ABSTRACT The relationship between brain activity and reading performance was examined to test the hypothesis that dyslexia involves a deficit in a specific visual pathway known as the magnocellular (M) pathway. Functional magnetic resonance imaging was used to measure brain activity in dyslexic and control subjects in conditions designed to preferentially stimulate the M pathway. Dyslexics showed reduced activity compared with controls both in the primary visual cortex and in a secondary cortical visual area (MT+) that is believed to receive a strong M pathway input. Most importantly, significant correlations were found between individual differences in reading rate and brain activity. These results support the hypothesis for an M pathway abnormality in dyslexia and imply a strong relationship between the integrity of the M pathway and reading ability.

Developmental dyslexia can be defined as an unexpectedly low reading ability given an individual's intelligence quotient that cannot be explained by other factors such as motivation, learning opportunity, sensory acuity, or brain injury. Estimates of dyslexia's prevalence range from 3 to 9% (1, 2). The etiology of dyslexia as well as specific sensory deficits in dyslexia remain controversial.

A particularly controversial issue is whether dyslexia involves a visual deficit. One subdivision of the visual system, known as the magnocellular (M) pathway, begins at the level of the ganglion cells in the retina, projects through the M layers of the lateral geniculate nucleus, and terminates in the primary visual cortex (V1) (3, 4). There are several lines of evidence for an M pathway deficit in dyslexia, including abnormally small cells in the M layers of the LGN (5), impaired perceptual performance (6–11), and reduced electrophysiological responses (5, 12–14) to stimuli processed mainly by the M pathway. Furthermore, a recent functional MRI (fMRI) study (15) reported that dyslexics showed essentially no significant activity in a cortical visual area (MT+) that consists of area MT along with adjacent motion sensitive areas) that is believed to receive a strong M pathway input. Several perceptual and electrophysiological studies have, however, failed to find evidence for an M pathway deficit (16–20).

Our study was designed to test two predictions of the M deficit hypothesis. First, the degree of the M pathway deficit should be strongly correlated with the severity of reading difficulty. Second, it should be possible to demonstrate physiological differences at least as early as V1.

MATERIALS AND METHODS

Blood oxygenation level-dependent fMRI (21–23; for review, see ref. 24) was used to measure brain activity in five dyslexic and five control subjects. Each subject participated in several scanning sessions: one to obtain a standard, high resolution, anatomical scan, one to define the early visual areas including V1, and at least three more sessions to measure fMRI response amplitude as a function of stimulus contrast (contrast is defined as the maximum minus the minimum intensity in the image divided by twice the mean).

fMRI response vs. contrast functions was measured using two sets of stimuli: (i) Test stimuli were designed to emphasize the M pathway inputs to cortex, and (ii) control stimuli were designed to stimulate multiple pathways. Lowering the mean luminance of a visual stimulus increases the responsiveness of the M pathway relative to other visual pathways, especially at low mesopic and scotopic luminances (25). Test stimuli, therefore, had low mean luminance (2 cd/m²), and control stimuli had high mean luminance (36 cd/m²). Visual stimuli were displayed on a screen, made of rear-projection material, and positioned at the opening of the bore of the MR scanner near the subject’s knees. The subjects, lying on their backs, looked directly up into an angled mirror to see the rear-projection screen. The display subtended 14 × 14° of visual angle. A bite bar was used to stabilize the subject’s head, and a small high contrast square in the center of the stimulus served as a fixation mark to minimize effects of eye movements. Control stimuli were 0.4 cycle/° contrast-reversing (8.3 Hz) sinusoidal gratings with high mean luminance (36 cd/m²) at several contrasts. Test stimuli were 0.4 cycle/° sinusoidal gratings that moved (20.75°/s) with low mean luminance (2 cd/m²) at several contrasts. The orientation and direction of motion of the test stimuli changed every 500 ms to minimize orientation- and direction-selective visual adaptation. The two halves of the test stimuli on either side of the fixation point moved in opposite directions (away from or toward the fixation point) to help minimize eye movements.

