The Brain Structural Hub of Interhemispheric Information Integration for Visual Motion Perception

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We investigated the key anatomical structures mediating interhemispheric integration during the perception of apparent motion across the retinal midline. Previous studies of commissurotomized patients suggest that subcortical structures mediate interhemispheric transmission but the specific regions involved remain unclear. Here, we exploit interindividual variations in the propensity of normal subjects to perceive horizontal motion, in relation to vertical motion. We characterize these differences psychophysically using a Dynamic Dot Quartet (an ambiguous stimulus that induces illusory motion). We then tested for correlations between a tendency to perceive horizontal motion and fractional anisotropy (FA) (from structural diffusion tensor imaging), over subjects. FA is an indirect measure of the orientation and integrity of white matter tracts. Subjects who found it easy to perceive horizontal motion showed significantly higher FA values in the pulvinar. Furthermore, fiber tracking from an independently identified (subject-specific) visual motion area converged on the pulvinar nucleus. These results suggest that the pulvinar is an anatomical hub and may play a central role in interhemispheric integration.

Keywords: diffusion tensor imaging, Dynamical Dot Quartet, individual difference, interhemispheric integration, pulvinar

Introduction

Integration of information from the left and right sides of the body and its surroundings involves interhemispheric interactions in the brain (Gazzaniga 2000; Kandel et al. 2000). Investigating the key anatomical structures underlying interhemispheric information transmission during specific cognitive tasks is important for understanding how both hemispheres contribute to information processing. In the present study, we investigate a hub for interhemispheric interaction for the apparent motion perception across the retinal midline. Previous studies have suggested that apparent motion perception across the retinal midline is processed by the bilateral human middle temporal (hMT)/V5+ regions (Muckli et al. 2002; Sterzer et al. 2003) and recently observed the neural correlates of electroencephalography (EEG) gamma-band synchrony with the interhemispheric interaction (Rose and Buchel 2005).

A critical hub for interhemispheric exchange between these regions has not, however, been definitively described. The corpus callosum (CC) is widely perceived to be the most plausible anatomical candidate mediating interhemispheric transmission between hMT/V5+ regions (Maunsell and van Essen 1983; Gazzaniga 1987). Ramachandran et al. (1986) reported, however, that commissurotomized patients can perceive apparent motion when they are shown a stimuli consisting of 2 dots presented in succession on opposite sides of the retinal midline. This finding was confirmed by Naikar and Corballis (1996) in a detailed psychophysical experiment with commissurotomized patients. Their results revealed that the perceptual integration of apparent motion is mediated by a subcortical brain node not by the CC (Naikar and Corballis 1996). In addition, they suggested that the subcortical brain node might be superior colliculi (SC) or pulvinar nucleus (PN). The key subcortical structure underlying this brain node remains unknown after many decades.

This report proposes several approaches to determine the brain region. Here, healthy participants are used because the locus of injury is generally different among individual brain-injured patients and because the periphery of the locus can compensate cognitive functions of the injured brain region even in adult brains (Kaas et al. 1990; Ramachandran 1993). Moreover, the recovery of cognitive function significantly depends on the rehabilitation of the individual (Taub et al. 1993; Dromerick et al. 2000).

We used Dynamic Dot Quartet (DDQ), which is one of ambiguous stimuli. Viewing DDQ typically induces either vertical or horizontal apparent motion. When a stimulus is presented around the center of visual field, horizontal motion across the retinal midline requires interhemispheric interaction (Ramachandran and Anstis 1983; Rose and Buchel 2005). All the healthy participants were able to perceive apparent horizontal motion. The amount of time during which horizontal motion was perceived in the experiment, however, differed among individuals (Chaudhuri and Glaser 1991). Therefore, we can use the ratio of time length of horizontal motion perception to that of vertical motion perception in evaluating the bias to horizontal motion perception for this ambiguous stimulus. This also quantifies the individual differences of the interhemispheric interaction. In using the ambiguous stimulus, physical properties such as brightness and positions of dots remain unchanged; therefore, we can extract neural signals relating to the contents of apparent motion perceptions.

