

Title

Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between ADHD, dyslexia, dyspraxia and the autistic spectrum.

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Summary

There is increasing evidence that abnormalities of fatty acid and membrane phospholipid metabolism play a part in a wide range of neurodevelopmental and psychiatric disorders. This proposal is discussed here in relation to ADHD, dyslexia, developmental coordination disorder (dyspraxia) and the autistic spectrum. These are among the most common neurodevelopmental disorders of childhood, with significant implications for society as well as for those directly affected. However, controversy still surrounds both the identification and management of these conditions, and while their aetiology is recognised as being complex and multifactorial, little progress has yet been made in elucidating predisposing factors at the biological level.

An overview is provided here of the contents of this Special Issue, which contains a selection of reports from a unique multidisciplinary workshop involving both researchers and clinicians. Its purpose was to explore the possibility that ADHD, dyslexia, dyspraxia and autism fall within a phospholipid spectrum of disorders. This proposal could explain the high degree of comorbidity between these conditions, their aggregation within families and relation to other psychiatric disorders, and a range of associated features that are already well known at a clinical level. The existing evidence for fatty acid abnormalities in these disorders is summarised, and new approaches are outlined that have the potential to improve both the identification and the management of these and related neurodevelopmental and psychiatric conditions.

Introduction

There is a high degree of overlap between a range of neurodevelopmental disorders that includes attention-deficit hyperactivity disorder (ADHD), dyslexia (specific reading difficulties), dyspraxia (developmental co-ordination disorder), and the autistic spectrum. Although these are all neurodevelopmental disorders of childhood, they all persist into adulthood, causing serious problems not only for those affected, but for society as a whole.

Between them these conditions may affect as many as 10% of the population, and although they often go unrecognised, it is widely acknowledged that the earlier the problems can be identified, the better are the chances of successful management and remediation. However, a major problem is that formal diagnoses of ADHD, dyslexia, dyspraxia and autism not only involve different sets of operational criteria (many of which are acknowledged to be less than satisfactory), but also tend to involve specialists from different professional disciplines. Practitioners dealing with any one of these conditions are often unfamiliar with at least some of the others, and may therefore be unaware of co-morbidity issues and their implications.

In research there is even more compartmentalisation, owing to the very wide range of disciplines involved at this level. There is thus a clear need for better integration across clinical and research perspectives, and a compelling case for interdisciplinary approaches to both. A new perspective is offered here which it is hoped could help towards achieving this. There is currently little firm agreement regarding the key etiological factors in any of these conditions, and this situation places serious limitations on existing methods of both diagnosis and management.

The papers collected together in this special issue represent the output from a unique workshop on 'New Approaches to Neurodevelopmental Disorder', held in Inverness in September 1999. The specific purpose was to bring together experts from a wide range of different disciplines to present and discuss their research and its relevance to a new paradigm that has the potential to transform our current understanding of ADHD, dyslexia, dyspraxia and the autistic spectrum. Each of these disorders is characterised and defined by a different set of core features that are obviously central to clinical diagnosis, and these will be outlined very briefly below. However, various associated features are common to many or all of these conditions, and familial aggregation is also apparent. Together, these factors could provide important clues to the aetiology of these complex disorders.

The proposal under consideration at this workshop was that abnormalities of fatty acid and phospholipid metabolism could help to account for many of the features that are common not only to these conditions but also to some other neurodevelopmental and psychiatric disorders (1). This approach not only represents a new paradigm for research into dyslexia, dyspraxia, ADHD and the autistic spectrum, but also has implications that cut across - and could help to unite - almost all of the relevant disciplines. Moreover, there is already evidence that it could provide new leads with respect to both the identification and the management of these conditions.

ADHD, dyslexia, dyspraxia, and autistic spectrum disorders: core and associated features

Attention-deficit Hyperactivity Disorder (ADHD)

ADHD is one of the most common disorders of childhood and adolescence, and it is now clear that problems usually persist into adulthood. However, the validity of the ADHD syndrome is often called into question, as it involves a rather disparate range of behavioural and learning problems with no clear discontinuity from normal function. Formal diagnosis lies in the province of psychiatry, and the current criteria used by the American Psychiatric Association (2) involve an age-inappropriate level of a number of symptoms from one or both of two major dimensions, namely inattention and hyperactivity-impulsivity. These symptoms must also be of early onset, persistent over time, and must occur across more than one situation. Prevalence estimates vary from around 2% for the most severe forms of ADHD to 10% or more when less stringent criteria are used, and the disorder is much more common in males than females. The most common treatment approach is pharmacological, involving stimulant medications such as methylphenidate, but their widespread and increasing use remains a controversial issue. The relative success of these drugs in managing symptoms does not constitute evidence that dopaminergic abnormalities are the primary problem in ADHD, and they are ineffective in up to one third of cases. Further details are given by Richardson and Puri (3), who review and evaluate the potential role of fatty acids in this condition.

