Pre-treatment by lamotrigine attenuates the ketamine-induced BOLD response in healthy volunteers: A phMRI study

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Introduction

N-methyl-D-aspartate (NMDA) receptor hypofunction is thought to be a primary or contributory cause of schizophrenia pathophysiology[1, 2] and NMDA receptor channel blockers, such as ketamine, have been shown to mimic some schizophrenia symptoms[3]. However, it is unclear whether the effects of ketamine are due to direct glutamate blockade, or to increased glutamate release as a result of decreased inhibitory tone from the NMDA neuron. Other studies have shown that agents such as lamotrigine, an inhibitor of pre-synaptic glutamate release, block some of the ketamine-induced effects in healthy volunteers.

Using a combination of pharmacological challenge and fMRI (pharmacoMRI; phMRI), we first investigated the direct changes in blood oxygen level dependent (BOLD) signal due to the intravenous administration of ketamine in healthy volunteers. We then examined the effects of lamotrigine pre-treatment on this ketamine-induced BOLD signal change and hypothesized that it would modify responses in brain areas implicated in schizophrenia.

Methods

Study 1 - 12 healthy volunteers (aged between 18 and 45) were tested on two occasions receiving placebo (saline) or ketamine (bolus 0.26mg/kg over 1-minute, maintenance infusion 0.25mg/kg/hr for the rest of the scan) in a randomised, balanced order, double-blind fashion.

Study 2 - 19 different healthy volunteers (aged between 18 and 45 years) were tested on two occasions receiving either placebo or lamotrigine (300mg) 2 hours prior to the same ketamine infusion above in a randomised, balanced order, double-blind fashion.

In both studies, subjects underwent a 16 minute fMRI scan, 8 minutes into which they received the infusion. Images were acquired on a 1.5T Philips scanner with a multi-slice, single shot EPI sequence to achieve whole brain coverage. Data were analysed using SPM2 (Friston, The Welcome Department of Cognitive Neurology, London, UK). Data analysis identified voxels showing significant changes in successive 1 minute time-bins compared to pre-infusion baseline and compared to either saline infusion responses (study 1) or lamotrigine pre-treatment responses (study 2).

Results

Ketamine induced psychological symptoms in healthy individuals similar to those seen in psychosis. These symptoms were attenuated by pre-treatment with lamotrigine. Ketamine-induced BOLD signal was observed in several areas including medial frontal gyrus (BA6), cingulate gyrus (BA24), inferior frontal gyrus (BA45/47), superior temporal gyrus (BA22/42) , thalamus, whilst the mid frontal gyrus (BA46), precentral gyrus (BA4), postcentral gyrus (BA2/3) and parahippocampal gyrus (BA18/36). These areas were blocked or attenuated by lamotrigine pre-treatment. Figure 1 shows two example time series in areas where BOLD is attenuated and blocked due to lamotrigine pre-treatment.

Discussion

Ketamine-induced BOLD responses were observed in regions implicated in schizophrenia. We hypothesise that the significant changes observed are mediated by enhanced glutamate release. This was verified as lamotrigine pre-treatment attenuated or blocked the ketamine BOLD signal in areas that have been implicated in psychosis symptoms. We hypothesise that the ketamine-induced effects are a result of a glutamatergic stimulation at non-NMDA glutamate receptors. This study demonstrates that direct infusion of ketamine combined with fMRI (phMRI) offers a potential new tool for localising and pharmacologically dissecting the subjective effects of NMDA receptor modulation.

References

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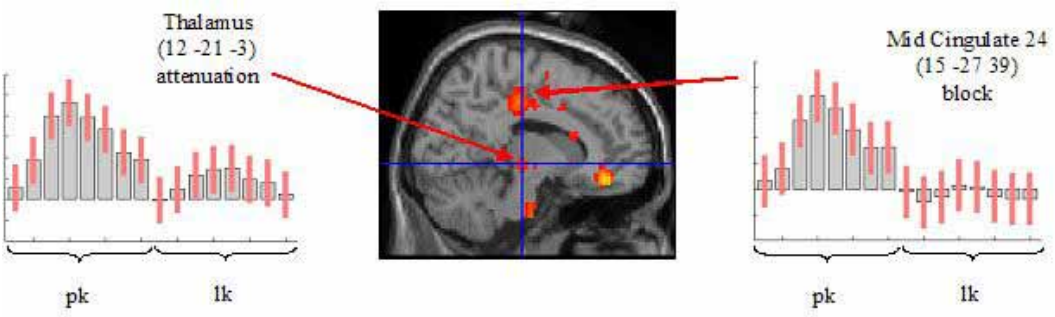

Figure 1. Ketamine BOLD signal changes due to placebo pre-treatment (pk) and lamotrigine pre-treatment (lk)