NEAR INFRARED SPECTROSCOPY AS A NON-INVASIVE ASSESSMENT OF CORTICAL ABNORMALITY IN MIGRAINE?

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1. INTRODUCTION

Migraine is a brain disorder associated with debilitating episodic head pain that afflicts approximately 7% of men and 20% women. It has been estimated to cost US employers about $13 billion per annum.[1, 2] There is an abnormal haemodynamic response to strong visual stimuli in migraine that has been measured using functional magnetic resonance imaging (fMRI).[3] An alternative optical technique, near infrared spectroscopy (NIRS), is more suitable than fMRI for mass studies because of its low cost. Its simplicity and portability offer the potential for widespread use in outpatient clinics. We report preliminary work designed, ultimately, to evaluate the use of NIRS as a screening and therapy evaluation tool in migraine.

2. BACKGROUND: MIGRAINE

2.1. Strong patterns

Patterns of stripes (gratings) vary predictably in only one dimension and have been widely used in vision research. The gratings that have parameters optimal for visibility at low contrast[4] are also those that at high contrast interfere maximally with the visibility of

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other stimuli with which they are combined (in studies of visual masking[5]). Patterns with the same characteristics induce the highest amplitude evoked potentials[6] and are associated with the greatest fMRI blood oxygenation level dependent (BOLD) signal[7]. In brief, they are stimuli to which the visual system is in a general sense maximally sensitive, and will be referred to here as *strong* patterns.

2.2. Aversion, perceptual distortions and seizures in response to strong patterns

Strong patterns can induce a variety of perceptual distortions – illusions of colour, shape and motion. The origin of the illusions is unknown, despite a century of study, although various mechanisms have been proposed.[8] Some individuals are far more susceptible than others to these distortions, usually individuals with frequent headaches.[8] The illusion susceptibility increases in the 24 hours prior to a headache.[9] If the headaches are unilateral, the distortions predominate in one lateral visual field.[8] Individuals with migraine find the patterns aversive[10] and these individuals are particularly susceptible to the perceptual distortions that the patterns evoke.[8] In migraine with aura, the distortions tend to occur interictally in the visual field affected by the aura.[8]

Strong patterns can induce seizures in patients with photosensitive epilepsy.[11, 12] The patterns that induce paroxysmal epileptiform EEG activity in patients with photosensitive epilepsy are very similar indeed to the characteristics of patterns that provoke perceptual distortions in normal observers and, to a greater extent, those with migraine.[8]

2.3. Cortical abnormality in migraine

The cerebral cortex responds abnormally in migraine. The abnormality is poorly understood, although there are several disparate but convergent lines of evidence, recently reviewed,[13] consistent with the hypothesis that the cortex is hyperexcitable: migraine and epilepsy are co-morbid conditions[14] and several anticonvulsant drugs have been shown to prevent migraine in randomised controlled trials[15]. In migraineurs (1) magnetic stimulation of the visual cortex stimulates phosphenes more readily,[16] (2) the evoked potential fails to show the usual habituation with repeated stimulation,[17, 18] (3) *strong* (epileptogenic) patterns are aversive,[10] (4) the fMRI BOLD response to *strong* patterns is selectively elevated.[3]

We hypothesise that the perceptual distortions occur because a spread of excitation causes visual neurons to fire inappropriately. According to this hypothesis, the degree of susceptibility to distortions increases with, and reflects, the degree of cortical hyperexcitability.

2.4. Triggering of headaches

When they are asked, about 40% of patients with migraine will report visually provoked attacks.[19] A substantial proportion report that flicker induces attacks, and a smaller proportion are aware that patterns of stripes can also be a problem. The role of vision in the induction of migraine attacks has received only one investigation in a dozen epidemiologic studies of migraine with a sample size of 1,000-20,000 patients.[19]

The possibility that many headaches are visually provoked has been suggested by (1) double-masked studies that have shown the imperceptible high frequency flicker from fluorescent lighting to be responsible for many headaches experienced by office workers,[20] and (2) the success of recent ophthalmic techniques for headache prevention.[21]

3. BACKGROUND: NEAR INFRARED SPECTROSCOPY

Near infrared spectroscopy exploits the relative transparency of biological tissue to light between 700-1000nm. The most important tissue chromophores within this region are oxyhaemoglobin (HbO2), deoxyhaemoglobin (HHb) and oxidised cytochrome oxidase (CytOx), which display significantly different absorption characteristics, enabling spectroscopic measurements of their relative concentrations in the adult brain.[22] A major advantage of the technique is its non invasive and continuous nature - the light intensity levels used being well below those associated with damage. Systems are portable and measurements can be made easily and repeatedly, without the need for a dedicated laboratory. This makes the technique of potential use in outpatient clinics. Recent technical advances have led to the development of NIRS systems that can measure a variety of oxygenation and haemodynamic parameters in quantitative absolute units, with high temporal resolution and a degree of localisation. Many previous studies have demonstrated the suitability NIRS for measurements of functional activation in adults, particularly over the visual cortex.[23, 24]

4. PURPOSE OF THE STUDY

The purpose of the present study was to determine whether we would be able in normal volunteers to measure the haemodynamic response of the visual cortex to patterns of stripes, both those associated with illusions (*strong* patterns) and those of higher spatial frequency. According to the data obtained by fMRI BOLD,[3] any difference between the response to strong patterns and those of higher spatial frequency should be marginal in normal volunteers but greater in migraineurs.

5. METHODS

5.1. Participants

Six male and two female students and staff of the University of Essex aged 20-57 served as unpaid volunteers. All had normal or corrected-to-normal visual acuity. The volunteers gave written, informed consent, and the study was approved by the University of Essex Ethics committee.

