Brief Communications

Strong Motion Deficits in Dyslexia Associated with *DCDC2* Gene Alteration

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Dyslexia is a specific impairment in reading that affects 1 in 10 people. Previous studies have failed to isolate a single cause of the disorder, but several candidate genes have been reported. We measured motion perception in two groups of dyslexics, with and without a deletion within the *DCDC2* gene, a risk gene for dyslexia. We found impairment for motion particularly strong at high spatial frequencies in the population carrying the deletion. The data suggest that deficits in motion processing occur in a specific genotype, rather than the entire dyslexia population, contributing to the large variability in impairment of motion thresholds in dyslexia reported in the literature.

Key words: ***DCDC2*; dyslexia; magnocellular; psychophysics; visual motion**

Introduction

Dyslexia is a specific developmental disorder characterized by severe difficulties in learning to read and spell, despite adequate schooling, normal visual acuity, and normal intelligence. Dyslexia has been reported in every culture studied, with prevalence ranging from 5 to 17%. Longitudinal studies have shown that the disorder is stable with age, and in contrast to popular opinion, does not disappear after adolescence, thus posing a lifelong socio-economical burden.

Current theories propose that dyslexia might originate from deficits in phonological processing, in visual attention, or in visual perception (Galaburda and Livingstone, 1993; Stein and Walsh, 1997; Vidyasagar and Pammer, 2010). Early evidence pointed to a selective deficit of the magnocellular-dorsal system, (Galaburda and Kemper, 1979; Galaburda et al., 1985; Livingstone et al., 1991) and consistently several aspects of motion processing are impaired in reading disabilities (Lovegrove et al., 1980; Cornelissen et al., 1995; Stein and Walsh, 1997; Demb et al., 1998; Slaghuis and Ryan, 1999, 2006). However, these motion perception deficits are on average small (0.1–0.3 log-U; Cornelissen et al., 1995, Stein and Walsh, 1997; Slaghuis and Ryan, 1999; Amitay et al., 2002; Ramus et al., 2003; Williams et al., 2003; Wilmer et al., 2004; Slaghuis and Ryan, 2006; Main et al., 2014) and there is considerable variability over the population (Hogben, 1996; Amitay et al., 2002; Ramus et al., 2003; Roach et al., 2004).

A wealth of prior information from familial aggregation and twin studies suggests a substantial inherited component, with heritability ranging from 0.4 to 0.8 (Schumacher et al., 2007; Carrion–Castillo et al., 2013). In particular, a deletion within intron 2 of the gene *DCDC2*, capable of modulating whole gene expression, has been considered a risk for genetic alteration in dyslexia (Meng et al., 2005; Harold et al., 2006; Brkanac et al., 2007; but see Ludwig et al., 2008; Wilcke et al., 2009; Meng et al., 2011; Powers et al., 2013). The *DCDC2* alteration (henceforth *DCDC2*d+) is present in ~10–17% of dyslexics, as opposed to 4% of normal readers (Meng et al., 2005; Wilcke et al., 2009), making it a condition affecting ~1–2% of the entire population.

Mice knockdown *in utero* has suggested that *DCDC2* might play a role in neuronal migration (Meng et al., 2005; Burbridge et al., 2008) reminiscent of human cyto-architectonic anomalies in dyslexics (Galaburda and Kemper, 1978, 1979; Galaburda et al., 1985), and the diffuse and specific white matter alterations of *DCDC2*d+ dyslexics (Darki et al., 2014; Marino et al., 2014).

More recent studies have shown that neuronal firing in *DCDC2* knock-out mice is highly noisy, with variable and sluggish delays and low temporal coherence (Che et al., 2014). These deficits could lead to severe visual consequences when the alterations affect the visual system: in particular for motion detection, which requires temporal precision.

