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Differential Processing of the Direction and Focus of Expansion of Optic Flow Stimuli in areas MST and V3A of the Human Visual Cortex.

RunningTitle: Cortical Analysis of Optic Flow Stimuli

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Abstract

Human neuropsychological and neuroimaging studies have raised the possibility that different attributes of optic flow stimuli, namely radial direction and the position of the focus of expansion (FOE), are processed within separate cortical areas. In the human brain, visual areas V5/MT+ and V3A have been proposed as integral to the analysis of these different attributes of optic flow stimuli. In order to establish direct causal relationships between neural activity in V5/MT+ and V3A and the perception of radial motion direction and FOE position, we used Transcranial Magnetic Stimulation (TMS) to disrupt cortical activity in these areas whilst participants performed behavioural tasks dependent on these different aspects of optic flow stimuli. The cortical regions of interest were identified in seven human participants using standard fMRI retinotopic mapping techniques and functional localisers. TMS to area V3A was found to disrupt FOE positional judgements, but not radial direction discrimination, whilst the application of TMS to an anterior sub-division of hV5/MT+, MST/TO-2, produced the reverse effects, disrupting radial direction discrimination but eliciting no effect on the FOE positional judgement task. This double dissociation demonstrates that FOE position and radial direction of optic flow stimuli are signalled independently by neural activity in areas hV5/MT+ and V3A.

Key Words: transcranial magnetic stimulation, fMRI, psychophysics, V5/MT+, V3A.

New and Noteworthy

Optic flow constitutes a biologically relevant visual cue as we move through any environment. Using neuro-imaging and brain-stimulation techniques this study demonstrates that separate human brain areas are involved in the analysis of the direction of radial motion and the focus of expansion in optic flow. This dissociation reveals the existence of separate processing pathways for the analysis of different attributes of optic flow which are important for the guidance of self-locomotion and object avoidance.

Introduction

When we move through our environment visual cues about the nature and direction of this motion are provided by the changing pattern of images formed on our retinae – so called optic flow. The ability of the human visual system to analyse optic flow is of crucial biological significance as it provides key visual cues that can be used for the guidance of self-motion and object avoidance (Gibson, 1950). Movement by an individual (typically forwards) generates a focus of expansion (FOE) in optic flow from which all motion vectors expand and this provides crucial information about heading direction (Warren & Hannon, 1988). Analysis of the global nature and direction of radial motion, on the other hand, constitutes a very different type of cue to that offered by the analysis of FOE position. The signalling of radial motion provides information that can be used to globally subtract or parse flow motion, which is essential for the tracking and avoidance of independently moving objects during self-motion (Warren & Rushton, 2009).

Visually presented moving stimuli elicit neural activity across an extensive network of human brain areas including: V1, V2, V3, V3A, V3B, hV5/MT+, V6, IPS0-4 (Zeki et al., 1991; Watson et al., 1993; Tootell et al., 1997; Smith et al., 1998; Culham et al., 2001; Claeys et al., 2003; Sieffert et al., 2003; Pitzalis et al., 2010). In the human brain, two cortical areas within this network exhibit a particularly high sensitivity to visual motion. The first of these is human V5/MT+ (hV5/MT+), and is the visual area most closely associated with motion processing (Zeki et al., 1991; Watson et al., 1993; Tootell et al., 1995; Dumoulin et al., 2000; Culham et al., 2001). hV5/MT+ forms a complex comprising at least two, but possibly more visual areas (see: Kolster et al., 2010). These subdivisions have been tentatively proposed as human homologues of areas MT and MST, which form constituents of V5/MT+ in the monkey brain (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 2009). In this study we have adopted the terms MT/TO-1 for the posteriorly located area and MST/TO-2 for the anterior sub-division. This nomenclature reflects the suggested functional homology with the

macaque as well their differentiation in the human brain on the basis of their retinotopic characteristics (Amano et al., 2009). The other human visual area with a high degree of motion selectivity is area V3A which contains a representation of the full contra-lateral visual hemi-field and lies anterior and dorsal to area V3 in the occipito-parietal cortex. V3A is second only to hV5/MT+ in terms of its sensitivity to motion stimuli (Tootell et al. 1997; Smith et al., 1998; Vanduffel et al., 2002; Sieffert et al., 2003). This is in contrast to the monkey brain where it is neurons in V3, rather than V3A, which are more responsive to motion stimuli (Felleman & Van Essen, 1987).

