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Normal and abnormal fMRI activation patterns in the visual cortex after recovery from optic neuritis

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Recovery to normal or near normal visual acuity after an optic neuritis episode is common, despite frequent persistence of conduction abnormalities, evident in prolonged visual evoked potential (VEP) latencies. Improvement of visual function is commonly attributed to peripheral nerve recovery. However, central reorganization processes may also be involved. To assess this, we compared the patterns of fMRI activation, elicited by stimulation of the affected and the normal eye, along the visual cortical hierarchy. Activation was assessed in 8 subjects, which recovered clinically from an episode of optic neuritis but still had prolonged VEP latencies. In all patients, reduced fMRI activation was seen in V1 during stimulation of the affected eye, compared to the normal eye. The fMRI signal difference decreased in magnitude with progression along the visual hierarchy, and in some regions within the lateral occipital complex even showed the opposite preference (for the affected eye). These results may indicate a built-in robustness of the object-related areas to disruption of the visual input. Alternatively, it could reflect an adaptive functional reorganization of the cortical response to an abnormal input.

Optic neuritis is an acute inflammatory optic neuropathy, a common condition that causes a loss of vision, which is typically transient. The inflammatory process causes demyelination which leads to conduction blocks in the axon. The annual incidence is 5/100,000 and the prevalence is of more than 1/1000 of the general population (Rodriguez et al., 1995). The most frequent setting is one in which a young adult notes a rapid diminution of vision in one eye, sometimes progressing within hours or days. The maximal visual loss can vary from minor blurring to no light perception. In addition to blurred vision, abnormal color vision, reduced contrast sensitivity and visual field loss are usually present in the affected eye. In clinical practice, the presence of a delayed but well-preserved P100 wave of the visual evoked potential (VEP) is most useful for confirming the diagnosis of optic neuritis. Responses are considered abnormal when the latency of the P100 is above 114 ms (Halliday et al., 1972).

Optic neuritis can be clinically isolated but more often can arise as one of the manifestations of multiple sclerosis and as time progress approximately half of the patients develop other symptoms and signs of the disease.

The treatment of optic neuritis has been investigated in several trials, the results of which have shown that corticosteroids speed up the recovery of vision without affecting the final visual outcome. Improvement usually begins within 2 weeks of onset, perhaps sooner with corticosteroids treatment. After several weeks recovery to normal or near normal visual acuity occurs in more than two thirds of instances. The initial period of recovery is rapid and probably is due to the resolution of the acute inflammation. In the later phase, proliferation of sodium channels and remyelination of the nerves takes place, leading to improvement of visual function (i.e. peripheral effects). This clinical improvement occurs despite the frequent persistence of conduction abnormalities as evidenced by prolonged VEP latencies (Hickman et al., 2002).

A few previous fMRI studies on patients who recovered from optic neuritis showed that the patients had a smaller extent of activation in the visual cortex compared to controls (Rombouts et al., 1998; Gareau et al., 1999; Langkilde et al., 2002; Werring et al., 2000; Toosy et al., 2002). Significant positive correlation was found between the patients' psychophysical performance (such as contrast sensitivity or visual acuity) and the BOLD signal level in occipital cortex (Langkilde et al., 2002). The occipital fMRI signal was also negatively correlated with the interocular difference in latency of the visual evoked response (Gareau et al., 1999). Therefore, the emerging picture is that the function of early visual areas is affected by the peripheral damage. These results, however, were limited by their crude anatomical localization. Therefore, we still do not know how the various cortical areas along the visual hierarchy are affected by optic neuritis.

In the past decade important tools have been developed to identify different visual areas in the human brain (Van Essen and Drury, 1997). It is commonly accepted that these regions are

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generally organized in hierarchical pathways, in which the early processing areas analyze basic features of the visual stimuli (such as contour orientation), while later processing areas analyze more complex features (such as faces or objects). The sorting of different areas is made using one of two ways. The first is retinotopic mapping, which is based on the topographic organization that is characteristic of the early visual areas (V1–V4) (Wandell, 1999). The second method is based on the difference in the functional characteristics between areas. Higher visual areas lose their fine retinotopic organization but show clear functional specialization. For example, areas within the lateral occipital complex (LOC), located at the lateral–ventral aspect of the occipital lobe, show preferential activation to objects over scrambled versions of the same images (Malach et al., 1995).