In order to noninvasively investigate the brain structure of healthy participants, diffusion tensor imaging (DTI) was used. DTI measures random thermal motions of water molecules in brain tissue. The water molecules diffuse relatively freely along the neural fiber direction but are hindered in the fiber transverse direction (Tanner and Stejskal 1968). The hindrance of water diffusion in white matter is putatively due to the
diffusion barrier presented by the cell membrane and the myelin sheath (Le Bihan et al. 1993; Norris 2001; Beaulieu 2002). Therefore, DTI can quantify the neural structure in white matter (WM) indirectly. DTI created the opportunity for researchers to visualize connections of brain structure in detail (Le Bihan et al. 1986; Turner et al. 1990; Conturo et al. 1996; Pierpaoli et al. 1996; Iwasawa et al. 1997; Makris et al. 1997; Mori et al. 1999; Virta et al. 1999; Werring et al. 1999; Basser et al. 2000; Clark et al. 2000; Mori and van Zijl 2002; Hagemann et al. 2003; Wakana et al. 2004, 2005). From the DTI, we calculated the fractional anisotropy (FA) value. The FA value quantifies the coherence of the orientations of WM tracts in the living brain (Basser et al. 1994). Therefore, the FA value evaluates the coherence of neural fibers on WM tracts indirectly (Le Bihan et al. 2001). High FA represents more organized tissues (anisotropic diffusion) and low FA indicates a lack of directional tissue (isotropic diffusion). In other words, the FA value evaluates the "microstructural integrity" of WM tissue (Klingberg et al. 2000; Pfefferbaum et al. 2002; Head et al. 2004). The microstructural integrity of WM tissue reflects the "integrity of information" or "information transmission efficiency" in cognitive tasks, and DTI has provided information about structural variations in specific brain regions associated with particular behavioral traits, for example, reaction time of a button press (Tuch et al. 2005; Gold et al. 2007; Floel et al. 2009).

The aim of the current study was to identify a structural hub involved in the perception of apparent motion across the retinal midline. For this purpose, we evaluated the correlation between individual differences of the FA values of WM clusters and individual differences of one "bias to horizontal motion perception." The bias to horizontal motion perception was quantified by using the time length of perceiving horizontal motion, relative to vertical motion.

Materials and Methods

Participants and Experiment Design

Eleven healthy right-handed volunteers (aged from 20 to 29; 3 females) were recruited for the experiment. The experiment was performed twice on 2 different days separated by an interval of approximately 3 weeks.

On the first day, they performed the psychophysical experiment in a magnetic resonance imaging (MRI) room. We recorded functional magnetic resonance imaging (fMRI), while they are performing the psychophysical task. After the experiment, we recorded DTI too. On the second day, the psychophysical experiment was repeated to test the stability of psychophysical characteristics. All procedures were approved by the AIST MRI Safety and Ethics committee, and informed consent was obtained from all participants before the experiment was conducted.

Stimulus

In the DDQ paradigm, a pair of dots is presented alternately in the upper left and lower right or the lower left and upper right corners of the visual field. At the center of them, a white fixation cross was set at 10.0° wide and 2.0° high. The center of the visual field was displayed in the center of the visual field. At the start of the psychophysical experiment, a fixation cross (2 perpendicular lines, each 4.0° long and 0.2° wide) was displayed in the center of the screen (30 s), followed by pairs of DDQ (luminance: 60 cd/m², diameter: 3.0°) at diagonally opposite corners of a rectangle around the center of the screen in alternating sequences. The duration of a single animation frame was 250 ms. These frames were shown repeatedly in alteration through each session.

Participants were asked to respond according to whether the motion was horizontal or vertical, by identifying the upper-side dots with right-hand dots or by identifying the lower-side dots with left-hand dots. (b) Ten courses of stimuli for all experiments. On the first day, we requested participants to perform a psychophysical task and recorded their fMRI data. After this psychophysical task, we recorded their DTI data. On the second experiment, we recorded only the psychophysical data of the same participants. The interval time between 2 days was 2-3 weeks. The sequence of stimulus presentation for 1 day during the whole experiment is enlarged on the second arrow. The psychophysical experiment for 1 day involves 8 sessions. Each session is also enlarged on the third arrow. During the first minute of each session, the visual stimulus is stationary, and the next 15 min, the stimulus flashes alternately between 2 different pairs of dots (upper right and lower left or upper right and lower left).

