Is pH a biochemical marker of IQ?

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SUMMARY

We have measured intracellular brain pH *in vivo* in 42 boys and found a significant correlation between this biochemical parameter and samples of intelligent behaviour. To the best of our knowledge this is the first reported relation between a biochemical marker which is within normal physiological values and intellectual ability. pH is one of the most accurate parameters that can be measured by ^{31}P magnetic resonance spectroscopy and it reflects sensitively cellular ionic status and metabolic activity. The observed correlation, although not implying a causal relation, raises the possibility that intelligent behaviour may be influenced by the ionic status of brain tissue, or vice versa.

1. INTRODUCTION

A recent study on brain metabolism in Duchenne muscular dystrophy suggested there might be correlations between markers measureable in the brain by ^{31}P magnetic resonance spectroscopy (MRS) and measures of intelligent behaviour (Tracey *et al.* 1995). We have examined the relation of brain biochemistry and function in greater detail by studying normal subjects with Full Scale IQs ranging from 63 to 138.

2. METHODS

(a) *Subjects*

The study group comprised 42 volunteer boys who acted as a control group for other studies on cognitive ability in Duchenne muscular dystrophy. The mean age of this group was 122 months (range 89–158) and subjects were drawn, with informed consent, from five Oxfordshire schools. The study had the approval of the Central Oxford Research Ethics Committee.

(b) *Magnetic resonance spectroscopy*

All spectroscopy was done in a 2T whole body magnet, using a Bruker Biospec spectrometer. All spectra were obtained at 34.49 MHz using a spectral width of 2 kHz on a duty cycle of 15 s using a single, transmit–receive butterfly surface coil (10 cm × 14 cm) mounted on a curved perspex sheet. This geometry produces a B_1 flux orthogonal to the coil axis, which allows the coil to be placed coaxially with the magnet bore, against the top of the subject's head and well away from the temporalis muscles. The anatomical area excited by the coil is shown in figure 1. Free induction decays were zero-filled and transformed with 8 Hz of exponential multiplication. Baseline correction, line-fitting and automatic peak-picking were achieved using standard NMR1 software (New Methods Research Inc, East Syracuse, New York, U.S.A.). pH was determined using the difference in chemical shift between phosphocreatine resonance and inorganic phosphate (Moon & Richards 1973). In 12 subjects, two or more spectra were obtained and the pH values in any one subject differed from each other by no more than 0.01 pH units. Where two or more pH values were available, the mean value was used. Estimates for the relative volume of extracellular space in the cortex vary from around 10% in white matter, to 20% in grey matter. The concentration of inorganic phosphate is comparatively low in extracellular space (Buchilli *et al.* 1994). Therefore, the pH measured by this technique represents intracellular pH. The pH of the cortex does not vary significantly with depth in normal subjects (Cadoux-Hudson *et al.* 1989).

(c) *Statistical analysis*

Data are presented as means ± s.d. Spearman's correlation coefficient (corrected for ties) was calculated for each data set. Statistical significance was assumed if $p < 0.05$.

(d) *Neuropsychological assessment*

Age-scaled scores from the Wechsler Intelligence Scale for Children (WISC-III) were obtained from all 42 boys; 30 of these boys also completed tests of memory, visuo-spatial/constructional ability, manual dexterity, verbal fluency and reading.

3. RESULTS

A significant positive correlation (see table 1; figure 2) was found between the regional sampling of brain pH (represented in figure 2) and WISC-III Full Scale

