# **Dyslexia and familial high blood pressure: an observational pilot study**

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**<u>Abstract</u>**

Purpose: Developmental dyslexia is a neurodevelopmental learning disability characterised by unexpectedly poor reading and unknown aetiology. One hypothesis proposes excessive platelet-activating factor, a potent vasodilator, as a contributor. This implies a negative association between dyslexia and high blood pressure (HBP). Since both conditions have a partial genetic basis, this association may be apparent at the familial level. Methods: The prediction was tested in dyslexic and nondyslexic children by comparing individuals and families with and without a family history of high blood pressure (HBP+/HBP-). Findings: Proportionately fewer dyslexics (49/112) than controls (11/12) were HBP+. Families with multiple, all-dyslexic children were less likely to be HBP+ (7/16) than those with a non-dyslexic child (11/11). Within families, mean child scores on reading were higher in the HBP+ group (mean 44.3, SE mean 0.95) than in the HBP- group (mean 40.3, SE mean 0.87). Interpretation: HBP+ family history is associated with better performance on reading. The prediction of a negative association between dyslexic status and familial high blood pressure is therefore confirmed.

**<u>Introduction</u>**

Developmental dyslexia is a neurodevelopmental learning disability which has been estimated to affect 5-10% of UK children [1]. It is characterised by unexpectedly poor reading relative to the child's general intelligence, not explained by other factors such as socio-economic background or gross neurological deficit. Developmental dyslexia is known to have a considerable genetic component [2-4], but the mechanisms which give rise to the condition remain unclear. However, it seems increasingly clear that dyslexia is a neurobiological syndrome characterised by both structural [5] and functional [6] brain differences.

Abnormalities of phospholipid metabolism may play an important role in neurodevelopmental disorders such as schizophrenia [7], autism [8] and also dyslexia [9,10]. Phospholipids are the basis of cell membranes; in the brain the type of phospholipid present in neuronal membranes can affect neuronal function [11,12]. Evidence that phospholipid metabolism may be relevant to dyslexia includes abnormal phospholipid metabolism in dyslexics *in vivo* [13], significantly more clinical signs of fatty acid deficiency in dyslexics than controls [14] and overactivity in dyslexics of the enzyme phospholipase A2, which is involved in the remodelling of phospholipid membranes [15]. Extending this hypothesis, we recently proposed that levels of the phospholipid platelet-activating factor (PAF) could be raised in dyslexia [16], and that this could account for some of the differences seen in dyslexic individuals' brains. PAF is a neuroimmune mediator with multiple functions,

including cell signalling [17], stimulation of leucocyte adhesion [18], and vasodilation [19,20].

Given that dyslexia is a syndrome with a biological basis, it is likely to interact with other biological syndromes, and the pattern of these interactions may provide clues to the underlying aetiology. The PAF hypothesis makes certain predictions about the association of dyslexia with some common clinical conditions. In particular, PAF is a potent vasodilator which is known to lower blood pressure in a rat model, an effect which can be prevented by pre-administration of the PAF-inactivating enzyme platelet-activating factor acetylhydrolase [20]. Human patients with borderline hypertension have significantly raised levels of antibodies to PAF compared with normotensive controls [19]. A negative association would therefore be expected between high levels of PAF in dyslexia and the presence of high blood pressure (HBP). Given the contribution of genetic factors to both dyslexia and HBP [21], we assumed further that any associations between dyslexic status and high blood pressure should be apparent at the familial level as well as within individuals. Therefore, children at risk for dyslexia who do show a characteristic dyslexic phenotype (dyslexics) should be less likely to have a family history of HBP than children at risk who do not show the dyslexic phenotype (controls). Conversely, dyslexic children with a family history of HBP should be "less dyslexic" – i.e. should perform better on reading, working memory and spelling tasks – than those without a family history of HBP.

