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Combining clinical assessment scores and in vivo MR spectroscopy neurometabolites in very low birth weight adolescents

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Summary

Objective: Very low birth weight (VLBW) survivors are at increased risk of neurological impairments that may persist into adolescence and adulthood. The aims of this study were to identify the most important clinical assessments that characterize differences between VLBW and control adolescents, and to look at the relationship between clinical assessments and the metabolites in in vivo MR spectra.
Methods: At 14—15 years of age, 54 VLBW survivors and 64 term controls were examined clinically. Several neuropsychological and motor assessments were performed. The magnetic resonance (MR) brain spectra were acquired from volumes localized in the left frontal lobe and contained mainly white matter.
Results: Probabilistic neural networks and support vector machines demonstrated that clinical assessments rendered a possibility of the classification of VLBW versus control adolescents. The most important clinical assessments in this classification were visual—motor integration, motor coordination, stroop test, full scale IQ, and grooved pegboard.

Through the use of outer product analysis-partial least squares discriminant analysis on a subset of adolescents ($n = 36$), the clinical assessments found to most

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strongly correlate with the spectral data were the global assessment scale, Wisconsin card sorting test, full scale IQ, grooved pegboard test, and motor coordination test. Clinical assessments that relate to spectral data may be especially dependent on an intact microstructure in frontal white matter.

1. Introduction

Children born prematurely with very low birth weight (VLBW) are at increased risk of brain injury and subsequent motor, perceptual, cognitive, and behavioural impairments and disabilities [1]. Different types of magnetic resonance techniques have revealed both grey and white matter abnormalities in these children [2—4]. Magnetic resonance spectroscopy (MRS) provides the non-invasive in vivo detection of a number of biologically important cellular metabolites in the brain, and it is an imaging modality that has been widely used to measure neuronal integrity in asphyxiated term infants and VLBW children [5—8]. Most MRS studies in VLBW children have been performed during the neonatal and infant period, although brain injury in these high risk groups persists into adulthood, as shown by other imaging modalities [9—13]. A few studies have looked at MRS findings in VLBW children later in childhood; however, these studies have yielded no or weak relationships between metabolite ratios and clinical findings [14,15].

Probabilistic neural network (PNN) [16] and support vector machines (SVMs) [17] are methods frequently used for the analysis and interpretation of spectroscopic and other multivariate data. We have already reported that PNN distinguished between VLBW adolescents or adolescents born small for their gestational age at term and control adolescents based on small, yet systematic, differences in the brain metabolite distribution described by MRS [18]. Data fusion, the process of combining information from different sources to establish a single decision, is a relevant tool in the search for connections between specific variables within these sources. Outer product analysis (OPA) was introduced as a method to detect the co-evolution of spectral regions from two sets of measurements on the same samples [19]. In the present study, we extend the approach to calculate outer product matrices from clinical assessments and in vivo MR spectra from the same subjects.

The purpose of this study was, first, to identify the most important clinical assessments that characterize differences between VLBW and control adolescents. Secondly, the relationship between clinical assessments and metabolites in the in vivo MR spectra was assessed.

2. Methods

2.1. Subjects

The subjects, aged 14—15 years, were recruited from a follow-up study of VLBW children (birth weight $\leq$ 1500 g) and term control children (birth weight $>$ 10th percentile). The VLBW children had been admitted to the neonatal intensive care unit at the University Hospital in Trondheim, Norway from 1986 to 1988. The control children were born to mothers living in the Trondheim region. Further details of the study population and design are given in previous articles [18,20]. The regional committee for Medical Research Ethics approved the study. Written informed consent was obtained from both the adolescents and their parents.

2.2. Clinical assessment

The clinical assessment consisted of an extensive battery of neuromotor and neuropsychological tests performed by a multidisciplinary team. Of 118 subjects included in the clinical assessments, the VLBW group consisted of 27 girls and 27 boys and the controls consisted of 39 girls and 25 boys. The clinical and MRS evaluations were all blinded. The clinical assessments (with abbreviations) and their numerical order in further analyses are summarized in Table 1.

2.2.1. Cognitive evaluation: assessments 1—5

An estimate of the adolescents' intelligence quotient (IQ_{est}) was calculated using four subtests of the Wechsler intelligence scales (WISC-III) [21]. The four subtests were arithmetic (IQ_{arith}), vocabulary (IQ_{voc}), block design (IQ_{block}), and picture arrangement (IQ_{pict}) [22].

2.2.2. Fine motor speed evaluation: assessments 6 and 7

Manual dexterity was estimated using the grooved pegboard tests for both the dominant and non-dominant hand [23].

2.2.3. Psychiatric evaluation: assessment 8—12

The psychiatric assessments included the autism spectrum screening questionnaire (ASSQ) [24] and mother-report on attention deficit hyperactive disorder