Human neuropsychological studies have raised the possibility that the analysis of FOE position and radial motion direction of optic flow stimuli occurs within separate cortical areas. Beardsley & Vaina (2005), for example, demonstrated that a patient with damage to hV5/MT+ was impaired in terms of their ability to perceive radial motion direction but their ability to detect FOE position remained intact. Neuroimaging data also point to a segregation of function with regards to the analysis of the radial direction of optic flow and FOE position. Consistent with the functional specialisations that have been reported for monkey MT and MST (Saito et al., 1986; Mikami et al., 1986; Komatsu and Wurtz, 1988; Duffy and Wurtz, 1991a; b; Tanaka et al., 1993, Lagae et al., 1994; Eifuku and Wurtz, 1998; Duffy, 1998) the anterior subdivision of hV5/MT+, MST/TO2, has been shown to be selectively responsive to radial motion or optic flow stimuli. MST/TO-2 appears to be more specialised for encoding the global flow properties of complex motion stimuli in comparison to its posterior counterpart MT/TO-1 (Smith et al., 2006; Wall et al., 2008). In terms of the analysis of FOE position, neural activity in area V3A has been identified as potentially important. Koyama et al. (2005) in their fMRI experiments demonstrated that activity within human V3A is closely correlated with the position of FOE. Cardin et al. (2012) have also demonstrated sensitivity in V3A to FOE position.

Both neuropsychological and neuroimaging data have their limitations. In the case of the former, lesions are rarely confined to discrete visual areas, whilst the latter provide only correlative measures of brain function. As a result it is neither possible to ascertain from these results whether the perception of FOE position is causally dependent on neural activity in area V3A, nor whether a similar causal relationship exists between neural activity in hV5/MT+ and the perception of radial direction in optic flow. Therefore the purpose of this study was to test the hypothesis that human cortical areas hV5/MT+ (more specifically its anterior sub-division, MST/TO-2) and V3A perform distinct and separable contributions to the perception of radial motion direction and FOE position of optic flow stimuli. In order to establish causal dependencies, we used repetitive Transcranial Magnetic Stimulation (rTMS) to disrupt neural function within hV5/MT+ and V3A whilst participants performed behavioural tasks that assessed the ability of human observers to discriminate the direction of radially moving dots or changes in the position of FOE in optic flow stimuli. All cortical target sites were identified in each of the participants using fMRI retinotopic mapping procedures (Sereno et al., 1995; DeYeo et al., 1996; Engel et al., 1997) combined with functional localisers (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 2009).

Materials and Methods

Participants

Seven volunteers participated in this study (five male; ages 21-48). All participants had normal or corrected-to-normal vision at the time of testing and gave written informed consent. Experiments were approved by ethics committees at both the University of Bradford and York Neuroimaging Centre, and were carried out in accordance with the Declaration of Helsinki and accepted TMS safety protocols (Wassermann, 1998; Lorberbaum and Wassermann, 2000; Rossi et al., 2009).

Figure 1 here

Visual Stimuli

Visual stimuli were presented on a 19-inch Mitsubishi DiamondPro 2070SB monitor (refresh rate 75Hz; 1024 x 768 resolution) and consisted of moving white dots (size: ~0.2°; density: 4.69/deg^2) within a 10° (diameter) circular aperture. The constituent dots moved at a speed of 7°/s (with a flat speed gradient) and were presented for 200ms on each trial. In experiment 1, the radial motion stimuli comprised signal and noise dots. A percentage of the dots were signal dots that moved coherently in a radial direction (expanding/contracting). The exact percentage of signal dots was set (for each individual) at a level corresponding to the 75% correct performance threshold for the radial direction discrimination task. This was determined in preliminary psychophysical experiments. Across all the observers 75% correct performance typically required relatively low percentages of signal dots (range: 10.1 - 24.4%). The remaining (noise) dots moved in random directions and had a uniform density across the stimulus aperture. In experiment 2 a similar radial motion aperture stimulus was placed within a hemi-field of randomly moving dots and FOE position of this stimulus could be moved upwards or downwards (see Figure 1). The magnitude of the FOE displacement corresponded to 75% correct performance, which was also determined in preliminary psychophysical experiments. In order to prevent any confounding effects that could arise if the signal dots created a perceptual border at the intersection with the noise dots, a coherence level of 70% for the signal dots in the radial motion aperture stimulus was used. When the stimulus was placed within the hemi-field of randomly moving noise dots, this effectively masked the presence of any motion-defined border between the aperture stimulus and the background. To control for any potential cues arising from the difference in density of the expanding dots at the FOE versus the periphery; 10% of the 70% coherent signal dots were contracting towards a common focal point whilst the remainder were expanding in the opposite direction.

