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Morphological differences in the lateral geniculate nucleus associated with dyslexia

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ABSTRACT

Developmental dyslexia is a common learning disability characterized by normal intelligence but difficulty in skills associated with reading, writing and spelling. One of the most prominent, albeit controversial, theories of dyslexia is the magnocellular theory, which suggests that malfunction of the magnocellular system in the brain is responsible for the behavioral deficits. We sought to test the basis of this theory by directly measuring the lateral geniculate nucleus (LGN), the only location in the brain where the magnocellular and parvocellular streams are spatially disjoint. Using high-resolution proton-density weighted MRI scans, we precisely measured the anatomical boundaries of the LGN in 13 subjects with dyslexia (five female) and 13 controls (three female), all 22–26 years old. The left LGN was significantly smaller in volume in subjects with dyslexia and also differed in shape; no differences were observed in the right LGN. The functional significance of this asymmetry is unknown, but these results are consistent with the magnocellular theory and support theories of dyslexia that involve differences in the early visual system.

1. Introduction

Developmental dyslexia is a specific learning disability of reading and spelling that cannot be attributed to low intellectual ability or inadequate schooling (Shaywitz, 1998). Prevalence estimates depend on whether the diagnostic thresholds are relative to age or IQ. However, approximately 7% of the population is identified as having dyslexia in both cases where IQ and age discrepancies are taken into account (Peterson and Pennington, 2012).

The cause of dyslexia is a subject of intense debate (e.g. Franceschini et al., 2012; Goswami, 2011; Stein, 2014; Vidyasagar and Pammer, 2010), and contradictory results may be found in the literature (e.g. Eden and Zeffiro, 1998; Gori et al., 2014a, 2014b; Olulade et al., 2013). Based initially on post-mortem measurements showing a reduction of 27% in the size of the magnocellular but not parvocellular cell bodies in the lateral geniculate nucleus (LGN) of a small (five) sample of subjects with dyslexia (Livingstone et al., 1991), a magnocellular theory (Stein, 2001; Stein and Walsh, 1997) that suggests that malfunction of the magnocellular system in the brain is responsible for the behavioral deficits in dyslexia.

The magnocellular stream in the human visual system is specialized to convey temporal information (Derrington and Lennie, 1984; Solomon et al., 2004). It begins in the parasol retinal ganglion cells, projects to the two inferior layers of the LGN, the primary visual nucleus in the thalamus, and thereafter intermingles with the other streams to varying degrees throughout the cortex (Merigan and Maunsell, 1993). The LGN is therefore the only location in the brain where the magnocellular stream is spatially isolated, permitting a unique structural test here. It is also difficult to isolate the magnocellular pathway using particular visual stimuli (e.g. Skottun, 2001a; Skottun, 2001b, 2004; Skottun and Skoyles, 2007; Skottun and Skoyles, 2006a,b). Although Livingstone et al. (1991) examined the LGN in a small sample of post-mortem brains, their findings have never been replicated nor measured *in vivo*.

Dyslexia has been associated with deficits in behaviors associated with the magnocellular stream, such as motion discrimination (Demb et al., 1998a; Solan et al., 2003; Wilmer et al., 2004), contrast sensitivity for stimuli with higher temporal and lower spatial frequencies (Lovegrove et al., 1982; Martin and Lovegrove, 1984, 1987; Mason et al., 1993), temporal processing (Eden et al., 1995; Laycock and Crewther, 2008; Lovegrove et al., 1980), and visuospatial attention (Facoetti et al., 2000; Franceschini et al., 2012; Franceschini et al., 2013; Gabrieli and Norton, 2012; Ruffino et al., 2014; Steinman et al., 1998; Vidyasagar, 2004; Vidyasagar and Pammer, 1999, 2010).

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Although there is a consensus in the existence of a connection between deficiencies in the magnocellular system and dyslexia, there is still disagreement on the causal relationship (e.g. Gori et al., 2014a; Olulade et al., 2013).

Since the magnocellular theory originated from findings of a reduction in the size of neurons in the magnocellular layers of the LGN in a small group of post-mortem dyslexia brains, we sought to test the generality of this finding *in vivo* in a larger sample. We compared the volume and morphology of the LGN in subjects with dyslexia to a set of IQ-matched controls.

2. Materials and methods

2.1. Subjects

This study included 13 subjects (five female) with dyslexia and 13 IQ-matched controls (three female), all 22–26 years old. None had other neurological disorders, their native language was English and all were right-handed. The subjects with dyslexia were recruited from the university Learning Center, where they had been registered as having reading disorders on the basis of professional assessments. All subjects provided informed written consent, and the University of Missouri ethics committee approved the research protocol.

