IS THE MOTOR CORTEX HYPEREXCITABLE IN MOTOR NEURON DISEASE – A STUDY USING PHARMACOLOGICAL fMRI

S. Azam[1], B. Koritnik[3], M. Mehta[2], S. C. R. Williams[2], P. N. Leigh[1]
[1] MRC Centre for Neurodegeneration Research and
[2] Centre for Neuroimaging Sciences, King's College London, Institute of Psychiatry, London, UK
[3] Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, Ljubljana, Slovenia

BACKGROUND

In motor neuron disease (MND) functional studies have shown altered intracortical inhibition and excitation. Excess glutamate induced corticomotor excitability has been proposed as a possible mechanism for this imbalance. More recent anatomical studies showing a global loss of GABAergic interneurones and an alteration in the GABAA receptor mRNA expression pattern in pyramidal cells have highlighted that GABAergic mediated inhibition may also play an important role in the pathophysiology of MND. Midazolam (MZ), a selective GABAA agonist allows us to probe the functional status of post-synaptic GABAA receptors, allowing us to investigate the role of the GABAergic system in MND. Increased motor effort in MND patients, and subsequent cortical reorganisation as an adaptive phenomenon where greater effort is exerted in carrying out a motor task may explain some of the altered cortical activation. Therefore in this study we have examined the effects of MZ on motor task activation, controlling for effort.

METHODS

Using functional imaging (fMRI) we studied 12 patients with MND as defined by the El-Escorial Criteria of definite, probable or possible MND and two control groups: 12 healthy volunteers (HV), and 12 patients with multifocal motor neuropathy (MMN) matched for weakness with the MND group. A visually paced motor task was performed, requiring responses of 5%, 10%, 20% and 30% of maximum grip strength thereby controlling for effort. Subjects were scanned while they received an intravenous challenge of normal saline and on a separate visit an infusion of MZ. Image pre-processing and statistical analysis were carried out using SPM5. Regions of interest (ROI) were defined to extract representative data for the contralateral motor cortex, ipsilateral cerebellum and bilateral subcortical areas.

RESULTS

BOLD signal changes in cortical and subcortical motor networks during motor task under control conditions were comparable between all groups. In contrast to previous studies, we did not see a greater increase in BOLD signal in the cortex of MND patients compared to HV. Following MZ, direct group comparisons revealed a decreased BOLD response in the contaralateral motor cortex (sensorimotor, premotor and supplementary motor areas) in HV, but not MND or MMN. In contrast, after MZ, the BOLD response was increased in the putamen of all groups.

CONCLUSION

The use of a graded motor task matched to individual maximum grip strengths may be a more precise way of providing comparable data on cortical activation between groups in whom motor effort can play an important role in observed results. Suppression of BOLD signal in the motor cortex of HV is likely to be a direct result of post-synaptic GABAA receptor mediated inhibition or due to an indirect reduction of glutamatergic output from the motor cortex. The increase in BOLD signal in the subcortical areas following MZ in all three groups may reflect a compensatory response from parallel motor loops when the task is made more "difficult". The lack of cortical BOLD signal suppression following MZ in the MND group and in the MMN group who have importantly been matched for weakness, may reflect further compensatory changes due to increased motor effort. In the MND group this means that during a motor task GABAA receptor mediated effects seen are likely to be a compensatory response to effort.