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Neural compensation in adulthood following very preterm birth demonstrated during a visual paired associates learning task

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ABSTRACT

Very preterm birth (VPT; < 33 weeks of gestation) is associated with an increased risk of learning disability, which contributes to more VPT-born children repeating grades and underachieving in school. Learning problems associated with VPT birth may be caused by pathophysiological alterations in neurodevelopment resulting from perinatal brain insult; however, adaptive neuroplastic processes may subsequently occur in the developing preterm brain which ameliorate, to an extent, the potential sequelae of altered neurophysiology. Here, we used functional magnetic resonance imaging (fMRI) to compare neuronal activation in 24 VPT individuals and 22 controls (CT) in young adulthood during a learning task consisting of the encoding and subsequent recognition of repeated visual paired associates. Structural MRI data were also collected and analysed in order to explore possible structure-function associations. Whilst the two groups did not differ in their learning ability, as demonstrated by their capacity to recognize previously-seen and previously–unseen visual pairs, between-group differences in linear patterns of Blood Oxygenation Level Dependant (BOLD) activity were observed across the four repeated blocks of the task for both the encoding and recognition conditions, suggesting that the way learning takes place differs between the two groups. During encoding, significant between-group differences in patterns of BOLD activity were seen in clusters centred on the cerebellum, the anterior cingulate gyrus, the midbrain/substantia nigra, medial temporal (including parahippocampal) gyrus and inferior and superior frontal gyri. During the recognition condition, significant between-group differences in patterns of BOLD activity were seen in clusters centred on the claustrum and the posterior cerebellum. Structural analysis revealed smaller grey matter volume in right middle temporal gyrus in VPT individuals compared to controls, however volume in this region was not significantly associated with functional activation. These results demonstrate that although cognitive task performance between VPT individuals and controls may be comparable on certain measures, differences in BOLD signal may also be evident, some of which could represent compensatory neural processes following VPT-related brain insult.

1. Introduction

Very preterm birth (VPT; < 33 completed weeks of gestation) is associated with an increased risk of cognitive disability in childhood and adolescence. Studies have found modest but statistically significant deficits in areas including perceptual–motor skills (Taylor et al., 2000), language ability (Taylor et al., 2000; Rushe et al., 2004; Nosarti et al., 2008), executive functions (Nosarti et al., 2008; Giménez et al., 2006) verbal and visual memory (Taylor et al., 2000; Omizzolo et al., 2014; Caldú et al., 2006) and IQ (Isaacs et al., 2000; Hack et al., 2002). The cognitive deficits resulting from VPT birth are associated with later academic difficulties (Aarnoudse-Moens et al., 2009; Schneider et al., 2004) and potentially have a role in the higher incidence of behavioural and psychiatric difficulties seen in these populations in childhood and adulthood (Johnson, and Marlow, 2011; Nosarti et al., 2012).

The extensive structural brain alterations seen in VPT populations, from infancy through to young adulthood, likely represent an underlying cause of cognitive impairment (Nosarti et al., 2008; Omizzolo et al., 2014; Woodward et al., 2006; Ball et al., 2012). However, recent research on the functional sequelae of VPT birth has led to the hypothesis that adaptive neuroplastic processes may allow some VPT born individuals to attain levels of cognitive functioning which are less deficient than might otherwise have been expected given these pathophysiological occurrences (Giménez et al., 2005; Schafer et al., 2009; Gozzo et al., 2009; Narberhaus et al., 2009; Lawrence et al., 2010; Salvan et al., 2013).

Postulated compensatory neural pathways can be observed when VPT born individuals and controls complete the same behavioural tasks, whilst their brain activity is measured using functional magnetic

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resonance imaging (fMRI). Studies investigating Blood Oxygen Level Dependent (BOLD) signal fluctuations during tasks involving language functions, for example, have identified altered patterns of neural interconnectivity between task-specific brain areas (i.e. frontal and temporal cortices) in individuals born VPT compared to controls. During a passive auditory language task, stronger connectivity was observed in VPT-born children between left Wernicke's area and the right inferior frontal gyrus (the homologue of Broca's area) and the supramarginal gyri bilaterally (Gozzo et al., 2009); whereas during a semantic association task, VPT-born children demonstrated stronger connectivity between typical language processing and sensorimotor areas, whilst also showing weaker connectivity within areas of the prefrontal cortex (Schafer et al., 2009).

Other studies have investigated brain structure and function simultaneously, to elucidate how damage to the former could effect the latter. Salvan et al. (2013) demonstrated functional differences between VPT born young adults and controls using a verbal paired associates learning task. During the task, pairs of word-stimuli were presented four times (encoding), intercalated with four blocks of cued-recall trials. Equivalent performance on the behavioural measures was seen, but between-group differences in patterns of BOLD activity were apparent in the right anterior cingulate-caudate body during encoding and in the thalamus and hippocampus/parahippocampal gyrus during recall. This study also reported reduced white matter integrity in the VPT group in tracts passing through the thalamic/hippocampal region that was differently activated during recall, suggesting that functional activation is partly accounted for by anatomical differences in regions displaying BOLD signal change. In another study, Gimenez and colleagues (Giménez et al., 2005), using a declarative 'face-name' memory task, demonstrated significantly greater right hippocampal activation in VPT adolescents than controls, which was associated with a significant decreased volume of the left hippocampus. The authors interpreted this as evidence of a compensatory mechanism in the VPT individuals. Interestingly, in this study, despite the proposed neural compensation, behavioural performance in the VPT group was still poorer than the control group, indicating that such plasticity may not always be fully effective.

