

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

Marina Bedny,<sup>1,2,\*</sup> Talia Konkle,<sup>1</sup> Kevin Pelphrey,<sup>3</sup> Rebecca Saxe,<sup>1</sup> and Alvaro Pascual-Leone<sup>2</sup>

<sup>1</sup>Brain and Cognitive Sciences Department, Massachusetts Institute of Technology, Room 46-4021, 43 Vassar Street, room 46-4021, Cambridge, MA 02139, USA

<sup>2</sup>Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue Kirstein Building KS 158 Boston, MA 02215, USA

<sup>3</sup>Yale Child Study Center, Yale University, 230 South Frontage Road, New Haven, CT 06520, USA

## 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: after long-standing 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 time course of this plasticity is not known. To test for a sensitive period in MT/MST development, we used fMRI to compare MT/MST function in congenitally blind, late-blind, and sighted adults. 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 long-standing blindness.

## Results

In sighted individuals, the middle temporal complex (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 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 [5–9], 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 long-standing 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 functional magnetic resonance imaging (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](#) available online 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 because 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. For assessment of this pattern, left and right MT/MST ROIs were defined based on data from a separate group of 12 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 ( $t(19) \leq -2.4$ ,  $p < 0.05$ ) and activated MT/MST above baseline in congenitally blind adults ( $t(9) \geq 3.2$ ,  $p < 0.05$ ). 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 ( $F[1,28] \geq 23.4$ ,  $p < 0.0001$ ; [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 a complete summary of statistics.)

\*Correspondence: [mbedny@mit.edu](mailto:mbedny@mit.edu)

**Table 1. Demographic Information of Participants**

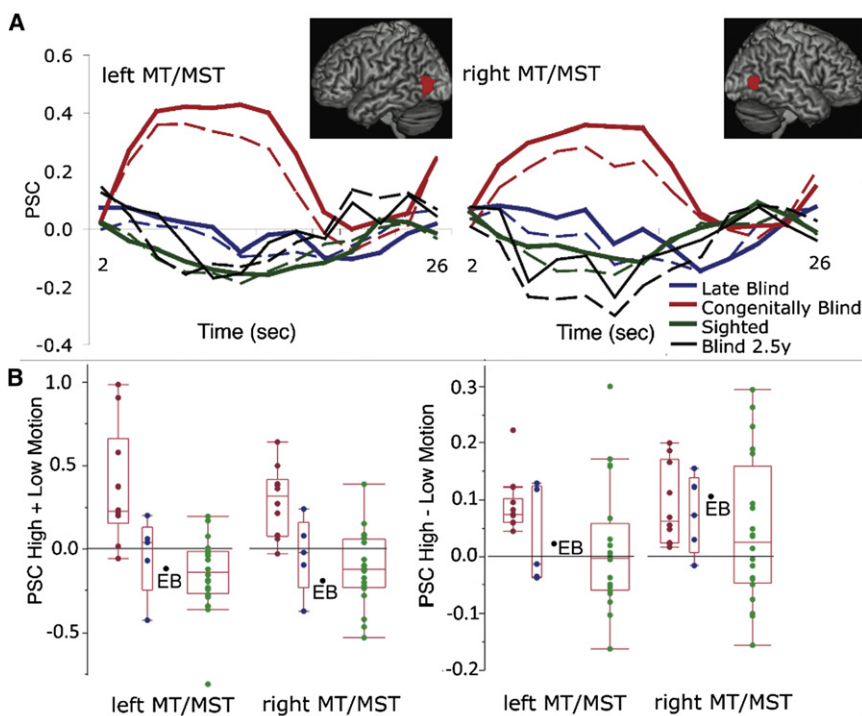
Participant	Gender	Age (yr)	Age of Blindness	Cause of Blindness	Residual Light Perception	Highest Level of Education (yr)
EB1	F	43	Birth	Premature birth/RLF	none	BA (16)
EB2	F	47	Birth	Premature birth/RLF	none	3 yr of college
EB3	M	40	Birth	Congenital bilateral cataracts	none	some college (13)
EB4	M	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

CB denotes congenitally blind, LB denotes late blind, and EB denotes early blind. Sighted participants are matched in mean age and years of education to the CB group. RLF denotes retrolental fibroplasia.

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 ( $t(9) \geq 4, p < 0.005$ ). 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 ( $F[1,28] = 4.3, p = 0.05$ ). This difference between groups was not reliable in right MT/MST. In general, the high-versus-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 (Figure 1B).

Like the ROI analyses, whole-brain analyses revealed group differences between sighted and congenitally blind individuals in MT/MST (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



**Figure 1. Activity in Left and Right MT/MST ROIs for Sighted, Congenitally Blind, and Late Blind**

(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. CB denotes congenitally blind (red), LB denotes late blind (blue), and sighted is in 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 box plot indicates sample size. The box plots 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.

