

**Sensitive period for a multimodal response in human visual motion area
MT/MST.**

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Running head: Sensitive period for human MT/MST development.

Summary

The middle temporal complex (MT/MST) is a brain region specialized for the perception of motion in the visual modality [1-4]. However, this specialization is modified by visual experience: following longstanding blindness, MT/MST responds to sound [5]. Recent evidence also suggests that the auditory response of MT/MST is selective for motion [6, 7]. The developmental timecourse of this plasticity is not known. To test for a sensitive period in MT/MST development, we compared MT/MST function in congenitally blind, late blind and sighted adults using fMRI. MT/MST responded to sound in congenitally blind adults, but not in late blind or sighted adults, and not in an individual who lost his vision between ages of 2 and 3 years. All blind adults had reduced functional connectivity between MT/MST and other visual regions. Functional connectivity was increased between MT/MST and lateral prefrontal areas in congenitally blind relative to sighted and late blind adults. These data suggest that early blindness affects the function of feedback projections from prefrontal cortex to MT/MST. We conclude that there is a sensitive period for visual specialization in MT/MST. During typical development, early visual experience either maintains or creates a vision-dominated response. Once established, this response profile is not altered by longstanding blindness.

Highlights

1. MT/MST responds to moving sounds in congenitally but not late blind adults.
2. MT/MST of congenitally blind adults has higher connectivity with prefrontal cortex.

Results

In sighted individuals, MT/MST supports motion perception in the visual modality, and does not respond to sound [4, 8]. In contrast, MT/MST of adults who have been blind since birth (congenitally blind) responds to auditory and tactile motion [5-9]. Thus, blindness can lead to a multimodal response in MT/MST; or put another way, visual experience is required in order for MT/MST to develop into a modality-specific visual area. Must this visual experience occur during a sensitive period of development? Alternatively, is the recruitment of MT/MST for auditory perception in congenitally blind adults the result of attending to auditory motion throughout the lifespan? We studied this question by comparing activity in MT/MST in sighted, congenitally blind and late blind individuals.

Based on prior studies, we predicted that MT/MST of congenitally blind individuals would respond to sounds, whereas MT/MST of sighted individuals would not. The key question of the present study was whether MT/MST of late blind individuals would respond to sound. If visual experience *early* in life (or early blindness) affects the response of MT/MST, then MT/MST of adults who become blind later in life should not respond to sound, just as in sighted individuals. By contrast, if MT/MST responds to sound as a result of longstanding visual deprivation anytime during the lifespan, then MT/MST should respond to sounds in adults who have been blind for many years, regardless of whether they became blind early or late in life.

Sighted, congenitally blind and late blind adults (Table 1) listened to receding and approaching motion sounds while undergoing fMRI. All blind participants had been totally blind with at most minimal light perception for at least 9 years. To produce the sensation of motion (receding or approaching), we modulated the volume of the sounds over time (see Experimental Procedures for details). Motion sounds were of two types: high motion (footsteps) and low motion (tones). A separate group of sighted adults rated the sounds on the extent to which they conveyed motion. (See Figure S2 for motion ratings). The ratings confirmed that both, the high and low motion sounds appeared to move, and that the high motion sounds produced a stronger percept of motion. Note that the present stimuli are not sufficient to establish motion selectivity of MT/MST since they vary in many low-level sound properties in addition to motion content. Rather these motion sounds allow us to test a cross-modal response profile in MT/MST, because motion sounds activate MT/MST in early blind subjects [6, 7].

In each group (sighted, congenitally blind and late blind), we looked for two kinds of evidence of an MT/MST response to motion sounds: 1) a greater average response of both motion sound conditions relative to rest, and 2) a greater response to the high than low motion sounds. To assess this pattern, left and right MT/MST ROIs were defined based on data from a separate group of twelve sighted subjects who performed a visual motion task. (For ROI definition and verification see Supplemental Experimental Procedures.)

Does the MT/MST of congenitally blind but not sighted individuals respond to sound?

First, we established that MT/MST in congenitally blind but not sighted adults responded to receding and approaching motion sounds. As predicted, sounds deactivated MT/MST below baseline in sighted adults ($t(19) \leq -2.4$, $p < .05$) and activated MT/MST above baseline in congenitally blind adults ($t(9) \geq 3.2$, $p < .05$). In a direct comparison of congenitally blind to sighted individuals, bilateral MT/MST responded more to motion sounds (relative to rest) in the congenitally blind group than in the sighted group ($F(1,28) \geq 23.4$, $p < .0001$, Figure 1B). Figure 1 shows the time course of activation in left and right MT/MST. (We present t-values summarized over left and right MT/MST, unless these regions showed different effects. See Table S1 for complete summary of statistics.)

