
Peer Review File

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Reviewer A

The manuscript describes a comprehensive explorative study that has an overall aim of defining “Visual Dyslexia”. It is an ambiguous aim considering the history of research in this area (ie. Stein, J. What is Developmental Dyslexia? Brain Sci. 2018, 8, 26.) Nonetheless, the investigators have performed an innovative experiment testing specific traits of dyslexic children, with promising results towards a better understanding of the role of visual perception in dyslexia. Their main hypothesis is that people with visual dyslexia show a positive correlation between reading speed and interletter spacing, called a ‘visual marker’. This hypothesis is tested in an experiment where dyslexics with and without visual abnormalities is recruited, and grouped according to their visual abnormality. The results show that there is moderate correlations in some of the visual groups, but that only a proportion of the individuals had the visual marker.

General comments:

COMMENT 1: Although this is a well-written manuscript, it could be argued whether or not this study makes a significant contribution to the already existing literature. The authors also recognize this: they make the necessary reservations in their conclusion.

REPLY 1: This study does not pretend to draw definitive conclusion, but its publication could contribute to open up new directions of investigation, advancing a novel approach to address the issue of vision and dyslexia. This consideration has been pinpointed in the conclusion section.

CHANGES IN THE TEXT: this clarification has been added in the conclusion section.

COMMENT 2: The link between the magnocellular pathway and/or dorsal stream with dyslexia is mentioned in the introduction, but it is not thoroughly explained how this experiment is connected to a possible altered dorsal stream activity.

REPLY 2: in effect, if abnormal magnocellular function has been introduced by many authors to address the results found in previous investigations, I acknowledge that theorizing the way altered dorsal stream generates the defects reported in this study would be too speculative. So, references to this aspect have been removed from this manuscript. I intend to investigate this possible relationship in my next study.

CHANGES IN THE TEXT: references to this aspect have been removed from the manuscript.

COMMENT 3: The research group have previously defined a condition called spatial relationship anisotropy, more prevalent in dyslexics than in controls, it would be interesting to know how the prevalence of this condition changes through development, and if it is related to reading experience instead of dyslexia.

REPLY 3: This is a good point, indeed. According to previous studies, spatial relationship anisotropy in young adults (mean age 29.3 ± 11.6 years) was half the value found in non-dyslexic children (mean age 9.2 ± 2.0 years: SRA: 1.13 ± 2.19 vs 2.36 ± 1.75 : references 25 and 85, respectively). It is therefore arguable that spatial relationship perception matures through development, and this maturation may be a requisite for normal reading acquisition.

CHANGES IN THE TEXT: this consideration has been added in the discussion section. I am grateful to the Reviewer for the suggestion.

COMMENT 4: The main concern is that there is a circular argument: they test and recruit dyslexics with “anisotropic perception of visual space”, meaning that they perceive letters more crowded and closer together. Then they find a (moderate) positive correlation between reading speed and interletter spacing in those dyslexics. This seems like no surprise, since the people they recruited already had showed problems with crowding. I suggest the authors justify in the introduction the relevance of their work and their differences with respect to previous published work.

REPLY 4: with the term “anisotropic perception of visual space”, we do not mean that dyslexics perceive letters more crowded and closer together. There is no way, in fact, to establish this by measuring the amount of anisotropy of the visual space. Actually, within the clinical setting, central crowding can be deduced if there is a difference in visual acuity when presenting isolated and sequential optotypes, as it occurs in amblyopes. But the recruited children did not show problems with crowding under a clinical perspective: their visual acuity was normal and none of them had conditions predisposing to amblyopia. So, the anisotropic perception of the visual space would *contribute* to increased lateral masking in this dyslexic sample *not in the classical sense of “increased central (or foveal) crowding”*, as it occurs in amblyopia, but in terms of its abnormal distribution across the paracentral visual field. As the consequence of this redistribution, the effect is exerted in the paracentral area of the visual field, that is a crucial region as it pre-processes each line of text during reading [Bouma & Legein, 1977 [28]; Geiger & Lettvin, 1987 [29]; Atkinson, 1991 [26]; Martelli et al, 2009] [30].

In sum, abnormal spatial relationship perception is not equal to saying increased crowding, but it subtends a disturbed distribution of the lateral masking across the paracentral visual field responsible, in turn, for the reading problems. In my

opinion there is no circularity in this assumption as this is, indeed, to be demonstrated by checking for the visual marker in subjects with abnormal SRA. As far as we know, in previous published works this aspect has not been considered.

CHANGES IN THE TEXT: This explanation has been included in the introduction section.

COMMENT 5: The strongest finding is possibly that in the group of dyslexics with unstable ocular dominance, 50% had the visual marker, supporting previous findings of unstable ocular dominance in dyslexics. It would be interesting to know if people without dyslexia but with unstable ocular dominance also had the same correlation between reading speed and interletter spacing. I understand this is not possible to answer in the present study, but suggest that the authors consider the question for future studies.

REPLY 5: another interesting point to be addressed. I will consider this issue for future studies.

CHANGES IN THE TEXT: thanks to the anonymous Reviewer, this suggestion has been added in the discussion section.