Of relevance to this study is a report by Narberhaus et al. (Narberhaus et al., 2009), which used the same visuo-perceptual learning task we investigated and described the mean BOLD signal response during four encoding and four recognition blocks of visual stimuli-pairs in VPT-born adults compared to controls. They reported that, despite no significant performance differences between the groups, during encoding VPT subjects showed increased activation compared to controls in the left caudate nucleus, right cuneus and left superior parietal lobule and a mean decreased signal in the right inferior frontal gyrus. During recognition, VPT individuals showed a mean increased BOLD signal response compared to controls in the right cerebellum and in the anterior cingulate gyrus bilaterally. The authors argued that these differential activation patterns represented neural compensation following perinatal brain injury subsequent to very preterm birth. However, as noted by the authors, an important methodological limitation with their analysis concerned the averaging of activations across the four repeated blocks of the task. This had the potential to mask more 'pure' memory effects with repetition effects and retrieval with encoding effects.

Therefore, in this study, we extended the work of Narberhaus et al. (Narberhaus et al., 2009) by reanalysing their data to study the adaptation of neural resources during the learning and recall processes. We aimed to investigate whether the way learning of visual paired associates takes place differs between very preterm-born adults and control participants. In order to explore this we determined brain regions, in a sample of VPT young adults and separately in a control group, that demonstrated either increasing or decreasing linear activation patterns over the four repeated blocks of the encoding and recognition phases. We then looked for any patterns of functional adaptation that differed significantly between the groups.

In normative samples, paired associates learning tasks typically activate a fronto-parieto-occipital network (Neuner et al., 2007), as well as a hippocampal-diencephalic circuitry and medial temporal lobe structures (Neuner et al., 2007; Stark, and Squire, 2000; Strange et al., 2002).

Specifically, decreased activation in thalamus and superior frontal gyrus has been associated with repeated stimuli presentations in humans (Neuner et al., 2007). A possible explanation could be that activation during the first learning blocks reflect a direct access to the associations learnt during encoding which exploit areas of the thalamus projecting to the prefrontal cortex (Klein et al., 2010) and hippocampus (Aggleton et al., 2010). With practice and successful retrieval of the paired associates, subsequent retrieval may become more automatic and thus may not require access to regions centrally involved in encoding.

We hypothesized that VPT born young adults would display altered linear patterns of BOLD signal response compared to controls during the processes of encoding and recognition in components of the fronto-parieto-occipital, hippocampal-thalamic and temporal lobe networks, which include areas found to be particularly impacted in VPT cohorts, both at a functional (Giménez et al., 2005; Narberhaus et al., 2009; Salvan et al., 2013; Scheinost et al., 2014) and a structural level (Nosarti et al., 2008; Ball et al., 2013; Northam et al., 2012; Eikenes et al., 2011). We further conducted exploratory analyses to investigate whether structural alterations (using a whole-brain analysis approach) in the VPT group would be significantly associated with functional activation (Narberhaus et al., 2009; Salvan et al., 2013).

2. Materials and methods

2.1. Participants

In 1983–84, 147 infants born at less than 33 weeks gestation and admitted consecutively to the Neonatal Unit at University College London Hospital (UCLH) within 5 days of birth, survived, were discharged, and were enrolled for long-term follow up. Of this cohort, 78 individuals were born at 28 or less weeks of gestation and 69 were born between 29 and 33 weeks of gestation. At age 15 years, 113 (76.9%) of these individuals received a cognitive, behavioural and neurological assessment and 90 (61.2%) had an MRI. At age 20, 94 (83.2%) of the individuals assessed in adolescence agreed to participate in follow-up (Allin et al., 2008). For the current fMRI study, 24 young adults of both sexes who were born VPT with no history of cerebral palsy, grade 3/4 intraventricular haemorrhage or periventricular leukomalacia as assessed by neonatal cranial ultrasound, were randomly selected from the cohort described above. These are the same subjects who participated in the study by Narberhaus et al. (2009), with the addition of three VPT individuals who were previously not analysed due to image corruption issues which were successfully fixed prior to this analysis).Twenty-two controls (CT) were recruited from advertisements in the local press and university and were selected according to age, handedness and gender. Inclusion criteria were full-term birth (37–42 completed weeks of gestation); exclusion criteria were birth complications (e.g. low birth weight defined as < 2500 g, endotracheal mechanical ventilation), prolonged gestation (greater than 42 weeks), history of psychiatric illness, severe hearing deficits and motor impairment. All participants were English native speakers and right handed. The experiments were undertaken with the understanding and written consent of each subject, with the approval of the appropriate local ethics committee, and in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki).

2.2. Functional MRI task: Visual paired associates

The task used here is identical to that used by Narberhaus et al. (2009) and contained the following conditions: encoding, recognition, same/different discrimination and low-level baseline, presented in that order (see Fig. 1). During the encoding condition, participants were presented with pairs of coloured abstract pictures on black squares and