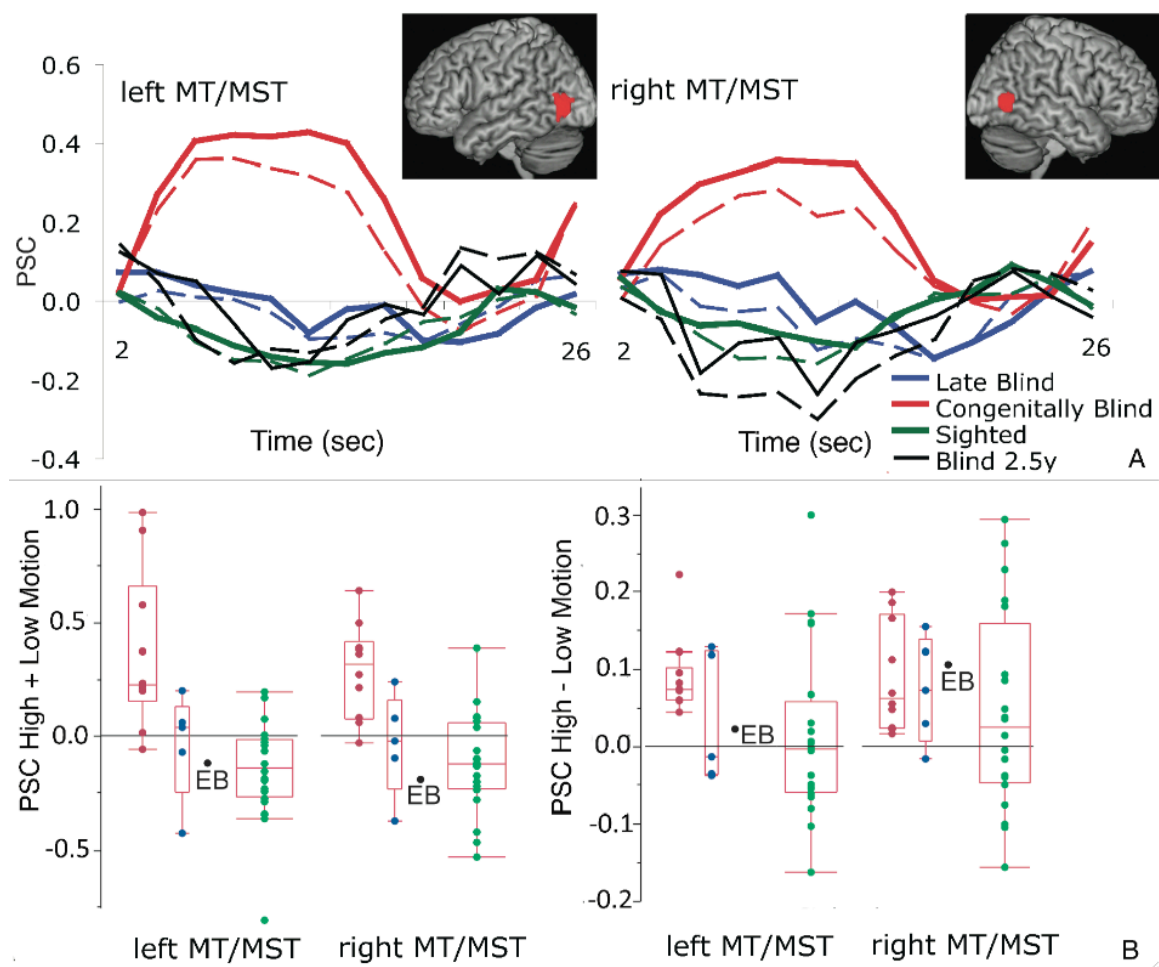


Figure 1. Activity in left and right MT/MST ROIs for sighted (green), congenitally blind (red) and late blind (blue). A: Activity to the high motion condition (footsteps) is shown in solid lines, and activity to the low-motion condition (tones) is shown in dashed line. The data reflect percent signal change relative to baseline, plotted as a function of time in seconds. Inset figures display the MT/MST ROIs overlaid on a normalized template. B: Percent signal change (PSC) in left and right MT/MST ROIs

for individual subjects. On the left, PSC for the mean of the high and low motion conditions relative to rest. On the right, PSC difference between the high and low motion conditions. Each point represents a single subject. Congenitally Blind: CB (red), Late Blind: LB (blue), Sighted (green), EB is the single participant who lost his vision between the ages of 2 and 3 (black). In the box plots of the data the middle line marks the 50th percentile (median), the lowest edge of the box marks the 25th percentile and the upper edge of the box marks the 75th percentile. The box whiskers terminate at 1.5 standard deviations away from the median (10th and 90th percentiles). The width of the boxplot indicates sample size. The boxplots illustrate that EB is different from the congenitally blind population, but not from the sighted or late blind populations in mean the high motion+low motion > rest contrast bilateral MT/MST, and in the high motion>low motion contrast of left MT/MST, but not right MT/MST.

Similarly, in the congenitally blind group, but not in the sighted group, there was a larger response to the high-motion than the low-motion sounds in MT/MST ($t(9) \geq 4$, $p < .005$). The difference between the high and low motion conditions was significantly larger in the congenitally blind adults than in the sighted in left MT/MST ($F(1,28) = 4.3$, $p = .05$). This difference between groups was not reliable in right MT/MST. In general, the high-vs-low motion difference was highly variable across sighted individuals, and even in left MT/MST some sighted participants showed a larger difference than congenitally blind participants (see Figure 1B).

Like the ROI analyses, whole-brain analyses revealed group differences between sighted and congenitally blind individuals in MT/MST (See Figure 2). While listening to motion sounds (relative to rest), congenitally blind adults showed increased signal in right MT/MST (middle temporal/lateral occipital gyri) as well as in the superior temporal gyrus. Neither left nor right MT/MST were active above rest in sighted adults. In this contrast, sighted individuals activated bilateral prefrontal cortex (inferior/middle frontal gyri and precentral gyrus, insula), right inferior parietal lobule, bilateral cerebellum, and left putamen. Congenitally blind adults also showed activity in the right prefrontal and bilateral parietal cortices (See Figure 2B, Table S2 for within-group results). The primary auditory cortex was not significantly active above rest in either group at the corrected threshold. However, bilateral auditory activity did emerge at an uncorrected threshold of $p < .001$ (Brodmann areas 22, 41, 42). The weakness of this effect is likely due to the effect of scanner sound on resting state activity. In the motion-vs-rest contrast, congenitally blind individuals had greater activation than sighted adults in bilateral MT/MST, as well as left superior parietal lobule and left cuneus.

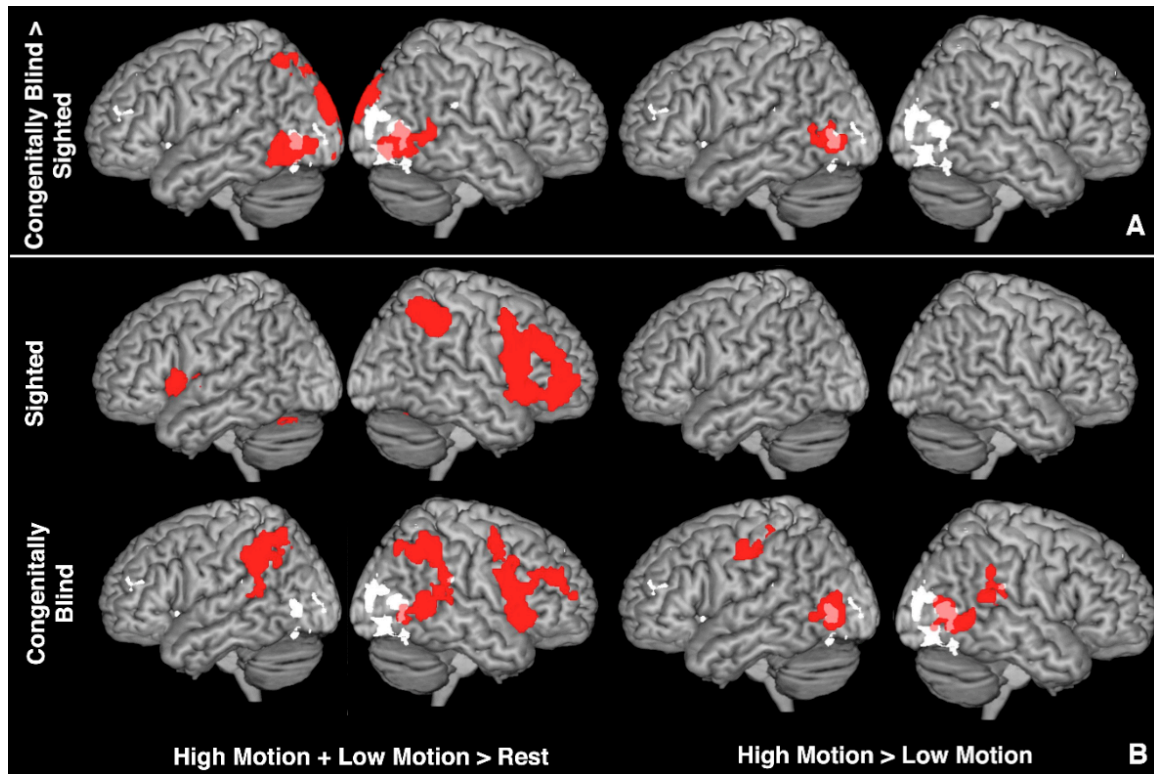


Figure 2. Brain regions active during auditory motion task. Results of whole-brain analyses showing greater BOLD signal in the congenitally blind, relative to the sighted groups (A) and activity in congenitally blind and sighted groups separately (B) both shown in red. High and low motion conditions relative to rest (left) and in the high motion condition relative to the low motion condition (right) ($p < .05$, corrected). Activation during a visual motion task in a separate group of participants is presented in white. Overlap of activation during motion sound task and visual motion task appears pink. As can be seen in panels A and B, motion sound activation and visual motion activation overlap in the region of MT/MST. Additionally, MT/MST activation in the congenitally blind group is similar to previous reports of MT/MST activity in sighted individuals. The average coordinates from five representative studies fall within the auditory motion activation in the congenitally blind group (mean left MT/MST -45, -70, 4, mean right MT/MST 43, -69, 5 [2, 10-13]). This overlap suggests similar MT/MST localization in the sighted and congenitally blind, but does not preclude the possibility that the location of functional area MT/MST is subtly different with respect to anatomy in congenitally blind individuals. For list of brain regions depicted in this figure, see Table S3.