Psychophysical Experiment

Psychophysical experiment was repeated on 2 different days, separated by a gap of several weeks (Fig. 1b). This is because we needed to confirm the stability of ratios within individuals (Fig. 2c). On the first day, we recorded fMRI when participants performed psychophysical task, and on the second day, same participants performed psychophysical experiment in a darkroom without recording fMRI. The design of psychophysical experiment is, however, totally same between these 2 days.

Figure 1. Schematic of DDQ paradigm. (a) The DDQ stimuli consist of alternately presented pairs of dots at one position (the upper left and lower right of the visual field) and an alternative position (at the lower left and upper right of it). Participants recognized horizontal motion or vertical motion by identifying the upper side dots with the lower side dots or by identifying the right-hand dots with left-hand dots. (b) Time courses of stimuli for all experiments. On the first day, we requested participants to perform a psychophysical task and recorded their fMRI data. After this psychophysical task, we recorded their DTI data. On the second experiment, we recorded only the psychophysical data of the same participants. The interval time between 2 days was 2-3 weeks. The sequence of stimulus presentation for 1 day during the whole experiment is enlarged on the second arrow. The psychophysical experiment for 1 day involves 8 sessions. Each session is also enlarged on the third arrow. During the first minute of each session, the visual stimulus is stationary, and the next 15 min, the stimulus flashes alternately between 2 different pairs of dots (upper right and lower left or upper right and lower left).
We used the FMRIB Software Library of FSL (http://www.fmrib.ox.ac.uk/fsl) for analyzing DTI for each subject as follows. Images were preprocessed to correct for eddy current and head motion. Their diffusion tensors were fitted independently to each voxel in the corrected image, then used to calculate FA maps (Basser et al. 1994; Jenkinson and Smith 2001). T1-weighted images were spatially normalized to the Montreal Neurological Institute (MNI) template brain. The resulting normalization parameters were subsequently applied to the DTI for reorienting the gradient directions accordingly. Normalized FA images were smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel using SPM (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8) software to increase statistical sensitivity to correlations equal to or larger than the kernel width.

To assess the dependence of the WM region on the duration of horizontal and vertical motion perception, we used nonparametric Spearman’s rank tests of the correlation coefficients between the FA values in WM clusters and the psychophysical measure (the ratio of the sum of durations of horizontal perception compared with vertical perception). Clusters were defined with an uncorrected threshold of \( P < 0.005 \), and the null distribution of the correlation coefficient was determined using Monte Carlo simulations in the usual way (Nichols and Holmes 2002). Crucially, by using the maximum cluster size, we implicitly correct for the multiple comparisons over the search volume considered. The Monte Carlo calculation used 10 000 permutations.

For subsequent analyses, we focused only on significant voxels (at a corrected level) with a correlation greater than 0.7 (Gold et al. 2007; Floel et al. 2009). The statistical parametric map of Spearman’s correlation coefficient revealed 6 regions of interest (ROIs) with significant correlations in the WM. The study included fast spin echo T2-weighted pulse sequence with the following parameters: 27 axial slices, TR 3 s, TE 9.8 ms, flip angle 70°, field of view (FOV) 256 mm (covering the whole telencephalon), acquisition matrix 128 × 128, reconstructed to 256 × 256, 3-mm slice thickness with no interslice gap. Diffusion-sensitizing gradients were applied along 16 directions with a diffusion sensitivity of \( b = 0 \) and 1000 s/mm².

The studies also included fast spin echo T1-weighted pulse sequence with the following parameters: 51 axial slices, TR 16 s, TE 8.85 ms, number of excitations (NEX) 1, FOV 320 mm (covering the whole cerebrum), acquisition matrix 128 × 128, constructed to 256 × 256, 2.5-mm slice thickness with no interslice gap. Diffusion-sensitizing gradients were applied along 10 directions with a diffusion sensitivity of \( b = 0 \) and 1000 s/mm².

