Niacin skin test response in dyslexia

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Abstract

The niacin skin test reflects a flush and oedema owing to the production of prostaglandin D2 from arachidonic acid. A diminished response may indicate abnormalities in the phospholipid metabolism, which has been shown in schizophrenia. There is evidence that dyslexia might also involve phospholipid abnormalities, therefore we examined the skin response in 51 dyslexics and 45 controls. Four concentrations of aqueous methyl nicotinate were applied topically to the forearm. Flushing was rated using a seven-point scale at 3 min intervals over 21 min. Repeated measures ANOVA for the four concentrations across all seven time-points showed no significant effect of subject group, but when analyses were confined to the first 9 min, flushing was reduced in dyslexics. Significant group differences were also found for the lowest niacin concentration (0.0001 M) across six out of seven time-points. The results indicate a slightly reduced and delayed response to niacin in dyslexia.

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1. Introduction

There is mounting evidence that abnormalities of omega-3 and omega-6 highly unsaturated fatty acids (HUFA) can play a part in dyslexia and related neurodevelopmental disorders of childhood [1,2], as well as in many adult psychiatric conditions [3,4]. Omega-3 and omega-6 fatty acids are both crucial for normal brain development and function, and are recognised as essential nutrients because they must be provided by the diet. However, many diets consumed in modern developed countries are rich in processed foods that contain relatively low levels of key HUFA. Furthermore, it has been suggested that the biological predisposition to certain neurodevelopmental and psychiatric disorders, including dyslexia and schizophrenia, may include metabolic abnormalities that increase dietary requirements for omega-3 and/or omega-6 fatty acids [5].

Dyslexic individuals show a higher frequency of physical signs consistent with essential fatty acid deficiency than controls [6–9]. Cerebral 31-Phosphorus Magnetic Resonance Spectroscopy has provided further evidence of membrane lipid abnormalities in dyslexia [10], as have studies using blood biochemical measures. Membrane fatty acid concentrations have been found to correlate with some traits and symptoms associated with dyslexia [6,11,12]. Elevated levels of a cytosolic phospholipase A2 (PLA2) enzyme (consistent with an excessive loss of HUFA from membrane phospholipids) have also been reported in dyslexic adults relative to matched controls [13]. Preliminary evidence from treatment trials also suggests some benefits from fatty acid supplementation in dyslexia and related conditions [14–16], although the extent to which these findings reflect actual abnormalities of fatty acid metabolism in dyslexia is not yet clear.

A simple measure that has been used to index one aspect of HUFA metabolism is the niacin skin patch
test. Topical application of niacin (methyl nicotinate) to
the forearm induces skin vasodilatation and sometimes
oedema in around 85–90% of normal subjects [17–20].
This reaction arises from the release of the omega-6
HUFA arachidonic acid (AA) from membrane phos-
pholipids in dermal macrophages [4]. The subsequent
conversion of AA to prostaglandin D$_2$ via the cyclo-
oxigenase pathway is thought to produce the erythema
and oedema, which has the advantage of combining the
two aspects of the skin reaction into one assessment.

To date, the niacin test has not been used in dyslexia,
therefore this study aimed to assess the response to
topical niacin in dyslexic and control adults, with the
hypothesis that dyslexic adults will show impaired niacin
flushing relative to controls.

2. Methods and materials

2.1. Subjects

All subjects were assessed using a battery of psycho-
metric measures widely used in the assessment of
dyslexia. Six subtests from the Wechsler Adult Intelli-
gence Scales (WAIS) were used, four assessing general
ability: Similarities, Vocabulary, Block Design, Picture
Arrangement; and two working memory: Digit Span
and Digit Symbol [35]. Literacy skills were measured
with the Wide Range Achievement Test (WRAT) Word
Reading, Spelling [36], and the Gray Oral Reading Test
(GORT) Passage Reading [37].

Exclusion criteria for all subjects were: low general
ability (IQ pro-rated from WAIS Similarities, Vocabu-
lar, Block Design and Picture Arrangement < 80), any
neurological, psychiatric or other major medical dis-
order, or any use of fatty acid supplements within the
last 6 months. Subjects using non-steroidal anti-inflam-
matory drugs (e.g. aspirin) on a regular basis, or subjects
who had taken these on the day of the test were also
excluded.

Dyslexic subjects were selected according to the
following criteria: (1) previous history/assessment, (2)
discrepancy between general ability (pro-rated IQ) and
reading of at least 1.5 SD; and (3) positive indicators
including particular impairments in auditory working
memory (Digit Span), and a score of more than 8 on the
adult dyslexia screening checklist. Controls were selected
for no history of reading difficulties, reading and
spelling within the normal range, and a score of less
than 8 on the adult dyslexia screening checklist. The
study was approved by the Oxfordshire Psychiatric
Research Ethics Committee. All subjects gave written
informed consent before taking part in the study.