Materials and Methods

Subjects. Subjects with dyslexia who have been genotyped for the deletion within the *DCDC2* gene by genetic association tests were recruited from an ongoing genetic study cohort (Marino et al., 2012). Inclusion criteria at the time of recruitment for the genetic study were as follows: (1) either

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Table 1. Summary neuropsychological and psychophysical scores of dyslexics groups

	*DCDC2*d+	*DCDC2*d−	Group difference
Summary group characteristics			
Age	17.7 ± 3.3	16.7 ± 1.3	0.40
Males/females	5/6	6/4	0.69
IQ	106.6 ± 15.7	93.8 ± 5.5	0.03
Word reading (Z-score)	−3.45 ± 3.0	−2.69 ± 2.0	0.52
Non-word reading speed (Z-score)	−4.45 ± 4.8	−2.95 ± 2.5	0.39
CBCL attention problem subscale	70 ± 12	67 ± 11	0.67
Motion direction sensitivity (log-U)			
Vertical motion 0.5 c/°	0.25 ($p = 0.027$)	0.05 ($p = 0.60$)	
Horizontal motion 0.5 c/°	0.4 ($p = 0.21$)	0.004 ($p > 0.9$)	
Vertical motion 4 c/°	1.4 ($p < 0.0001$)	0.6 ($p = 0.026$)	
Horizontal motion 4 c/°	1.5 ($p = 0.001$)	0.5 ($p = 0.06$)	
Motion sensitivity at 4 c/° (Z-scores)			
Vertical motion	−6.0 ± 3.1	−2.7 ± 2.9	0.02
Horizontal motion	−5.9 ± 4.3	−2.3 ± 3.5	0.03

Main neuropsychological indexes for the two groups and summary psychophysical performance expressed either as log-units sensitivity (with significance vs controls) or as Z-scores.

accuracy or speed Z-scores ≤−2.0 SD on timed text-reading tests, (2) either accuracy or speed Z-scores ≤−2.0 SD on timed reading of single unrelated words or pronounceable non-word lists (Cornoldi and Colpo, 1995, 1998; Sartori et al., 1995), (3) full-scale IQ ≥85 (Wechsler Intelligence Scale for Children, revised; Wechsler, 1981), and (4) absence of neurological or sensorial disorders. For summary scores see Table 1.

Control subjects were contacted by word of mouth among high school and university students of Vita-Salute San Raffaele (that has very selective admission standards), 16–21 years old (8 total, 4 females, age 19.7 ± 1.8). Normal readers with *DCDC2* deletion were recruited from a genetic study of emotional and behavioral problems in adolescents (Frigerio et al., 2006). Two (one female) participated in the present study (age 23.5 ± 2).

The protocol was approved by the Scientific Review Board and the Ethics Committee of the "Eugenio Medea" and "San Raffaele" Scientific Institutes. All subjects who participated in the study were right-handed, had normal or corrected-to-normal acuity, color vision (Ishihara Color Vision Test), and stereovision (Frisbee Stereotest). Only one subject lacked stereovision and had strabismus, and was tested monocularly. For this subject, we report the average sensitivity of the two eyes.

Motion direction sensitivity. We measured contrast sensitivity with one-interval two-alternative forced-choice motion discrimination paradigms. The stimuli were small drifting grating patches (spatial frequency 0.25–8 c/°; temporal frequency 8 Hz) windowed by a stationary Gaussian (2° SD, 150 ms duration, positioned at screen center), drifting either horizontally or vertically starting at random phase at each trial. The subject fixated a spot (0.1°) at the center of the display and reported the motion direction (left-right or up-down), completing at least two sessions of 40 trials each per each condition. The very short exposure ensured that subject made no visually driven eye movements. Stimulus contrast during the session was varied from trial to trial according to an adaptive QUEST algorithm (Watson and Pelli, 1983). The stimulus contrast that yielded 75% correct responses was taken as threshold. If the subject was not able to perform 75% correct for contrasts in the range 30–100%, a sensitivity value of 1 (maximum) was assigned (see inset of Fig. 1*A*,*C*). Because of time restrictions, in a few subject we could not test all the spatial frequency range, but for all we acquired sensitivities at 0.5 and 4 c/° for vertical or horizontal motion.