Dyslexia

Developmental dyslexia is sometimes regarded as synonymous with 'specific reading difficulties', i.e. underachievement in reading in relation to general ability. However, the term properly refers to a specific neurodevelopmental syndrome with a constitutional basis. Dyslexia involves much more than just reading difficulties, and any reliable diagnosis requires additional indicators (4). Core psychological features include specific weaknesses in working memory, especially for auditory-linguistic material, and difficulties with direction and sequencing. Early signs typically include visuo-motor problems and slow or abnormal spoken language development despite no obvious impairment of general ability. This condition affects around 5% of the population in a severe form, and is more common in males.

The primary domains involved in the identification and management of dyslexia are psychology and education. There remains resistance to a 'medical model' within these professions (although this usually reflects a misunderstanding to the point of caricature of current biological approaches). The evidence for sensory problems in dyslexia is now undeniable, but there is still controversy over their significance. In this issue, John Stein (5) discusses the neurobiology of reading difficulties. He explains how a mild abnormality of the development of 'magnocellular' systems specialised for very rapid neural processing probably underlies the low-level visual and auditory problems that are common in dyslexia, and he also outlines how these problems may actually contribute to difficulties in learning to read. Despite substantial research into the physiological causes of dyslexia, however, biochemical approaches have so far been conspicuous by their absence.

Dyspraxia

Dyspraxia or developmental co-ordination disorder (DCD) is probably the least known and least understood of the conditions under discussion here. Dyspraxia is primarily defined in terms of problems with planning and motor co-ordination, while the DCD diagnosis adopted by the DSM-IV (2) is somewhat broader. Debates over terminology are likely to continue, and the term dyspraxia is used here for convenience. Attentional, perceptual and spoken language problems are frequently associated, and there is a high degree of overlap with ADHD and dyslexia as well as with non-verbal learning difficulties (6). Other notable features include excitability or instability of mood, anhedonia and/or hypersensitivity to touch, as well as minor physical symptoms such as digestive problems, all of which are also common in autistic spectrum disorders.

Dyspraxia often goes undiagnosed, although recognition by parents, teachers or GPs of a 'clumsy child' syndrome may lead to referral to a paediatrician or neurologist. Intervention from physiotherapists or occupational therapists may be recommended, but management is more often from within educational and psychological services. The best estimates of prevalence are around 5% for severe cases, but as with ADHD and dyslexia, milder forms are more common, and males are disproportionately affected. Problems persist into adulthood, and there appears to be a high rate of associated psychiatric disorder (7), usually attributed to the persistent social difficulties and very low self-esteem associated with dyspraxia.

Autism

Autistic spectrum disorders fall within the sphere of psychiatry. The core deficits involve social and communication problems, and autism usually appears in the first two years of life although the earliest signs can be subtle. Autistic infants appear indifferent or averse to affection and physical contact, but often show inappropriate attachment to objects. Speech usually develops slowly and abnormally if at all. There is often extreme sensitivity to auditory or visual stimulation, yet a lack of appropriate reactions to sound or genuine danger, and little reaction to pain. An obsessive desire to prevent environmental change is typical, as are rhythmic body movements such as rocking or hand-clapping. Autism is about three to four times more common in males than females, and prevalence estimates range from 1 to 15 per 10,000 children, depending on the criteria used.

Definitional and diagnostic problems surrounding the autism syndrome and associated disorders are thoughtfully discussed by Graham Jones in this volume (8). As with ADHD, the autistic spectrum probably involves complex and potentially multiple etiologies with a final common pathway with respect to symptom expression. Colwyn Trevarthen provides further perspectives on this (9), highlighting the very complex and multiple interacting factors involved in the development and emergence of autism.

