

Adaptive Changes in Response Inhibition BOLD Responses following Antidepressant Treatment

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Introduction

The neurotransmitter serotonin (5-HT) is closely associated with a number of psychiatric conditions including depression, anxiety and impulse control disorders. Previous research has highlighted the role of the orbito-frontal (OFC) and prefrontal cortices (PFC) in performance monitoring and response inhibition. Acute changes to the availability of 5-HT has been shown to modify the normal brain response during response inhibition supporting the central role of serotonin in this process. However, clinically significant effects of antidepressants are typically observed only 10-14 days after starting treatment suggesting an adaptation in the brain response with sustained treatment. Citalopram, a standard selective serotonin reuptake inhibitor (SSRI) antidepressant, has been used both as an acute 5-HT challenge (by intravenous injection) and through daily administration as a chronic inhibitor of 5-HT reuptake. It remains unclear whether increased duration of SSRI usage will lead to greater changes in serotonergic systems that are recruited during response inhibition and monitoring. We aim to explore adaptive changes in 5-HT signalling following sub-chronic SSRI treatment in healthy controls performing a response inhibition paradigm.

Methods

24 healthy, right handed, age and sex matched volunteers were recruited (mean age=21.1, sd=1.7 years). Participants were provided, in a randomised, balanced order, single blind design, with either 20mg citalopram or placebo for 11 days and tested after 14 days from first dosage following a 3 day drug washout. They then underwent a six minute behavioural inhibition fMRI task where they were asked to press a button in response to a letter being displayed, but not respond if that letter was a 'V'. Four blocks, each of 26 letters were interspersed with 13 No-Go 'V' cues along with 4 Go blocks with no 'V' stimuli. Data were analysed and compared using two sample t-tests in SPM5. Whole brain images were acquired on a Philips *Intera* 1.5T scanner using single-shot echo-planar (EPI) pulse sequence. Each volume comprised 29 ascending axial slices (TR=2s, TE=40ms, 4.5mm thickness with 0.5mm slice gap, in-plane resolution of 3.5x3.5mm).

Results

The main effect of response inhibition (No-Go) compared to monitoring (Go) led to bilateral activation of the inferior frontal gyrus (BA47), medial temporal gyrus (BA21) and right medial frontal gyrus (BA8) ($p < 0.001$ uncorrected). 11 days of citalopram treatment compared to placebo was associated with a reduced response bilaterally in the inferior frontal gyrus (BA47) and relative increases in the right middle frontal gyrus (BA10), mid cingulate (BA24), precuneus (BA7) and posterior cingulate (BA30) when inhibiting responses ($p < 0.001$ uncorrected).

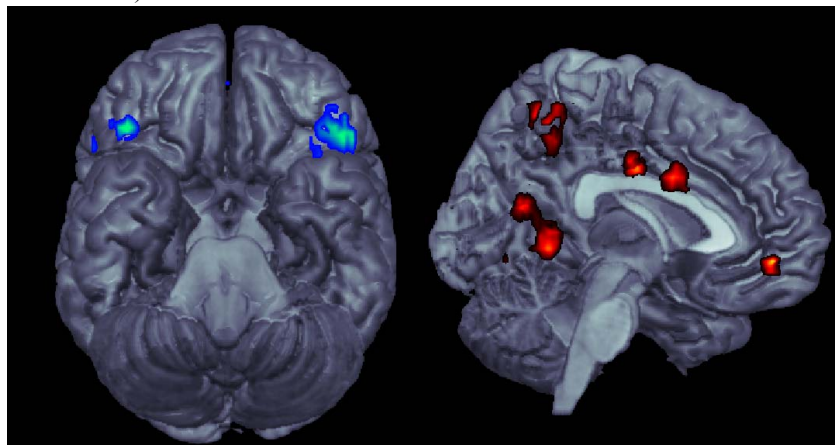


Fig 1: Citalopram treated versus placebo bilateral BOLD signal decreases in the inferior frontal gyrus (BA47) (left) and relative increases in right medial frontal gyrus (BA10), mid cingulate (BA24), precuneus (BA7) and posterior cingulate (BA30) (right) when inhibiting responses compared to responding.

Discussion

Sustained citalopram treatment appears to diminish the response of the lateral OFC when that brain area is required to process the inhibition of an ongoing action. Acute administration of SSRIs have been shown to enhance this response using the same task (Del Ben et al, 2005; Völlm et al., 2006). Chronic SSRI treatment may therefore desensitize the lateral OFC to serotonin mediated responses even after a 3 day drug washout. Additionally, the relative increases in responses in the posterior and mid-cingulate as well as the precuneus and medial frontal gyrus may be due to a reduction in default mode network processing following drug treatment. These findings may relate to enhanced post synaptic signalling or down regulation of 5-HT receptors following chronic increases in central 5-HT availability.

Conclusion

Antidepressant SSRI treatment in healthy volunteers causes adaptive changes in serotonin signalling compared to placebo when performing a 5-HT mediated response. These findings suggest that chronic SSRI use modifies 5-HT pathways involved in cognitive flexibility and inhibitory control.

References

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