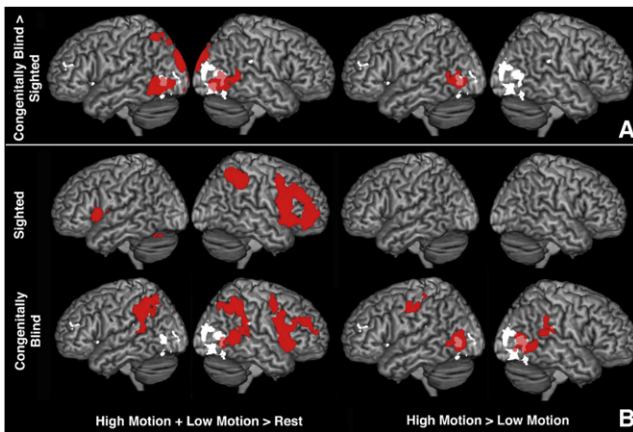


Figure 2. Brain Regions Active during Auditory Motion Task

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) ( $p < 0.05$ , 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 (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.

as in the superior temporal gyrus. Neither left nor right MT/MST were active above rest in sighted adults. In 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 and 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  $p < 0.001$  (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-versus-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.

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-versus-low motion sounds) (Figure 2 and 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-versus-rest  $F[1,13] \geq 5.3$ ,  $p < 0.05$ ). MT/MST ROIs in late-blind adults did not respond to sound more than MT/MST ROIs of the sighted ( $p > 0.3$ ). For the high-versus-low motion response, late-blind adults were not significantly different from either congenitally blind or sighted groups ( $p > 0.1$ ).

#### 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 versus not congenital blindness onset ( $F[1,12] \geq 2.3$ ,  $p < 0.05$ ), but no effect of residual light perception ( $p > 0.1$ ) (Table S1).

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 versus not congenital blindness ( $F[1,12] \geq 5.3$ ,  $p < 0.05$ ), but not number of years of blindness ( $p > 0.3$ ), predicted MT/MST activity across blind participants. Thus, the difference among congenitally and noncongenitally 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 ( $r < 0.2$ ,  $p > 0.3$ ). 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 ( $t(9) \geq 4.3$ ,  $p = 0.001$ ), 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 ( $t(9) = 4.2$ ,  $p < 0.005$ ). 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 a false discovery rate (FDR)-corrected threshold of 0.05. When the threshold was lowered to an uncorrected level of 0.01, 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.

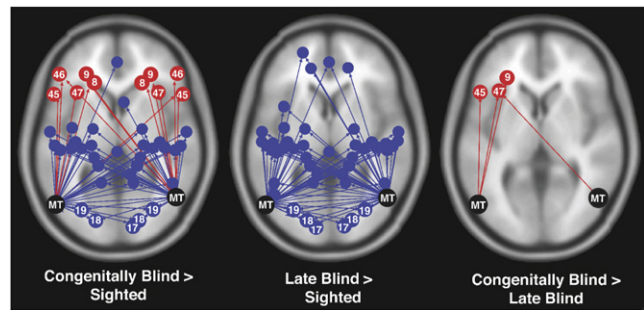


Figure 3. Functional Connectivity Results from Experiment 2

All maps are FDR corrected for multiple comparisons at  $p < 0.05$ . Regions more correlated with MT/MST across groups are shown in red, regions less correlated with MT/MST are shown in blue.

(Left) Regions differentially correlated with MT/MST in the congenitally blind relative to sighted adults.

(Center) Regions less correlated with MT/MST in late blind relative to sighted adults.

(Right) 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](#).

To confirm these exploratory findings, we examined MT/MST functional connectivity during resting blocks of a separate data set 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 ( $p < 0.05$ , FDR-corrected) ([Figure 3](#) and [Table S3](#)). These were the same lateral prefrontal regions observed in the first data set.

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](#) and [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. After 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 nonvisual inputs for influence over MT/MST activity. In the absence of early vision, nonvisual cortical structures establish a greater influence over MT/MST activity, whereas 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 nonvisual 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 2 and 3. 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 noncongenitally blind. Twenty-one sighted adults, ten congenitally blind adults, and five late-blind adults participated in experiment 2. (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 9 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, we made sounds louder or quieter, respectively. Footstep stimuli were created by recording the sounds of female and male individuals walking toward 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 ~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 decibels relative to full scale (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](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 2 s 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 1 s delays and played in random order. The blocks were 12 s long, and separated by 10 s 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 min 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 backward speech [37]. Blocks were 18 s long and were separated by 14 s of fixation. The experiment was broken up into five runs of 7.7 min each. Each run had a total of 15 rest blocks. The total duration of resting state data was therefore 17.5 min.

