

## Re-Defining Dyslexia: Accounting for variability

### Redefiniendo la dislexia: explicando la variabilidad

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The scientific effervescence that reigns around developmental dyslexia is explained by the difficult challenge that consists of ascribing this handicap to a single cause whilst multiple profiles of dyslexic patients can be observed. In this chapter, we start by presenting the main neuro-cognitive hypotheses that aim to explain dyslexia. We then review the multidimensional nature of dyslexia, and discuss the necessity of using a common diagnostic criteria to improve our understanding of its true nature. We then conclude by presenting promising work connecting cerebral endophenotypes and behavioral phenotypes highlighting the need for a multi-factorial rather than mono-theoretical account of developmental dyslexia.

Keywords: Developmental dyslexia; Multi-factorial deficit; Review.

La efervescencia científica que reina en torno a la dislexia evolutiva se explica por el difícil desafío que implica atribuir esta dificultad a una causa simple al tiempo que se observan pacientes disléxicos con múltiples perfiles. En este capítulo, empezamos presentando la hipótesis neurocognitiva principal que persigue explicar la dislexia. Revisaremos la naturaleza multidimensional de la dislexia y discutiremos la necesidad de utilizar un criterio diagnóstico común para mejorar nuestra comprensión de su verdadera naturaleza. Concluiremos con la presentación de un trabajo prometedor que conecta endofenotipos cerebrales y fenotipos conductuales, resaltando la necesidad de un enfoque multifactorial más que monoteórico de la dislexia evolutiva.

Palabras clave: Dislexia Evolutiva; Déficit Multifactorial; Revisión.

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### Back to basic: what is dyslexia?

According to the World Health Organization (WHO, 1997 - ICD 10), dyslexia is a specific reading disorder: “The main feature is a specific and significant impairment in the development of reading skills that is not solely accounted for by mental age, visual acuity problems, or inadequate schooling. Reading comprehension skill, reading word recognition, oral reading skill, and performance of tasks requiring reading may all be affected. Spelling difficulties are frequently associated with specific reading disorder and often remain into adolescence even after some progress in reading has been made. Specific developmental disorders of reading are commonly preceded by a history of disorders in speech or language development. Associated emotional and behavioural disturbances are common during the school age period.” Strikingly, this definition relies mainly on exclusion criteria, i.e. dyslexia is not diagnosed because of the reading impairment per se but because the learning difficulties cannot be explained otherwise; that is reading disorder cannot be explained by basic sensory deficits, evident brain abnormalities, or primary psychological deficits. Importantly, the ICD 10 definition does not exclude those deficits: it points out that they cannot ‘solely’ explain the reading disorder. Indeed, specific reading disorders have been associated with deficits in related domains such as oral language (dysphasia and Specific Language Impairment), writing skills (dysgraphia), mathematical abilities (dyscalculia), motor coordination (dyspraxia), temporal orientation (dyschronia), visual abilities, Attention-Deficit/Hyperactivity-Disorder (Habib, 2000) and increased internalizing, anxious and depressive symptomatology (Mugnaini et al., 2009).

### Multiple deficits in dyslexia?

There are many competing neuro-cognitive hypotheses aiming at explaining dyslexia, each one highlighting one type of behavioural deficit in relation with abnormal brain structures and/or functional responses. Among those hypotheses, one can identify three major approaches (Démonet et al., 2004; Pernet & Démonet, in press). A first approach relates reading to phonology, an essential part of the reading process. A second approach relies on identifying subtle visual or visuo-attentional deficits which would explain the specific reading disorder. Finally, a third approach is to conceive dyslexia as a specific learning / memory disorder.