Stimuli were generated via a Cambridge ViSaGe graphics card and displayed on a calibrated CRT display running at 120 Hz with mean luminance of 30 cd/m^2. Subjects sat at 57 cm from screen up to 4 c/° and at 114 cm for 8 c/°.

Sensitivity for stationary gratings. Contrast sensitivity was measured for static gratings (2° SD, 0 Hz, 150 ms exposure) tilted at ±45° from vertical and presented at fixation. All other procedures were identical to the motion direction discrimination task except that the subject judged orientation.

Coherence motion thresholds. Sensitivity for motion coherence (inverse of the proportion of the points with coherent trajectory) was assessed for circular motion (clockwise or counterclockwise), radial motion (expanding or contracting), and translational motion (up-down and left-right). The stimuli comprised 100 small dots (each 35 arcmins), half black and half white, presented for 250 ms to subjects in a dimly lit room on a 21 inch Sony CRT monitor (50 cd/m^2), subtending 40 × 30° when viewed from viewing distance 60 cm. A proportion of dots drifted coherently at local speed of 10°/s (limited lifetime of 10 frames, framerate 75 Hz), whereas the remainder were displayed at random positions on each frame. Viewing was binocular. Sensitivity was defined as the motion coherence that produced 75% correct direction discrimination, obtained by fitting data (from 30 to 40 trials) with a cumulative Gaussian.

Motion energy in Fourier domain. We simulated the effect of coarse spatial sampling (10–13 samples/° with 4–16% of spatial jitter) on sinusoidal gratings of various spatial frequencies drifting at 8 Hz displayed transiently for 150 ms. We calculated the spatiotemporal spectra of the sampled waveforms and the average root mean square (RMS) energy in the rightward and leftward quadrants of the 2D spectra in the range between 0 and 10 c/°. The difference between RMS energy in the correct and aliased motion direction was taken as an estimate of motion-direction discrimination. Examples of patterns after sampling and filtering are displayed in Figure 3*a*. Sampling rate and spatial jitter were free to vary to best fit the individual subject contrast sensitivity.

Results

We measured motion perception in two groups of dyslexics, with (+) and without (−) deletion in *DCDC2*, but otherwise matched for age, IQ, and reading disabilities (Table 1). Figure 1 shows contrast sensitivities for motion direction discrimination for gratings drifting vertically (top) or horizontally (bottom) for a brief period of time (150 ms), over a wide range of spatial frequencies. Dyslexic carriers of intron 2 deletion (*DCDC2*d+; Fig. 1*a*,*c*) showed marked impairment in motion discrimination compared with normal readers (thin line with ±1SD interval in shaded gray area), with a dramatic drop of performance at spatial frequencies >2 c/°. In contrast, dyslexics without *DCDC2* deletion (Fig. 1*b*,*d*) showed only a mild impairment in motion discrimination.

To quantify this effect further we considered motion sensitivity at two spatial frequencies, 0.5 and 4 c/° (Fig. 1*e*,*f*; Table 1). At the lower spatial frequency, *DCDC2*d+ with dyslexia showed only mild impairment (Fig. 1*e*, red bars). However, at 4 c/° the deficit was large and highly significant (Fig. 1*f*, red bars). In contrast, dyslexics without deletion (*DCDC2*d−) showed much less impairment in sensitivity, which reached significance only at high spatial frequencies. Interestingly, two normal readers with deletion of *DCDC2* had sensitivities for motion in the typical range (white bars), although the sample size is too small to draw firm conclusions.