A whole brain analysis of high versus low motion sounds also revealed bilateral MT/MST in congenitally blind adults as well as the right middle/superior temporal gyri and the right insula. In contrast, sighted individuals did not have any brain regions more active for the high motion than low motion sounds (Figure 2B). Only the left MT/MST showed greater activity in congenitally blind than the sighted group (group-by-condition interaction) (Figure 2A).

The auditory MT/MST activation in congenitally blind individuals overlapped with visual MT/MST in a separate group of sighted participants, as well as with visual MT/MST identified in prior studies [2, 10-13] (Figure 2, and Supplemental Experimental Procedures). No brain regions were more active in sighted than congenitally blind adults (either for sounds relative to rest or high-vs-low motion sounds) (Figure 2, Table S2).

The above analyses confirmed that (1) MT/MST responds to motion sounds in congenitally blind adults; (2) the region identified by these analyses overlaps with visual area MT/MST identified in a separate group of sighted participants; and (3) MT/MST does not respond to motion sounds in sighted adults.

Does the MT/MST of late blind adults respond to sound?

Next, we addressed the key question of whether MT/MST of late blind adults (blind age 9 or later) show a response similar to sighted adults or to congenitally blind adults. Due to the small number of late blind individuals who are totally blind and because whole-brain random effects analyses require a large number of participants [14], only ROI analyses were used to compare late blind adults to the remaining groups.

In late blind adults, MT/MST ROIs responded like MT/MST ROIs of the sighted. That is, activity for motion sounds was below rest, and BOLD responses for the high and low motion sounds were not different from each other (Figure 1). The late blind group showed a smaller MT/MST response to sound than the congenitally blind group (motion-vs-rest $F(1,13) \geq 5.3$, $p < .05$). MT/MST ROIs in late blind adults did not respond to sound more than MT/MST ROIs of the sighted ($p > .3$). For the high-vs-low motion response, late blind adults were not significantly different from either congenitally blind or sighted groups ($p > .1$).

Could the MT/MST response to sound be explained by either residual light perception or total duration of blindness?

Some blind adults had minimal residual light perception. We therefore asked whether the difference between congenitally blind and not congenitally blind adults could be explained by whether or not participants had any residual light perception. In both right and left MT/MST ROIs we found a reliable effect of congenital vs. not congenital blindness onset ($F(1,12) \geq 2.3$, $p < .05$), but no effect of residual light perception ($p > .1$) (Table 2).

Individuals who become blind later in life are likely to be blind for less time than individuals who are blind from birth (assuming equal ages across groups). We therefore asked whether the difference between congenitally blind and non-congenitally blind adults could be explained by the total number-of-years-blind (multiple regressions). Congenital vs. not congenital blindness ($F(1,12) \geq 5.3$, $p < .05$),

but not number of years of blindness ($p>.3$), predicted MT/MST activity across blind participants. Thus, the difference among congenitally and non-congenitally blind adults cannot be explained by the total duration of blindness.

In sum, MT/MST responded to sound only in individuals who were blind early in life. MT/MST did not respond to sound in sighted individual or blind individuals who lost vision late in life. The selective effects of early experience could not be explained by differences in residual light perception among groups. These data suggest that early blindness results in a multimodal response in MT/MST. Put another way, *early* visual experience is necessary to produce or maintain a vision-dominated response.

When is the sensitive period for specialization of MT/MST?

The late blind participants in the present study had all lost their vision after age 9. Within this late blind group, there was no relationship between age of blindness onset and amount of MT/MST activity ($r<.2$, $p>.3$). These data suggest that blindness onset before age 9 determines whether MT/MST becomes multimodal. To get a further sense for the time range of the MT/MST sensitive period, we compared MT/MST activity in our groups of congenitally and late blind adults to an early blind participant who became completely blind between the ages of 2 and 3 years. The MT/MST of this early blind individual was less active than any of the congenitally blind participants. His MT/MST ROIs responded less to sound than the MT/MST ROIs of the congenitally blind adults ($t(9)\geq 4.3$, $p=.001$), and responded no more than the MT/MST ROIs of the late blind adults. Relative to the congenitally blind group, this participant also showed a smaller difference between the high and low auditory motion conditions in left MT/MST ($t(9)=4.2$, $p<.005$). He was not different from any of the groups in right MT/MST.

In sum, despite having been completely blind for the vast majority of his life, the MT/MST of this 55-year-old male behaved more like that of a sighted individual than that of congenitally blind adult. Moreover, as described above, years of blindness did not predict the auditory response in MT/MST, across all of the blind participants. These data are suggestive of an early sensitive period within the first couple of years of life in MT/MST development [but see 6].

How does auditory information get to MT/MST of congenitally blind adults?: Resting State Functional Connectivity Analysis

We reasoned that in the congenitally blind group the MT/MST response to sound might reflect altered inputs from other brain regions. For example, there might be increased connectivity between auditory cortex and area MT/MST in congenitally blind participants, given the auditory response in MT/MST. To gain insight into what brain regions might be carrying auditory motion information to MT/MST, we compared resting state functional connectivity of MT/MST across groups. Prior work has shown that low frequency fluctuations in the BOLD signal are correlated

across brain regions with monosynaptic or polysynaptic anatomical connectivity [15-17]. We therefore examined correlations between spontaneous fluctuations of BOLD signal in MT/MST ROIs and the rest of cortex as a measure of functional interactivity in the absence of task.

First, we examined functional connectivity of MT/MST during the rest blocks of the current experiment. We found no differences between sighted and congenitally blind groups at an FDR corrected threshold of .05. When the threshold was lowered to an uncorrected level of .01, we observed lower correlations in the congenitally blind group between MT/MST and several retinotopic visual areas (left BA18, right BA19), as well as other sensory brain regions. We also observed increased correlations between MT/MST and regions of the dorsolateral prefrontal cortex (bilateral BA8, left BA9, left BA45). There were no changes in MT/MST connectivity with auditory cortices, relative to the sighted group or relative to the late blind group. This is despite the fact that connectivity of A1 and MT/MST in congenitally blind adults could be overestimated in functional connectivity analyses due to scanner noise during the rest blocks (See Supplemental Experimental Procedures for further details.). Therefore, A1 and MT/MST connectivity may in fact be reduced in the congenitally blind individuals. These data suggest that the multimodal response of MT/MST in congenitally blind individuals is not a result of greater input from A1.