### Phonological and auditory hypotheses

The phonological hypothesis, which is the most influential account for reading problems, postulates deficits related to the access or the manipulation of phonemic information, or both, preventing efficient learning of graphemes/phonemes correspondences that are crucial to reading (e.g. Bradley & Bryant, 1983; Ramus, 2004; Shaywitz & Shaywitz, 2005). One possible explanation for those deficits and in particular the deficit in phonemic categorization is that dyslexic subjects have too many representations, i.e. they have many non-pertinent

or allophonic representations (Serniclaes et al., 2001). These hypotheses are supported by the frequently observed presence of phonological disorders in dyslexic readers as for instance reduced performances for short-term verbal memory tasks, phonemic awareness (Ramus et al., 2003) and/or deficits in phonemic categorization (Serniclaes et al., 2001). Such behavioural deficits have been linked with abnormalities of the left posterior temporal cortex, the supramarginal gyrus and the inferior frontal cortex (Dufor et al., 2007; Dufor et al., 2009).

By contrast with the phonological hypothesis, the auditory processing deficit theory proposes that phonological deficits are secondary to a more basic impairment in rapid acoustic transition perception (Tallal, 2004; Tallal et al., 1985). Such deficits have been linked with microscopic abnormalities in the auditory cortex (Galaburda & Kemper, 1979), the frontal and perisylvian areas (Kaufman & Galaburda, 1989) and soma atrophies of magnocells in the medial geniculate nuclei of the thalamus (Galaburda et al., 1994). Abnormal functional responses to speech sounds have also been observed in the brainstem and the left inferior frontal cortex. For instance, Banai et al. (2009) showed abnormal timing and harmonic information contents in the brainstem response to the sound /da/. Such abnormal response is likely to be due to an interaction with other sub-cortical (thalamus) and cortical (auditory cortex) structure via cortico-fugal projections since no ‘basic’ deficits are observed when using clicks rather than complex sounds (Song et al., 2006). Those deficits in temporal and spectral coding of complex auditory stimuli would thus explain phonological deficits. This hypothesis is further supported by the fact that (1) slowing down the acoustic features in rolling /ma na/ /na ma/ stimuli (vs. /ma ma/ /na na/) enhances the left inferior frontal cortex response of dyslexic subjects to a level comparable to controls in normal situation (Ruff et al., 2002) and (2) training in auditory temporal processing improves reading performances (Merzenich et al., 1996).

### Visual hypotheses

The visual hypothesis posits the existence of low level visual disorders related to abnormal thalamic magno-cells. These cells are involved in the processing of low contrast information and fast moving stimuli and would thus be important for reading activities related to saccadic eye movements. Histological studies revealed soma atrophies of magno-cells in the lateral geniculate nuclei of the thalamus (Livingstone et al., 1991) and cyto-architectonic abnormalities of the primary visual cortex (Jenner et al., 1999) have been observed alongside abnormal functional brain responses of visual areas receiving magnocellular inputs (i.e. MT and dorsal regions - Demb et al., 1997, 1998). Favoursing this hypothesis, behavioural studies also showed increased thresholds on detection of low contrast, low spatial or high temporal frequencies (Lovegrove et al., 1980), and poor sensitivity to visual motion (Demb et al., 1998) in dyslexic readers (see however, Skotun, 2000).

As an alternative or complementary explanation, the visuo-attentional hypothesis situates the impairment in the encoding of letter sequences. For instance, Valdois and collaborators showed that dyslexic readers have a shorter visuo-attentional span, i.e. they cannot process simultaneously as many elements in an array as control readers (Bosse et al., 2007; Valdois et al., 2003). Although these visuo-attentional deficits are likely to be related to abnormal inferior parietal responses, they can also impact on reading areas mediating orthographic and phonological system. For instance, the inability to encode several letters simultaneously could impair sublexical procedures as well as grapheme/phoneme correspondence. Such attentional deficits could then explain (indirectly) altered brain responses often observed in the infero-temporal cortex (sublexical processes), angular/supramarginal gyri and inferior frontal gyrus (phonological processes - Demonet et al., 2004; Hoeft et al., 2007; Paulesu et al., 2001; Pugh et al., 2000; Peyrin et al., 2010). Finally it is worth noticing that the visual magnocellular pathway is involved in directing attention, eye movements and visual search, all three processes being relevant to reading and therefore magno-cell impairment might account for many signs observed in dyslexic readers (Stein & Walsh, 1997).