In control subjects, thresholds for vertical and horizontal motion are highly correlated. This also occurs in dyslexics without *DCDC2* deletion. In Figure 2*a*, the blue symbols show that sensitivity for vertical and horizontal motion is correlated at both low spatial (Pearson's $\rho = 0.735$, $p = 0.06$) and high spatial frequencies ($\rho = 0.88$, $p = 0.003$; Fig. 2*b*). However, *DCDC2*d+ dyslexics showed no significant correlation between sensitivities to horizontal and vertical motion, either at low or high spatial frequencies (red symbols; $\rho = 0.167$, $p = 0.69$ at 0.5 c/° and $\rho = 0.395$, $p = 0.33$ at 4 c/°). The anisotropy for motion direction in the percep-

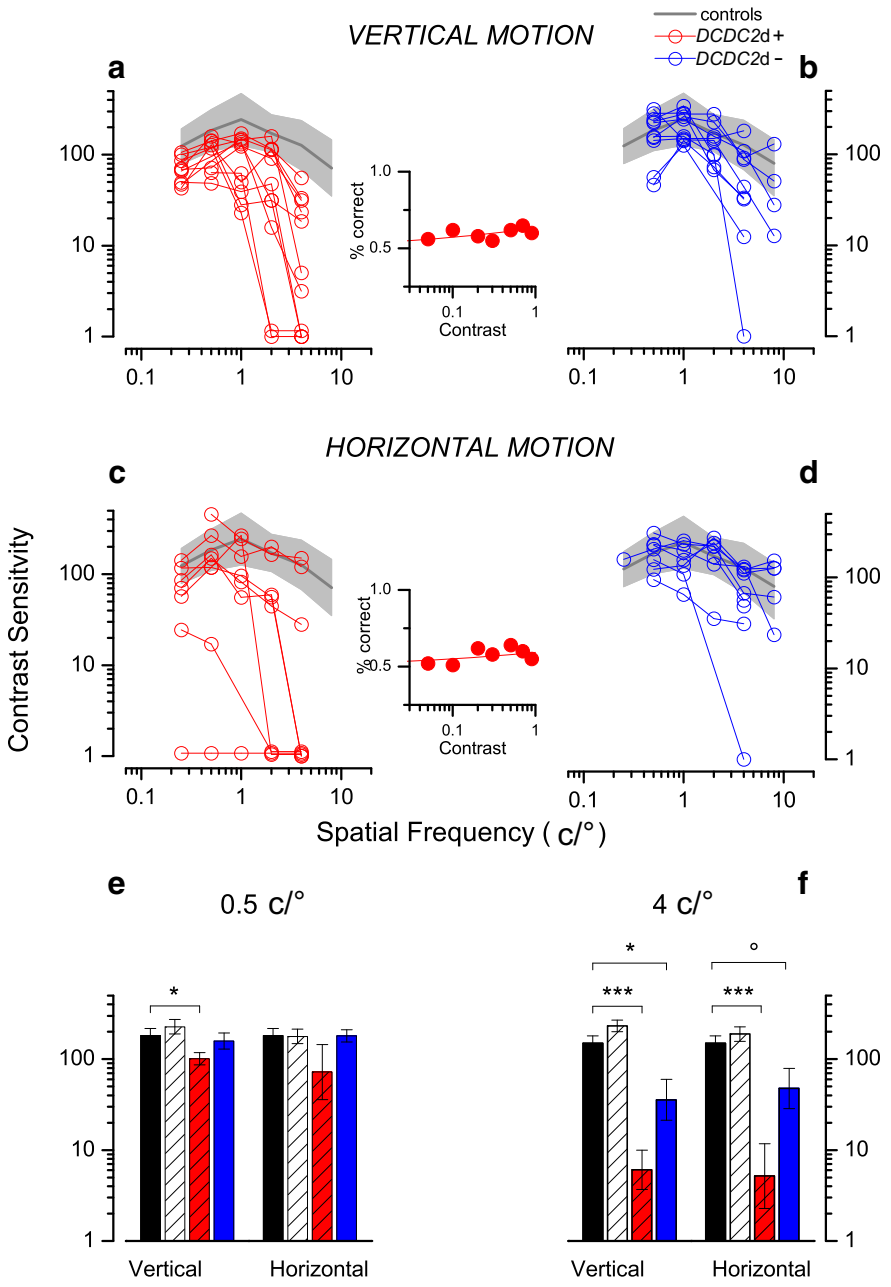

Figure 1. Motion Contrast Sensitivities for *DCDC2*d+ dyslexics. ***a–d***, Vertical (top row) and Horizontal motion (middle row) for dyslexics with a deletion within the *DCDC2* gene (***a***, ***c***) and dyslexics without the deletion (***b***, ***d***). Average sensitivities of normal readers are shown with a thin gray line along with a ± 1 SD band. The central inset shows the group *DCDC2*d+ performance for the stimuli for which a sensitivity of one was assigned. Each dot is the average at least of 15 trials. ***e***, ***f***, Average sensitivity at 0.5 and 4 c/° for four groups: normal readers (black), normal readers with *DCDC2* deletion (white), dyslexics with *DCDC2*d+ (red), and dyslexics without *DCDC2*d− (blue). Error bars are 1 SEM; °$p = 0.06$, *$p < 0.05$, ***$p < 0.001$).

tual deficit of *DCDC2*d+ points to an alteration at an early stage of visual analysis. To examine the impact of loss of visual sensitivity on perception of more complex stimuli, we measured motion coherence thresholds in a subset of seven *DCDC2*d+ dyslexics for various flow-motion patterns (Fig. 2*c*). They were required to discriminate expansion from contraction, or clockwise from counterclockwise rotation, or direction of translation, as a function of contamination by randomly moving dots. DCDCd+ dyslexics showed significant impairment of coherence thresholds (Vertical: $t_{(12)} = 2.94$ $p = 0.012$; Horizontal: $t_{(9)} = 0.89$ $p = 0.39$; Expansion: $t_{(12)} = 3.78$ $p = 0.0026$; Rotation: $t_{(12)} = 2.51$ $p = 0.027$), reaching significance except for horizontal motion. As expected from the deficit in contrast sensitivity, the effect is small given that low spatial frequencies provide much information about the direction of flow.