Many of the points Trevarthen makes are equally applicable to other neurodevelopmental disorders. The need to look beyond the cognitive and behavioural level to consider the actual brain structures and processes involved - and to do so from a developmental perspective - is particularly relevant, yet this is easily forgotten in the focus on discrete categories and labels based primarily on clusters of presenting symptoms. The fact that sensorimotor, emotional and motivational factors are effectively inseparable from cognition and behaviour is also self-evident from a biological perspective. These 'lower-level' factors are clearly fundamental during early development, when all of these disorders first start to become apparent. We propose that the study of phospholipid metabolism could help to elucidate the nature and origins of these and other neurodevelopmental and psychiatric disorders, as it provides a

framework that could bridge many of the gaps in our current knowledge of the complex relations between brain and behaviour (1).

Comorbidity issues - a phospholipid spectrum of disorders?.

The clinical overlap between ADHD and dyslexia is around 30-50% in both directions (10). It seems higher for the inattentive rather than the hyperactive-impulsive form of ADHD, possibly reflecting a common dysfunction of parietal mechanisms (11). A similar degree of overlap is found between dyslexia and dyspraxia, which is interesting in view of the mounting evidence that cerebellar dysfunction may be a key factor in dyslexia (12,13). The comorbidity between ADHD and dyspraxia appears to be equally high (7). Autism - if narrowly defined - is the rarest of these disorders, and would always be the primary diagnosis. Nonetheless, it is evident that many features of the autistic spectrum are also characteristic of the other disorders under consideration here.

Associated features in all of these conditions include pregnancy and birth complications, minor physical anomalies, and developmental delay in achieving milestones for motor, visuo-motor and/or language development. An increased frequency of allergic or auto-immune disorders in affected individuals and their relatives is another recurring theme which offers possible clues to shared aspects of biological predisposition, as discussed by Stein (5). And perhaps the most striking feature is the clear excess of males affected by each of these conditions, for which there is as yet no satisfactory explanation. All of these features - often regarded as peripheral or irrelevant to the central diagnosis - are potentially explicable in terms of mild abnormalities of fatty acid metabolism, as noted by Richardson and Puri (3).

The importance of certain highly unsaturated fatty acids (HUFA) for brain development and function is well known (14-18) but cannot be discussed in any detail here. In this volume, Richardson and Puri (3) provide a very brief overview, describing the synthesis of HUFA from their essential fatty acid (EFA) precursors and possible blocks to these conversion processes. Bennett and Horrobin (19) discuss phospholipid metabolism and membrane turnover with particular reference to the PLA2 cycle. The HUFA necessary for normal brain structure and function are constantly replaced and recycled, both during the normal turnover and remodelling of membrane phospholipids and in the cascades triggered by normal cell signalling processes. The action of PLA2 in removing HUFA from membrane phospholipids creates potentially damaging interim products including free fatty acids, which are highly susceptible to oxidation. These have to be recycled in at least two further enzyme steps in order to complete the full cycle. PLA2 over-activity has been repeatedly implicated in schizophrenia (20) but this is unlikely to be specific to this condition, as evidenced by the recent finding of elevated PLA2 in dyslexia, reported here by MacDonnell et al (21). It seems probable that the most damaging effects of elevated PLA2 activity will occur only when this is compounded by abnormalities of at least one of the other enzymes responsible for completing the PLA2 cycle.

As Bennett and Horrobin (19) make clear, PLA2 and many other phospholipid enzymes are good candidates for contributing to the genetic predisposition to neurodevelopmental disorders, because they are strongly expressed during brain growth and development. However, gene-environment interactions are clearly crucial at every stage, and phospholipid metabolism is also at the interface of these, depending as heavily as it does on the dietary intake of fatty acids.

The importance of an adequate dietary supply of HUFA in early development has already been the subject of much research (22). This issue is covered here in the paper by Willatts & Forsyth (23). They have carried out very careful studies of the effects of HUFA supplementation on the cognitive development of infants, and as well as reporting their recent findings they highlight some of the difficulties involved in distinguishing cognitive from sensorimotor abnormalities. In a theoretical paper, Taylor and Richardson (24) discuss some of the ways in which fatty acid abnormalities could plausibly account for the visual magnocellular deficits that have been well documented in dyslexia, and which may well play some role in related conditions.