### Learning hypotheses

The cerebellar hypothesis relates dyslexia to a general learning disorder that includes a failure to automatize reading and writing skills (Fawcett et al., 1996, Nicolson et al., 2001, Nicolson & Fawcett, 2007), i.e. dyslexia is regarded as an impaired automatization of high-order sensory-motor procedures essential in reading that would reflect an abnormal functioning in the lateral cerebellum (Doyon et al., 2002). According to Nicolson and colleagues, procedural learning difficulties could either appear in the language system (dyslexia), or the motor system (dyspraxia) or both. Supporting this hypothesis histological (Finch et al., 2002) as well as structural (Pernet et al., 2009a, 2009b) abnormalities have been observed in the cerebellum of dyslexic readers.

Another type of deficit relying on the ability to « learn » or more precisely to fix the perceptual properties from the immediate context is explained by the anchoring deficit hypothesis (Ahissar, 2007, Banai & Ahissar, 2010). The authors propose a functional dynamic process as a possible origin of disorders encountered in dyslexic individuals. The idea comes from the observation that it is more difficult for dyslexic participants to process a second stimulus after a first one when the perceptual properties of the first stimulus could be used as an anchor to process the second one. The same authors tested this phenomenon with either auditory or visual material whatever its lexical or non-lexical nature. Moreover, the results of these studies show that when the cognitive load is not heavy enough, both control and dyslexic performances are the same. The anchoring deficit is a dynamical process which does not rely on long term stored representations. Only the immediate information is use-

ful for the control participants to correctly process the stimuli. Another account of this theory comes from a study which discusses the existence of phonological troubles when the context of the experimental condition does not sufficiently load the working memory (Ramus & Szenkovits 2008).

### One theory fits all

The general magnocellular theory (Stein, 2001) encompasses the basic auditory, basic visual, part of attentional and cerebellar ones by discussing each deficit as a consequence of a general magnocellular defect. Importantly, according to this theory, phonological deficits are secondary in comparison to other deficits. This idea of a multifocal cerebral deficit originating in magno-cells is supported by histological abnormalities of M cells in the lateral (Livingstone et al., 1991) and medial (Galaburda et al., 1994) geniculate nuclei of the thalamus and possibly other cerebellar/Purkinje cells abnormalities.

### Multiple dyslexias for one reading deficit?

The multiplicity of hypotheses reflect the multiplicity of behavioural deficits observed in dyslexia raising an obvious question: Are there different forms or subtypes of dyslexia?

This question is not new and it has been proposed several distinctions between dyslexic readers. Three popular classifications have been proposed. (i) Boder in 1973 proposed to distinguish between dyslexic children on the basis of their 'sensory' deficit, i.e. they would either be classified as dysphonetic (having phonological problems), or dyseidetic (having visual problems). (ii) Based on the classification of patients with acquired dyslexia, Castles & Coltheart (1993) proposed to distinguish phonological from surface developmental dyslexic children. Accordingly, dyslexics are split into patients with assembling problems, i.e. grapheme/phoneme association, vs. patients with addressing problem, i.e. lexicon access. (iii) More recently, Wolf and Bowers (1999) proposed, on the basis of what is referred to as the double deficit hypothesis (Compton et al. 2001; Lovett et al. 2000; Wolf & Bowers 1999, 2000), three subtypes: phonological, rate, and phonological-rate. The double-deficit hypothesis asserts that impaired readers have some combination of two deficits. The first type of deficits is an impaired phonological awareness and the second one is an impairment deficit of rapid naming capacity (or visual naming speed), which involves the rapid access and retrieval of names of known objects or visual symbols, such as digits, and letters. The double deficit hypothesis therefore distinguishes dyslexic readers based on phonological processes per se and phonological lexical access. However useful, e.g. for clinical purposes, those classifications do not reflect the variety of behavioural deficits and neural abnormalities mentioned in section 2.