To confirm these exploratory findings, we examined MT/MST functional connectivity during resting blocks of a separate dataset from the same participants. The pattern of results in the second experiment confirmed findings from the first experiment. There were no changes in MT/MST connectivity with A1. However, compared to sighted individuals, the congenitally blind adults had decreased correlations between bilateral MT/MST and retinotopic visual cortices (BA17, BA18, BA19) as well as the contralateral MT/MST and other primary and secondary sensory regions. Correlations were increased between MT/MST and lateral prefrontal regions including BA8, BA9 and BA45 ($p < .05$, FDR corrected) (Figure 3, Table S3). These were the same lateral prefrontal regions observed in the first dataset.

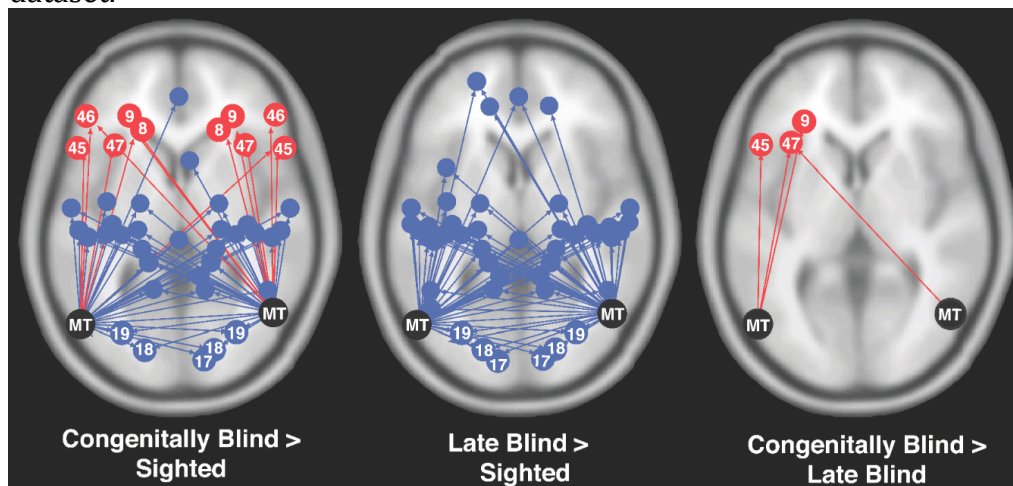


Figure 3. Functional connectivity results from experiment 2. All maps are FDR corrected for multiple comparisons at $p < .05$. Regions more correlated with MT/MST across groups are shown in red, regions less correlated with MT/MST are shown in blue. A. Regions differentially correlated with MT/MST in the congenitally blind relative to sighted adults. B. Regions less correlated with MT/MST in late blind relative to sighted adults. C. Regions more correlated with MT/MST in the congenitally blind relative to late blind adults. Numbers correspond to approximate Brodmann areas in dorsolateral prefrontal and retinotopic visual areas. For a complete list of Brodmann areas see Table S3.

Given the two differences we observed in connectivity between the congenitally blind and sighted individuals (increases with prefrontal regions and decreases with early sensory regions), what connectivity changes occur in the late blind adults? Relative to sighted adults; late blind adults had reduced correlations between bilateral MT/MST and retinotopic visual cortices (BA17, BA18, BA19) as well as the contralateral MT/MST and other primary and secondary sensory regions. These are similar to reductions in connectivity observed in congenitally blind adults. In contrast, unlike the congenitally blind adults, the late blind adults did not show increased correlations between MT/MST and prefrontal regions (relative to sighted individuals). Late blind adults had significantly lower correlations between MT/MST and left lateral prefrontal regions including BA9 and BA45 than congenitally blind adults (See Figure 3, Table S3). These data imply that the auditory response in MT/MST of congenitally blind adults is associated with changes in functional connectivity to *prefrontal* areas, rather than early sensory areas.

Discussion

MT/MST responded to motion sounds only in congenitally blind adults and not sighted adults, late blind adults, and not in a participant who became blind between the ages of 2 and 3 years. The difference among late and congenitally blind individuals could not be explained by the duration of blindness or the presence of residual light perception. Thus, early blindness leads to a multimodal response profile in MT/MST. Following early visual experience, MT/MST does not become responsive to sound even after decades of visual deprivation in adulthood. It has also previously been shown that individuals who grow up blind, but have their vision restored in adulthood, continue to have a multimodal response in MT/MST [6]. Together, these data suggest that MT/MST acquires or maintains a vision-dominated response profile as a consequence of early visual experience. Our findings are consistent with a body of prior work demonstrating different effects of early and late visual experience on the visual system [18-22].

A sensitive period for MT/MST development is consistent with evidence for early maturation of MT/MST and an early sensitive period in the development of global motion vision. Children who have bilateral visual deprivation during the first eight months of life due to congenital cataracts, but not later, show protracted deficits in global motion perception long after the cataracts have been removed [23-27]. Our

data suggest that these behavioral deficits might stem from cross-modal changes in MT/MST function.

A key outstanding question concerns the exact timing of this early sensitivity of MT/MST to blindness. There is one report in the literature of an individual who became blind at age 3, and nevertheless has a multimodal response in MT/MST [6]. Therefore, there is case-by-case variability in the exact timing of this MT/MST sensitive period. Future group studies with multiple early blind individuals are needed to accurately delineate the time window for cross-modal functional plasticity in MT/MST.

A possible developmental mechanism for cross-modal plasticity in MT/MST is suggested by the results of the connectivity analysis. Both early- and late-blind participants had reduced correlations between MT/MST activity and retinotopic visual regions. During development, afferents from retinotopic visual regions (and possibly visual afferents from subcortical structures) may compete with non-visual inputs for influence over MT/MST activity. In the absence of early vision, non-visual cortical structures establish a greater influence over MT/MST activity, while visual regions have less influence [28]. As a consequence MT/MST might become responsive to stimuli from other modalities. In this regard, competition among cortical areas may be analogous to competition between the right and left eye within the primary visual cortex [6, 24].

What are the non-visual competitors for MT/MST connectivity? One might initially have predicted that MT/MST receives cross-modal information directly from other primary or secondary sensory regions such as the auditory cortex. On this account, one would expect enhanced connectivity between auditory cortex and MT/MST in the congenitally blind group. The results of the connectivity analyses do not support this interpretation. Correlations between MT/MST activity and auditory cortex and other primary and secondary sensory regions were no higher in congenitally blind than sighted participants. On the other hand, we did observe increased correlations between several lateral prefrontal regions (BA8, BA9, BA45, BA46, BA47) and MT/MST in congenitally blind adults relative to both sighted and late blind individuals. Thus across groups, an auditory response of MT/MST is associated with increased functional connectivity with prefrontal regions.

