Imaging cerebral energy metabolism in healthy infants

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Abstract Broadband near-infrared spectroscopy (bNIRS) has the potential to provide non-invasive measures of cerebral haemodynamic changes alongside changes in cellular oxygen utilization through the measurement of mitochondrial enzyme cytochrome-c-oxidase (oxCCO). It therefore provides the opportunity to explore brain function and specialization which remains largely unexplored in infancy. We used bNIRS to measure changes in haemodynamics and changes in oxCCO in 4-to-7-month-old infants over the occipital and right temporal and parietal cortices in response to social and non-social visual and auditory stimuli. Changes in concentration of oxygenated-haemoglobin ($\Delta[HbO_2]$), deoxygenated haemoglobin ($\Delta[HHb]$) and change in the oxidation state of oxCCO ($\Delta[oxCCO]$) were calculated using changes in attenuation of light at 120 wavelengths between 780-900nm, using the UCLn algorithm. For 4 infants, the attenuation changes in a subset of wavelengths were used to perform image reconstruction, in an age-matched infant model, for channels over the right parietal and temporal cortices, using a multispectral approach which allows direct reconstruction of concentration change data. The volumetric reconstructed images were mapped onto the cortical surface to visualize the reconstructed changes in concentration of HbO_2 and HHb and changes in metabolism for both social and non-social stimuli. Spatially localized activation was observed for $\Delta[oxCCO]$ and $\Delta[HbO_2]$ over the temporo-parietal region, in response to the social stimulus. This study provides the first reconstructed images of changes in metabolism in healthy, awake infants.

1 INTRODUCTION

NIRS is a non-invasive neuroimaging technique that provides measures of changes in cerebral haemodynamic activity and oxygenation. Due to its feasibility, it has become an established research tool in the field of Psychology to study neurodevelopment and investigate both typical [1] and atypical brain development [2]. NIRS uses near-infrared light to quantify changes in the concentration of oxygenated $\Delta[HbO_2]$ and deoxygenated haemoglobin $\Delta[HHb]$. More recently, broadband NIRS [3]–[5] systems have been developed to allow for the measurement of changes in metabolic activity alongside haemodynamic activity. This is performed by measuring changes in the oxidation state of mitochondrial enzyme cytochrome-c-oxidase $\Delta[oxCCO]$, which is responsible for 95% of energy metabolism. oxCCO is a more direct marker of brain activity. Compared to haemoglobin based measures, oxCCO can potentially provide a more direct marker of brain activation, and animal studies [6] have found a significant correlation between oxCCO measures and phosphorus magnetic resonance spectroscopy biomarkers of cerebral energy metabolism.

More recently in the field of fNIRS, technological advancement has allowed the reconstruction of images of $\Delta[HbO_2]$ and $\Delta[HHb]$ (in both adults and infants) [7] and $\Delta[oxCCO]$ (in adults) [8]. To date, no studies have reconstructed images of changes in haemodynamics and metabolism in infants. These reconstructed images could provide the opportunity to investigate the spatial specificity of cerebral energy metabolism during development and to understand its role in functional cortical specialisation. In this study, we used a broadband NIRS system to measure changes in the redox state of CCO alongside haemodynamic changes in typically developing infants. We performed image reconstruction for four of the infants in the study, to visualize, for the first time, reconstructed broadband NIRS measured changes in response to functional activation.

2 MATERIALS AND METHODS

The study protocol and procedures were approved by the Birkbeck Psychology Research Ethics Committee. Forty-two healthy 4-to-7-month-old infants participated in the study (22 males, 20 females: age 179 ± 16 days old). All parents volunteered and gave written, informed consent to participate.

2.1 Instrumentation

Measurements were performed using a broadband system developed in-house at University College London [3]. The system consisted of four light sources (at the subject-end) which were controlled using a time multiplexed mechanism whereby one pair of light sources was on every 1.4 s. The system also consisted of fourteen detector fibres (at the subject-end). The attenuation signal was obtained from changes in attenuation of light at 120 wavelengths between 780 – 900 nm. The sources and detectors were positioned on the head using custom-built, 3-D printed arrays (all source/detector separation 2.5 cm, with three additional long-separation channels at 4.3 cm used for image reconstruction) which were positioned over the occipital and the right temporo-parietal regions. A NIRS-MRI co-registration map [9] was used to position the temporo-parietal array such that two channels were located over the superior temporal sulcus – temporo-parietal junction (STS-TPJ) region which has been shown to be activated to social stimuli [10]. Figure 1a shows the placement of the array on a participant and Figure 1b shows the locations of each of the channels on the head, including the long-distance channels used for image reconstruction.