We recently compiled 10 recent articles looking at cognitive subtypes in dyslexia (Pernet and Démonet, in press). Data are from studies across different languages although mainly in English. Results show that on 763 dyslexic subjects studied,

only 654 subjects could be classified according the various criterion used in the different studies, leaving 14.28% of participants with a literacy problem but no clear perceptual or cognitive deficit. Overall, our analysis also reveals that no clear-cut dyslexia subtypes can be obtained from behavioural subtyping although phonological (>40%) and rapid serial processing (>10%) are common disorders observed in dyslexia, although too often in association with other signs. This points out to the weak ability to find clear behavioural markers of dyslexia beyond reading difficulties. One can interpret this problem either as our inability (as researcher and clinicians) to come up with a good diagnostic test or as evidence that no behavioural test will be able to capture the core deficit in dyslexia because dyslexia is a made up category reflecting various brain disorder leading to various reading related deficits.

### Re-defining dyslexia: a research agenda

#### Research criterion for dyslexia

Looking at the multiplicity of behavioural deficits related to reading and often associated with other neuro-cognitive disorders, there is an urgent need for objective criteria to define dyslexia. One issue that arises when compiling multiple studies is subject selection. Some studies rely on the discrepancy definition of the ICD 10. Participants are selected such as they show reading deficits, no associated deficits, and normal IQ. Although this selection ensure that participants suffer from dyslexia, this limits the range of individuals and may result in groups with patients suffering mainly from phonological deficits (Bishop & Snowling, 2004). One option is to relax the criteria and allow associated deficits. Although it means studies will need larger groups, association/dissociations are by themselves interesting and likely to help separating dyslexia subtypes. Another option, is to study dyslexia based entirely on reading ability, ignoring associated deficits (as long as they cannot solely explain the deficit) and IQ (provided it is greater than 80) (Fletcher et al., 1992, Siegel, 1992, 2006). This second approach indeed stresses the reading disability and leads to study ‘poor readers’ rather than ‘specific reading impairment’. A second issue that needs to be addressed to be able to compare studies and therefore fully understand dyslexia, is the behavioural performance characterization. Among the 10 subtyping studies that we reviewed (Pernet & Démonet, in press), only phonological awareness has been systematically studied. This reveals the influence of the phonological hypothesis but also a bias leading to overestimate the presence of phonological disorders and/or underestimate the presence of other deficits. The only option left for the time being is to systematically investigate each aspect of deficits observed: phonological awareness, rapid acoustic perception, low level visual disorders, visuo-attentional disorders, procedural learning and working memory. It is only at the price of larger samples (and testing time) with a better and broader characterization of the reading disorder (issue 1) and cognitive deficits (issue 2) that subtypes of patients with deficits in learning to read will be identified.

### Looking for endo-phenotypes

To our knowledge, only 2 studies so far enquired sample heterogeneity in dyslexia from a brain perspective. Because many studies found supporting evidences for one or several hypotheses, current positions however shift toward a multifactorial view on dyslexia. As briefly reviewed above (see also Eckert, 2004) studies revealed that dyslexia relates to brain abnormalities in areas relevant to reading (lateral cerebellum, infero-temporal cortex, angular/supra marginal gyrus, auditory and superior temporal cortices, inferior frontal cortex). In the following we briefly present these 2 studies to illustrate how one can study heterogeneity in an attempt to account for a common disorder in reading.

