doi:10.1093/brain/awv036 BRAIN 2015: 138; 1–3 | e378

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Cortical differences in preliterate children at familiar risk of dyslexia are similar to those observed in dyslexic readers

Indra Kraft,[1] Riccardo Cafiero,[1] Gesa Schaadt,[1,2] Jens Brauer,[1] Nicole E. Neef,[1] Bent Müller,[3] Holger Kirsten,[3] Arndt Wilcke,[3] Johannes Boltze,[3,4] Angela D. Friederici[1] and Michael A. Skeide[1]

1 Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Department of Psychology, Humboldt-Universtität zu Berlin, Berlin, Germany
3 Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany
4 Translational Centre for Regenerative Medicine, Leipzig, Germany

Correspondence to: Indra Kraft,
Department of Neuropsychology,
Max Planck Institute for Human Cognitive and Brain Sciences,
Stephanstraße 1A, 04103 Leipzig, Germany
E-mail: ikraft@cbs.mpg.de

Correspondence may also be addressed to: Michael A. Skeide. E-mail: skeide@cbs.mpg.de

Sir,

In their recent report in *Brain*, Clark *et al.* (2014) presented cortical thickness data obtained from a cohort of 27 children that were compared longitudinally at three time points (first grade: ages 6–7, third grade: ages 8–9, sixth grade: ages 11–12) categorized as either dyslexic or not according to their reading outcome in sixth grade. Based on their observations, the authors conclude that the neuroanatomical precursors of developmental dyslexia are found predominantly in primary sensory cortices and that structural abnormalities in the reading network only emerge after children have learned how to read and write. This study is indeed invaluable as it follows preliterate children longitudinally until the disorder is diagnosed, providing a unique picture of structural cortical changes in dyslexic and non-dyslexic children during this time. However, there are a number of discrepancies between the presented findings and results from other groups including our own. These differences might be explained by the relatively low statistical power of the analyses carried out by Clark and colleagues. Moreover, because genetic and environmental factors are not included in their analyses, it remains unclear how the data can be integrated into a comprehensive account of developmental dyslexia.

The first limitation is based on the experimental design of the study. Although the subsamples compared by Clark *et al.* (2014) are small for a neuroimaging study [MRI time point 1: children who later were identified as dyslexic ($n = 7$) and those who were not ($n = 10$); MRI time point 3: children who were identified as having dyslexia ($n = 11$) and those who were not ($n = 13$), male dyslexic children ($n = 5$) and male control children ($n = 8$), female dyslexic children ($n = 6$) and female control children ($n = 5$)], the authors do not report results from a pretest power analysis. Hence, it is hard to determine whether the observations are truly significant or whether the effects were randomly detected and might not be reproducible in larger samples. The chosen whole-brain significance threshold of $P < 0.05$ (cluster size corrected to $P < 0.05$) is the most liberal confidence level possible in a neuroimaging study. The consequences of a potential power problem may be aggravated by substantial subsample size variations across measurement points. In particular, at MRI time point 1, $<64\%$

Advance Access publication February 20, 2015

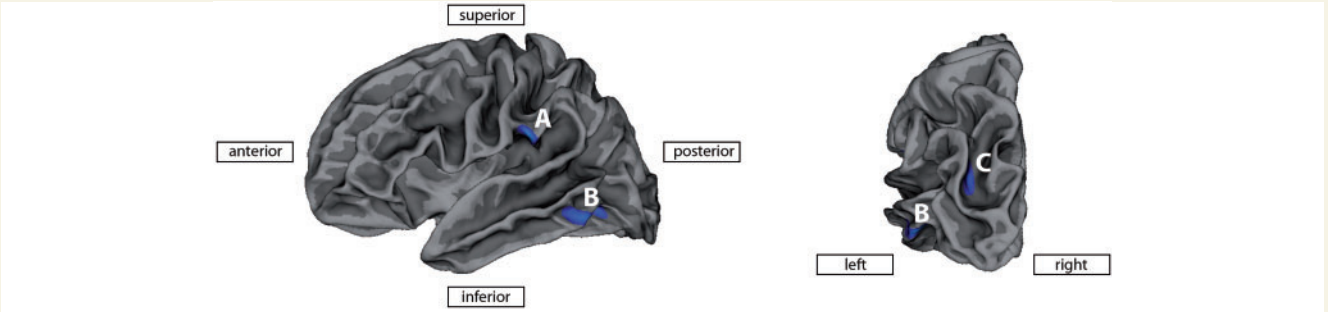

Figure 1 Cortical thickness differences between 5-year-old preliterate children at familial risk of developmental dyslexia and non-risk controls. Compared to children without a family history of developmental dyslexia, individuals with a family history of developmental dyslexia showed a significantly reduced cortical thickness ($P < 0.05$, false discovery rate corrected) in the left supramarginal gyrus (**A**), the left inferior temporal gyrus (**B**), and the left superior and transversal occipital sulci (**C**), but not in right-hemispheric regions. The opposite contrast (non-risk children versus at-risk children) did not reveal any significant results. Depicted are *z*-transformed cortical thickness values on the white matter surface of the group-averaged left hemisphere.

of the data about the children with dyslexia and <77% of the control data were available compared to MRI time point 3. We understand that such variations are almost unpreventable as they primarily emerge from the complex logistics of longitudinal surveys enrolling children in the given age range. Nevertheless, these variations compromise the longitudinal comparability of the data, even given very good scan-rescan reliability, and would therefore have deserved more detailed discussion.