The centres of motion stimuli were positioned 15° to the left of fixation for both TMS/behavioural experiments. This placement was used in order to minimise involvement of ipsi-lateral V5/MT+ in the performance of the motion discrimination tasks as Amano et al (2009), for example, have demonstrated that the receptive fields of hV5/MT+ neurones can extend well beyond the vertical meridian into the ipsi-lateral (in this case the left) visual field.

fMRI Localisation of Cortical ROIs

All functional and structural magnetic resonance imaging scans were acquired using a GE 3-Tesla Sigma Excite HDX scanner. The multi-average, whole-head T1-weighted structural scans for each participant encompassed 176 sagittal slices (repetition time (TR) = 7.8ms, echo time (TE) = 3ms, inversion time (TI) = 450ms, field of view (FOV) = 290 x 290 x 276, 256 x 256 x 176 matrix, flip angle = 20°, 1.13 x 1.13 x 1.0mm^3). The functional MRI scan used a gradient recalled echo pulse sequences to measure T2 weighted images (TR = 3000ms, TE = 29ms, FOV = 192cm, 128x128 matrix, 39 contiguous slices, 1.5 x 1.5 x 1.5mm^3, interleaved slice order with no gap).

Two sub-divisions of hV5/MT+ (MT/TO-1 and MST/TO-2) were identified using techniques similar to those described previously (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 2009). Briefly, localiser stimuli consisting of a 15° aperture of 300 moving white dots (8°/s) were centrally displaced 17.5° relative to a central fixation target into either the left or right visual field. By contrasting responses to moving with those to static, MST/TO-2 was identified by ipsi-lateral activations to stimulation of either the right or left visual field. MT/TO-1 was located by subtracting the anterior MST/TO-2 activity from the whole hV5/MT+ complex activation found for contra-lateral stimulation (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 2009; Strong et al., 2016). Stimuli in this case were projected onto a rear-projection screen and viewed through a mirror (refresh rate 120Hz; 1920 x 1080 resolution; viewing distance 57cm).

Standard retinotopic mapping techniques (Sereno et al., 1995; DeYeo et al., 1996; Engel et al., 1997) using a 90° anti-clockwise rotating wedge (flicker rate 6Hz), and an expanding annulus (≤15°radius), both lasting 36s per cycle, were used to identify area V3A and the control site LO-1, in each participant. Area V3A, located in superior occipito-parietal cortex, contains a complete hemi-field representation of the contra-lateral visual field. This differentiates it from dorsal and ventral V2 and V3, which map only a quadrant of the contra-lateral field (Tootell et al., 1997). LO-1 lies ventral to V3A and contains a lower contra-lateral visual field map posteriorly, and an upper contra-lateral visual field representation anteriorly (see Figure 2). LO-1 was chosen as a control site because it lies in close proximity to areas V3A and hV5/MT+, but unlike them, is largely unresponsive to visual motion (Larsson & Heeger, 2006) and exhibits only weak activation in response to moving stimuli (Bartels et al., 2008). Brainvoyager QX (Brain Innovation, Maastricht) was used to analyse the fMRI data and to identify target sites for the TMS, which were selected as centre-of-mass co-ordinates for identified ROIs. Table 1 provides Talairach co-ordinates for each of the target sites (right hemisphere only) in all 7 participants.

Figure 2 here *Table 1 here*

TMS Stimulation

The TMS coil was positioned over the cortical test and control sites identified from the fMRI localisation and retinotopic mapping experiments described above. In these experiments TMS was delivered to the target sites in the right hemisphere. Following identification of these target points in 3D space, co-registration between the subject's head and the structural scans was achieved using a 3D ultrasound digitizer (CMS30P (Zebris)) in conjunction with the BrainVoyager software. This allowed coil position to be monitored and adjusted throughout the experiment by creating a local spatial co-ordinate system which links the

spatial positions of ultrasound transmitters on the subject and the coil with pre-specified fiducials on the structural MRIs (see: McKeefry et al., 2008).