Responses to each test/control stimulus contrast were measured in separate scans that each lasted 254 s. The first 36 s of data were discarded to minimize effects of magnetic saturation and visual adaptation. During the remaining 216 s of each scan, a visual stimulus alternated six times (once every 36 s) with a uniform gray field of equal mean luminance. A sequence of 72 functional images (1 every 3 s) was recorded for each slice and for each stimulus condition.

For a given fMRI voxel, the image intensity changes over time and comprises a time series of data. This time series is periodic with a period equal to the 36-s stimulus temporal period. We quantify the fMRI response by: (i) removing any linear trend in the time series, (ii) dividing each voxel’s time series by the voxel’s mean intensity, (iii) averaging the time series over a set of voxels corresponding to a particular brain region, either V1 or MT+ (defined as described below), and then (iv) calculating the amplitude and phase of the (36-s

Abbreviations: fMRI, functional MRI; M, magnocellular; MT+, motion-sensitive area in lateral human occipital lobe; V1, primary visual cortex.

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bars represent plus to preferentially stimulate the M pathway, but responses were well matched in control conditions designed to stimulate multiple pathways. Error bars represent estimates of the noise in the fMRI functions. Error bars represent plus/minus 1 SEM across subjects in each group.

The data were analyzed separately in two brain regions corresponding to visual cortical areas V1 and MT+ (however, the slice selection did not include MT+ in the control conditions, so those data were analyzed only in V1). Area V1 was defined in each subject’s brain using standard techniques that locate reversals in the retinotopic map of visual cortex (28–32). Specifically, we adopted the methods exactly as described by Engel et al. (32). Area MT+ was defined, following previous studies (33–36), by measuring fMRI responses to stimuli that alternated in time between moving (10°/s, radially inward and outward) and stationary dot patterns (white dots on a black background). Specifically, area MT+ was selected as a contiguous group of voxels lateral to the parieto-occipital sulcus and beyond the retinotopically organized visual areas, which surrounded a cluster of voxels with a time series that correlated (r > 0.35, with a 0 to 9-s time lag) with the temporal alternation (moving vs. stationary) of the stimulus. These procedures to define the distinct brain areas were performed only once per subject.

To improve signal-to-noise in the response vs. contrast measurements, the least responsive voxels (e.g., voxels that contained a high proportion of white matter) were removed from the V1 and MT+ regions, based on responses to a reference stimulus. Reference scans were run at the beginning of each scanning session. The reference stimulus for V1 was a contrast-reversing 8.3-Hz 1 cycle/° checkerboard that alternated with a mid-gray field of equal mean luminance (36 cd/m²). The reference stimulus for MT+ was the moving dot condition described above. For both regions, voxels with correlations above a liberal threshold (r > 0.23, with 0- to 9-s time lag) were included in further analyses.

The reference stimulus also was used to determine the sign of the responses. Responses within ±90° of the reference phase were considered positive; otherwise, they were negative. Note that in this way the expected value for a scan with no visual stimulus would be 0.

fMRI was performed on a standard clinical GE 1.5 T Signa scanner with a custom designed head coil (low mean luminance test conditions and moving dots condition) or a 5-in diameter surface coil (high mean luminance control conditions and further vector-averaged across subjects. The error bars for the individual subject analysis in Fig. 1 were determined by fitting an exponential function to the nonharmonic frequency components of each average time series to estimate the noise amplitude at the 6 cycles/scan signal frequency. The error bars for the group analysis in Fig. 2 represent plus/minus 1 SEM across subjects in each group.

Reddish voxels show regions with greater activity to moving vs. stationary dots in a control subject and a dyslexic subject, respectively. MT+ (indicated by the white arrows) was defined to include active voxels outside the retinotopically organized visual areas. MT+ extended across three slices in both subjects, but only one slice is shown. Slices were parallel to and slightly ventral to the calcarine sulcus. (C) Individual differences in MT+ activity are strongly correlated with individual differences in reading rate (r = 0.80, P < 0.005, one-tailed). The solid line is a regression line through the data. MT+ responses are the fitted values at 30% stimulus contrast. Reading rates are reported as percentile scores. The dyslexic subject with a high reading rate scored quite poorly on other reading measures including the reading comprehension score of the Nelson–Denny reading test.