We suggest that MT/MST may respond to sound in congenitally blind individuals through altered top-down feedback from prefrontal cortex. There is evidence that in sighted adults prefrontal regions interact with MT/MST during visual motion tasks [29]. MT/MST activity is modulated by top-down frontally mediated processes, such as imagery and attention [30, 31], as well as by task-relevant information from other sensory modalities [8, 32-34]. In nonhuman primates there are direct projections from prefrontal regions to MT/MST [35]. In humans, the prefrontal cortex may influence MT/MST activity directly, or by modulating the interaction between MT/MST and parietal regions [36]. We hypothesize that this top-down influence of

prefrontal cortex on MT/MST is altered by early visual experience, possibly leading to a multimodal response profile.

In summary, early visual experience is required to render MT/MST a vision-dominated brain region. In congenitally blind individuals, reduced visual input during a sensitive period in development both alters functional connectivity in MT/MST, and leads to a multimodal functional profile.

Experimental Procedures

Participants

Twenty-one sighted, ten congenitally blind, and five late blind adults, took part in the auditory motion experiment. One additional early blind participant lost his vision between the ages of two and three. His data were analyzed separately and were also included in analyses of residual light perception and duration of blindness where his data were coded as non-congenitally blind. Twenty-one sighted adults, ten congenitally blind adults, and five late blind adults participated in experiment two. (For demographic information see Table 1.) All blind participants reported having no usable vision (could not see motion, shape or color or detect objects in their environment, and none of the participants had measurable acuity). Recruiting only individuals who had no usable vision severely restricted our pool of participants, particularly for the late blind group, as total blindness later in life is uncommon. However, total blindness was important component of the experiment because any sensitive period effects could otherwise be attributed to differences in residual vision. A small subset of participants in both groups had faint light perception in one or more eyes sufficient to distinguish a brightly lit environment from an entirely dark environment; we therefore include an analysis modeling MT/MST activity as a function of residual light perception (see Results). All blind participants had no usable vision for at least nine years and had all lost their vision due to pathology in or anterior to the optic chiasm. None of the participants suffered from neurological disorders or had ever sustained head injury. This study was approved by the institutional review board and all subjects gave written informed consent.

Tasks

Experiment 1 (Auditory Motion)

Participants heard motion in depth: a high motion condition (footsteps) and a low motion condition (tones). To induce percepts of approaching motion and receding motion, sounds got louder or quieter respectively. Footstep stimuli were created by recording the sounds of female and male individuals walking towards a computer, the volume gradient was then digitally altered to produce away sounds. Tone sounds were synthesized in Audacity software (<http://audacity.sourceforge.net/>).

The volume of the sounds presented in the scanner ranged approximately between 50 and 90 dBA SPL, depending on the participant and the stimulus. The magnitude of the increase/decrease in loudness in each motion stimulus was approximately 15 dBA SPL. The differences in volume among stimuli from different conditions are too

small to accurately measure in the scanner. Therefore, to precisely characterize the change in loudness for the high and low motion conditions we report dBFS, which measures volume changes relative to the maximum output of the amplifying device being used. In the high motion condition, the quietest footstep had an average volume of RMS=-18.6 dBFS and the loudest footstep had an average volume RMS=-13.1 dBFS (average range from loudest to quietest footstep=5.5 dBFS, $SD=2$ dBFS, overall file volume: A-weighted RMS=-30.3 dBFS). In the low motion condition, the quietest tones had an RMS=-8.8 dBFS and the loudest tones RMS=-2.7 dBFS (average range in RMS=6.2 dBFS, $SD=1.4$ dBFS, overall file volume: A-weighted RMS=17.75 dBFS). There was no binaural aspect to the stimuli. Stimuli can be downloaded at http://saxelab.mit.edu/resources/stimuli/motion_sounds.zip

Ratings from a separate group of sighted participants confirmed that the percept of motion induced by the sound was stronger in the high motion footsteps condition, and that the low motion sounds also appeared to move (See Figure S2). As the high motion sounds did not have a larger volume range, the stronger motion percept is likely due to the participants recognizing the high motion sounds as footsteps. However, to unambiguously establish that the MT/MST of congenitally blind individuals responds to motion, future studies will need to match acoustic stimuli such that they only differ in implied motion (and not for example low level aspects of the sound or salience).

During the fMRI experiment, participants were instructed to decide whether each sound was getting closer or getting further away, and responded by pressing one of two buttons after each sound clip. There were four variants of the footstep sound clips (male/female footsteps either approaching or receding) and four variants of the tone sound clips (two unique sounds either approaching or receding). Sounds were each two seconds long. (For further details on the sound stimuli see Supplemental Experimental Procedures). The blocked design consisted of four sound-clips from either the high or low motion condition per block separated by one-second delays and played in random order. The blocks were 12 seconds long, and separated by ten seconds of rest. There were four blocks of each condition (footsteps, tones) in every run. Each participant completed four runs of the task (each 7.5 minutes long). Items did not repeat within block. (Behavioral data for Experiment 1 are summarized in Figure S1.)

Experiment 2 (Resting Function Connectivity Only)

Participants made semantic judgments about aurally presented words and perceptual similarity judgments about strings of backwards speech [37]. Blocks were 18-seconds long and were separated by 14 seconds of fixation. The experiment was broken up into five runs of 7.7 minutes each. Each run had a total of 15 rest blocks. The total duration of resting state data was therefore 17.5 minutes.

Sighted participants were instructed to keep their eyes closed during the scans for all experiments.

fMRI Data Acquisition and Analyses

Data preprocessing and analysis of mean BOLD signal differences were performed in SPM2 (SPM2 <http://www.fil.ion.ucl.ac.uk/>) and Matlab-based in-house software. Whole-brain analyses were corrected for multiple comparisons at an $\alpha < .05$ by performing Monte-Carlo permutation tests on the data in SnPM3 using a combined voxel-cluster threshold [38, 39].

For all ROI analyses, bilateral MT/MST ROIs were defined based on data from a visual motion task in a separate group of twelve sighted adults [37]: right MT/MST [50 -66 4], left MT/MST [-52 -72 2] (see Supplemental Materials for details). Within the ROIs PSC was averaged from TR 4 through 7, the time of the block compensating for hemodynamic lag. This time window covered the peak response for all groups and conditions. We used t-tests to look for effects of sound condition within groups, and 2x2 ANOVAs to compare groups across sound conditions.

In functional connectivity analyses, we measured the correlations between low frequency fluctuations in BOLD signal in MT/MST, and BOLD signal fluctuations in the rest of cortex. Resting data were obtained from rest blocks of Experiments 1 and 2 and bandpass filtered (.01 to .08). BOLD signal from CSF and white matter as well as SPM generated motion parameters were used as nuisance regressors (Functional Connectivity SPM8 toolbox, conn <http://web.mit.edu/swg/software.htm> [40]; Connectivity analyses were FDR corrected at $\alpha < .05$. (Further details on neuroimaging procedures and analysis are provided in Supplemental Experimental Procedures.)

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Tables

Table 1

Demographic information of participants. CB: Congenitally Blind, LB: Late Blind, EB: Early Blind. Sighted participants are matched in mean age and years of education to the CB group. RLF: retrolental fibroplasia.