It is clear that ADHD, dyslexia, dyspraxia and autism are all complex neurodevelopmental syndromes with a biological basis. Moreover, they not only show a high degree of clinical overlap but often cluster together in families, suggesting common elements at the level of genetic predisposition. In fact, a family history of other neurodevelopmental or psychiatric disorders is one of the most striking features of all of these conditions. Familial associations in ADHD include depression, bipolar disorder, substance abuse and antisocial personality disorders (25,26) while dyslexia appears to show some degree of familial association with the schizophrenia spectrum, in which phospholipid abnormalities have already been well-documented (27). Of particular interest is the substantial co-morbidity between ADHD and disorders of mood. Recent evidence suggests that as many as one third of children who currently receive an ADHD diagnosis may actually be suffering from early onset bipolar disorder (28), although this can rarely be diagnosed in children owing to the current reliance on criteria for the adult form of this disorder. This kind of misdiagnosis could be extremely significant, because omega-3 fatty acids have already shown considerable promise in the treatment of bipolar disorder (29), while stimulant medications are likely to exacerbate this condition.

Epidemiology and genetics of neurodevelopmental disorders

In the first paper in this collection, Julian Little (30) describes the epidemiology of a wider range of developmental disorders, including those involving neural tube defects such as spina bifida where nutritional factors during pregnancy are believed to play a critical role. There is currently little reliable epidemiological data concerning neurodevelopmental disorders such as dyslexia, dyspraxia, ADHD and autistic spectrum disorders, at least partly owing to problems of awareness, accurate identification and diagnosis. His paper clarifies the difficulties involved in epidemiological research and the potentially serious methodological confounds. It is clear that further work in this area is required, but equally clear that an interdisciplinary approach is not only desirable, but necessary.

The genetics of specific language impairment (SLI) and dyslexia are discussed in two papers by Nasir and colleagues (31) and Francks and colleagues (32) respectively. These common neurodevelopmental conditions present particular problems to molecular geneticists seeking to identify the actual genes underlying disorder, although advances in methodology are starting to improve the prospects (33, 34). Very rare conditions that are transmitted in an autosomal dominant manner, such as Huntington's Disease, present a much simpler task; and in this case the gene responsible has already been identified. In disorders such as schizophrenia, with a lifetime population risk of around 1%, at least a few - and probably many - different genes are likely to be involved. Heritability for schizophrenia is around 50%, but despite extensive study, no reliable linkage has yet been established, and the best strategies will probably involve narrowing the search by first identifying candidate genes.

With even more common conditions such as ADHD, dyslexia, SLI and dyspraxia, the genes involved are likely to be not only many, but widely distributed in the general population. Even in autism, where the severest forms of disorder are rare and show very high heritability, the genetic picture appears complicated (34). In all these disorders, the mode of inheritance still remains unknown. Other problems include *genetic heterogeneity* (the condition may arise from any of several different 'genotypes'), *incomplete penetrance* (individuals with the genotype may fail to develop the condition or 'phenotype') and *phenocopy* (individuals without the genotype may show problems that resemble the phenotype). Accurate definition of the phenotype is a major problem for research, and better diagnostic procedures are sorely needed, especially if these could be linked to biological markers of predisposition.

Nonetheless, recent advances in both genotyping technology and quantitative statistical methods have now made it possible to investigate the genetic correlates of quantitative traits using large samples of sibling pairs. In the study of neurodevelopmental disorder these strategies clearly offer much more promise than conventional methods requiring arbitrary categorical classifications of affected versus non-affected individuals. As Francks and colleagues report here (32), a site on chromosome 6p has now been implicated by several independent studies of dyslexia, making this a robust finding. Work underway now includes screening the entire genome for further linkages, and the next steps will involve narrowing down those regions enough to begin physical mapping or candidate gene studies.

Horrobin and Bennett (35) recently reviewed the evidence for candidate genes in a range of psychiatric disorders, showing where proposed sites of linkage for these conditions coincide with those for genes known to be important in phospholipid and fatty acid metabolism. Molecular genetics is of course a very rapidly expanding field of knowledge, so a valuable update of this work is provided in this volume (19). These authors highlight many interesting correspondences, including the fact that the same region of chromosome 6 now firmly associated with dyslexia has also been implicated in ADHD, autism and schizophrenia. Moreover, genes encoding several enzymes important in phospholipid metabolism have also been linked to the same region, including a lyso-phospholipid coenzyme-A acyl transferase (36). This family of enzymes is important in completing the PLA₂ cycle, making this a good potential candidate for investigation in relation to these disorders. However, there are many other plausible candidates, and supportive evidence would be needed from basic biochemical studies prior to any such investigations.