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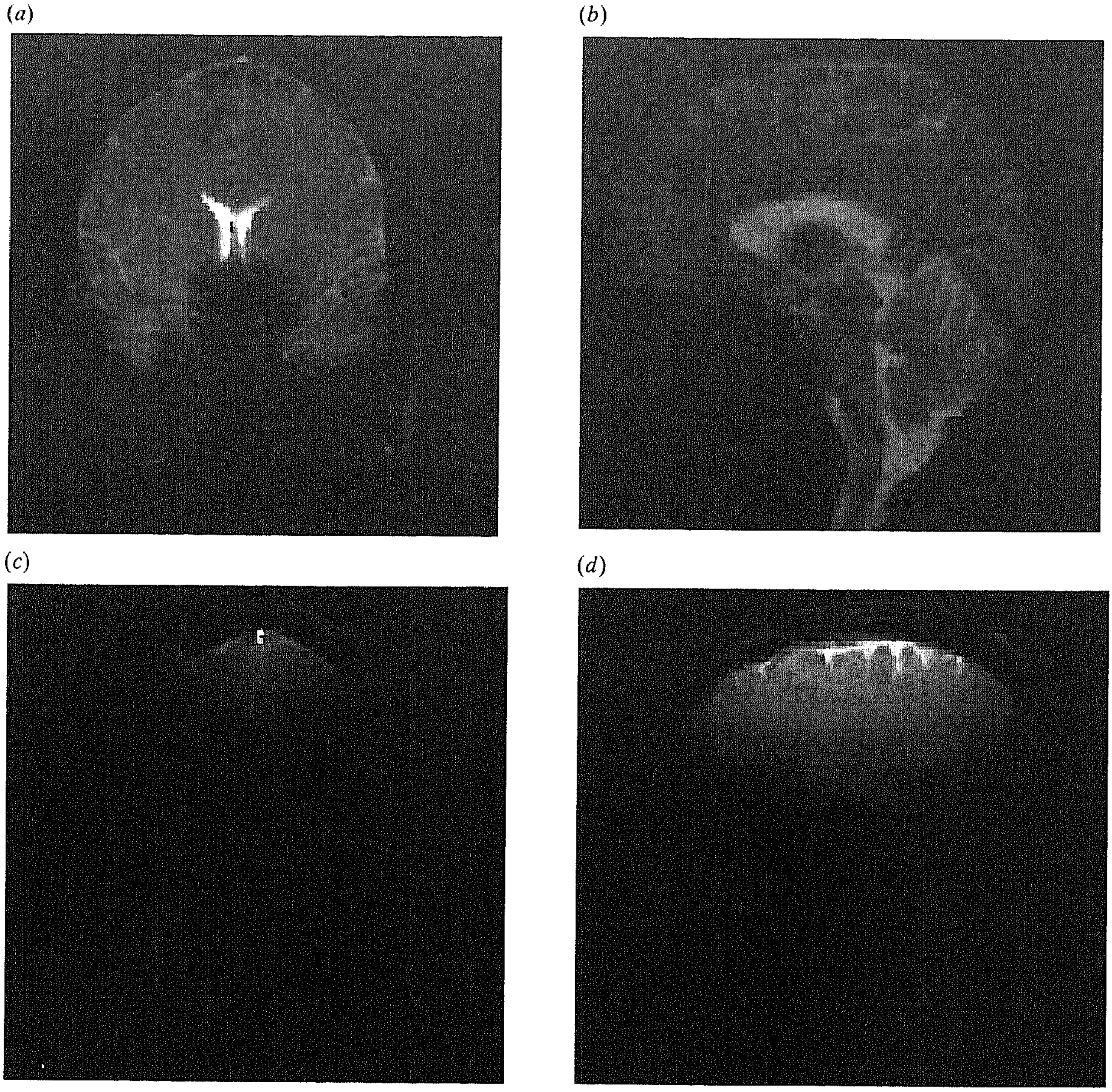

Figure 1. T_2-weighted gradient refocussed images showing the region excited by the coil. (*a*) Complete coronal section obtained using a birdcage quadrature head coil. (*b*) Sagittal section using the same coil. (*c*) Coronal section as in (*a*), obtained using a ^{1}H MRS butterfly surface coil of identical dimensions to the one used to obtain ^{31}P MRS spectra. (*d*) Sagittal section obtained as in (*c*). The upper two images are presented to assist interpretation of the lower images.