COMMENT 6: I enjoyed reading the manuscript but the methods in the experiment was sometimes difficult to follow. In particular: abnormal spatial relationship atropy, anisotropic perception, SRA, SRP – seemed to be a roundel and I am not sure if abbreviations were consistently used. The definition of SRA should include information about how much poorer these individuals were in distinguishing ellipses from circles, and the prevalence of SRA in dyslexics.

REPLY 6: The use of the terms SRP and SRA has been revised in the manuscript. It has been clarified that increased SRA is an expression of abnormal (unbalanced) spatial relationship perception. One percent point equals to a difference of 3.3 arc min between the x,y at the adopted viewing distance. So, subjects with an anisotropic perception above the cutoff were unable to identify ellipses with difference between the two axes lower than 16.5 min arc. The Average SRA in each class of dyslexics is reported in table 2. The prevalence of SRA above the cutoff of normality was 22.7%.

CHANGES IN THE TEXT: The use of the terms SRP and SRA has been revised in the manuscript (section 1 and 1.1), and the need for clarification reported by Reviewer 1 has been fulfilled in section 1.1. Information about how much poorer subjects with abnormal SRA were in distinguishing ellipses from circles, and the prevalence of SRA in dyslexics has been added in section 2.6.

COMMENT 7: With regards to the sample, the authors should consider if the refer from professionals with an interest in visual-perceptual impairment could have biased

the sample. However, it is not a main concern since the study is case-control rather than population based.

REPLY 7: as reported in section 2.5 of the manuscript, “Children were referred to our service from neuro-psychiatrists and speech therapists interested in obtaining information about the co-occurrence of a visual-perceptual impairment”. We suppose the sample is not representative of the dyslexic population but is biased towards subjects with visual-perceptive alterations: in fact, the suspect of professionals was the occurrence of visual-perceptive alterations in their patients. However, as recalled by the Reviewer this is not important as reporting the prevalence of our finding in the dyslexic population was not a goal of the study.

CHANGES IN THE TEXT: none.

COMMENT 8: Exclusion criteria includes some visual parameters possible tested by an ophthalmologist or optometrist. It would be interesting to know some more details about visual status, for instance if cycloplegic refraction was not used, significant hypermetropia may have been overlooked.

Also, accommodation levels are not mentioned and I assume it has not been measured, unfortunately these are parameters that may influence the results.

For future studies, the authors should keep in mind that visual input is important to visual perception, and that vision or accommodation problems may contribute to reading performance. For instance, accommodation problems (or uncorrected hypermetropia) may lead to intermittent blur and fixation instability, which may influence the ocular dominance result. The same problem yields for phorias.

Phorias is not mentioned in the exclusion criteria, and I assume individuals with different levels of phorias is included in the sample, as it is included in analysis (line 411). It would be interesting to know the levels of phoria acceptable to the authors, and also how phorias are measured, in particular with respect to compensation.

REPLY 8: to rule out the possibility of undetected hyperopic defects, all the children referred to our service undergo a routine cycloplegic refraction (tropicamide 0.5%) and, in case, adequate correction is prescribed. Likewise, accommodation and convergence is always scored as “poor”, “fair” or “normal” but, honestly, they are not quantified. In line with the suggestion of the Reviewer, from now on we will quantify the near point of convergence and accommodation. The same applies to phorias that were not considered an exclusion criterion unless they were judged as severe (exophorias higher than 13 pd and esophorias higher than 2 pd measured with adequate refractive correction). None of the children in the sample had severe phorias or poor convergence.

CHANGES IN THE TEXT: these details have been added in the method section.

Specific comments:

COMMENT 9: 1.36 Disabled readers and dyslexics are not the same. Please rephrase or explain.

REPLY 9: rephrased.

CHANGES IN THE TEXT: “disabled readers” deleted.

COMMENT 10: 1.44 Good point. Could this magno/parvo discussion be included in the current experiment?

REPLY 10: I think that spatial relationship perception, acting on a global scale, could be a magnocellular function. However, theorizing the way altered magnocellular function generates the defects reported in this study would be too speculative in my opinion.

COMMENT 11: 1.84-92 Use the term SRP and SRA consistently. Is having an abnormal SRP the same as qualifying for having SRA? I understand this might be obvious to the authors, but it is not to me.

REPLY 11: The use of the terms SRP and SRA has been revised in the manuscript. It has been clarified that increased SRA is an expression of abnormal (unbalanced) spatial relationship perception.

CHANGES IN THE TEXT: The use of the terms SRP and SRA has been revised in the manuscript (section 1 and 1.1), and the need for clarification reported by Reviewer 1 has been fulfilled in section 1.1.

COMMENT 12: 1. 205-207 Is this really enough to conclude a causality?

REPLY 12: “abnormal interocular inhibition as well as unbalanced sensory input affect the positional coding of letter and syllables in dyslexic readers. We postulate that the detrimental effect of this function on the readability of the characters depends on their spatial density”. I believe that in general binocular interference has something to do with struggling to read. Stein, Fowler and their theory of unfixed reference and unstable dominance strongly point toward this direction. So, it is worthwhile expanding the investigation from the oculomotor to the sensory interaction to establish if it is there a causal simply a correlational relationship.