Current evidence for abnormalities of fatty acid metabolism in ADHD, dyslexia, dyspraxia and the autistic spectrum

ADHD

Deficiency in certain HUFA as a factor in ADHD was first proposed almost twenty years ago (37). Supporting evidence from blood biochemical and other studies has been accumulating since then, as reviewed by Richardson and Puri in this issue (3). Findings are broadly in line with the original proposal that ADHD involves difficulties in the synthesis of HUFA, rather than a lack of their EFA precursors, although other mechanisms may well be operating. Given the heterogeneity of ADHD it seems probable that fatty acid abnormalities would affect only a subset of individuals receiving this diagnosis. However, biochemical studies have shown that even in a combined sample of ADHD boys and controls, omega-3 deficiencies were associated with behavioural and learning problems as well as with some

aspects of general health, notably allergic conditions (38). The fact that these relationships held irrespective of clinical diagnosis suggests that a dimensional perspective may well be more appropriate than a reliance on categorical classifications of disorder.

Dyslexia

In dyslexia, the proposal of fatty acid abnormalities is more recent, and followed from reports that certain visual deficits in dyslexic adults could be corrected via treatment with omega-3 fatty acids (39). Brain imaging using 31-phosphorus magnetic resonance spectroscopy further indicates some kind of lipid abnormality in dyslexia (40). Important new supporting evidence has come from the recent finding of elevated levels of a PLA₂ enzyme in dyslexia, as discussed by MacDonell et al in this volume (21), consistent with an abnormally high rate of removal of HUFA from the sn-2 position of membrane phospholipids.

In one early case report, fatty acid deficiency in a dyslexic child was confirmed by biochemical testing, and benefits from fatty acid treatment were noted (41). This child showed the same clinical signs that were first reported in ADHD such as dry, dull skin and hair, and soft, brittle nails. Moreover, their disappearance following nutritional intervention to correct the fatty acid deficiency was followed by reported improvements in schoolwork. Stevens et al (1995) created a simple scale to assess these signs, and demonstrated that scores were indeed related to blood biochemical measures of HUFA deficiency, particularly of n-3 fatty acids (42). In this volume Taylor, Richardson and colleagues report recent studies confirming that scores on this scale also relate to dyslexia in both adults (43) and children (44), although in each case some interesting sex differences are apparent.

Dyspraxia

Of the conditions under consideration here, dyspraxia has probably been the least studied in relation to fatty acid metabolism. However, the high co-morbidity of dyspraxia with both ADHD and dyslexia has not yet been factored out in studies of fatty acid metabolism in these conditions. It is quite possible that dyspraxic features may help to identify relevant subgroups within dyslexia or ADHD, and this is currently under investigation. Meanwhile, in the study reported here by Taylor et al (43), self-reported motor problems were among the features associated with clinical signs of fatty acid deficiency in dyslexic adults.

There is already evidence that HUFA deficiencies relate to movement disorders both in the general population (45) and in psychiatric patients treated with neuroleptics (46). In dyspraxic children, both anecdotal reports and open studies of treatment with LC-PUFAs further suggest that fatty acid abnormalities in this condition deserve serious investigation (47,48).

Autistic spectrum disorders

In relation to autistic spectrum disorders (ASD) there is again plenty of suggestive evidence that abnormalities of fatty acid metabolism may play a role (49) but very little in the way of formal study. One previous report has suggested an impairment of peroxisomal function to account for an apparent accumulation of very long chain fatty acids in some autistic individuals (50).

In this volume, Bell and colleagues (51) report a single case study of an individual with ASD

that revealed reduced HUFA concentrations in red blood cell membranes. In addition, they found evidence of an instability of membrane HUFA that has also been observed in schizophrenia. The mechanisms underlying this are not yet known, but it is consistent with the abnormal elevation of PLA2 found in schizophrenia (20,52) and more recently in dyslexia (21). Excessive oxidative stress could also be involved, as discussed below, and these two possibilities are by no means mutually exclusive (53). Intriguingly, Bell and colleagues also studied two individuals with Asperger's syndrome, a milder form of ASD, and found that red cell membrane HUFA concentrations in these subjects showed instead a remarkable *stability* relative to control samples, consistent with earlier speculations that phospholipase activity may be reduced in this condition (49). They also report evidence that abnormalities of tryptophan metabolism linked to ASD and related disorders have implications for HUFA metabolism. Clearly this is an area that deserves further study, and a biochemical approach of this kind has obvious potential in helping to clarify some of the heterogeneity in ASD.