2.2 Protocol and measurements

During the study, infants were seated on their parent's lap at an approximate viewing distance of 65 cm. A 35-in screen was used to display the experimental stimuli. These were visual and auditory stimuli comprising a "social" condition which consisted of dynamic videos of actors performing nursery rhymes such as "incy-wincy" and a "non-social" condition which consisted of moving mechanical toys. The baseline condition consisted of still images of transport vehicles. Both the social and non-social stimuli were presented for a varying duration of 8 – 12 s while the baseline was presented for 8 s. Figure 2 shows the order of stimulus presentation. The study began with a rest period (10 s minimum) to draw the infant's attention towards the screen, during which the infant was shown shapes in the four corners of the screen. Following this, the baseline and experimental conditions were alternated until the infant became bored or fussy. Alerting sounds were occasionally played during the baseline period to draw the infant's attention back to the screen.

2.3 Data analysis

Data analysis was carried out in MATLAB (Mathworks, USA) and has been described elsewhere [4]. Image reconstruction was performed at the individual subject level. A four-layer volumetric infant head model was built using average MRI data from a cohort of 12-month old infants [7], [13] using the iso2mesh software [14]. A grey matter (GM) surface mesh was built similarly and used to display the reconstructed images. Images of HbO_2, HHb and ΔoxCCO were reconstructed from the block-averaged attenuation changes at 13 discrete wavelengths (from 780 – 900 nm at 10 nm intervals) using the multispectral approach [15] as described elsewhere [8]. Toast++ [16] was used to compute wavelength-specific Jacobians on the tetrahedral mesh. Optical properties were assigned to each tissue type and for each wavelength by fitting all published values for these tissue types [17]–[19]. The inverse problem was solved employing the LSQR method (maximum number of iterations: 50; tolerance: 10^{-5}) to solve the matrix equations resulting from the minimization and using first-order Tikhonov regularization, with the parameter covariance matrix containing the diagonal square matrices with the background concentration values of the three chromophores (23.7 for ΔHbO_2, 16 for ΔHHb and 6 for ΔoxCCO) [20], [21] and the noise covariance matrix set as the identity matrix. The regularization hyper-parameter was set to 10^{-2}. The volumetric reconstructed images were mapped to the GM surface mesh; changes in concentration for HbO_2 and HHb were normalized to the maximum change in HbO_2 while oxCCO was normalized to its maximum change.

3 RESULTS

Figure 3 shows reconstructed images from a single infant at three different time points for both social and non-social conditions. Figure 4 shows reconstructed images from three different infants at time point 14 s post-stimulus onset (the response is expected to have reached a maximum around this time). Figure 5 shows the reconstructed images of the group average (averaging across the four infants shown in Figures 3 and 4) at three different time points. In general, in response to the social condition, a widespread initial decrease in $\Delta[HbO_2]$ and Δ[oxCCO] was observed over the temporal and parietal brain regions which was followed by a more spatially localized increase in $\Delta[HbO_2]$ and Δ[oxCCO]. Δ[oxCCO] displayed activity which was more localized to the parietal region. Meanwhile Δ[HHb] showed an initial increase in response to the stimulus followed by a decrease. Moreover, in response to the non-social condition, both $\Delta[HbO_2]$ and Δ[oxCCO] displayed a decrease with Δ[oxCCO] showing a more widespread decrease over the temporal and parietal regions.

4 CONCLUSIONS

In this study, we used a broadband NIRS system to explore the feasibility of reconstructing images of changes in haemodynamic and metabolic activity in awake infants, during functional activation. Broadband data were acquired in forty-two healthy infants during a social/non-social experimental paradigm that is known to elicit strong activation over the temporal and parietal brain regions [23]. Spatially localized activation was observed for $\Delta[HbO_2]$ and Δ[oxCCO] over the temporal and parietal regions during the period of maximum response to the stimulus in the four reconstructed infants. These results are in line with each infant's channel-wise data which show a clear increase in $\Delta[HbO_2]$ and Δ[oxCCO] in channels over the temporo-parietal region in response to the stimulus.

We have demonstrated for the first time in awake, healthy infants, the reconstruction of simultaneous changes in the concentration of HbO_2, HHb and oxCCO. Image reconstruction of changes in oxCCO provides the opportunity to investigate cerebral energy metabolism during neurodevelopment and to understand its role in specialisation of brain function. While in the healthy brain, such as in the case of the infants in this study, HbO_2 and oxCCO showed similar patterns of activation, the same pattern may not be observed and needs to be studied in clinical

populations. This technique is therefore useful to understand not only typical brain development, but atypical brain development in disorders such as autism spectrum disorders (ASD) where studies have shown a link to mitochondrial dysfunction [24].

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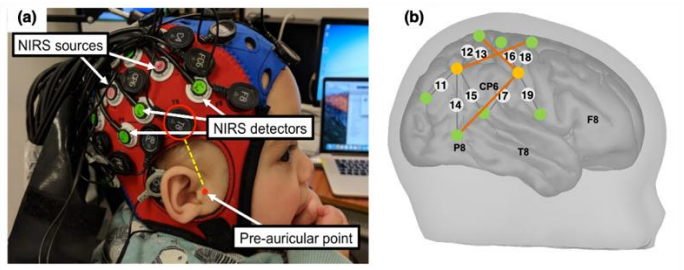

Figure 1: (a) The headgear is shown positioned on an infant's head with NIRS sources and detectors indicated. The black electrodes/fibres are EEG electrodes for concurrent EEG measurements that are not discussed in this paper. (b) Locations of the bNIRS channels (grey circles) and locations of the sources (orange circles) and detectors (green circles) over the right hemisphere. The grey lines show each source-detector pair that forms each channel (separation 2.5 cm) and the dark orange lines shows the long-distance channels used for image reconstruction (separation 4.3 cm)

Figure 2: Order of stimulus presentation.