Our aim in the study was to evaluate the degree to which the various cortical areas along the ventral pathway are affected by optic neuritis. To this end, we compared the pattern of fMRI activation elicited by visual stimulation of the affected and normal eye. In all previous studies, cortical activation was measured using a flickering checkerboard stimulus, which is optimally suitable to activate V1, but is sub-optimal for generating activation in the higher level, object related areas. Previous studies indicated that the function of early visual areas is affected by the peripheral damage, (as is the prolonged VEP), although behavioral performance recovered to normal levels. This behavioral recovery may possibly be due to compensation at higher-level visual areas, which may be manifest in similar activation in LOC during stimulation of either eye. This may occur in spite of persistent physiological abnormalities in the early processing stages (such as a prolonged VEP) that probably reflect the sustained damage in the retino-geniculo-striatal pathway.

Methods

Subjects

We examined 8 patients after acute episode of unilateral optic neuritis. (5 women and 3 men, median age 30, range 19–53). The interval between the episode and the scan ranged between 10 days to 5 years.

Control subjects

We examined additional 4 control subjects (4 women; median age 29.5 range 25–37), sorting them by their eye dominance (3 were with right eye dominance and one with left eye dominance); to ensure that the difference between the two eyes in the patients does not reflect a normal pattern of response preference for the dominant eye. Eye dominance was determined by the "hole in the card" test (Durand and Gould, 1910).

Investigation of vision

Neuro-ophtalmological examination was performed including: Snellen visual acuity, Pelli–Robson contrast sensitivity chart 4L (Metrotopia Ltd. in UK), visual field mapping by automatic perimetry (Humphrey systems) and visual evoked potentials (VEPs). VEPs were recorded monocularly to pattern reversal full-field checkerboards. The latency of the major positive component (P100) was measured in all subjects. Responses were considered abnormal when the latency of the P100 was above 114 ms (Halliday et al., 1972). Interocular latency difference (affected eye VEP− intact eye VEP) was calculated. In four patients, the contrast sensitivity function was further evaluated using a staircase procedure to find the threshold contrast of a sine wave grating at different spatial frequencies. (See Supplementary Fig. 1).

Patients' data

We examined 5 patients after their first event of acute optic neuritis and 3 patients after recurrent episodes. Patient GC had previously suffered from a very mild attack of optic neuritis in the "intact" eye, and therefore did not show a significant inter-ocular difference in the VEP (131 ms in both eyes). We therefore assigned the more recent affected eye as her AE (Affected eye.). As her data analysis showed the same trend as the other patients, we included her data in the group analysis. VEP information for patient YC is missing. Patient OS had delayed VEP in his unaffected eye without clinical history of optic neuritis in that eye. This is a common situation in MS patients. However, since OS still had a marked inter-ocular latency difference, (i.e. his affected eye showed an even greater delayed VEP) he was included in the study group. All patients had normal or near normal visual acuity, contrast sensitivity function and visual field mapping. They suffered from either no or little load of white matter disease as evident from their anatomical MRI. A summary of the patients' data is presented in Table 1.

MRI acquisition

The BOLD fMRI measurements were performed in a whole-body 1.5-T, Signa Horizon, LX8.25 General Electric scanner.

Table 1

	Age (gender)	Time after episode (months)	Affected eye	VEP (ms)			Visual acuity		Contrast sensitivity function (log CS)
				Rt	Lt	Inter-ocular difference	Rt	Lt	
ER	19 (m)	0.3	Left	105	132	27	20/20-	20/20-	Rt −1.95, Lt −1.95
AD	44 (f)	0.5	Left	105	117	12	20/25	20/25	Rt −1.80, Lt −1.80
OT	19 (f)	1	Left	98	135	37	20/20	20/20	Rt −1.80, Lt −1.65
GC	38 (f)		Left (S/P Rt)	131	131	–	20/20	20/20	Rt −1.35 −1.50, Lt −1.35
AR	25 (f)	24	Left	103	122	19	20/20	20/20	Rt −1.80, Lt −1.80
YC	30 (m)	1	Right	MD	MD		20/20	20/25	Rt −1.80, Lt −1.65
NA	39 (f)	69	Left (3rd episode)	112	128	16	20/25	20/20	Rt −1.65, Lt −1.65 −1.80
OS	29 (m)	12	Left (2nd episode)	133	175	42	20/20	20/20	Rt −1.80, Lt −1.35

m—male; f—female; MD—missing data; Rt—Right; Lt—Left; S/P—status post; VEP—visual evoked potential; CS—contrast sensitivity; The lower bound of the normal range of log CS is 1.65.