Figure 2. Results of psychophysical experiment. (a) Histograms of durations of horizontal/vertical perception of a typical participant. (b) The relationship between mean duration of perception of horizontal compared with vertical motion. Blue dots indicate the results of the first experiment and red dots indicate the results of the second. (c) The relation between the ratio of the sum of durations (vertical perception/horizontal perception) in the first experiment and the ratio in the second experiment. The ratio was stable between these 2 experiments.

In the psychophysical experiment of each day, all participants performed 8 sessions in each day. The duration of each session was 15 min. In each session, we asked participants to look at the dots and to press an appropriate button momentarily when they perceived a change in the direction of motion. In 1 min of the beginning of all sessions, one of stationary pairs of dots (upper right and lower left or lower left and higher left) was presented in the 4 sessions per each pair. The order of selection between them is random. We call them stationary control period (the middle time axis in Fig. 1b).

The representative psychophysical measure used in this report is the ratio of the sum of durations of horizontal perception compared with vertical perception.

Participants were instructed to maintain steady fixation and not attempt to change (or hold) their perception (Kohler et al. 2008; Kaneoke et al. 2009; Shimono et al. 2011), and their eye movements were carefully monitored during the experiment using a SensoMotoric Instruments Eyelink system (Teltow, Germany). Eye movements of >0.5° of visual angle occurred very rarely and were not systematically related to perceptual switches. We compared the frequency of eye movements during psewriswitch time spans of ±1 s with that during periods of stable perception and found no significant increase in eye movements around perceptual switches (two-tailed test, \( P = 0.53 \)) (Sterzer et al. 2003; Shimono et al. 2011).
We then included 3 additional control regions (in the splenium and bilateral SC) in addition to these 6 regions. Splenium and bilateral SC were suggested as potential hubs like PN for interactions between bilateral hMT regions by Naikar and Corballis (1996). The splenium was defined using MRicro (Hofer and Frahm 2006; Inoue et al. 2008) as the posterior one-fourth of the CC, to avoid the inclusion of the cerebral ventricle. The SC is anatomically well defined and clearly visible on a standard anatomical MRI image. Therefore, the SC was defined as a spherical ROI (diagonal size of 5 mm) according to previous research (Schneider and Kastner 2005; Himmelbach et al. 2007; Wall et al. 2009).

We used Matlab for analysis.

Functional Activity Relating to Apparent Motion Perception
Next, we extracted MT+ ROIs by using fMRI data and T1-weighted data (Fig. 3a). The fMRI data were analyzed using SPM8. All functional image volumes were realigned, corrected for slice timing, coregistered to the initial scan, and smoothed using a 6-mm FWHM Gaussian kernel.

Our aim was to define the white matter regions associated with motion-sensitive responses in human MT+ (Dumoulin et al. 2000). These regions were then used as subject-specific seed regions in subsequent tractography. Motion-sensitive areas were identified using standard whole-brain SPM analyses at the within-subject (first) level. These analyses used general linear models and boxcar stimulus functions convolved with a hemodynamic response function. We tested for the onset of illusory motion by modeling the first minute of (stationary) control stimulation and the first minute of illusory motion as 2 experimental effects. We tested for illusory motion effects using random field theory-corrected P values in the usual way to identify significantly activated voxels. These were then masked with a white matter mask from segmented T1-weighted structural MRIs. The ensuing white matter regions were used for subsequent tractography in the described next section.

Probablistic Tractography
The probabilistic tracts were drawn from selected ROIs in individual’s diffusion space using a Bayesian multifiber tractography technique (Behrens et al. 2007), which assesses the most likely distribution of fibers and the directions of fiber orientations for the data at each voxel. We created 5000 tracts from seed ROIs, and only tracts entering the target ROI were retained. Tracts were normalized from individual space to the NMI space by SPM8 and threshold to show only those present in at least 7 of 11 participants, and FA values of all participants exceeded 0.2 (Fig. 4; Floel et al. 2009).