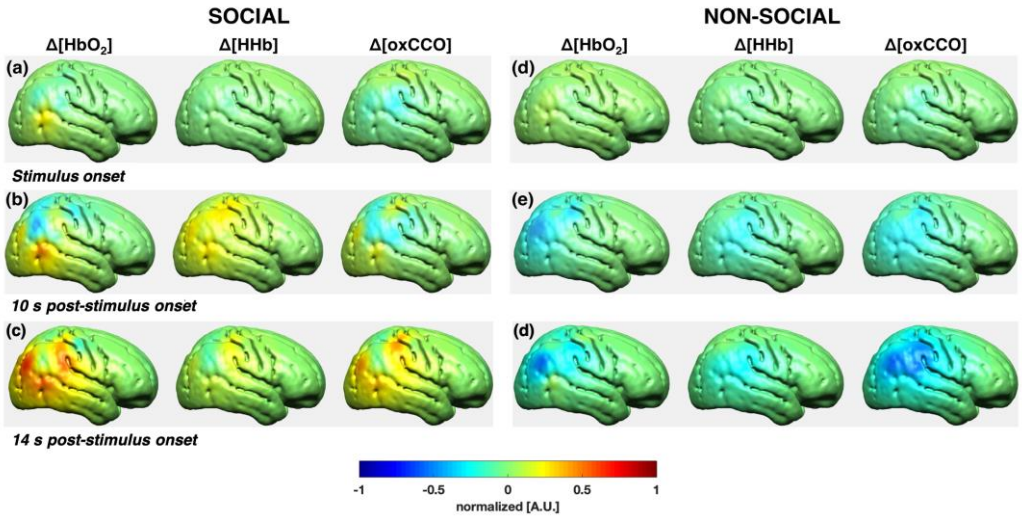

Figure 3: Reconstructed images from one infant at three different time points; stimulus onset, 10 s post-stimulus onset and 14 s post-stimulus onset for both social ((a) – (c)) and non-social conditions ((d) – (f)). The concentration changes of HbO_2 and HHb have been normalised to the maximum of HbO_2 and changes in oxCCO have been normalised to its maximum.

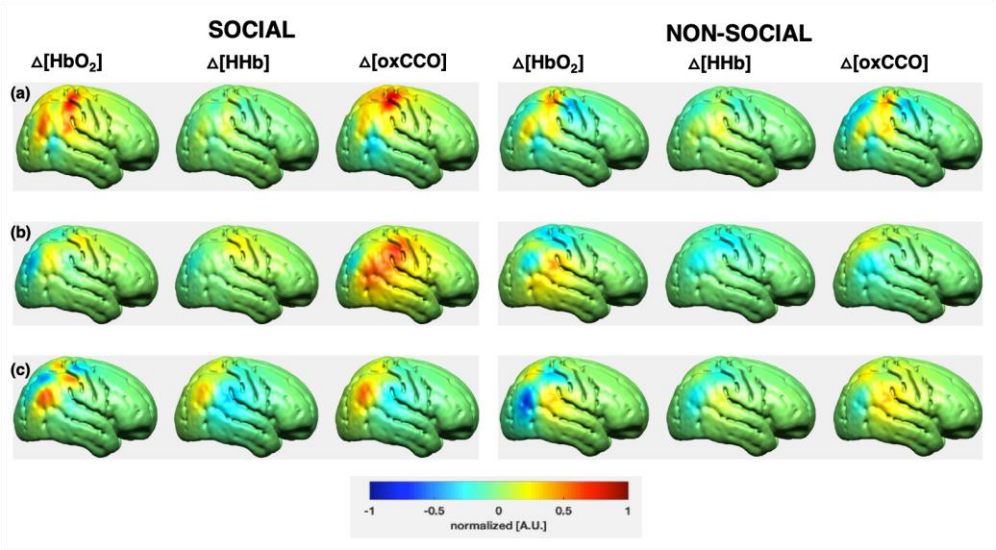

Figure 4: Reconstructed images from three different infants ((a) – (c)) at time-point 14 s post-stimulus onset for both social and non-social conditions.

Figure 5: Group average reconstructed images of the infants shown in Figures 3 and 4 at three different time points; stimulus onset, 10 s post-stimulus onset and 14 s post-stimulus onset for both social ((a) – (c)) and non-social conditions ((d) – (f)). The concentration changes of HbO_2 and HHb have been normalised to the maximum of HbO_2 and changes in oxCCO have been normalised to its maximum.