To verify that the loss of sensitivity was specific to motion, we measured contrast sensitivity of the *DCDC2*d+ dyslexics to static gratings, and found no impairment compared with normal readers (Fig. 2*d*). Furthermore, for almost all *DCDC2*d+ subjects, the best sensitivity for motion direction at 4 c/° was always worse than the sensitivity for static gratings (Fig. 2*e*, red circles; average difference 0.95 log-U, $t_{(8)} = 4.2$, $p = 0.003$), showing that subjects could detect the stimulus and perceive its orientation, but could not perceive its direction of motion. For control subjects the contrast sensitivities to motion and orientation were very similar (Fig. 2*e*, gray symbols; $t_{(7)} = 1.35$, $p > 0.2$).

That the deficit is particularly large at higher spatial frequencies and is anisotropic for motion direction suggests that it might be due to a lack of spatiotemporal information necessary for motion computation, possibly because of signal aliasing. Aliasing arises from under-sampling of the signal, either in the temporal or spatial domains. Given that temporal under-sampling would generate similar disruption at all spatial frequencies, we investigated the role of spatial under-sampling, which has been successful in explaining other motion perception anomalies (Morrone et al., 2008).

Figure 3*a* shows a simulation of spatial under-sampling of drifting gratings of low and high spatial frequency. Under-sampling has little effect at low spatial frequencies, but causes major disruptions at higher frequencies, with the introduction of aliased motion in the opposite direction. To quantify the effect, we measured the RMS energy in the two directions of motion up to a frequency of 10 c/° to simulate the function of contrast sensitivity that filters out the aliasing at very high frequencies. We computed the difference of motion energies for the correct and incorrect motion directions. This steadily decreased with spatial frequency for under-sampling between 10 and 13 samples/°. Figure 3*b* show examples of the fitted contrast sensitivity: in all cases it was possible to obtain a close match to *DCDC2*d+ dyslexic performance by changing the sampling or the noise jitter rate.

Note that the total energy of the sampled input is constant with spatial frequency up to 10 c/°, predicting a constant detection of the moving grating and hence a dissociation between discrimination and detection.