**Methods**

As part of an ongoing investigation into the genetics of developmental dyslexia [22,23], a cohort of families was collected in which at least one child is dyslexic. The children (age range 6-18 years) of these families were tested on a psychometric battery including British Ability Scales [24] Similarities (verbal reasoning), Matrices (non-verbal reasoning), Recall of Digits (verbal working memory), single word Reading and Spelling. Parents of 90 families participated in a consensual pilot study in which they filled in a questionnaire asking whether they or their close relatives (not defined) had ever to their knowledge had various clinical conditions, including HBP. Individuals were classified as having a family history of HBP (HBP+; N = 60) if they or at least one relative had suffered from it; otherwise they were considered not to have a family history of HBP (HBP-; N = 64). In practice, none of our children were reported as having HBP. The relatives who had HBP were as follows: child's parents (N = 12 children), parents' siblings and parents (N = 6), parents' parents only (N = 41) and parents' grandparent (N = 1).

Classification of individuals: Individuals were classified as dyslexic if their BAS Reading was at least 10 T-score points (1 standard deviation) below their BAS Similarities, or if they had an educational psychologist's report stating that they were dyslexic. Most individuals in our sample fell into this category.

Individuals were classified as control if they did not meet the above dyslexic criteria. There were 12 individuals in this category.

Questions: Two questions were asked. Firstly, were dyslexics and controls unevenly distributed between the HBP+ and HBP- groups? Fisher's exact test was used to assess this for individuals.

Some of the 90 families in our study have one child participating, others more than one. However, since the families were selected for dyslexia in the children, including families with only one child could distort the analysis; since controls are concentrated in the multiple-child families, family size is a potential confound[1]. A better comparison is to take families with more than one child (N = 27), and look at the history of HBP in families where all the children were dyslexic ("all-dyslexic": N = 16) with families where not all children were not dyslexic ("part-dyslexic": N = 11). We predicted that "part-dyslexic" families would be more likely than "all-dyslexic" families to have a history of HBP. Fisher's exact test was used to test this prediction.

Secondly, we asked whether the mean scores on age, sex (coded as male = 1, female = 2) and psychometric measures (expressed as age-adjusted T-scores with mean 50, standard deviation 10) differed significantly between the HBP+ and HBP- groups. If measures of general ability (BAS Similarities and Matrices) did not differ greatly, while measures of reading, spelling and working memory (BAS Reading, Spelling and Recall of Digits) did differ, that would suggest that the group with lower mean reading/spelling/working memory ability was "more dyslexic". We note that not all individuals completed every task. For the HBP- group (N = 63), Recall of Digits N = 57; Spelling N = 60. For the HBP+ group (N = 49), Recall of Digits N = 42.

Since the number of controls was small, and since they were from families at risk of dyslexia rather than from the general population, they could have had dyslexic tendencies or other characteristics which could distort the results. We therefore restricted the analysis to dyslexics only. To take account of family size, the unit of analysis was taken to be the family, and mean psychometric values were calculated for each family (dyslexic children only). An unpaired Student's t-test was used to compare the groups, because statistical tests of normality indicated data were near-normal (Shapiro-Wilk statistic: $p = 0.024$ for HBP- Spelling) or normal (Shapiro-Wilk statistic: $p > 0.05$ for all other HBP/psychometric groups). In all cases $p < 0.05$ was considered as statistically significant.

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[1] All the children from families with only one child are dyslexic except for one control, whose dyslexic sibling was excluded from the study on grounds of age.

## Results

The HBP+ and HBP- groups did not differ significantly on age (HBP+ mean: 10.8 (2.15); HBP- mean: 11.5 (2.20)) or sex (HBP+: 33 males, 27 females; HBP-: 40 males, 24 females). Dyslexics and controls did not differ significantly on age (dyslexic mean: 11.3 (2.23); control mean: 10.3 (1.67)) or sex (dyslexic: 69 males, 43 females; control: 4 males, 8 females).

Fisher's exact test: Despite the small numbers in our sample, we found significant differences (2-sided significance level $p = 0.002$) in the distribution of HBP+ and HBP- individuals between the dyslexic (49 HBP+; 63 HBP-) and control groups (11 HBP+ ; 1 HBP-). Because of the small numbers of controls, these results should be interpreted with caution. However, they are suggestive of a significant interaction between familial HBP and dyslexic status, such that the dyslexic group contains a smaller proportion of HBP+ group members.