2.2. Niacin test administration

Niacin (aqueous methyl nicotinate) was applied
simultaneously in four dilutions (0.1, 0.01, 0.001,
0.0001 M). A card strip with four pockets of absorbent
paper was used, and 50 µl of each solution (approxi-
ately one drop of a standard eye-dropper) were
delivered to the paper. The strip was applied firmly to
the skin of the inner forearm for 60 s and then removed.
Skin reaction was noted at 3-min intervals up to
21 min.
2.3. Descriptive assessment of the skin reaction

The skin reaction was assessed using a seven-point scale developed by Berger and colleagues [33,34]. The assessment of the skin reaction comprises two aspects: erythema and oedema. Berger’s scale incorporates the intensity, homogeneity and confluence of the erythema, as well as occurrence, intensity and spread of oedema:

1. No skin reaction;
2. Confluence of red spots in less than 50% of total patch area;
3. Slight redness/confluence of red spots in more than 50% of patch area;
4. Moderate redness/homogeneous erythema of whole patch area;
5. Spreading redness and/or visible oedema;
6. Visible oedema encompassing whole patch area;
7. Visible oedema that starts to spread out/oedema bigger than original patch area.

In addition, at each time-point, a digital picture was taken using a high resolution digital camera in front of a black background (Nikon CoolPix 4.2MegaPixels), in order to rate the skin reaction by an independent assessor. Four raters were included in the assessment of niacin flushing. All were initially trained using Berger’s scoring criteria via live demonstrations.

3. Results

3.1. Psychometric assessments and demographics

Subjects were 51 dyslexic adults (24 male, 27 female) and 45 controls (23 male, 22 female); 92 were White/Caucasian and 4 were Asian/Indian. Eighteen percent of the control sample and 12% of the dyslexic sample were smokers (chi square = 0.0694, \( p = 0.293 \)). The control group consumed more alcohol on average than the dyslexic group (MW U, \( z = -1.958 \), \( p = 0.05 \)). All subjects tolerated the test well; none refused to participate, showed any adverse reaction or reported any discomfort.

The two groups were matched as closely as possible for age and general ability. As shown in Table 1, there were no significant differences between groups on general ability, but as expected, the dyslexic group had significantly lower scores on measures of literacy skills (WRAT Reading and spelling, GORT), and working memory tasks (WAIS Digit Span and Digit Symbol). There were no significant difference between the groups (dyslexic/control) in age (MW U, \( z = -0.934 \), \( p = 0.351 \)), or sex (chi square = 0.032, \( p = 0.510 \)).

3.2. Niacin flushing

Fig. 1 shows the main scores for niacin reactions for all seven time-points in both dyslexic and control groups. Agreement between raters was very strong both between live and photographic ratings. Intra-class correlations were performed including the live and photograph ratings (0.986), and within the four photograph ratings (0.988).

There were no significant differences in flushing response by sex for the whole sample, or within the dyslexic and control group. There was no relationship between age and niacin flushing for the whole sample, although there was a slight trend for a weaker niacin response with age in the control group (total skin flush at 9 min \( r = -0.317 \), \( p < 0.05 \)). This should not impact our findings as the two groups do not differ by age.

Results were analysed using a repeated measures ANOVA, with one between-subjects factor (GROUP

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics for psychometric measures</th>
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<tbody>
<tr>
<td></td>
<td>Control ( N = 45 )</td>
</tr>
<tr>
<td>Sex</td>
<td>23 M, 22 F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>33.5 (10.2)</td>
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<tr>
<td>General ability</td>
<td>Similarities</td>
</tr>
<tr>
<td></td>
<td>13.7 (2.7)</td>
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<tr>
<td></td>
<td>13.9 (3.2)</td>
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<tr>
<td>Block design</td>
<td>13.2 (2.5)</td>
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<tr>
<td></td>
<td>10.8 (1.8)</td>
</tr>
<tr>
<td>Literacy skills</td>
<td>Word reading</td>
</tr>
<tr>
<td></td>
<td>112.8 (6.6)</td>
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<tr>
<td></td>
<td>110.3 (9.2)</td>
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<td></td>
<td>111.4 (18.4)</td>
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<tr>
<td>Working memory</td>
<td>Digit span</td>
</tr>
<tr>
<td></td>
<td>11.6 (2.8)</td>
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<td></td>
<td>12.4 (2.3)</td>
</tr>
</tbody>
</table>

All group comparisons were Mann–Whitney.
{dyslexic/control}) and two within-subjects factors (TIME \{7\}, and CONCENTRATION \{4\}). As expected, significant main effects were found for the factors TIME and CONCENTRATION, i.e. longer time produced stronger reaction \((F = 92.116, p < 0.001)\), and similarly, stronger niacin concentration produced more pronounced reactions \((F = 423.080, p < 0.001)\), as shown in Fig. 1. Additionally, there was a significant \(\text{TIME} \times \text{CONCENTRATION} \) interaction \((F = 18.043, p < 0.001)\).

