

Short-long functional polymorphism of serotonin transporter gene modulates the acute citalopram challenge phMRI response

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Introduction

Citalopram, a standard antidepressant, is a selective serotonin reuptake inhibitor (SSRI) and acts on the serotonin (5HT) transporter (5HTT) to inhibit reuptake in order to increase 5HT in terminal synapses. We previously demonstrated that an intravenous infusion of citalopram (7.5mg) evoked increases in blood oxygen level dependent (BOLD) signals in areas rich in the 5HTT; notably the caudate, amygdala and cingulate cortex. The 5HTT has a functional polymorphism in the promoter region, the short form (S) of which has been associated with increased risk of depression and poor treatment response. However, there does not appear to be a reduction in the density of uptake sites as they are unaffected by the polymorphism in human PET and post-mortem 5HTT radioligand binding studies. We investigated whether citalopram-challenge phMRI, as a probe of 5HT transporter function, would detect functional variants of the gene and how this may influence normal serotonergic function.

Methods

Forty two normal volunteers (15 Long-Long (LL), 19 Short-Long (SL) and 8 Short-Short (SS) genotypes; 25 female) were recruited. Each subject was scanned for 25-minutes whilst receiving 7.5mg of citalopram infused over 7.5 minutes. Whole brain images were acquired on a Philips *Inera* 1.5T scanner using single-shot echo-planar (EPI) pulse sequence. Data were analysed using SPM5. The last 2 minutes of the pre-infusion baseline was compared to successive 2 minute time bins covering the infusion and post infusion using regression analysis. A random effects factorial ANOVA of time x genotype was then conducted with gender and age as covariates.

Results

Homozygous SS carriers showed bilateral BOLD signal increases in the superior frontal gyrus ($p=0.003$ uncorrected) when compared to LL carriers. The SS carriers also showed significantly reduced BOLD responses ($p \leq 0.001$ uncorrected) bilaterally in the caudate, mid-cingulate gyrus and parietal cortex compared with the LL genotype group. Heterozygous SL/LS carriers responded to acute intravenous citalopram similarly to that of the LL group.

Discussion

The results offer the first direct evidence that the short and long variants of the 5HTT promoter region indeed influence synaptic 5HT function in the living human brain. Areas that are implicated in psychomotor function, motivation, emotional processing and attention were less activated in SS carriers in response to an acute increase in serotonin availability and this may explain their less favorable response to SSRI treatment.

Conclusion

Citalopram-challenge phMRI as a probe of the direct effects of drug action and in-vivo synaptic 5-HT function provides a means to investigate functional effects of genetic variation in serotonin-related genes. Furthermore, analysis of haplotype variation within the groups may provide greater detail into how the management of serotonin is influenced by genetic factors. Moreover, research into how genes interact with chronic antidepressant therapy may highlight how treatment response is mediated.

References

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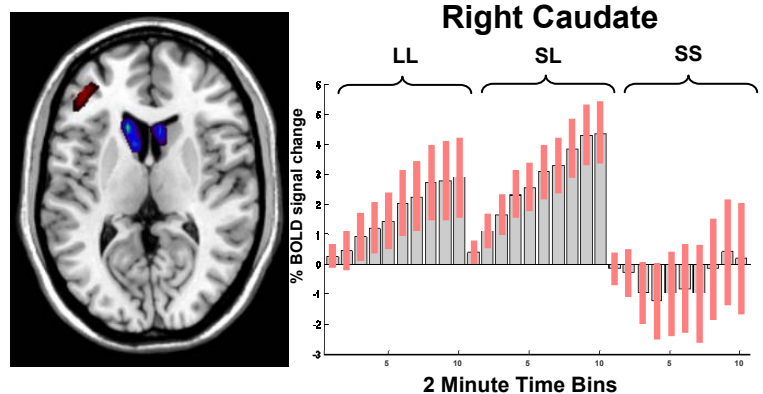


Fig 1: Bilateral caudate BOLD signal decrease and right superior frontal gyrus signal increase in the SS group compared to LL (left). Right caudate percentage BOLD signal change in each 2 minute time bin over 20 mins in response to an acute citalopram challenge (right).