Participant	Gender	Age (y)	Age of blindness	Cause of blindness	Residual Light Perception	Highest Level of Education (years)
EB1	F	43	Birth	Premature birth/RLF	none	BA (16)
EB2	F	47	Birth	Premature birth/RLF	none	3 y of college
EB3	M	40	Birth	Congenital bilateral cataracts	none	some college (13)
EB4	M	44	Birth	Congenital rubella syndrome	none	BA (16)
EB5	M	46	Birth	Retinoblastoma (enucleated)	none	MA (18)
EB6	F	53	Birth	Premature birth/RLF	minimal	MA (18)
EB7	F	61	Birth	Not known	minimal left eye	multiple MAs (22)
EB8	F	59	Birth	Premature birth/RLF	minimal	BA (17)
EB9	F	57	Birth	Premature birth/RLF	none	MA (18)
EB10	M	37	Birth	Retinitis pigmentosa	none	BA (16)
LB1	M	54	9	Retinoblastoma (enucleated)	none	MA (18)
LB2	F	53	30	Retinitis pigmentosa	minimal	MA (18)
LB3	M	48	20	Retinitis pigmentosa	minimal	MA (18)
LB4	M	53	16	Glaucoma	none	MA (18)
LB5	M	43	34	Optic nerve degeneration	none	BA (16)
B1	M	55	2.5 y	Retinoblastoma	none	JD (19)
Sighted	10F	46±16	-	-	-	17±2

Sensitive Period for Multimodal Response in Human Visual Motion Area MT/MST

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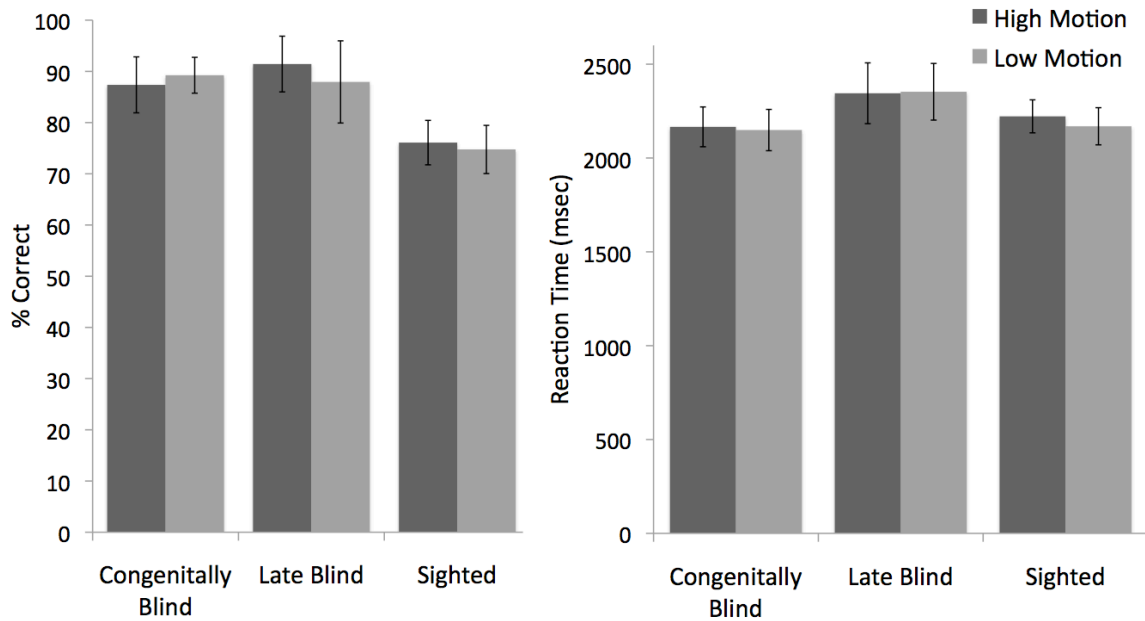


Figure S1

Accuracy and reaction time data for the towards/away responses to the motion sounds (Experiment 1). Error bars depict the standard error of the mean for each group. Data are presented from 12 sighted, 5 congenitally blind and 3 late blind participants. Due to a technical error, the behavioral data for the remaining participants were not saved. There were no reliable differences in accuracy either between groups or conditions (ANOVA p 's > .10). There was a main effect of group in the reaction time analysis ($p < .01$). In post-hoc t -tests late blind participants were reliably slower than sighted participants ($p < .05$).

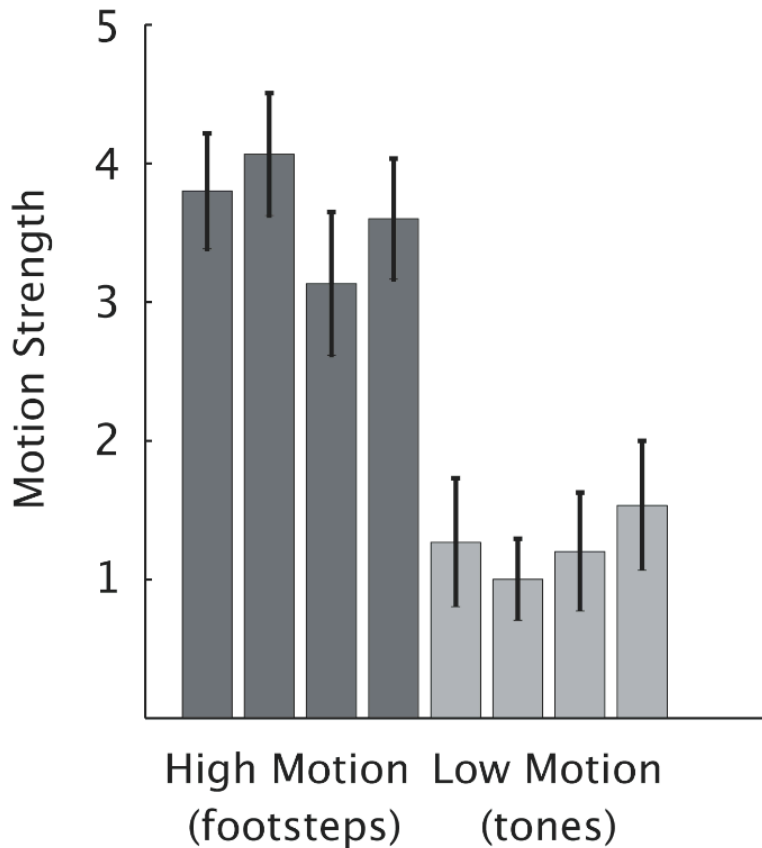


Figure S2

Motion ratings for the eight motion sounds presented during Experiment 1. In a separate norming experiment, 15 naïve sighted participants rated the motion strength of each of the 8 stimuli outside the scanner. The exact instructions were to “judge how much the sound in the sound clip sounds like it’s moving using a scale from 0 (no motion) to 5 (strong sense of motion).” In the figure above, each bar is the rating for one sound. Error bars represent standard deviations of the mean for that sound. The average motion strength of the footstep stimuli was 3.7 (min=3.1, max=4.0) while for the tone stimuli the average motion strength was 1.2 (min=1.0, max=1.3), showing a robust and significant difference between these conditions ($t(14)=5.0, p<0.001$). Furthermore, the low motion condition was significantly different from 0 ($t(14)=4.1, p<0.001$).