2.2. Behavioral measures

In all subjects we measured the Full Scale (4) IQ, Performance IQ, Verbal IQ and Digit Span (scaled) from the Wechsler Adult Intelligence Scale (WAIS-III) test (Wechsler, 1997); Word Attack, Letter-Word Identification, Spelling and the composite Basic Reading Skills (percentile) from the Woodcock–Johnson Tests of Achievement (Woodcock et al., 2001); and Phonological Awareness, Rapid Naming (digits and letters) and Alternate Rapid Naming (colors and objects) from the Comprehensive Test of Phonological Processing (CTOPP) (Wagner et al., 1999). We report all measures as standardized scores obtained from the norm-referenced instruments. For each test score, we performed a two-tailed *t*-test between subjects with dyslexia and controls.

2.3. Imaging parameters

For each subject, 40 proton density (PD) weighted turbo spin echo images [acquisition time 83 s, $0.75 \times 0.75 \times 1$ mm^3 resolution, 48 coronal slices, TR = 2970 ms, TE = 22 ms, flip angle = 120° and a 2× parallel imaging acceleration factor (GRAPPA)] were acquired with a Siemens (Erlangen, Germany) Trio 3 T MRI scanner at the Brain Imaging Center at the University of Missouri. These images were registered using an affine transformation (Jenkinson et al., 2002) to correct for displacement between acquisitions, upsampled to twice the resolution in each dimension, and averaged to create a mean image with high signal-to-noise that clearly revealed the anatomical boundaries of the LGN. A high-resolution T_1-weighted scan was also obtained for each subject (MPRAGE, isotropic 1 mm^3 resolution), and white and gray matter were segmented (Zhang et al., 2001) and summed to calculate total brain volume.

2.4. LGN volume measurements

The anatomical extent of each LGN was traced manually on the mean PD images by six independent raters blind to group membership. A mask was created for each LGN in every subject by calculating the median of the six individual binary masks (Fig. 1). The volume of each LGN was calculated from these median masks, with any values of 0.5 in the median mask adding one half voxel to the volume. We conducted a repeated measures analysis of covariance (ANCOVA) to compare the volume of the LGN between the dyslexia and control groups, with the volume of the left and right LGN as the repeated factor, group membership as a between-subjects factor, and gender, total brain volume and age as covariates. Since there were no significant effects or interactions for age or gender, these variables were excluded from subsequent analyses. The height, width, depth, and lateral distances from the midline were similarly examined. All measures passed Levene's test of equality of error variances. Statistics were calculated using SPSS 20 for Mac (IBM, Inc.).

2.5. LGN morphology

To test whether any differences in LGN volume could be determined to be specific to one region of the LGN, as would be expected by the magnocellular hypothesis, we conduced detailed morphological analyses of the LGN comparing the two groups, using two different methods. First, we aligned all of the LGN by their centers of mass, to compare the LGN shape in the native space of each subject. We rigidly (no scaling) oriented the PD images in native space to the AC–PC line and inter-hemispheric plane, preserving the original dimensions of the native brain. This transformation was applied to the median LGN masks, which were then registered by their centers of mass and averaged to create a probability map for each group in native space. To compare these probability distributions, in each hemisphere, the set of individual LGN masks for each subject were compared voxel-wise with permutation-based non-parametric testing, correcting for multiple comparisons using threshold-free cluster enhancement (Smith and Nichols, 2009).

Second, to test for differences in location of the LGN relative to standard coordinates, we computed a probabilistic atlas of LGN location. The PD images were transformed into a standard space (MNI) via a nonlinear transformation (Avants et al., 2008). The output transformations were then applied to the median LGN masks. The transformed median LGN masks were averaged to calculate the probability in standard space of each voxel belonging to the LGN. To insure that the nonlinear transformation did not alter the volume of the LGN differently between groups, we performed a three-way ANOVA with hemisphere and volume before and after the transformation as within-subject repeated measures, and group membership as a between subjects factor. The total brain volume was not significantly correlated with either the left or right LGN volume before or after the transformation and was therefore excluded from the analysis. Both left and right LGN volumes significantly increased during the transformation, as did total brain volume, but there was no significant interaction with hemisphere ($F_{1,24} = 0.001$, $p = .98$) or group ($F_{1,24} = 0.82$, $p = .38$).

3. Results

3.1. Behavioral measures

The behavioral assessments used to verify the subject classifications are summarized in Table 1. As the two groups were matched on the measures of age and IQ, there were no significant group differences for these measures. As expected, there were significant differences between the groups on skills related to reading.

3.2. LGN volume

The main effect of group (dyslexia vs. controls) on the LGN volume was marginally significant ($F_{1,24} = 3.13$, $p = .089$). A Tukey post-hoc test revealed that the volume of the left LGN was significantly smaller in subjects with dyslexia, 98.9 ± 8.0 mm^3, than controls, 120.7 ± 6.2 mm^3 ($F_{1,23} = 6.12$, $p = .02$). The volume of the right LGN followed the same trend, 103.8 ± 7.0 mm^3 vs. 112.3 ± 7.0 mm^3, but the difference was only marginally significant ($F_{1,23} = 2.89$, $p = .10$). As can be seen in Fig. 2, the statistical difference between the two groups is weakened by two LGN outliers (>2σ), one in each hemisphere but belonging to different subjects in the dyslexia group. Our volume measurements of