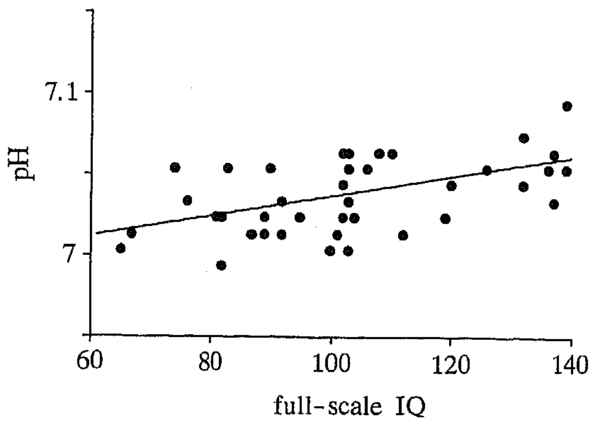

Figure 2. Relation between brain pH and full-scale IQ.

IQ; we also note that the association is the same direction for all tests administered but greatest with tests of verbal ability (tables 1 and 2).

Mean Full Scale (102.3 ± 19.6), Verbal (105.1 ± 22) and Performance (98.4 ± 16.3) IQs fell in the average range. The ages of the subjects ranged from 6.11 to 13.1 years (mean 124 ± 17 months); the data showed no random correlation of age with Full Scale IQ.

4. DISCUSSION

While the temporo-spatial stability of our pH measure remains uncertain and we do not assume we have exhaustively sampled intelligent behaviour, we note that both pH and behaviour samples were obtained under fixed experimental conditions and that the WISC-III has excellent psychometric properties (Little 1992; Bracken & McCallum 1993). We are not aware of any previous reports of brain–behaviour relations in non-invasive human studies where the normal brain-referent is at the biochemical level.

Table 1. *Spearman's Rank correlation coefficients (corrected for ties) between brain pH and age-scaled scores on WISC-III, Wechsler Objective Reading Dimensions (WORD) and Wide Range Assessment of Memory and Learning (WRAML) subtests*

(Subtest numbers (1–12) that comprise WISC-III quotients and indices are contained in parentheses. Subtests marked * are those with a relatively high verbal loading. Unless otherwise stated, $n = 42$, n.s; not significant ($p > 0.05$).)

	correlation	significance (p)
WISC-III quotients		
full scale IQ (1[10])	0.523	0.0008
verbal IQ (1–5)	0.5576	0.0004
performance IQ (6–10)	0.3041	n.s.
WISC-III indices		
verbal comprehension (1–4)*	0.5313	0.001
perceptual organization (6–9)	0.2047	n.s.
freedom from distractibility (5+12)	0.2899	n.s.
processing speed (10+11)	0.2361	n.s.
Subtests		
1. similarities*	0.6288	0.0001
2. vocabulary*	0.5883	0.0002
3. comprehension*	0.5415	0.004
4. information*	0.3746	0.015
5. arithmetic	0.1645	n.s.
6. block design	0.3668	0.017
7. picture completion	0.1727	n.s.
8. object assembly	0.1553	n.s.
9. picture arrangement	0.0341	n.s.
10. coding	0.2034	n.s.
11. symbol search	0.255	n.s.
12. digit span*	0.4228	0.006
Kauffman crystallized (Gc) and fluid (Gf) formulae		
Gc (1+2+3+4+9)	0.604	0.001
Gf (1+5+6+8+9)	0.44	0.006
WORD ($n = 30$)		
basic reading*	0.3574	n.s.
WRAML ($n = 30$)		
A – design memory	0.1276	n.s.
B – picture memory	0.0933	n.s.
C – story memory*	0.2014	n.s.
D – verbal learning*	0.2103	n.s.
Memory screening index (A+B+C+D)	0.235	n.s.

Table 2. *Partial correlations (controlling for age) between raw scores from neuropsychological tests ($n = 30$) and brain pH*

(Subtests marked (*) are those with a relatively high verbal loading.)

verbal fluency*	correlation	significance (p)
categorical 1	0.4682	0.005
categorical 2	0.4602	0.005
Annette's peg moving task		
left hand speed – time to criterion	−0.1599	n.s.
right hand speed – time to criterion	−0.0973	n.s.
Rey complex figure	—	—
copy raw score	0.2616	n.s.

