Investigations of LGN activation during recovery from acute optic neuritis

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Background: Optic neuritis (ON) is the onset manifestation in 19% of patients with multiple sclerosis (MS)[1]. The main symptoms of ON are visual impairment and retrobulbar pain, and the signs include abnormal colour vision, decreased contrast sensitivity, abnormal VEP (visual evoked potentials), visual field defects and a decreased visual acuity. Inflammation and demyelination of the optic nerve causing conduction block are the major causes of the symptoms in ON.

Spontaneous recovery of vision occurs within weeks or months after onset of symptoms, and several factors may contribute to the recovery process[2] including 1) resolution of inflammation, 2) remyelination, 3) restoration of conduction to axons which persist in the demyelinated state and 4) adaptive cortical changes that compensate for the axonal loss and/or persistent conduction block.

Some functional magnetic resonance imaging (fMRI) studies have shown an altered cortical (extra-occipital) response during stimulation of the previously affected eye in patients with previous ON, indicating reorganization of the response at the cortical level[3].

Using high field scanners activation in the lateral geniculate nucleus (LGN) during visual stimulation has been demonstrated[4]. Previously, LGN activation has only been reported in *one* patient with acute ON: during stimulation of the affected eye no LGN activation was observed; this was in contrast to stimulation of the healthy eye which yielded bilateral LGN activation[5]. This indicates that measurements of LGN activation with fMRI could be used for monitoring optic nerve integrity during recovery from disease.

To further elucidate the mechanisms behind the recovery process in ON, we conducted a longitudinal fMRI study of LGN activation in patients during recovery from an acute attack of ON. If the recovery of visual function is caused by regeneration of the optic nerve, this would be reflected in the LGN activation.

Methods: Sixteen patients with acute ON were included. At the time of inclusion six of the patients had MS. The patients were examined at baseline (less than six weeks after onset of symptoms), and follow-up examinations were performed two weeks, three and six months later. Each examination included a structural and a functional MRI on a 3 T scanner, VEP, visual acuity and a visual field examination.

To minimize partial volume effects due to the small size of LGN, we delineated LGN on 3D-T1W images (MPRAGE) using 'DISPLAY' (http://www.bic.mni.mcgill.ca/) prior to statistical analysis. Prior to drawing, the MPRAGEs were re-sliced to provide coronal images in the PC-Obex-plane; hereafter the LGN was delineated according to the landmarks published by Horton et al[6] (Fig.1).

Echo planar imaging (EPI) of 42, 3 mm slices positioned parallel to the calcarine sulcus, were acquired with the following parameters: TR=2.49s, TE=30ms, flip-angle 90°. Visual stimulation was performed using the IFIS system (Psychology Software Tools, Inc., 1999). The patients viewed a flickering checkerboard reversing at 8 Hz with each eye separately (block design, 10 sec of flickering checkerboard, 10 sec pause, total scan time per eye 5 min 6 sec). Pre-processing, consisting of motion correction and registration to the MPRAGE of the first examination, was performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). Statistical analysis was performed using a general linear model with RETROICOR and expanded motion parameters as nuisance regressors[7]. The effect size maps were re-sliced to match the resolution of the structural images. At each time point we calculated, within the LGN region, the average BOLD signal change during stimulation of the affected and the unaffected eyes and computed the differences between these two values.

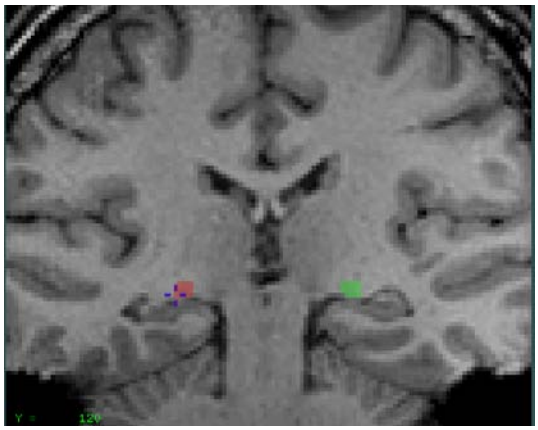

Fig. 1. Delineation of the LGN; e.g. the left LGN is green

Results: The differences in LGN activation between the affected and the unaffected eyes over time for the different patients are depicted in Fig.2. There is a clear tendency towards smaller differences in LGN activation between the affected and the unaffected eyes over time.

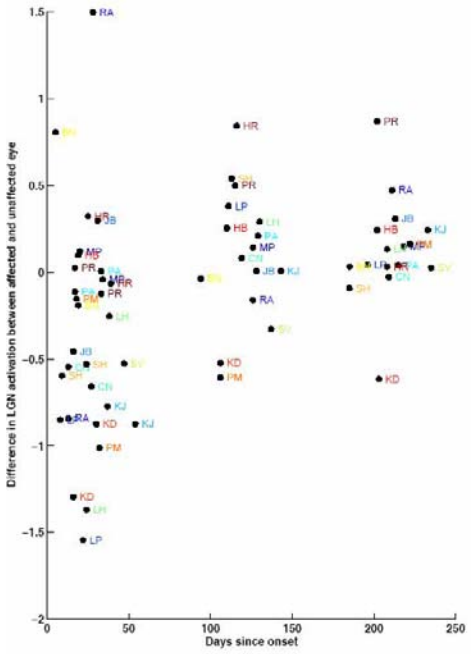

Fig. 2. Differences in LGN activation between affected and unaffected eye over time. Each patient has his/her own colour

Discussion: Our results indicate that during regeneration of vision after acute ON the amount of impulses reaching LGN from the affected eye increases and with that the LGN activation. This is likely to be caused by restoration of conduction through the optic nerve and/or remyelination of the optic nerve. However, other brain areas also project to the LGN, among others the visual cortex, so we cannot exclude that an altered input from the visual cortex to LGN could have an influence.

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