Table S1

	MT/MST ROI within group t-tests					
	High Motion + Low Motion > Rest			High Motion > Low Motion		
	Mean	SD	One sample t-test	Mean	SD	One sample t-test
Sighted						
lMT/MST	-0.15	0.22	$t(19)=-3.13, p=.01$.01	.11	$t(19)=-.58, p=.57$
rMT/MST	-0.12	0.22	$t(19)=-2.42, p=.03$.05	.13	$t(19)=1.54, p=.14$
Congenitally Blind						
lMT/MST	0.36	0.35	$t(9)=3.27, p=.01$.09	.05	$t(9)=5.61, p=.0003$

rMT/MST	0.29	0.21	$t(9)=4.34, p=.002$.09	.07	$t(9)=-4.02, p=.003$
Late Blind						
lMT/MST	-0.04	0.24	$t(4)=-.39, p=.72$.03	.08	$t(4)=.84, p=.34$
rMT/MST	-0.04	0.23	$t(4)=-.34, p=.75$.08	.07	$t(4)=2.36, p=.08$
MT/MST ROI group*condition 2 by 2 ANOVA						
	Effect of Group		Effect of Condition		Interaction	
Congenitally Blind > Sighted						
lMT/MST	$F(1,28)=24.58, p<.0001$		$F(1,28)=8.05, p=.008$		$F(1,28)=4.28, p=.05$	
rMT/MST	$F(1,28)=23.46, p<.0001$		$F(1,28)=9.36, p=.005$		$F(1,28)=1.08, p=.31$	
Late Blind > Sighted						
lMT/MST	$F(1,23)=.51, p=.61$		$F(1,23)=.74, p=.40$		$F(1,23)=1.32, p=.32$	
rMT/MST	$F(1,23)=.59, p=.45$		$F(1,23)=3.78, p=.06$		$F(1,23)=.22, p=.64$	
Congenitally Blind > Late Blind						
lMT/MST	$F(1,13)=5.31, p=.04$		$F(1,13)=12.47, p=.004$		$F(1,13)=2.90, p=.11$	
rMT/MST	$F(1,13)=7.46, p=.02$		$F(1,13)=17.94, p=.001$		$F(1,13)=.20, p=.66$	
MT/MST ROI Residual Light Perception Regression						
	Effect of Group		Effect of Light Perception		Interaction	
lMT/MST	$F(1,12)=3.15, p=.008$		$F(1,12)=1.01, p=.33$		$F(1,12)=.88, p=.40$	
rMT/MST	$F(1,12)=2.37, p=.04$		$F(1,12)=1.63, p=.13$		$F(1,12)=-.55, p=.59$	
MT/MST ROI Years of Blindness ANOVA						
	Effect of Group		Effect of Years Blind		Interaction	
lMT/MST	$F(1,12)=5.70, p=.03$		$F(1,12)=.02, p=.89$		$F(1,12)=.03, p=.87$	
rMT/MST	$F(1,12)=5.32, p=.04$		$F(1,12)=.63, p=.44$		$F(1,12)=.36, p=.56$	
MT/MST ROI EB relative to Congenitally Blind and Late Blind groups						
	Relative to CB group			Relative to LB group		
	Mean	SD from Mean	One sample t-test	SD from Mean	One sample t-test	
lMT/MST	-.12	-2 SD	$t(9)=4.36, p=.001$	-.37 SD	$p>.3$	
rMT/MST	-.19	-1.6 SD	$t(9)=7.25, p<.0001$	-.65 SD	$p>.3$	

Table S2, Supplements Figures 2

Brain regions showing increased signal at a corrected threshold of $p<.05$, Corrected. Column headers abbreviations: k – number of active voxels; w – combined voxel and cluster statistic; p_{combo} – cluster-voxel corrected p -value; x, y, z – peak MNI coordinates; Voxel peak t -peak t -statistic in the cluster, Brain Area (Brodmann area) – description of brain regions encompassed in cluster and approximate Brodmann areas with activation.

Table S3, Supplements Figure 3

Brain regions with increased and decreased connectivity in congenitally blind group relative to the sighted group, late blind group relative to sighted group, and congenitally blind group relative to late blind group. Column headers are: Source - brain regions for which correlations are being computed, left MT/MST or right MT/MST; beta and t-value for correlation difference, p -FDR – significance level for difference in correlations among

groups (corrected for the number of Brodmann area ROIs tested); BA – target Brodmann area with changed correlation, in that group.

Tables one and two in Excel Files (Attached)

Supplemental Experimental Procedures

Motion Sound Stimuli (Experiment 1)

There were eight distinct motion stimuli used in the motion experiment, with four variants of the high motion footstep sound clips (male/female footsteps either approaching or receding) and four variants of the low motion tone sound clips (two unique sounds either approaching or receding). Motion ratings collected outside the scanner from a separate group of subjects confirmed that the high motion sounds produced a stronger sensation of movement than the low motion sounds, and that all the high and low motion stimuli sounded as if they were moving (See Figure S4). Sound files were 32-bits and 44,100 sample rate. Stimuli can be downloaded at http://saxelab.mit.edu/resources/stimuli/motion_sounds.zip.

Motion Sound Task (Experiment 1)

Sounds were presented through Sensimetric MRI Compatible Insert Earphones. These headphones provide good isolation from scanner noise and high sound fidelity details can be found at <http://www.sens.com/s14/index.htm>. Padding was used to further attenuate the sound of the scanner. All sighted participants were instructed to keep their eyes closed during the fMRI experiment.

Prior to beginning the scanning session each participant practiced the task for at least 8 trials. When the first run of the task began, the experimenter watched to make sure the participant was responding accurately on most of the trials. This was almost always the case. If this was not the case, instructions were reiterated and the experiment started over again. Throughout the study, an experimenter watched the responses of the participant as they were made to ensure that the subject was not falling asleep during the study. No participants ever stopped making responses during the task. After the study, we asked each participant what the sounds in the scanner sounded like. All participants reported hearing footsteps. Some participants also thought the tone stimuli sounded like a jackhammer and provided various other descriptions for the tone stimuli.

Experiment 2 Task

Participants heard pairs of words over headphones and indicated how related in meaning the words were on a scale of one to four by pressing buttons on a respond pad. On one-fifth of the blocks participants heard backwards speech strings and decided how similarly they sounded. Five pairs from one condition made up a block. Blocks were 18-seconds long and were separated by 14 seconds of fixation. The experiment was broken up into five runs of 7.7 minutes each. The same participants took part in Experiments 2 as Experiment 1, with one additional sighted participant in Experiment 2.

MRI Data Acquisition and Analyses

Structural and functional data were collected on a 3 Tesla Siemens scanner using an MPRAGE pulse sequence. Anatomical data were collected with 1.33 mm isotropic voxels, while functional blood-oxygenation-level-dependent (BOLD) data were acquired in 3x3x4 mm voxels. T1- weighted structural images were collected in 128-axial slices (TR=2ms, TE=3.39ms). Functional, blood-oxygenation-level-dependent (BOLD) data were acquired in using a gradient echo EPI sequence with 30 near-axial slices (TR=2sec, TE=30ms). The first four seconds of each run were excluded to allow for steady-state magnetization. Prior to modeling, data were realigned, smoothed with a 5 mm smoothing kernel, and normalized to a standard template in Montreal Neurological Institute (MNI) space (in SPM2).