The second limitation relates to the conceptual framework for interpreting the results. Developmental dyslexia is moderately to highly heritable with rates of inheritance ranging from 30% in families with low levels of parental education to 70% in families with high levels of parental education (Scerri and Schulte-Körne, 2010). Unfortunately, the authors accounted for neither the impact of genetic nor environmental variance, particularly parental education, in their analyses. This is limiting because previous imaging genetics studies indicate that the direct effect of dyslexia susceptibility genes on cortical thickness phenotypes is stronger than on behavioural phenotypes such as reading level (Darki *et al.*, 2014). Accordingly, the statement from the authors that their 'results are specific to dyslexia *per se* rather than a family history of dyslexia' remains vague. Clark and colleagues do not provide an alternative account of the current best-supported integrative model of dyslexia introduced by Giraud and Ramus (2013). This model assumes that a certain set of genetic risk variants alters neuronal precursor migration to their cortical target layers *in utero,* which, in turn, leads to acoustic-phonological deficits detectable in newborns predicting the later reading and writing outcome (Giraud and Ramus, 2013).

The third limitation is that the authors categorize the participants according to their reading outcome at MRI time point 3, but do not directly relate the corresponding reading and spelling data to the cortical thickness data. Additionally, as no behavioural correlates of the brain measures obtained at MRI time points 1 and 2 are provided, it remains unclear whether the distinct cortical thickness patterns have any behavioural implications with respect to phonological awareness or reading and spelling.

Recently, we compared whole-brain cortical thickness in 53 pre-reading children (mean age: 5 years 5 months, range 4 years 9 months to 6 years 3 months) either with ($n = 25$, 11 females) or without ($n = 28$, 12 females) a familial risk of developmental dyslexia defined as having one or more first-degree relatives with dyslexia. This analysis revealed a significantly reduced cortical thickness in the left supramarginal gyrus and the left occipito-temporal cortex ($P < 0.05$, false discovery rate corrected) in children with a familial risk compared to non-risk children (Fig. 1), whereas the inverse contrast did not reveal any significant differences. The participants were tightly matched for their parents' education and profession and did not differ significantly ($P = 0.694$) with respect to this environmental factor most substantially contributing to the development of dyslexia (Peterson and Pennington, 2012). This supports the assumption that genetic factors but not parental education and profession are an important source of variance for explaining the observed cortical differences.

The anatomical confinement of these effects to temporo-parietal and occipito-temporal cortices is not only in line with the adult literature (Peterson and Pennington, 2012) but also supports all other comparably powered studies investigating brain structure and function in preliterate children at risk of dyslexia. Both regions were identified cross-sectionally with respect to familial risk in a functional MRI study on phonological processing at a pre-reading age (Raschle *et al.*, 2012). Additionally, the arcuate fasciculus as the long-distance white matter fibre tract connecting temporo-parietal cortical areas with temporal and frontal areas was not only shown cross-sectionally to be related to phonological awareness (Saygin *et al.*, 2013) but was also shown to predict reading outcome at third grade (Myers *et al.*, 2014).

In conclusion, the current literature and our own results obtained in larger samples suggest an endophenotypic developmental continuum of genetic risk factors affecting

temporo-parietal and occipito-temporal cortical maturation. This is assumed to be present in pre-reading children as well as in young and adult readers, which is in contrast to the results reported by Clark and colleagues. Given the relatively small sample size and longitudinal group variations in this study, it cannot be excluded that the absence of differences in several cortical areas, which form the later reading network, might be obscured by limited statistical power to detect such effects, whereas effects in other areas might be overestimated. Crucially, Clark and colleagues had only 57% power in their sample at MRI time point 1 to detect the clusters in the left supramarginal gyrus and the left occipito-temporal cortex identified in our analyses (effect size = 0.93; effect size in Clark *et al.* = 0.53; effect size is defined as the mean difference divided by common standard deviation). Despite the significant value of the longitudinal study by Clark and colleagues for the field, larger and statistically more powerful studies may be required to reveal ultimately which of the contrary hypotheses best approximates reality. This could comprise international collaborations to investigate larger samples collected from populations being comparable with respect to orthographic regularity and genetic background.

References

Clark KA, Helland T, Specht K, Narr KL, Manis FR, Toga AW, et al. Neuroanatomical precursors of dyslexia identified from pre-reading through to age 11. Brain 2014; 137: 3136–41.

Darki F, Peyrard-Janvid M, Matsson H, Kere J, Klingberg T. DCDC2 polymorphism is associated with left temporoparietal gray and white matter structures during development. J Neurosci 2014; 34: 14455–62.

Giraud AL, Ramus F. Neurogenetics and auditory processing in developmental dyslexia. Curr Opin Neurobiol 2013; 23: 37–42.

Myers CA, Vandermosten M, Farris EA, Hancock R, Gimenez P, Black JM, et al. White matter morphometric changes uniquely predict children's reading acquisition. Psychol Sci 2014; 25: 1870–83.

Peterson RL, Pennington BF. Developmental dyslexia. Lancet 2012; 379: 1997–2007.

Raschle NM, Zuk J, Gaab N. Functional characteristics of developmental dyslexia in left-hemispgeric posterior brains regions predate reading onset. Proc Nat Acad Sci USA 2012; 109: 2156–61.

Saygin ZM, Norton ES, Osher DE, Beach SD, Cyr AB, Ozernov-Palchik O, et al. Tracking the roots of reading ability: white matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. J Neurosci 2013; 33: 13251–8.

Scerri TS, Schulte-Körne G. Genetics of developmental dyslexia. Eur Child Adolesc Psychiatry 2010; 19: 179–97.