COMMENT 13. 1. 365 please state how ametropia was measured (was cycloplegic refraction done?)

REPLY 13: the refractive status of each child is always determined after cycloplegia (see reply to comment 8).

CHANGES IN THE TEXT: definition added in the method section.

COMMENT 14. 1. 367 please define poor convergence

REPLY 14: poor convergence as ≥ 8 cm from the nose, according to the operative definition provided by Horwood, Toor and Riddell (2014).

CHANGES IN THE TEXT: definition added in the method section.

COMMENT 15. l. 441 Should be “non words” ?

REPLY 15: “(in words modality, false positive rate: 6%).

COMMENT 16. Figure 5: takes up a lot of space and in my opinion does not add to the manuscript.

REPLY 16: figure 5 describes the linear model referred to the reading rate as a function of interletter spacing; in the nonvisual sample and in the anisotropic sample. It shows the difference in the slope that is not significant in the nonvisual sample (panel a and b) and significant in the anisotropic sample (panel c and d). Finally, it represents the rate of improvement of the reading speed as a function of spatial relationship anisotropy. For this reason, we judged it could be of avail to the reader for a better comprehension. If the reviewer believes this is not the case, figure 5 will be removed and figures 6 and 7 will be re-numbered.

Reviewer B

COMMENT 1- It is difficult to see what the purpose of this paper is. It states that its aim is to define 'visual dyslexia'. But as far as I can tell the paper starts with the questionable assumption that a child has visual dyslexia if increasing the spacing between letters increases his reading speed ie it assumes a definition before anything else, so that any subsequent argument will be circular.

REPLY 1: the working hypothesis is that a child has visual dyslexia if he or she shows at least one of the visoperceptive alterations investigated and that this alteration is not merely an epiphenomenon, but a causal role can be suggested based on the effect it can have on the positional coding of the letters, that, if hampered, is made easier by manipulation of the interletter spacing. I agree completely with the Reviewer: this assumption is questionable, in fact it is a working hypothesis, and therefore needs to be investigated, confirmed or rejected. However, its consideration is justified by previous literature supporting the putative role of abnormal spatial relationship anisotropy, unstable ocular dominance, abnormal crowding in a subgroup of dyslexics. For this reason, in my opinion there is no circularity. Due caution about the finding of the study has been pinpointed in the conclusion section.

I care to highlight that this study does not pretend to draw definitive conclusion, but in my opinion its publication could contribute to open up new directions of investigation, advancing a novel approach to address the issue of vision and dyslexia.

CHANGES IN THE TEXT: this clarification has been added in the conclusion section.

COMMENT 2: It then uses tests of letter spacing sensitivity, crowding sensitivity, binocular imbalance (unstable dominance) and interocular inhibition to classify children who had been diagnosed as dyslexic into 4 groups: nonvisual, crowding sensitive, unstable dominance and showing abnormal binocular inhibition. The authors then report that up to 75% of the children in each of the 3 visual groups did not increase their reading speed with increased letter spacing. This makes no sense.

REPLY: In many cases the sample effect does not match the individual outcomes. Statistics performed on averaged data reflects a general trend but may not reflect individual experimental behaviors. I understand (and appreciate as a scientist) the concern of the Reviewer, but, honestly, I do not think it definitely makes no sense: it is simply not so strong to support conclusive statements, and further investigation is needed. This study is merely intended to encourage researchers to investigate in this direction in order to clarify the moderate trend we have reported.

CHANGES IN THE TEXT: These considerations have been further pinpointed in the conclusion section.

Other points:

COMMENT 3: The abstract is incomprehensible.

REPLY: After reconsidering the abstract I have realized that in many points it is definitely not clear. So, I have modified many passages with the hope that, in its actual form, it can satisfy the requirement of clearness.

CHANGES IN THE TEXT: abstract rephrased.

COMMENT 4: Introduction. The discussion of the magnocellular theory is irrelevant to the rest of the paper

REPLY 4: I acknowledge that theorizing the way altered dorsal stream generates the defects reported in this study would be too speculative. So, references to this aspect have been removed from this manuscript.

CHANGES IN THE TEXT: references to this aspect have been removed from the manuscript.

COMMENT 5: p132 univocal - unequivocal?

REPLY 5: unequivocal, corrected

CHANGES IN THE TEXT: corrected

COMMENT 6: 203 what does negative to visual marker mean?

REPLY 6: “negative to the visual marker” = “...do not present the visual marker”.

CHANGES IN THE TEXT: corrected

COMMENT 7: The figures should have proper legends that describe the axes and

different symbols. All need much more explanation. The authors should not assume readers have detailed knowledge of their previous papers.

REPLY 7: the legends of the figures are reported at the end of the manuscript, according to the instructions for Authors. I apologize if the explanation reported in the legends of the figures turned out to be poor, but it was my concern to avoid repeating in the legends what explained in the text. Figure legends have been enriched according to the suggestion of the Reviewer.

CHANGES IN THE TEXT: Figure legends have been enriched according to the suggestion of the Reviewer.