Activation of inferior frontal gyrus during response inhibition: effects of citalopram and acute tryptophan depletion depend on neocortical 5-HT$_{2A}$ receptor levels

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Introduction. The inferior frontal gyrus (IFG) plays a critical role in response inhibition, as assessed with tasks like the Go/No-Go paradigm. It has also been shown that serotonergic input exerts a potent regulatory influence on neuronal processing in the frontal cortex including the neuronal circuits subserving response inhibition in the IFG. The present study was designed to elucidate the link between serotonergic binding levels of the main neocortical excitatory receptor subtype (5-HT$_{2A}$), response inhibition and activation of the IFG. We hypothesized that IFG circuits subserving response inhibition are sensitive to interventions that lead to acute changes in cerebral serotonin levels. We further predicted that the sensitivity of IFG to serotonergic challenges will depend on individual differences in serotonergic binding levels.

Methods. 17 subjects performed a variant of the classic Go/No-Go task during three fMRI sessions at 3T. The task included three types of conditions. (1) "Go" trials, pressing a button to a visual cue (2) "alternative Go", pressing a different button to a different visual cue and (3) "No-Go", requiring response inhibition (figure 1). In counterbalanced sessions, subjects received the SSRI citalopram (20 mg/h, iv, ~50 mg in total) or underwent acute tryptophan depletion (ATD) or no treatment. Participants also underwent 18-F altanserin Positron Emission Tomography (18-F altanserin PET) to map regional 5-HT$_{2A}$ receptor binding in terms of the outcome measure BP$_P$. Statistical analyses were performed in SPM5 using a repeated measures ANOVA design including the contrasts of interest from the three serotonergic challenges with linear and quadratic functions of 5-HT$_{2A}$ receptor BP$_P$ as covariates.

Results. IFG was bilaterally recruited while inhibiting pre-potent responses (figure 2 green). There were differences in inferior frontal activation among the three conditions, but these differences depended on the global 5-HT$_{2A}$ receptor BP$_P$ (figure 2, yellow). Specifically, individuals with low BP$_P$ showed greater activation in left IFG for No-Go (vs. alternative Go) after ATD, while subjects with high inferior-frontal BP$_P$ showed greater activation with No-Go trials (vs. alternative Go) after citalopram. In the control condition without pharmacological intervention, inhibition-related activity in left IFG was not significantly modulated by the 5-HT$_{2A}$ receptor level.

Conclusions. The inferior frontal regions that subserve inhibitory control are modulated by serotonergic treatments, but the effect of treatments depends on the individual differences in 5-HT$_{2A}$ receptor binding.

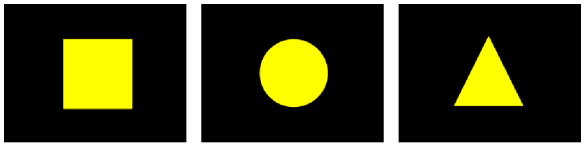

Fig. 1. The Go/No-Go task. The figures appeared in randomized order with 1000 ms duration and 500 ms ISI. Go and alternative Go trials required different button response.

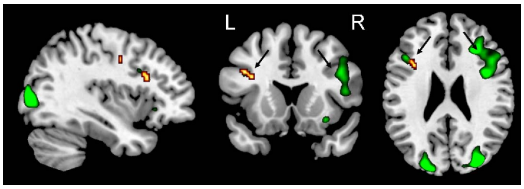

Fig. 2. Bilateral IFG activation with response inhibition (green). The left IFG response differed between Citalopram and ATD conditions, dependent on the trait 5HT2a level (yellow) (p<0.001).