Pernet et al. (2009a) investigated in 77 subjects (38 adult dyslexic subjects and 39 controls) the relationship between grey matter volumes and behavioural performance using a voxel-based morphometric approach. Results showed significant effects with phonemic deletion (metaphonology), irregular word spelling (lexicon) and pseudoword reading (grapheme-phoneme). Whilst in control subjects, language performances correlated with grey matter volumes in many known language related areas (including the cerebellum), no correlations could be observed in subjects with dyslexia suggesting a strongly disorganized cortical architecture in dyslexia. We then hypothesized that the absence of within-group correlations could be partly explained by the existence of multiple dyslexia sub-types in the brain. In a follow up analysis (Pernet et al. 2009b) we used the control group to construct a typical brain via bootstrapped confidence intervals, i.e. we estimated for each voxel of brain what was the normal range of variation. Next, we classified each voxel of each dyslexic brain individually to see whether subjects showed brain regions that were out of the normal range. Finally we pooled the results of each dyslexic subject to create a map indicating where the dyslexic group differed from controls. The main advantage of this technique, is of course that a brain region can be declared as showing a significant difference between groups even if the patient group has half of the subjects above the confidence interval and half below (i.e. this effect is non linear with regard to patient classification). Results showed that 100% of dyslexic subjects had higher or lower grey matter than controls over the right cerebellar declive, a cerebellar region showing systematic activation during language tasks (Stoodley & Schmahmann, 2009) and over the right striatum (lentiform nucleus). Importantly, about half of the subjects had lower volumes than controls and the other half had higher volumes therefore revealing four clear cut brain endo-phenotypes. In addition, these four sub-groups showed significant behavioural differences in terms of phonological and lexicon access performance. Overall, our results suggest that different brain phenotypes exist and that brain phenotypes support different behavioural phenotypes.

Giraud et al. (2005) and Pernet & Démonet (in press) investigated in 14 dyslexics participants the electrical evoked activ-

ity to the passive listening of /ba/ and /pa/ syllables. The whole point of using these syllables is that, although phonologically different, they are acoustically close. The main difference between these two sounds is that they are different regarding their Voice Onset Time (VOT - in fact the /pa/ syllable was obtained by extracting the initial low frequency activity constituting a short pre-burst voice segment occurring in French just before the consonant lip release burst in /ba/). The VOT is defined as the time between a phonetically relevant supra-laryngeal event, such as release, and glottal pulsing (Lisker & Abramson, 1964) and is the major phonetic determinant in the discrimination of consonants of the voiced-voiceless contrast. Auditory evoked potentials (AEPs) for each syllable were clearly distinguishable in control subjects (10 males). Following the N1/P2 complex (peaks at 80ms, 120ms and 180ms), a negative component peaking at approximately 240 ms is observed for the syllable /ba/ but not /pa/; this supplementary component is followed by an off-response at approximately 334 ms; this component is believed to represent the electrophysiological signature of the neural processing of the consonant lip release burst. For syllable /pa/, such pre-burst sound does not exist, the lip release and vowel voicing being simultaneous, and therefore the supplementary burst-related component is not observed in AEP. It follows that AEPs bring out a time course signature typical of either /b/ or /p/ depending on the presence versus absence of the lip release burst component. When compared to control participants, three subgroups of dyslexic readers could be identified: (1) participants with a standard N1/P2 complex followed by an earlier than controls negative component (220ms) plus by many late components without clear off-response; (2) participants with a standard N1/P2 complex but no release component for /ba/, i.e. /ba/ and /pa/ AEPs were not distinguishable on the basis of component number and latencies; (3) dyslexic participants with identical brain responses as controls. From a behavioural viewpoint these three subgroups could also be distinguished. In fact, participants in subgroups 1 and 2 showed marked reading deficits (reading age < 10 years and/or overall spelling < 60%) while participants of the 3rd subgroups show moderate reading deficits (reading age > 10 years) suggesting that severe dyslexia only is associated with impairment of phoneme coding in the auditory cortex. Again, these results show that different brain endophenotypes can be observed and that different endophenotypes support different behavioural phenotypes.

#### Linking up all levels of analysis

There are no doubts nowadays that dyslexia is related to genetic abnormalities. In fact, genetic studies have revealed multiple loci for chromosomal abnormalities and in particular on chromosomes 15 and 6, but also 2, 3, 1 and 18 (Brkanac et al., 2007; Chapman et al., 2004; Francks et al., 2003; Gayan and Olson, 2003; Raskind et al., 2005). Again, this multiplicity of candidate genes is likely to reflect the variability observed in dyslexia at the behavioural level. Thus, the multifactorial and

polygenic nature of developmental dyslexia strongly suggests the existence of various brain phenotypes (Goldberg & Weinberger, 2004; Gottesman & Gould, 2003).

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