Results

Psychophysical Measurement
In the psychophysical experiment, we recorded the timing sequence of perceptual switching between 2 directions of apparent motion (vertical and horizontal). Figure 2a shows histograms of the durations of each perception using sample data from each session. Figure 2b shows the relationship between mean durations of perception for horizontal and vertical motion. The ratio of the sum of durations of horizontal and vertical perception was significantly smaller than 1.0 (Wilcoxon matched-pairs signed-rank test, P < 0.01).

Figure 2c shows the plots of the ratio of total durations of each motion direction in the first and second experiments, confirming that the ratio was reliably stable between the 2 experiments within each individual.

Correlation between FA Data and Psychophysical Parameter
Next, we extracted the brain regions in which FA values in WM exhibited a significant correlation with the psychophysical measure (the ratio of the sum of durations of horizontal or vertical perception). The results revealed that FA values in bilateral MT+ regions and bilateral occipital visual areas showed a significant negative correlation, whereas FA in the bilateral PN showed a significant positive correlation (Fig. 3a). Figure 3b shows the correlations and peak positions in MNI coordinate. They involve results of control ROIs in the splenium and bilateral SC. Although the psychophysical measure did not exhibit a significant correlation with FA values in the control ROIs, it correlated significantly with FA values in bilateral occipital, MT+, and PN ROIs (Fig. 3b, P < 0.05). To explore the influence of outliers on the observed correlations, standardized z-scores were computed for FA values in each of the ROIs and plotted in Figure 3b. As the figure shows, there does not seem to be any substantial influence of the psychophysical measure or FA values on the observed significant correlations. Furthermore, we extracted each participant’s FA values in 7 ROIs and observed regression plots between their maximum values and their psychophysical measures (Fig. 3c). This analysis is conducted on unsmoothed FA images in individual’s native spaces. The reason why we used maximum values here is because we needed to avoid the problem of double dipping.

In addition, we checked that the increase of FA value is caused by the decrease of radial diffusivity, that is, the mean diffusivity of the nonprincipal eigenvectors (figures are not shown).

Tractography
The results of the ROI analysis revealed individual differences in the brain regions, in which FA was related to the frequency of horizontal motion perception. In addition, we observed connectivity between the ROIs selected in ROI analysis, using a probabilistic tracking technique.

Importantly, we confirmed the connectivity between left/ right MT+ ROIs and left/right PN ROIs (Fig. 4, blue regions). The MT+ ROIs were defined by significant activity of fMRI, and PN ROIs were defined by using their anatomical landmarks (Fig. 4, yellow regions). These tracts are common region for 7 of 11 participants in MNI coordinates, and FA values in the region exceeded 0.2 for all participants.

These results suggest the notion that ROIs naturally extracted by correlations with psychophysical parameters can reflect information transmission between MT+ regions.

In addition, we observed tracts between MT+ ROIs and occipital visual area ROIs (Fig. 4, red regions). These ROIs were expressed by yellow regions in Figure 4.

Discussion
Our primary findings advance the results of previous reports on commissurotomized and blindsight patients, suggesting that the hub for interhemispheric transmission during apparent motion perception is not the CC but is located subcortically (Ramachandran et al. 1986; Naikar and Corballis 1996; Forster et al. 2000). Naikar and Corballis 1996, in particular, suggested that the subcortical brain node might be SC or the PN.

In the current study, we examined healthy participants using 2 methodological strategies. First, we recorded DTI to evaluate individual differences in WM. Second, we used the bias of perceiving horizontal motion in an ambiguous perception paradigm (the DDQ) for evaluating individual differences. We found these psychophysical differences to be small but stable, over a period of several weeks. This finding suggests that short-
Figure 3. (a) The positions of ROIs in MNI space are shown in the left figure. In 6 of 9 ROIs (occipital visual area, MT+ areas, left and right pulvinar), the ratio of the sum of durations of the 2 directions of perceived motion (horizontal perception/vertical perception) showed a significant correlation with the mean FA value. Three of 9 regions (splenium, left and right SC) were selected as control ROIs. The right figure is MT+ ROIs defined by significant activity of fMRI. (b) The table shows peak positions, correlations, and $P$ values of these ROIs. (c) Regression plots between maximum FA value in 9 ROIs and the ratio of the sum of vertical phase durations and the sum of horizontal phase durations. These analyses were conducted on unsmoothed FA images in a native space.
term changes do not have a substantial influence on the psychophysical measures used herein.