Discussion

Our results show a specific loss of visual motion discrimination in dyslexic carriers of a deletion in the *DCDC2* gene. The deficit is

robust at low spatial frequencies, but it is even more dramatic at high spatial frequencies, where many subjects have virtual motion blindness. Previous research, performed before the age of genotype screening, has found on average a mild deficit in contrast sensitivity tasks at high temporal frequencies (typically 0.1–0.3 log-U) in dyslexics, which has been linked to a vulnerability of the magnocellular-dorsal system (Lovegrove et al., 1980; Galaburda and Livingstone, 1993; Stein and Walsh, 1997; Ben-Shachar et al., 2007). However, the finding has been rather controversial, and often the deficit has been reported only in a subset of individuals (Lovegrove et al., 1980; Hogben, 1996; Stein and Walsh, 1997; Amitay et al., 2002; Roach et al., 2004), or particular motion tasks (Demb et al., 1998; Wilmer et al., 2004; Main et al., 2014).

The present study shows that a particular subset of dyslexics with altered genotype, (~5–17% of dyslexics) suffers a strong motion deficit. This could contribute to the large intersubject variability in motion discrimination in dyslexia reported in the literature (Lovegrove et al., 1980; Stein and Walsh, 1997; Roach et al., 2004; Ben-Shachar et al., 2007). It is also possible that the anatomical deficit of LGN magnocellular cells observed post-mortem (Galaburda et al., 1985) might be in carriers of *DCDC2* alteration. A certain degree of variability is present also within *DCDC2*d+ dyslexics. However, we tested only two directions and cannot exclude that *DCDC2*d+ dyslexics with less severe deficits would have failed for some other directions of motion that have not been tested, explaining some of the variability. In addition, we cannot be certain that the specific gene is not the only factor at play.

Interestingly, many previous studies have measured contrast sensitivity for motion discrimination at low spatial frequency where a small deficit is observed (~0.1–0.2 log-U) (Demb et al., 1998; Wilmer et al., 2004). The only exception is Slaghuis et al. (2006) who observed a greater deficit (~0.3 log-U) at 4 c/°, in agreement with the present data for the *DCDC2*d− subjects. Measuring the limiting spatial resolution of the motion detectors may be a more sensitive test for motion anomalies.