Overall, dyslexic subjects showed a weaker response to topical niacin than controls, but no significant interaction was found between GROUP and CONCENTRATION \((F = 0.300, p = 0.826)\) or GROUP and TIME \((F = 1.737, p = 0.112)\) when all time-points and concentrations were considered together. However, as demonstrated in Fig. 1, there was a consistent separation between the dyslexic and control groups. The reaction to the weakest niacin solution showed the most pronounced separation, and this was true over six out of seven time-points. The greatest separation was after 9 min, staying consistent for the rest of the time observed. We examined these group differences separately—each time-point and each concentration—and the dyslexic group flushed significantly less to the weakest solution than the control group from 9 min (2nd time-point) onwards \((\text{MW U}, \; z = -3.088, p < 0.01)\).

4. Discussion

Previous studies have found some evidence of fatty acid abnormalities in dyslexia. A simple, non-invasive measure that has been used to study fatty acid metabolism in other conditions is the flushing response to niacin. Abnormalities have been well documented in schizophrenia, but to our knowledge this is the first study of niacin flushing in relation to dyslexia. Our results showed a slightly reduced and delayed response to niacin in a large sample of dyslexic adults compared with matched controls. The group difference was observed across all four concentrations of niacin used, although it was most pronounced for the weakest of these \((0.0001 \text{ M})\). At this concentration, the reduced flushing response of the dyslexic group was still evident at the final observation point, 21 min after topical application. For the stronger concentrations the group difference was apparent only for the first 9–15 min.

Care was taken to exclude subjects taking medications such as aspirin or non-steroidal anti-inflammatory drugs that are known to interfere with the niacin flushing response. Similarly, the weaker niacin response of dyslexic adults cannot be attributed to smoking or alcohol consumption, both of which are known to affect fatty acid metabolism \[38\], because these habits were slightly less common in the dyslexic group than in controls.

The aim of this study was to find out if the topical niacin test would reveal any differences between dyslexic adults and controls. Reduced niacin flushing has repeatedly been shown in schizophrenia spectrum disorders \[17,32,34\], and various common features as well as familial associations between dyslexia and schizophrenia led to the suggestion that each may involve separate but interactive abnormalities of fatty acid metabolism \[5\]. In both conditions, however, experimental studies have implicated elevations of a \(\text{PLA}_2\) enzyme that removes \(\text{HUFA}\) from membranes; and dyslexic adults showed cytosolic \(\text{PLA}_2\) values that were intermediate between schizophrenia patients and normal controls \[13\]. Similarly, our findings of reduced niacin flushing in dyslexia parallel to those from studies of schizophrenia, but indicate a milder degree of abnormality.

A diminished response to niacin indicates abnormalities somewhere in the pathway by which the omega-6 \(\text{HUFA}\) AA is released from the phospholipids in the cell.
membranes by PLA2 and then converted into prostaglandin D2 in the cyclo-oxygenase pathway. In schizophrenia, many studies have shown reduced AA concentrations in red blood cell membranes [39,40]. The lack of flushing to niacin in dyslexia might therefore reflect a lack of substrate, although to our knowledge, no published studies have yet shown abnormalities of blood fatty acid concentrations in dyslexia.

In schizophrenia, elevated PLA2 has been explicitly linked with reduced niacin flushing, suggesting that the niacin skin test may provide a simple way of identifying a subgroup of patients with disordered fatty acid metabolism [30]. Elevations of cytosolic PLA2 have also been reported in dyslexia [13], so our findings point to the need to study both niacin flushing and PLA2 in the same individuals with this condition, ideally together with blood fatty acid profiles.

With further validation, the niacin skin test could be a potentially useful clinical tool for indexing fatty acid abnormalities in a range of neurodevelopmental conditions, as it is safe, non-invasive, well-tolerated and easy to administer. Our results suggest that in dyslexia, the niacin test could be performed in a shorter time (10 min) by the use of only one concentration (0.0001 M), as the other time-points and concentrations have not provided any useful additional data. This metabolic pathway clearly deserves further investigation in dyslexia and other conditions, as the topical niacin test offers a quick and inexpensive way to identify possible subgroups with a specific biological abnormality that may cut across current diagnostic categories. However, the sample size studied here is not sufficiently large to undertake subgroup investigation. Further work is required to identify the actual abnormalities in phospholipid metabolism that the niacin skin test may index. It is even possible that this may help to predict responses to treatment with HUFA, and this hypothesis is currently under investigation in dyslexic adults.

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References