Correlations have been reported between averaged evoked potentials (AEP) and IQ (for examples, see Ellis 1969; Ertl & Schafer 1969; Callaway 1973). The amplitude of an evoked potential *in vitro* is known to be proportional to pH (Ellis 1969); indeed increasing intra- and extracellular pH increases the amplitude of nerve action potentials (Lehmann 1937) and decreases conduction time (Ellis 1969). More generally, the properties of receptors are also modulated by changes in pH; for example, the responsiveness of the *N*-methyl-D-aspartate receptor is improved with alkalinity (see, for example, Gottfried & Chesler 1994), gap junction conductance is a simple and positive function of pH (Spray *et al.* 1981), the channel permeability and gating properties of the acetylcholine receptor are also positively correlated with extracellular pH in the physiological range (Palma *et al.* 1991) as is the rate control of acetylcholine esterase (Taylor *et al.* 1994). Reuptake of the neurotransmitter glutamate is proportional to intracellular pH (Judd *et al.* 1996). Conversely, neuronal activity affects pH (Chesler & Kaila 1992). For example, glial cells regulate pH changes induced by neuronal activity (Rose & Dietmar 1994) and astrocyte pH has been shown to increase with cortical stimulation (Chesler & Kraig 1987). There are therefore grounds for suggesting that pH is associated with the efficacy of conductivity–transmission in the brain at the neuronal level, although we are unable to determine whether higher pH somehow accommodates this process or is a response to it. Although pH may merely be a marker of electrophysiological (e.g. AEP) function, it is likely to have greater temporal stability and be less sensitive to immediate environmental influences. Observations that diluted the impact of AEP-IQ correlations may not therefore equally apply to our findings. Namely, that the form of an AEP is influenced by the cognitive responses of the subject (Sutton *et al.* 1967; Callaway 1973) and that AEP measures confound information about the present state of the brain with enduring properties more likely to underlie the 'intelligence' trait (Robinson 1989).

Insufficient data are currently available to determine whether the pH range (or rate of change) and innate or environmentally mediated individual characteristics; it might though be argued that the cluster of higher correlation coefficients between brain pH and tests/indices with a relatively high verbal loading (tables 1 and 2*) suggests the latter. Similarities have for example been noted (Horn 1985; Kaufman 1994) between the verbal-performance intelligence dichotomy and Horn & Cattel's (1966) distinction between crystallized (Gc) and fluid (Gf) intelligence. Gc tasks are said to require previous education, training and acculturation, while Gf tasks demand a more flexible–adaptable response to unfamiliar stimuli. A stronger pH correlation with Gc might therefore imply that it is sensitive to changes in ability mediated more by environmental than hereditary factors. This hypothesis is not however supported by our data as both Gc and

Gf (operationalized in terms of WISC-III subtests according to Kauffman (1994)) correlate significantly with pH, and alternative measures of achievement-attainment (e.g. reading and arithmetic subtest scores) do not.

The pH measured is the averaged pH from the area delineated in figure 1. Imaging was not done on every subject so that identical regions of brain might not have been excited in all studies. In so far as our regional and unlocalized sample of pH is adequate, and a marker of the output-efficiency of a global, interactive biochemical system that is an underlying property of all brain regions, we would note that the particular association of this marker with a relatively selective cognitive domain (e.g. 'verbal' subtests) may lend support to connectionist modellers and neuropsychologists (Farah & McClelland 1991; Plaut & Shallice 1993) who have argued that functional modularity need not necessarily imply regional anatomical modularity.