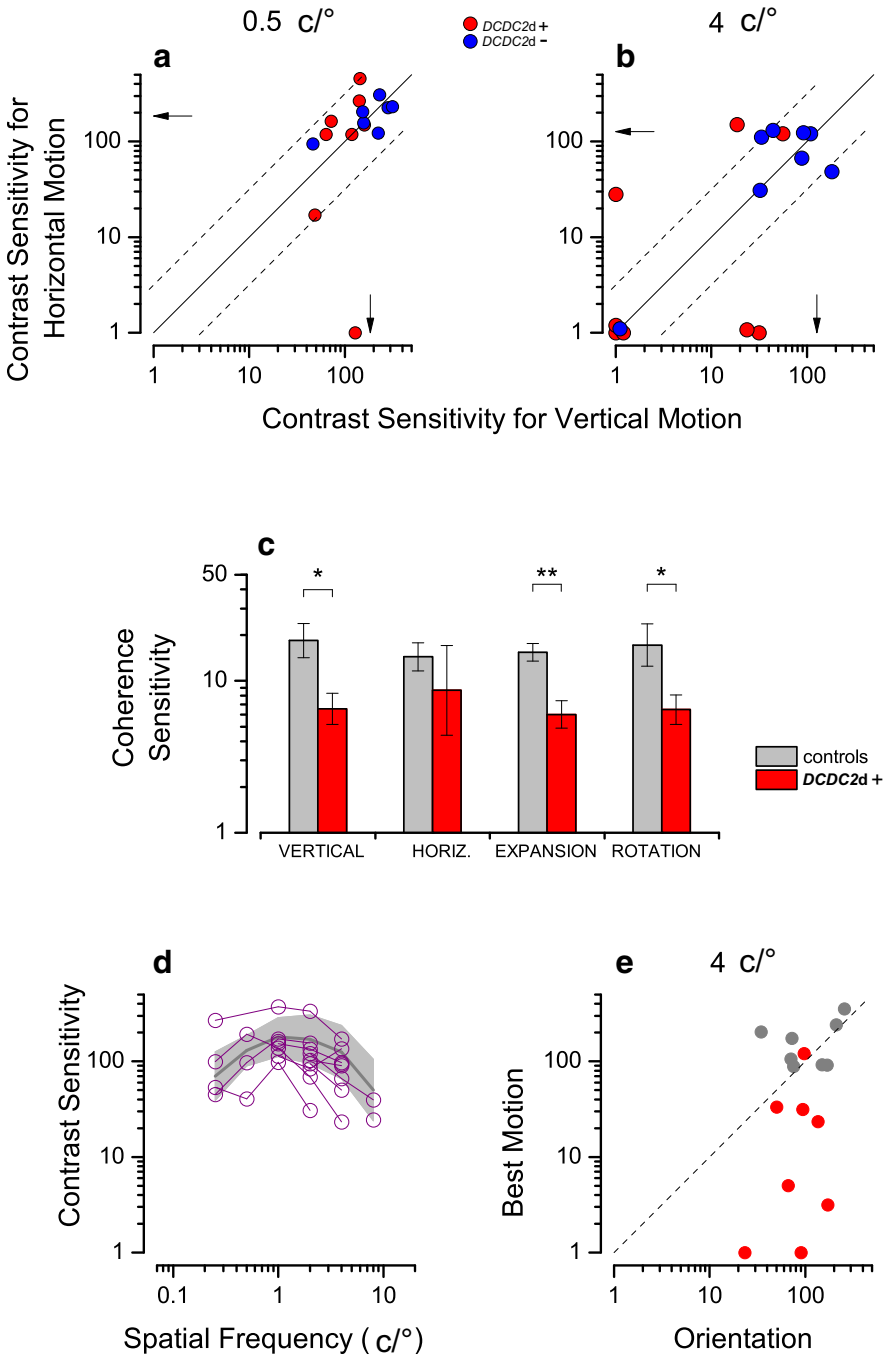

Figure 2. Contrast Sensitivity deficit anisotropy. Horizontal motion against vertical motion at 0.5 c/° (***a***) and 4 c/° (***b***). *DCDC2*d+ dyslexics in red, *DCDC2*d− dyslexics in blue, and averages of controls with arrows. Dashed lines indicate an anisotropy in motion sensitivity of 0.5 log-U. ***c***, Sensitivity to motion coherence for four motion patterns (*$p < 0.05$, **$p < 0.01$). ***d***, Contrast sensitivity for orientation discrimination of a static grating. Thin gray line along the ± 1 SD band is the average controls' sensitivity; purple indicates *DCDC2*d+ dyslexics. ***e***, Comparison of contrast sensitivity for the best estimate of motion sensitivity and orientation discrimination at 4 c/° for *DCDC2*d+ in red and control subjects in gray.

An increased deficit at high spatial frequency is not consistent with a homogeneous decrease of performance of magnocellular pathways, or more generally of the motion system, that it is well known to prefer low spatial frequencies (Burr et al., 1982). This necessarily calls in mechanisms that increase perturbation near the acuity limit of the motion detectors. Spatial under-sampling of the input to motion detectors induces high interference from aliased signals at high spatial frequency, simulating the observed deficit in the *DCDC2*d+ subjects. This could occur either because of paucity of number of LGN fibers projecting to the direction-selective neurons of V1, or from anomalies of the temporal code with erratic firing of some of the projecting neurons. In particular, an increase in the temporal noise of the neural discharge may cause local interference with transmission of visual information, with an effective loss of samples at specific positions. Interestingly, both anomalies have been observed in *DCDC2* knock-out mice (Meng et al., 2005; Che et al., 2014). Similar deficits might

