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Cortical visual function in premature infants

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Preterm birth is a major cause of neurological impairment in childhood and can lead to long-term clinical, educational and social problems [1]. Better understanding and measurement of cerebral function in infancy, would enable the functional consequences of brain damage to be identified at an earlier age.

Cortical visual processing is an early-developing aspect of brain function and is essential for the acquisition of cognitive, motor and social skills. We have devised a test battery for examining functional vision, the ABCDEFV [3] which includes two tests of cortical function for young infants: (i) orientation-reversal visual event-related potentials (OR-VERP); (ii) latency of saccadic fixation shifts (FS) under competition, a test of cortically based control of attention. Other studies have shown that development of the OR-VERP in term infants with hypoxic-ischaemic brain insult correlates with neonatal neuroimaging [4] and along with FS performance is predictive of later developmental outcome [5]. In this study, we examined these indicators in a group of 24 prematurely born infants (<32 weeks gestation) who had neonatal and term MRI scans to test whether these measures indicated early brain damage and predicted later cognitive outcome.

Infants were tested at between 3 and 7 months post-term. The OR-VERP was elicited with grating patterns switching between 45-135 deg orientations at 8 reversals s-1. The pass criterion was a statistically reliable OR-VERP (circular variance test) by 7 months post-term. In FS, the pass criterion was 80% correct refixations, and a difference between mean latencies for competition and non-competition trials of less than 0.5s. The Griffiths mental developmental scale was used as an outcome measure at 2 years.

Infants were divided into three groups, Mild/Normal (n = 8), Moderate (n = 7) and Severe (n = 9), according to extent of white matter damage seen on T2 images. The majority of infants in the mild lesion group (7/8) showed normal OR-VERP responses, but only 3/7 of the moderate group and 2/9 of the severe group met the pass criterion. On FS, 6/8 of the infants in the mild group showed typical attention responses by 7 months but less than half the moderate group and none of the severe group passed the test. Absence of an OR-VERP response before 7 months predicted a DQ < 80 at 2 years with a sensitivity of 86% and a specificity of 65%. Failure on the FS test was also associated with a low DQ score (sensitivity 100%; specificity 53%).

These results demonstrate that early visual cortical measures are useful diagnostic and prognostic tools to assess infants born prematurely. These measures provide not only a sensitive indicator of cortical visual function but also prediction of development across cognitive and motor domains.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

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Inflammation in the adult and developing brain

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Neural injury, in ischaemia, trauma or neurodegenerative disease, triggers wide-ranging inflammatory changes in neighbouring glia (astrocytes, microglia) and recruitment of leukocytes, particularly T-cells, which play an important role in the immune surveillance of the damaged neural tissue and in dealing with neural infection. Recent studies using cell cultures and transgenic animals have started to shed light on the identity of molecular factors that induce these inflammatory changes, particularly cytokines such as IL6, TNF-alpha and TGF beta 1 (Raivich et al. 1999; Makwana & Raivich, 2005). However, inflammation is also frequently associated with enhanced axonal damage and neuronal cell death. For example, recent epidemiological studies show strongly enhanced risk of cerebral palsy in the presence of maternal and/or fetal infection (Kendall & Peebles, 2005). Application of E. coli lipopolysaccharide (endotoxin), the standard bacterial inflammatory stimulus, strongly enhances the sensitivity to hypoxic/ischemic insults in the neonatal animal, particularly if the stimulus is applied some time before, with a maximum 12h preceding the insult (Kendall et al. 2005). Moreover, analysis of the cellular changes involved using cell surface activation markers showed that this enhanced sensitivity coincides with microglial activation, and is preceded by that of brain vessels, pointing to an endothelial → microglial → neuronal cellular cascade. Here, the availability of conditional mutants now allows us to address the cell type-specific and time dependent roles of cytokines such as TNF and TGFb1 and intracellular signals which include ras/MEK/ERK and JNK&Jun pathways as well as intracellular pH (Kendall et al. 2006), in mediating these detrimental inflammatory changes in the injured brain.

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Developmental programming of the brain: neuroinformatic approach

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Striking evidence from a number of disciplines has focused attention on the interplay between the developing organism and the circumstances in which it finds itself. The organism can express specific adaptive responses to its environment which include short term changes in physiology as well as long-term adjustments. Early life events may therefore affect any organ including the brain. With the progress in reproductive medicine and neonatal intensive care, we are confronted with an increasing number of newborns at high risk for modification of early brain development. Advanced Magnetic Resonance Imaging (MRI) techniques have recently provided us with new data on fine structural alteration of the brain in these high risk newborns. Volumetric analysis of 3D-MR imaging data sets are achieved by segmentation of the imaged volume into the different tissue types with 3-dimensional renderings. Applying these techniques to the study of the high risk newborn new insights into the modification of cortical development have been gained (2). Preterm infants exposed to postnatal corticosteroid treatment for chronic lung disease were found to have a 30% reduction in cortical gray matter development (3). A similar reduction in cortical development was found in preterm infants after intrauterine growth restriction (IUGR)(5). The hippocampus is known for its crucial role in cognitive function such as memory and learning. It is sensitive to hypoxia, and to stress hormones. The total volume of both hippocampal formations was found to be significantly smaller in IUGR preterm infants than in the control group. These modifications of cortical development were also found in preterm infants studied at 8 years and were correlated with neurofunctional deficits (4). Diffusion weighted imaging further allows assessment of microstructural development of the white matter structures (1). Factors influencing diffusion in the developing brain are related to anisotropy, which describes the preferential direction of water diffusivity. The geometric nature of the diffusion tensor can be used to display the fiber architecture of the brain white matter and its alteration due to modification of brain development. IUGR preterm infants showed microstructural alterations in major associative white matter tracts. To assess brain functioning early on, measurement tools of neurobehavioral functioning have been developed. The Assessment of preterm infant behaviour (APIB) as a newborn behavioral assessment methodology provides an integrated subsystem profile of the infant's current ability to process environmental input and assesses the level of brain functioning. Significant correlation of behavioral maturation and cortical brain development has be shown using APIB to assess brain function in newborns. Advanced MR-techniques such as 3D-MRI, diffusion tensor imaging combined with specific neurobehavioral testing allow us to study normal brain development in the newborn and assess effects of endogenous or exogenous insults with implications for longterm neuropsychological development.

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