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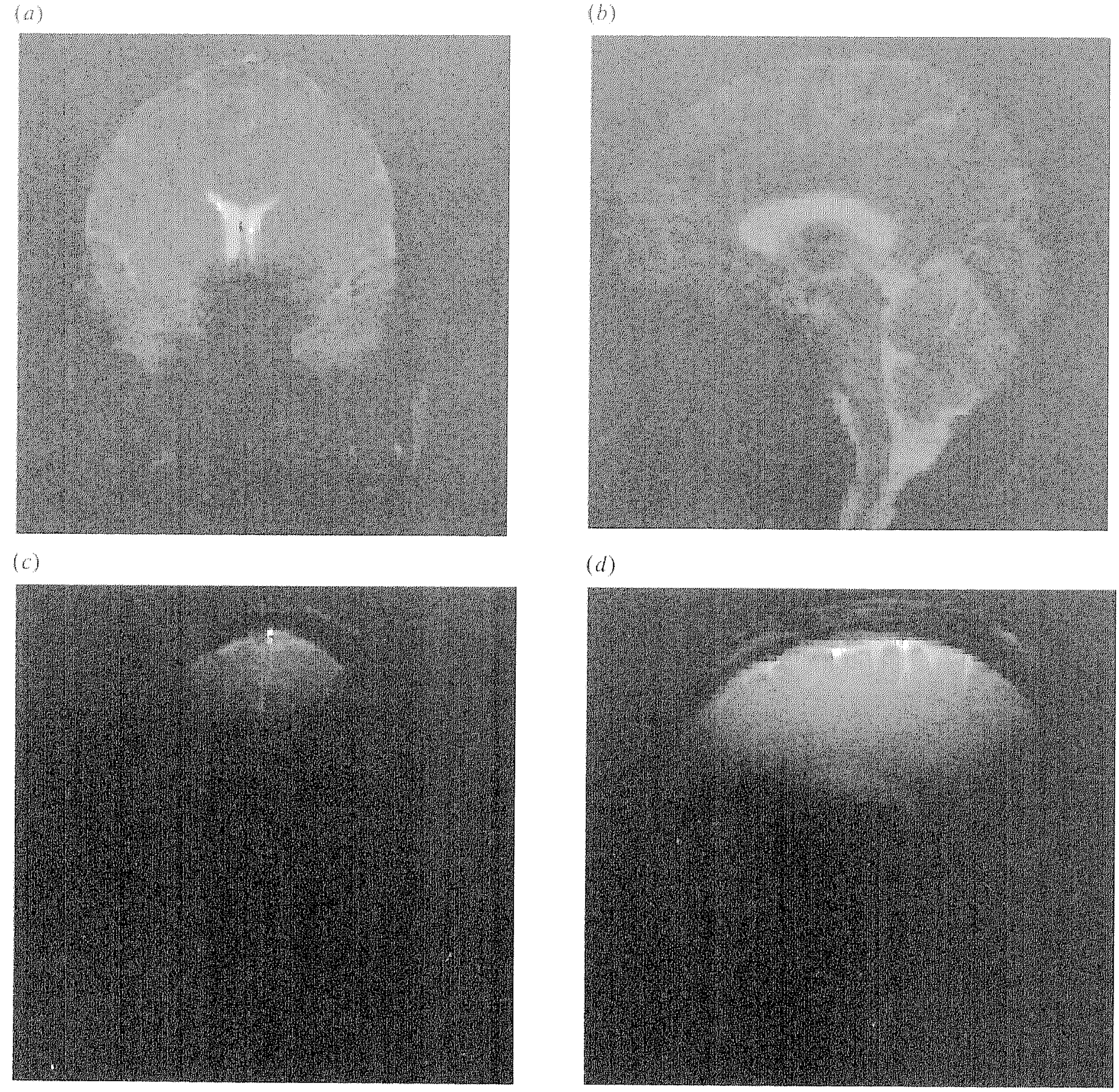

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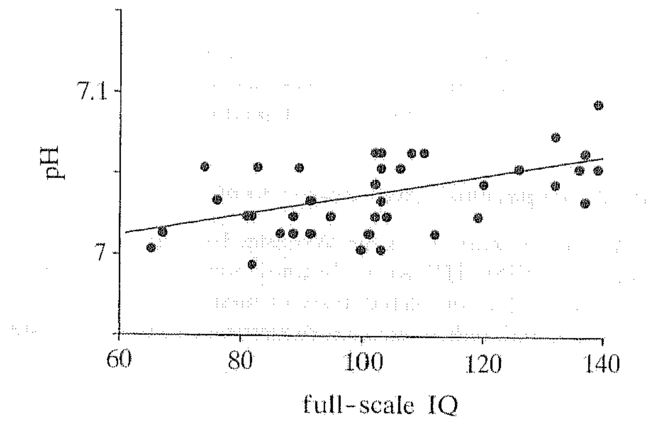

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