In our analysis of DTI data on healthy subjects, the significant positive correlation between the FA value and the bias to horizontal motion perception was observed only in PNs. The result suggested that the hub on the subcortical connectivity across the retinal midline is not SC but PN. Additionally, occipital visual areas showed significant positive correlation with the bias to vertical motion perception. Previous work has reported that the orbit of motion projects to a trace of activation on the V1 area, and it is suggested that it might be caused by feedback from MT+ to V1 (Muckli et al. 2005). Interpreting our results from his viewpoint, the feedback signal from MT+ might project on V1 separately in each hemisphere. For connecting between bilateral V1 areas, splenium might be the most important connection. If V1 is the most important region to integrate information of left and right visual fields, split-brain patients should have difficulty perceiving horizontal motion. Therefore, the result is consistent with Ramachandren et al. (1986).

Finally, using tractography, we observed bilateral tracts between PN ROIs and MT+ ROIs. Previous physiological studies have reported that the PN projects to a range of occipital areas but not the primary visual area. Most importantly, our tractography revealed some specific tracts between the PN and MT+. These results suggest that the local information transmission efficiency of bilateral PN influences individual differences in the probability of perceiving apparent horizontal motion across the retinal midline through bilateral PN-MT+ tracts. Note that the results in Figure 4 are not presented with significant anatomical connectivity between MT+ and the pulvinar. These results are presented to show the anatomical specificity of connections with this region using ad hoc criteria (Leh et al. 2008). Crucially, the spatial pattern of connectivity we found with these criteria includes the pulvinar.

There are some limitations of our study: First, correlations between FA values and information transmission efficiency have been reported in several studies (Wolbers et al. 2006; Floel et al. 2009). FA values, however, are influenced by many physiological features such as myelination, axon diameter, axon density, and ultrastructure (Beaulieu 2002). Therefore, further research is necessary for evaluating their influence on the FA values. Second, in our DTI study, we were unable to give perspectives about neural functional activity. An EEG study, Rose and Buchel (2005), however, showed that gamma-band synchrony was enhanced when perceiving horizontal motion than when perceiving vertical motion. Here, we focused on the individual difference of bias to horizontal motion perception. According to Rose and Buchel (2005), participants who easily perceive horizontal motion should show high gamma-band synchrony between their 2 hemispheres—a supposition which could be tested in future experiments. The gamma-band synchrony can be observed in magnetoencephalography (MEG) as well. By estimating the neuronal process in the brain from EEG and/or MEG, we will additionally be able to explore the relationship between electrical information flow and brain structure (Shimono et al. 2011).

Third, we set the spacing between the centers of the vertical and horizontal dots at 10.0° following Ramachandren et al. (1986). However, the dependency of visual size to the position of the hub is an interesting problem (Kohler et al. 2008). Long-ranged visual stimulus needs relatively more bilateral interaction than a short-ranged one, and medial superior temporal area will play a more important role than MT for information processing of long-range apparent motion. Fourth, in DDQ stimulus, a relative amount of time perceiving horizontal motion decreases the time perceiving vertical motion increases. Therefore, we are impossible to separate the factor of the easiness of horizontal motion perception and the difficulty of vertical motion perception. In the future study, we will need to separate these factors by designing other visual stimuli.

Fifth, we can expect that higher quality data will give more detailed information. For example, we will be able to understand the difference in cognitive roles among subdivided regions within PN by using higher magnetic field MRI and by increasing the number of participants. Sixth, hopefully, our noninvasive technique and several ideas give new approaches for predicting symptoms of brain-injured patients—a possibility which should be investigated further.

In conclusion, our results showed that the bilateral PN is a key subcortical structure, acting as a hub for perceiving apparent horizontal motion.

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