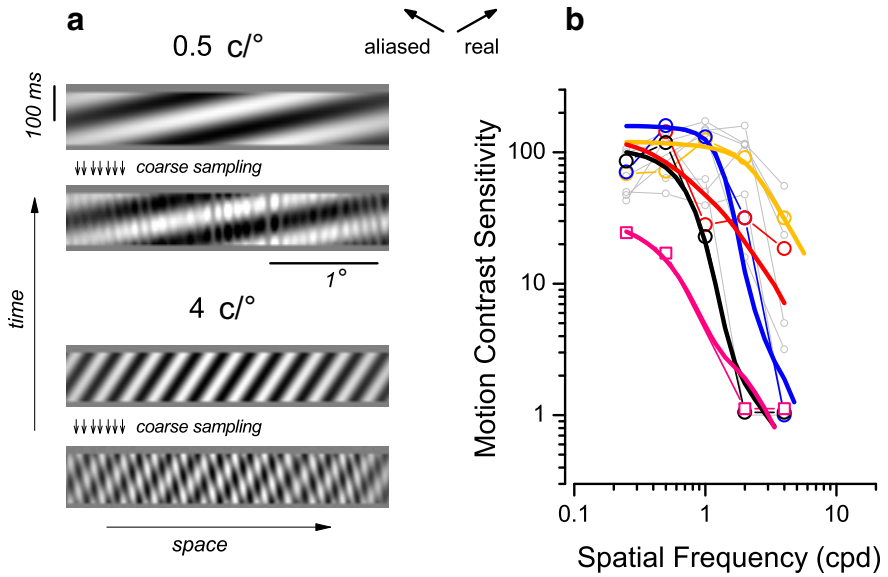

Figure 3. Under-sampling model. ***a***, Space–time diagram of 0.5 and 4 c/° drifting gratings (top) and sampled at coarse frequency (bottom), after low-pass filtering. The arrows at top indicate real motion in the North–East direction and aliased motion in the North–West. The small arrows indicate some sample positions. ***b***, Continuous curves: the difference between energy for the two motion directions as a function of spatial frequency of the grating. Model sampling parameters are as follows: 12.5 ± 2 (yellow curve), 11 ± 0.7 (blue), 10 ± 1.2 (red), 10.5 ± 0.6 (black), and 10 ± 1.4 (pink) samples/deg. The data are example subjects taken from Figure 1*a* (circles) or *c* (squares). The gray symbols plot the data of remaining subjects.

also occur between V1 and higher motion areas. However, contrast sensitivity for motion direction is a property that it is limited at V1 level in human. Our data reveal a severe motion deficit in humans with a similar genetic alteration of mouse models, and this might well underlie many reading disabilities.

It is currently debated whether motion deficits reported in dyslexics might result from a lower exposure to reading (Olulade et al., 2013). However, it is unlikely that this alone could explain the strong visual impairment of *DCDC2*d+ observed here: dyslexics without *DCDC2* deletion were matched for reading performance and many other cognitive indices, yet displayed only minor impairments in motion perception. Interestingly our group of *DCDC2*d− dyslexics had a lower IQ and yet performed better than the *DCDC2*d+ dyslexics. The sensory origin of the strong visual deficit reported here is consistent with recent data showing an impairment in visually evoked potentials in children of dyslexic parents (who carry a high chance of developing dyslexia) even before school age (Kevan and Pammer, 2008).

Our results suggest that *DCDC2*-deleted without the dyslexic phenotype may develop normal motion sensitivity. Although the sample is too small to draw firm conclusions, it is worth noting that normal readers with *DCDC2* deletion have a specific pattern of alterations in neuronal architecture, measured by DTI/FA, distinct from that of *DCDC2*d+ dyslexics (Marino et al., 2014). Anatomical anomalies in these subjects may mark some subthreshold developmental vulnerability to cognitive deficits that further specific studies need to address.

Together our data show high vulnerability of motion pathways in a subpopulation of dyslexic patients with a *DCDC2* genetic alteration, possibly associated with anomalies in the early visual motion pathways. Our data also stress the importance in the characterization of subpopulation of dyslexia to design target neurorehabilitative strategies of intervention and treatment specific for the sensory system.

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