In whole-brain random-effects analyses, the general-linear model was used to analyze BOLD signal as a function of condition. Covariates of interest were convolved with a standard hemodynamic response function. Nuisance covariates included run effects, an intercept term, and global signal. Data were subjected to a high-pass filter (1 cycle/128 sec).

MT/MST ROI Definition and Verification

ROIs were defined based on a visual motion task in a separate group of eleven sighted adults. Participants saw concentric rings moving outward and inward. In a control condition, participants saw concentric rings changing in luminance. Blocks were 16 seconds long and were separated by 16 seconds of fixation. We defined a left and right MT/MST ROI using the Motion-Luminance contrast, by growing 15mm spheres around peaks of activation within MT/MST in whole-brain maps thresholded at .01, $k = 10$. $r_{MT/MST}$, 522mm, $t_{max} = 5.60, 50, -66, 4$; $l_{MT/MST}$, 574mm, $t_{max} = 6.17, -52, -72, 2$. The peak coordinates of the MT/MST ROIs are consistent with prior reports of visual motion MT/MST activity in sighted individuals. Average peaks across five representative studies: $l_{MT/MST} - 45, -70, 4$, $r_{MT/MST} 43, -69, 5$ [1-5]. The average peaks from prior studies fall within the ROIs used in the present study, as well as within the whole-brain results from the auditory motion task in the congenitally blind group.

The MT/MST ROIs were validated using data from a new set of four sighted participants. These participants performed the same visual motion task described above but were not included in the analysis defining the ROI. In both of the MT/MST ROIs (left and right), we found that each of these four participants had a greater response to motion, relative to luminance change (see table below). Variability in the effect size across participants reflects both the extent to which the MT/MST ROI overlapped with that particular subject's MT/MST, and the size and statistical significance of the activation for that subject. To ensure that the motion effect was not general to any visual brain region, but specific to the MT/MST ROIs we performed the same analysis in BA17. This BA17 ROI was generated using the BIT software tool. Unlike the MT/MST ROI, BA17 showed no hint of an increased response to motion. In all four participants the effect was in the opposite direction (luminance > motion). These analyses illustrate that the MT/MST ROIs successfully localize motion selective MT/MST in sighted individuals. Therefore, we are able to ask about the function of the anatomical equivalent of MT/MST in congenitally blind individuals. Note however that four subjects is a small number of participants, therefore caution is warranted in generalizing the present data to the population of sighted individuals.

Subject	PSC	<i>t</i> -value	<i>p</i> -value
lMT/MST			
1	0.53	<i>t</i> (316)=1.96	<i>p</i> =.05
2	0.39	<i>t</i> (316)=2.82	<i>p</i> =.005
3	0.14	<i>t</i> (316)=1.08	<i>p</i> =.28
4	0.52	<i>t</i> (158)=2.37	<i>p</i> =.02
subject-wise t-test		<i>t</i> (3)=4.35	<i>p</i> =.02
rMT/MST			
1	0.92	<i>t</i> (316)=4.50	<i>p</i> =.00001
2	0.22	<i>t</i> (316)=1.86	<i>p</i> =.06
3	0.18	<i>t</i> (316)=1.51	<i>p</i> =.13
4	0.26	<i>t</i> (158)=1.53	<i>p</i> =.13
subject-wise t-test		<i>t</i> (3)=2.25	<i>p</i> =.11
BA17			
1	-0.07	<i>t</i> (316)=-.28	<i>p</i> =.94
2	-0.39	<i>t</i> (316)=-2.04	<i>p</i> =.04
3	-0.05	<i>t</i> (316)=-.71	<i>p</i> =.48
4	-0.17	<i>t</i> (158)=-.15	<i>p</i> =.88
subject-wise t-test		<i>t</i> (3)=-2.18	<i>p</i> =.11

Resting State Functional Connectivity Analyses

Low frequency fluctuations in BOLD are correlated among brain regions [6]. These correlations occur in the absence of task and are constrained by intrinsic anatomical connectivity among brain regions [6-9]: regions with monosynaptic or polysynaptic anatomical connections have higher correlations [e.g. 10, 11]. However, functional connectivity does not solely reflect anatomical connectivity, since BOLD signal co-fluctuations are influenced by task. For example, functional connectivity of MT/MST, parietal, and prefrontal regions increases with attention to motion [12].

We correlated BOLD signal in MT/MST ROIs with BOLD signal in all Brodmann areas (during the rest blocks of Experiments 1 and 2) [13]. Analysis was conducted using the Functional Connectivity SPM8 toolbox (conn <http://web.mit.edu/swg/software.htm>). To correct for co-fluctuations in BOLD signal due to physiological and scanner noise, BOLD signal from CSF and white matter as well as SPM generated motion parameters were used as nuisance covariates (CompCorr method [14]). Additionally a bandpass filter of .01 to .08 was used. Hanning within-condition weights were used to minimize effects of non-rest blocks on rest-block activity. This procedure preferentially weights data from the middle of the rest block relative to either the beginning or end of the block. Bivariate correlations were then computed between bilateral MT/MST and other Brodmann-area-based ROIs. Correlations were computed in the sighted, congenitally blind and late blind groups and compared across groups. Unless noted otherwise in the results section, False Discover Rate (FDR) was used to correct for multiple comparisons across the brain volume.

Possible Effects of Scanner Noise on Connectivity Analyses

Functional connectivity data were collected in the absence of a task, but in the presence of scanner noise. Because functional connectivity is influenced by task, our results reflect connectivity of MT/MST in a noisy environment. One possible consequence of this is

overestimation of the functional connectivity of MT/MST and A1 in the congenitally blind group, relative to the sighted. This is because sound leads to deactivation of MT/MST of sighted individuals, but activation of MT/MST of congenitally blind individuals. Thus the presence of sound may have similar effects on MT/MST and A1 in the congenitally blind, but different effects on MT/MST and A1 in the sighted. This could increase MT/MST and A1 correlations in congenitally blind, relative to the sighted. Like previous functional neuroimaging studies, we find that A1 and MT/MST connectivity is not altered in the congenitally blind group [15, see also 16]. But in fact A1 and MT/MST connectivity may be reduced in the congenitally blind (like connectivity with S1 and M1), and resting state functional connectivity studies are insensitive to this reduction. DTI studies are needed to determine whether or not anatomical connections between A1 and MT/MST are in fact weakened in congenitally blind individuals.

Another interesting possibility is that prefrontal functional connectivity with MT/MST is influenced by the presence of noise differently in the sighted and blind groups. The presence of sound may be a cue for PFC to increase MT/MST activity in the congenitally blind, but not in the sighted. This seems plausible because prefrontal regions modulate activity in sensory brain regions based on current task demands [17-19]. In this light, altered connectivity in the congenitally blind group may reflect altered contingencies in prefrontal feedback, rather than strengthened anatomical connectivity. DTI studies are necessary to distinguish between these interesting alternatives.

Supplemental References

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