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 statistical parametric mapping 2 (SPM2; <http://www.fil.ion.ucl.ac.uk/>) and MATLAB-based in-house software. Whole-brain analyses were corrected for multiple comparisons at an  $\alpha < 0.05$  by performing Monte-Carlo permutation tests on the data in SnPM3 with 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 12 sighted adults [37]: right MT/MST [50 -66 4], left MT/MST [-52 -72 2] (see [Supplemental Experimental Procedures](#) 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  $2 \times 2$  analyses of variance 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 (0.01–0.08). BOLD signal from CSF and white matter as well as SPM generated motion parameters were used as nuisance regressors (functional connectivity SPM8 toolbox, <http://web.mit.edu/swg/software.htm>) [40]. Connectivity analyses were FDR-corrected at  $\alpha < 0.05$ . (Further details on neuroimaging procedures and analysis are provided in [Supplemental Experimental Procedures](#).)

#### **Supplemental Information**

Supplemental Information includes Supplemental Experimental Procedures, two figures, and three tables and can be found with this article online at doi:10.1016/j.cub.2010.09.044.

#### **Acknowledgments**

We wish to thank the New England blind community and the research participants for making this project possible. We would also like to thank Athinoula A. Martinos Imaging Center for help with fMRI data collection and analyses. Work on this study was supported by the David and Lucille Packard Foundation (to R.S.) and grants from the National Center for Research

Resources: Harvard-Thorndike General Clinical Research Center at BIDMC (NCRR MO1 RR01032) and Harvard Clinical and Translational Science Center (UL1 RR025758); NIH grants K24 RR018875 and RO1-EY12091 (to A.P.-L.) The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Received: March 21, 2010

Revised: August 6, 2010

Accepted: September 13, 2010

Published online: October 21, 2010

#### **References**

1. Dubner, R., and Zeki, S.M. (1971). Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. *Brain Res.* 35, 528–532.
2. Tootell, R.B., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R., and Belliveau, J.W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J. Neurosci.* 15, 3215–3230.
3. de Jong, B.M., Shipp, S., Skidmore, B., Frackowiak, R.S., and Zeki, S. (1994). The cerebral activity related to the visual perception of forward motion in depth. *Brain* 117, 1039–1054.
4. Zihl, J., von Cramon, D., and Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain* 106, 313–340.
5. Poirier, C., Collignon, O., Scheiber, C., Renier, L., Vanlierde, A., Tranduy, D., Veraart, C., and De Volder, A.G. (2006). Auditory motion perception activates visual motion areas in early blind subjects. *Neuroimage* 31, 279–285.
6. Saenz, M., Lewis, L.B., Huth, A.G., Fine, I., and Koch, C. (2008). Visual motion area MT+/V5 responds to auditory motion in human sight-recovery subjects. *J. Neurosci.* 28, 5141–5148.
7. Wolbers, T., Zahorik, P., and Giudice, N.A. (2010). Decoding the direction of auditory motion in blind humans. *Neuroimage*, in press. Published online May 5, 2010. 10.1016/j.neuroimage.2010.04.266.
8. Lewis, J.W., Beauchamp, M.S., and DeYoe, E.A. (2000). A comparison of visual and auditory motion processing in human cerebral cortex. *Cereb. Cortex* 10, 873–888.
9. Ricciardi, E., Vanello, N., Sani, L., Gentili, C., Scilingo, E.P., Landini, L., Guazzelli, M., Bicchì, A., Haxby, J.V., and Pietrini, P. (2007). The effect of visual experience on the development of functional architecture in hMT+. *Cereb. Cortex* 17, 2933–2939.
10. Watson, J.D., Myers, R., Frackowiak, R.S., Hajnal, J.V., Woods, R.P., Mazziotta, J.C., Shipp, S., and Zeki, S. (1993). Area V5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb. Cortex* 3, 79–94.
11. Dumoulin, S.O., Bittar, R.G., Kabani, N.J., Baker, C.L., Jr., Le Goualher, G., Bruce Pike, G., and Evans, A.C. (2000). A new anatomical landmark for reliable identification of human area V5/MT: A quantitative analysis of sulcal patterning. *Cereb. Cortex* 10, 454–463.
12. Kourtzi, Z., Bulthoff, H.H., Erb, M., and Grodd, W. (2002). Object-selective responses in the human motion area MT/MST. *Nat. Neurosci.* 5, 17–18.
13. Campana, G., Cowey, A., and Walsh, V. (2006). Visual area V5/MT remembers “what” but not “where”. *Cereb. Cortex* 16, 1766–1770.
14. Friston, K.J., Holmes, A.P., and Worsley, K.J. (1999). How many subjects constitute a study? *Neuroimage* 10, 1–5.
15. Fox, M.D., and Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8, 700–711.
16. Dosenbach, N.U., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., et al. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc. Natl. Acad. Sci. USA* 104, 11073–11078.
17. Greicius, M.D., Supekar, K., Menon, V., and Dougherty, R.F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb. Cortex* 19, 72–78.
18. Burton, H., Snyder, A.Z., Diamond, J.B., and Raichle, M.E. (2002). Adaptive changes in early and late blind: A fMRI study of verb generation to heard nouns. *J. Neurophysiol.* 88, 3359–3371.
19. Burton, H. (2003). Visual cortex activity in early and late blind people. *J. Neurosci.* 23, 4005–4011.

