Accurate Predictive Models of Atomoxetine’s and Citalopram’s Effect on Motor Inhibition in Parkinson’s Disease

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Background

Motor inhibition deficits occur in Parkinson’s disease (PD) even in the absence of impulse control disorders. Their aetiology is multifactorial, including the loss of noradrenergic and serotonergic projections to the prefrontal cortex and structural change in frontostriatal circuits1-3.

Our recent studies have showed that selective noradrenaline (atomoxetine) and serotonin (citalopram) reuptake inhibitors improve motor inhibition in a subgroup of PD patients, in terms of both performance and brain activity4,5. However, the impact of treatment depends on individual differences in clinical characteristics and brain imaging.

This Study

We developed two predictive models to identify patients who are most likely to benefit from these new candidate therapies.

- **Clinical model** which used demographic (sex, age) and clinical measures (cognitive impairment, disease severity, levodopa equivalent dose, plasma concentration of each drug) in combination with structural brain imaging data.
- **Mechanistic model** which used the demographic and clinical data, plus functional brain imaging measures.

Methods & Results

- **Double-blind randomized placebo-controlled crossover study with 34 PD patients (three sessions: 40mg atomoxetine, 30mg citalopram or placebo) and 42 controls (1 session, no drug).**
- **Stop task**: 360 Go trials, 80 stop trials (tracking algorithm to 50% inhibition, figure); SSRT estimated by integration method; confirmed poor motor inhibition in PD (figure). Large individual variability led to no main effect of either drug.
- **DTI**: T - T, 63 directions, analysed with FSL; fractional anisotropy and mean diffusivity extracted from the anterior internal capsule (frontostriatal connection).
- **fMRI during the stop task**: T - T, whole-brain, 3 mm resolution, analyzed with SPM. See figure for main effects of task and PD; parameter estimates extracted from the right inferior frontal gyrus, bilateral pre-supplementary motor areas and striatum.
- **Benchmark for behavioural efficacy**: 30% reduction in the impact of PD on the SSRT.
- **Support vector machine with a radial function kernel; leave-one-out cross validation; inferences from 5000 permutations; 79-85% accuracy in predicting the drug response.**

**Features for optimal Atomoxetine prediction**

- **Clinical**: R fractional anisotropy, drug concentration, levodopa dose 79.4% <0.005
- **Mechanistic**: activation in R caudate nucleus, L caudate nucleus, R pre-SMA 85.3% <0.001

**Features for optimal Citalopram prediction**

- **Clinical**: R fractional anisotropy, age, R mean diffusivity, cognition 79.4% <0.005
- **Mechanistic**: activation in L caudate nucleus, R putamen, R pre-SMA 85.3% <0.005

Conclusion

- Increasing noradrenaline or serotonin improves stopping efficiency of a subgroup of patients with Parkinson’s disease.
- The clinical model is of relevance to prospective trialists and clinicians, to enable patient stratification in future clinical trials and for potential treatment decision for individual patients.
- The mechanistic model provides the link to preclinical and comparative studies noradrenergic and serotonergic systems for cognitive control.

References

2. Politis et al. 2010. Neurob Dis
3. Rae et al. 2014. Neuroimage
5. Ye et al. 2014. Brain