction: F(1,1)=3.12, p<0.001).

Conclusions
- Striatal disinhibition by picrotoxin reliably induced tic-like movements (in 15/16 infusion). We found a slight increase in locomotor activity after striatal disinhibition. This may reflect that the dorsal striatal neural activity facilitates locomotor activity (e.g. Barbera et al., 2016) and indicates that striatal disinhibition may contribute to hypervigilance, which is a common comorbidity of TS (El Mahany et al., 2015).
- We found an increase in fine motor counts after picrotoxin infusion which shows a similar time course to tic-like movements, suggesting an automated method to quantify these movements.
- Striatal disinhibition tended to reduce startle reactivity, but did not affect PPI. The latter contrasts with reduced PPI in TS (Swardlow et al., 2001). This does not support a direct contribution of striatal disinhibition to PPI deficits in TS, but may also reflect the difference between acute striatal disinhibition (in our rat model) and chronic striatal disinhibition (in TS).
- Our electrophysiological findings under anaesthesia showed that striatal disinhibition causes marked striatal spike-wave discharges, consistent with previous findings in freely moving rats (e.g. Israelashvili & Bar-Gad, 2015; Klaus & Plenz, 2016), and enhances neuronal burst firing, consistent with findings on neural disinhibition in prefrontal cortex and hippocampus (Bast et al., 2017).

References