Familial analysis for families with multiple children: Of the 16 "all-dyslexic" families, 7 were HBP+ and 9 were HBP-. Of the 11 "part-dyslexic" families, all 11 were HBP+. The distribution of familial HBP differed significantly between these two groups (Fisher's exact test: 2-sided significance level $p = 0.003$).

T-test: To account for family structure, we compared mean psychometric scores of (dyslexic only) children in HBP+ (N = 38) and HBP- (N = 52) families using a t-test. Statistically significant differences between HBP+ and HBP- families were seen for BAS Recall of Digits, Reading and Spelling. Scores were significantly higher for the HBP+ group than the HBP- group. Similarities (verbal reasoning) showed the same

pattern, though not to the same extent as Recall of Digits (working memory) and

Reading. In short, a family history of HBP was associated with better performance on

tests which dyslexics find comparatively difficult. Table 1 shows the mean

psychometric scores for the HBP+ and HBP- family groups (SD = standard deviation,

SE = standard error of the mean).


[Table 1 near here]

**Discussion**

We have proposed the hypothesis that the phospholipid platelet-activating factor (PAF) may play a role in developmental dyslexia [16]. This hypothesis predicts a negative association between dyslexia and high blood pressure (HBP). Results of our pilot study indicate clear differences, in the direction predicted by the hypothesis, between children at risk for dyslexia with and without a family history of HBP. Even when only the dyslexic individuals in our sample were analysed, our results indicate that children from families with a history of HBP perform significantly better on psychometric tests of reading and spelling.

Sources of bias: Any study such as this which uses self-report data from a questionnaire is open to problems. A common criticism is that some individuals may be more willing to report clinical conditions than others. In this case, individuals who themselves have a disorder may be more willing to report their clinical history; and women may be more willing to report than men. This form of bias can never be ruled out altogether in a questionnaire study. However, it is worth noting that:

1) At the time of the study, respondents to the questionnaires could not have been aware of the hypothesis specifically tested here, since it had not been published. Both parents in families with one or more dyslexic children were asked about a large number of clinical conditions. The aim of the study was to assess immune dysfunction, the prevalence of which is controversial in developmental dyslexia [25-29].

2) Since all families were taken from a cohort already investigated for dyslexia, there was unlikely to be a bias on the basis of dyslexic status.

3) A Fisher's exact test (data not shown for reasons of space) indicated no statistically significant difference between male and female response rates to the questionnaire.

4) HBP+ and HBP- groups did not differ significantly on age, sex and general ability, reducing the likelihood of bias due to these factors. Moreover, the families have a similar socio-economic background and come from the same geographic area (Central Southern England).

A potential source of bias which cannot be ruled out is that of non-response bias -- whether the families not asked about their clinical history differed from those who were asked with respect to the relevant variables. Given the total lack of awareness of the hypothesis among the families, it is difficult to see what this difference could be. However, we hope to address this problem, and the problem of self-report bias, in a study currently being planned which will not use questionnaire data.

Finally, given the small numbers, and the fact that the sample from which control subjects were taken was a sample at risk for dyslexia, it is likely that the controls themselves have dyslexic tendencies. However, this should tend to decrease the likelihood of observing a statistically significant association between dyslexic status and HBP. Moreover, even when controls were excluded from the analysis, children with and without a family history of HBP still showed significantly different performances on reading-related psychometric tasks. Families with a control child

among the children were significantly more likely to have a history of high blood pressure than families where all the children were dyslexic.

To summarise, we believe that this study is consistent with the PAF hypothesis of dyslexia. To our knowledge, no other hypothesis of developmental dyslexia has made this particular prediction or has proposed mechanisms which could explain this finding. That is not to say that there are not other mechanisms which could explain the observed relationship between dyslexia and familial high blood pressure. PAF is part of an extremely complex network of cytokines whose effects on intracellular signalling systems have yet to be disentangled. However, the prediction, which was specifically generated by the PAF hypothesis, has been confirmed; we consider therefore that the hypothesis may continue to serve as a basis for research. Whatever the causative mechanisms, we hope our study will help to make the important point that dyslexia is more than just a cognitive difference.