20. Sadato, N., Okada, T., Honda, M., and Yonekura, Y. (2002). Critical period for cross-modal plasticity in blind humans: A functional MRI study. *Neuroimage* 16, 389–400.
21. Voss, P., Gougoux, F., Zatorre, R.J., Lassonde, M., and Lepore, F. (2008). Differential occipital responses in early- and late-blind individuals during a sound-source discrimination task. *Neuroimage* 40, 746–758.
22. Noppeney, U., Friston, K.J., Ashburner, J., Frackowiak, R., and Price, C.J. (2005). Early visual deprivation induces structural plasticity in gray and white matter. *Curr. Biol.* 15, R488–R490.
23. Elleberg, D., Lewis, T.L., Maurer, D., Brar, S., and Brent, H.P. (2002). Better perception of global motion after monocular than after binocular deprivation. *Vision Res.* 42, 169–179.
24. Elleberg, D., Lewis, T.L., Defina, N., Maurer, D., Brent, H.P., Guillemot, J.P., and Lepore, F. (2005). Greater losses in sensitivity to second-order local motion than to first-order local motion after early visual deprivation in humans. *Vision Res.* 45, 2877–2884.
25. Lewis, T.L., and Maurer, D. (2005). Multiple sensitive periods in human visual development: Evidence from visually deprived children. *Dev. Psychobiol.* 46, 163–183.
26. Bourne, J.A., and Rosa, M.G. (2006). Hierarchical development of the primate visual cortex, as revealed by neurofilament immunoreactivity: Early maturation of the middle temporal area (MT). *Cereb. Cortex* 16, 405–414.
27. Wattam-Bell, J., Birtles, D., Nystrom, P., von Hofsten, C., Rosander, K., Anker, S., Atkinson, J., and Braddick, O. (2010). Reorganization of global form and motion processing during human visual development. *Curr. Biol.* 20, 411–415.
28. Dobkins, K.R. (2009). Does visual modularity increase over the course of development? *Optom. Vis. Sci.* 86, E583–E588.
29. Zaksas, D., and Pasternak, T. (2006). Directional signals in the prefrontal cortex and in area MT during a working memory for visual motion task. *J. Neurosci.* 26, 11726–11742.
30. Kourtzi, Z., and Kanwisher, N. (2000). Activation in human MT/MST by static images with implied motion. *J. Cogn. Neurosci.* 12, 48–55.
31. Recanzone, G.H., and Wurtz, R.H. (2000). Effects of attention on MT and MST neuronal activity during pursuit initiation. *J. Neurophysiol.* 83, 777–790.
32. Meyer, G.F., and Wuerger, S.M. (2001). Cross-modal integration of auditory and visual motion signals. *Neuroreport* 12, 2557–2560.
33. Meyer, G.F., Wuerger, S.M., Rohrbein, F., and Zetzsche, C. (2005). Low-level integration of auditory and visual motion signals requires spatial co-localisation. *Exp. Brain Res.* 166, 538–547.
34. Sadaghiani, S., Maier, J.X., and Noppeney, U. (2009). Natural, metaphoric, and linguistic auditory direction signals have distinct influences on visual motion processing. *J. Neurosci.* 29, 6490–6499.
35. Burman, K.J., Palmer, S.M., Gamberini, M., and Rosa, M.G. (2006). Cytoarchitectonic subdivisions of the dorsolateral frontal cortex of the marmoset monkey (*Callithrix jacchus*), and their projections to dorsal visual areas. *J. Comp. Neurol.* 495, 149–172.
36. Buchel, C., and Friston, K.J. (1997). Modulation of connectivity in visual pathways by attention: Cortical interactions evaluated with structural equation modelling and fMRI. *Cereb. Cortex* 7, 768–778.
37. Bedny, M., Caramazza, A., Grossman, E., Pascual-Leone, A., and Saxe, R. (2008). Concepts are more than percepts: The case of action verbs. *J. Neurosci.* 28, 11347–11353.
38. Nichols, T.E., and Holmes, A.P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Hum. Brain Mapp.* 15, 1–25.
39. Hayasaka, S., and Nichols, T.E. (2004). Combining voxel intensity and cluster extent with permutation test framework. *Neuroimage* 23, 54–63.
40. Behzadi, Y., Restom, K., Liu, J., and Liu, T.T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage* 37, 90–101.