Interpretation of the evidence

In attempting to interpret the current evidence for fatty acid abnormalities in these neurodevelopmental disorders, it is clear that many issues still remain to be resolved. Fatty acid and phospholipid metabolism is exquisitely complex and can be influenced by many factors, both constitutional and environmental. Any single biochemical measure is open to a range of interpretations, and until further evidence is available – ideally from a range of measure used concurrently in the same subjects – very few firm conclusions can be drawn. Having said this, the available evidence does suggest that fatty acid abnormalities are probably implicated to at least some extent in all of these conditions.

With respect to mechanisms, a constitutional inefficiency in the conversion of EFA to HUFA has been proposed as a factor not only in ADHD (37,42) but also in dyslexia and dyspraxia (47,48). However, other kinds of abnormalities are equally plausible. The recent finding of elevated PLA2 in dyslexia (21) makes that case clear, and a similar abnormality could help to explain the apparent instability of HUFA in autism (51). Other enzymes involved in membrane phospholipid synthesis and breakdown are discussed elsewhere in this volume (19), and it is obvious that much work remains to be done to elucidate precise patterns of abnormality that may underlie different symptoms or conditions.

Oxidative stress is another possible interpretation of the biochemical findings of low levels of HUFA in neurodevelopmental disorder, and this proposal is discussed in this volume by Marion Ross (53). Increased PLA2 activity could well be related to oxidative stress, and many studies of schizophrenia have indicated a pathology involving free radicals (54). There could certainly be parallels with this in other neurodevelopmental disorders, and this possibility clearly requires further investigation.

Implications for Diagnosis and Management

ADHD, dyslexia, dyspraxia and autism are all complex, multifactorial syndromes, but currently definition and diagnosis is based on their phenomenology - and from a limited perspective in each case. These issues are spelt out clearly by Jones in this volume with respect to the autistic spectrum (6), but the same problems apply equally to ADHD, dyslexia and dyspraxia, and they seriously hinder accurate identification and effective management.

All of these conditions clearly have a biological basis with a strong genetic component, so we

would argue that it makes sense to focus further research efforts on discovering more about this level. In this, phospholipid metabolism looks like an extremely promising paradigm. This approach has already led to the development of new tests for the identification of certain fatty acid abnormalities, and with further validation these could potentially become important diagnostic tools. Pauline Ward's paper in this volume (55) outlines some promising new measures that have already been used to assess the fatty acid abnormalities associated with schizophrenia. The niacin skin patch test, assessing abnormalities in the prostaglandin pathway, may provide an index of deficiency in certain HUFA, particularly arachidonic acid. A simple breath test has also been developed which measures alkanes, the end products of lipid peroxidation (56). Lipid peroxidation caused by oxidative stress could prove to be an important factor in neurodevelopmental disorders, as suggested by Ross in this volume (53). Both of these tests are non-invasive and would therefore be highly acceptable for use with children.

Another major attraction of this approach is the possibility that it raises of new, safe treatments for these disorders, particularly given the limitations of current methods of management. Benefits following treatment with omega-3 fatty acids have already been shown in the management of both schizophrenia (57-62) and mood disorder (29), both of which show some comorbidity with the neurodevelopmental disorders under discussion here. It is still too early to evaluate the potential of fatty acid treatments in these conditions, but there is sufficient rationale and preliminary evidence to warrant large-scale randomised controlled trials. A few small studies of ADHD have already yielded some positive results as well as some equivocal or negative findings, but further trials are indicated and these need to be carefully designed and hypothesis-driven (3). In dyslexia, no results from controlled trials are yet available, but several large-scale studies of this kind involving both dyslexic children and adults are approaching completion (62). Similar work is needed in relation to dyspraxia and the autistic spectrum.

Conclusion

At present, controversies over aetiology, diagnosis and management pervade both research and clinical practice with respect to ADHD, dyslexia, dyspraxia and the autistic spectrum. It is probably fair to say that the only point on which there is almost unanimous agreement is the need for better methods of early identification and management. The challenge is therefore to develop a better understanding of the nature and interaction of the genetic and environmental influences that produce the overlapping cognitive and behavioural profiles associated with these relatively common neurodevelopmental conditions. Given the extraordinary complexity of the inter-relationships between brain and behaviour, this is no easy task. However, at a biochemical level, we suggest that the study of fatty acid and phospholipid metabolism appears to have a great deal to offer.

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