Responses in the dyslexic subject were lower for the dyslexic subject (D) compared with the control subject (C). Continuous curves are fitted power functions. Error bars represent estimates of the noise in the fMRI responses. (E) Individual differences in MT+ activity are strongly correlated with individual differences in reading rate (r = 0.80, P < 0.005, one-tailed). The solid line is a regression line through the data. MT+ responses are the fitted values at 30% stimulus contrast. Reading rates are reported as percentile scores. The dyslexic subject with a high reading rate scored quite poorly on other reading measures including the reading comprehension score of the Nelson–Denny reading test.
retinotopy measurements). We used a T2*-sensitive gradient recalled echo pulse sequence with a spiral readout (26, 27). Parameters for the surface coil protocol were: 750 TR (repetition time), 40 TE (echo time), 70° FA (flip angle), four interleaves, inplane resolution = 0.94 × 0.94 mm, and slice thickness = 4 mm. Parameters for the head coil protocol were: 1500 TR, 40 TE, 90° FA, two interleaves, inplane resolution = 1.02 × 1.02 mm, and slice thickness = 4 mm. In all experiments, eight adjacent planes of fMRI data were collected either perpendicular to the calcarine sulcus and beginning at the occipital pole (surface coil experiments) or parallel to the calcarine sulcus with the lowest slice near the ventral surface of the occipital lobe (head coil experiments).

During each scanning session, structural images were acquired using a T1-weighted spin echo pulse sequence (500 TR, minimum TE, 90 FA) in the same slices and at the same resolution as the functional images. These inplane anatomical images were registered to a standard anatomical scan of each subject's brain so that all data (across multiple scanning sessions) from a given subject were aligned to a common three-dimensional coordinate grid.

Five dyslexic subjects (two females) were solicited from the Stanford Disabilities Resource Center (SDRC). All were students at Stanford University (mean age 22.2 years, SD = 2.9) and were assumed to be of above average intelligence. The subjects had a childhood history of dyslexia and were still experiencing reading difficulties in adulthood. All subjects were diagnosed with dyslexia in a neuropsychological evaluation administered by a clinical psychologist, as required by the SDRC. Subjects were tested by different clinical psychologists with slightly different test batteries, but all showed significant reading difficulty that warranted special treatment by the university (e.g., extra time on exams). Five control subjects (two females) were solicited from the Stanford University population (mean age 26.8 years, SD = 6.1). None of the control subjects had a history of reading difficulty. All subjects were right-handed, except one control subject who was left-handed. In addition, two of the dyslexic subjects (one female) were codiagnosed with attention deficit disorder. These subjects were taking Ritalin for attention deficit disorder but did not take it before the neuroimaging procedures. None of the other subjects was taking medication or had a neurological or psychiatric illness that would interfere with the study. Informed consent was obtained from all subjects.

The Nelson–Denny Reading Test (1960), a timed reading test (similar to that on the SAT or GRE exams), was used to measure reading rate and comprehension. Reading rate (words per minute) was determined by having subjects mark where they were in the text after the first minute of reading. A standardized percentile score was then derived from both the rate and comprehension measures. As expected from the SDRC classification, dyslexic subjects had significantly lower scores on both rate (control: mean = 63.4, SD = 13.8; dyslexic: mean = 17.2, SD = 15.3; P < 0.005, one-tailed t test) and comprehension (control: mean = 64.8, SD = 8.3; dyslexic: mean = 26, SD = 17.1; P < 0.005, one-tailed t test).