The instrument used in our study was a simple questionnaire asking whether parents of dyslexic children, or any of their relatives, had ever suffered from a range of clinical conditions (including immune disorders, developmental disorders and numerous other conditions). Given the unrefined nature of this assessment and the small numbers in the groups, so clear a result was unexpected. It is possible however that the small numbers may have affected the results (although any such effect would arguably be likely to blur distinctions rather than enhance them). A study is currently being planned to see if the result can be replicated with larger numbers. In the meantime, we hope that since developmental dyslexia is now widely accepted as a brain-based physiological condition, epidemiological studies of its comorbidity with

other diseases could provide much-needed clues to the underlying mechanisms

involved.

**<u>Acknowledgments</u>**

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**Table 1:** psychometric scores for HBP+ and HBP- family comparisons

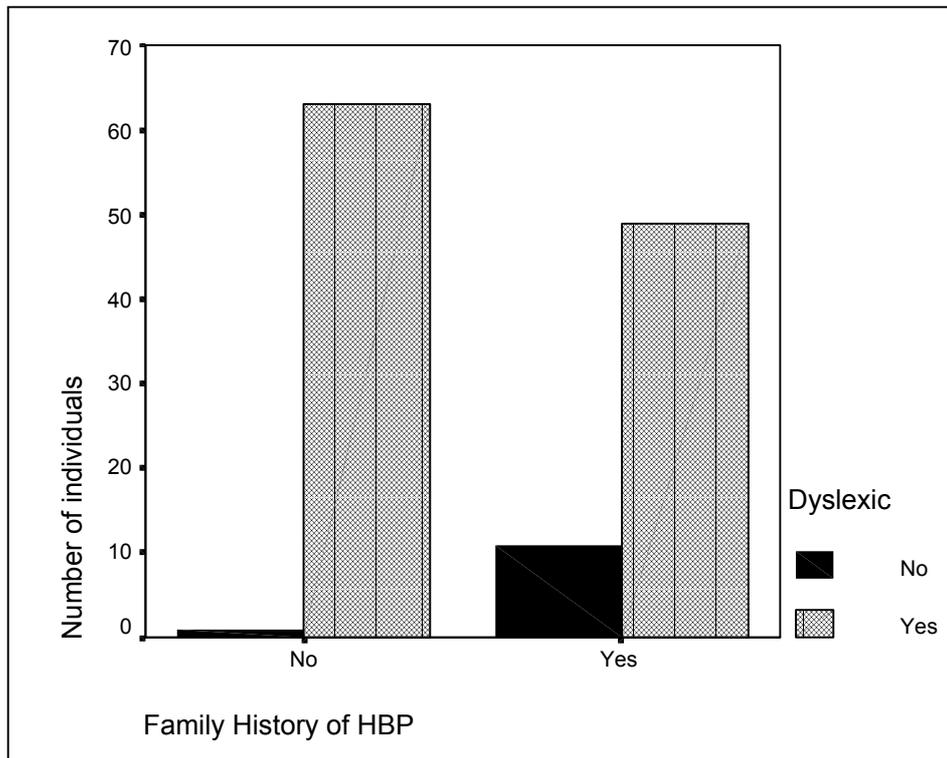| | HBP- | | | | HBP+ | | | *p* value |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | SE | N | Mean | SD | SE | |
| | | | | | | | | | |
| **Similarities** | 52 | 60.0 | 8.72 | 1.21 | 38 | 63.5 | 5.81 | 0.94 | 0.024 |
| **Matrices** | 52 | 53.1 | 6.25 | 0.87 | 38 | 55.7 | 6.74 | 1.09 | 0.062 |
| **Recall of Digits** | 47 | 40.0 | 8.28 | 1.21 | 33 | 45.6 | 10.3 | 1.80 | 0.009 |
| **Reading** | 52 | 40.3 | 6.25 | 0.87 | 38 | 44.3 | 5.84 | 0.95 | 0.003 |
| **Spelling** | 50 | 41.4 | 5.57 | 0.79 | 38 | 43.9 | 5.05 | 0.82 | 0.033 |

**Figure 1**: Numbers of dyslexics and controls in HBP- and HBP+ groups

**Figure 2**: Mean psychometric scores for HBP- and HBP+ dyslexic groups