5.2. Procedure

A commercially available NIRO 200 dual-channel spectrometer (Hamamatsu Photonics K.K) was used. Probes with interoptode spacing of 40mm incorporating the emitting and detecting fibres were fixed to the scalp. The optodes were placed with horizontal symmetry either side of two locations: O1 and 10mm above FP4 (measured according to the International 10-20 system of electrode placement.[25]). Optical attenuation data were acquired simultaneously from the frontal and occipital regions at 6Hz.

Horizontal square wave gratings, circular in outline, subtending 18 degrees, with spatial frequencies of 2.5 and 8.5 cpd (Michelson contrast >90%) were presented on the LCD TFT screen of a personal computer. The patterns were each presented for 27s with a 37s interval between presentations, during which the screen was uniformly illuminated with the same space-averaged luminance (48 $cd.m^{-2}$). Two test sessions were given with 5-20min rest between each. The patterns were presented in random order, 5 times each within a session, with the constraint that no pattern appeared more than twice in succession. The order of presentation in the second session was the reverse of that in the first. Each pattern was therefore presented a total of 10 times.

The recorded attenuation data were converted into changes in concentration of the chromophores HbO_2 and HHb.

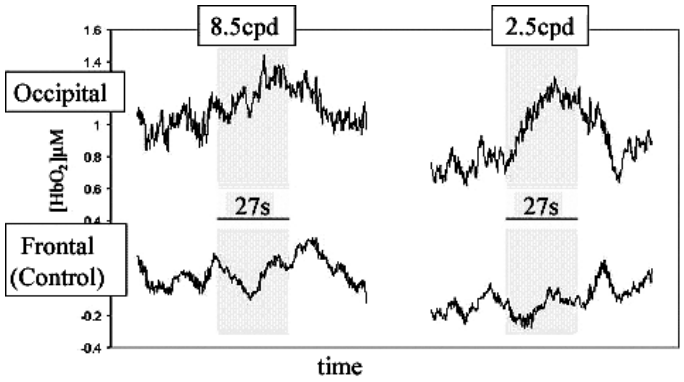

Figure 1. Micromolar oxyhaemglobin concentration changes (from arbitrary baseline) in response to a 8.5 cpd grating (left) and 2.5 cpd grating (right). Upper traces - probes over occipital region; lower traces - probes over frontal region (control). Average of ten sweeps in one representative participant. Periods of 27s stimulation (shown by horizontal bar) were preceded and followed by periods of 37s uniform screen (27s shown) with the same space-averaged reflectance as the stimulus.

6. RESULTS

Figure 1 shows, for a representative participant, the micromolar oxyhaemoglobin concentration changes over time (about an arbitrary baseline) before, during and after the presentation of a grating. The curves show the average of 10 sweeps and have been filtered using a running average of 1s. The curves on the left of the figure show the data

for the grating with spatial frequency of 8.5 cycles per degree and the curves on the right the data for the *strong* grating with spatial frequency of 2.5 cycles per degree. The concentration changes are greater over the occipital region (upper curves) than over the frontal region (lower curves). Note the slow decrease in signal following the pattern offset.

Table 1 shows the mean micromolar oxyhaemglobin concentration changes during the 27s presentation of the patterns. The data in Table 1 are differences in the signal obtained during the stimulus and during the latter 27s of each of the 20 periods lasting 37s that immediately preceded the stimuli (during which the screen was a uniform grey). (The 10s immediately following a stimulus was not included to avoid the slow offset of the haemodynamic response.) Over the occipital region both grating stimuli gave a significant increase in signal compared with the grey screen ($t(7)=1.88$, $p=0.05$, one-tail, for the 8.5cpd grating; $t(7)=2.44$, $p=0.02$, one-tail, for the 2.5cpd grating). The differences over the frontal region, which served as a control for systemic effects, did not approach significance. The occipital response to the 2.5cpd grating was marginally larger than that to the 8.5cpd grating ($t(7)=1.16$, $p=0.14$, one-tail).

Note that the data analysed here are raw and unfiltered. The relatively high standard deviations reflect the large differences between individuals. Some of the differences may be due to variation in optode placement relative to cortical structures, but according to the fMRI BOLD findings, the variation may also reflect stable differences in the cortical haemodynamic response from one individual to another.

Table 1. Micromolar oxyhaemoglobin concentration changes.

	Occipital region		Frontal region	
Participant	8.5cpd	2.5cpd	8.5cpd	2.5cpd
1	0.122	0.090	-0.014	-0.020
2	0.102	0.993	-0.039	0.363
3	-0.042	0.007	-0.134	-0.336
4	0.079	-0.026	0.034	-0.309
5	0.303	0.173	0.105	-0.094
6	-0.014	0.237	-0.217	-0.081
7	0.125	0.329	0.040	-0.007
8	0.855	0.828	-0.114	-0.026
Average	0.191	0.329	-0.042	-0.064
SD	(0.288)	(0.380)	(0.107)	(0.215)

7. DISCUSSION

The change in micromolar oxyhaemglobin concentration as a result of a grating stimulus was clearly measured using NIRS. As anticipated on the basis of fMRI BOLD findings,[3] the response to the two gratings was similar, though slightly larger for the *strong* stimulus. It now remains to be determined, in a much larger cohort of subjects, whether the individual differences can be explained at least in part by diagnostic

category, and whether the differences between the pattern stimuli will be greater in participants with migraine, as the fMRI BOLD findings would predict. The present findings indicate that NIRS has the potential to provide a non-invasive, portable and inexpensive monitor of visual disturbance in migraine.

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