**RESULTS**

Area MT+ was defined in each subject's brain by measuring responses to moving vs. stationary dot patterns. As mentioned above, a recent fMRI study reported almost no significant MT+ activity in dyslexics (15). We, however, found that it was possible to localize area MT+ in each hemisphere of all subjects. Examples are shown for individual control and dyslexic subjects in Fig. 1A and B, respectively. The discrepancy might be due to differences in the stimuli (e.g., higher contrast) or to differences in the subject populations.

Although MT+ regions were found in all subjects, the individual response vs. contrast functions tended to be lower for dyslexic subjects compared with controls. Fig. 1C and D shows representative response vs. contrast functions for a control and dyslexic subject, respectively.

One of the two goals of this study was to determine if the weakened MT+ responses predict individual differences in reading performance. We used reading rate because that is a good indicator of reading difficulty in our sample of university students with a childhood history of dyslexia (37). Fig. 1E plots each subject's reading rate vs. their fitted MT+ response to a 30% stimulus contrast. There was a very strong correlation (r = 0.80, P < 0.005, one-tailed) between individual differences in MT+ activity and reading rate. Of course, the 30% stimulus contrast was chosen arbitrarily for the purposes of this figure; the correlation is significant (P < 0.01) for contrasts ranging from 4 to 90%.

The second goal of this study was to determine if dyslexics showed reduced activity in V1, consistent with the hypothesis that the deficit is precortical. The correlation between individual differences in brain activity and reading rate was weaker in V1 than in MT+. Even so, there was a range of contrasts (from 30 to 100%) for which the correlation was significant at the P < 0.05 level.

The lower correlations between V1 activity and reading rate may be due to imperfect isolation of the M pathway signal in V1. After reaching the cortex, signals from the M and other pathways intermingle, and most layers of V1 receive a mixed input. Area MT+, on the other hand, is believed to receive a dominant input from the M pathway (38, 39), and that may explain why we found stronger correlations in MT+ than in V1.

A group analysis also was performed to determine if there was a difference (on average) in brain activity between the two (dyslexic and control) groups. The data were averaged across subjects in each group, and then a bootstrapping statistical analysis was used (40) to test for group differences. The procedure consisted of two steps: (i) randomly sample a value from the Gaussian distribution defined by the group mean and SE corresponding to each contrast level; (ii) fit the resampled data with a power function, R = Acn, where R is fMRI response amplitude, c is contrast, and A and n are free parameters that characterize the amplitude and shape, respectively, of the curves. These two steps were repeated 1000 times to form a bivariate distribution of the 1000 pairs of parameter values for each group. A final P value was obtained by testing the null hypothesis that the means of these bivariate distributions did not differ. Given the aforementioned strong correlations with reading rate, it is not surprising that there was also a significant group difference in brain activity both in MT+ (Fig. 2A, P < 0.02) and in V1 (Fig. 2B, P < 0.02).

As a control experiment, V1 activity was recorded for conditions (high mean luminance contrast-reversing grating stimuli) designed to stimulate multiple pathways. Activity in V1 was very similar in the two groups for these control conditions (Fig. 2C, P > 0.10), consistent with previous reports of impaired perceptual sensitivity at low, but not high, mean luminances (7, 10). Hence, the reduced responses in dyslexics' brains can be attributed to a specific deficit in the M pathway, rather than a general difference in activation levels between the groups.

**DISCUSSION**

Dyslexia may represent readers in the lower tail of a normal distribution of reading ability (41). Our subjects exhibited a wide range of individual differences in reading rate that were strongly correlated with MT+ brain activity. Hence, one can reasonably well predict reading rate from measurements of brain activity. Even disregarding any relevance to dyslexia per se, this is one of a few studies reporting strong correlations between individual differences in brain and behavior (42–47).
Our results are consistent with an M pathway deficit in dyslexia. This M pathway deficit may be only a marker for a more general deficit in fast temporal processing and have no direct causal relationship with reading difficulty (48). It is difficult, however, to imagine that an abnormality in such a significant visual pathway would fail to have consequences for complex visual behaviors, like reading.

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