During the behavioural experiments TMS pulses were delivered using a Magstim RapidPro 2 (Magstim, UK) figure-of-eight coil (50mm). During each trial a train of five biphasic pulses was applied (see Figure 1). This pulse train had a total duration of 200ms and the pulse strengths were set at 70% maximal stimulator output. The onsets of the pulse trains were synchronous with the onset of the presentation of test stimuli.

Psychophysical/TMS Experimental Procedures

Participants viewed the monitor with their right eye at a distance of 57cm with the left eye occluded and head restrained in a chin rest. All trials for Experiment 1 and Experiment 2 were set to the 75% threshold abilities of each participant. In these preliminary experiments, a method of constant stimuli (MOCS) was used to determine threshold, with 50 repetitions of each coherence level between 5-50% for the radial motion task, and 30 repetitions of each position change between -1 - +1 degree of visual angle for the FOE task.

In the combined behavioural/TMS experiments we employed a 2-AFC procedure and the order of conditions (each comprising 100 trials) was counter-balanced across participants and TMS was applied single-blind. In experiment 1, participants indicated whether the dots were moving inwards (contracting) or outwards (expanding). In experiment 2, participants viewed a reference stimulus comprising a similar aperture of radially expanding dots placed within a field of random dots (see figure paradigm). The FOE was level with fixation but was displaced in the left visual field. In a second presentation (test stimulus) the FOE was displaced either up or down at a distance set to threshold (75%) performance. Participants indicated the direction positional change perceived by an appropriate keyboard button press

and were instructed to respond as quickly and accurately as possible. Response time was measured as the time taken for the participant to press one of the decision keys on the keyboard following stimulus offset.

Statistical analysis of the results for each task was carried out using IBM SPSS Statistics 20, using repeated measure ANOVAs. The assumption of normal distribution was confirmed with Mauchly's Test of Sphericity. If this assumption was violated, the degrees of freedom (dF) were corrected to allow appropriate interpretation of the F value of the ANOVA. These corrections included the Greenhouse-Geisser when sphericity (ε) was reported as less than 0.75, and Huynh-Feldt correction when sphericity exceeded 0.75.

Results

Group averaged performance was expressed in terms of percent correct (pCorrect) for each of the TMS conditions as well as for a baseline condition (when no TMS was administered whilst the participants performed the task). Inspection of Figure 3 reveals that relative to all other TMS conditions, stimulation of MST/TO-2 results in a loss of performance in radial direction discrimination, whereas discrimination of FOE is impaired only for TMS applied to V3A. These effects are examined statistically below.

As these tasks were designed to measure two different aspects of optic flow processing, the data were interrogated for any interactions using a two-way ANOVA comparing TMS site with tasks in order to investigate independence from one another. This analysis highlighted a significant interaction between TMS site and the tasks we examined in experiments 1 and 2 ($F(3,48) = 5.98$, $p = 0.002$). Significant differences were also found across tasks ($F(1,48) = 4.57$, $p = 0.038$) and TMS sites ($F(3,48) = 5.08$, $p = 0.004$). This shows that results were significantly different between tasks and TMS conditions.

Figure 3 here

In order to examine the main effect of TMS site on performance for each task separately, repeated-measures ANOVAs were also used. For the radial motion direction discrimination, a significant effect of TMS condition on task performance was found ($F(3,18) = 13.55$, $p < 0.001$). Pair-wise comparisons (Bonferroni-corrected) for this task indicated that this effect was due to significant differences existing between Baseline and MST/TO-2 ($p = 0.018$), Control and MST/TO-2 ($p = 0.012$), and, crucially, V3A and MST/TO-2 ($p = 0.015$). All other comparisons failed to demonstrate any significant differences (Baseline *versus* Control, $p = 0.448$; all other comparisons, $p = 1.00$) (see figure 3a). These results demonstrate that neural processing in area MST/TO-2 appears to be essential for normal levels of performance for the radial motion direction discrimination task. Conversely, disruption to neural activity in area V3A has no effect on performance levels for this task.

Similar analyses applied to the data obtained in the FOE displacement experiment demonstrated show the opposite effects for areas MST/TO-2 and V3A. There is a significant main effect of TMS site on performance on the FOE task ($F(3,18) = 15.36$, $p < 0.001$). Subsequent pair-wise comparisons (Bonferroni-corrected) highlighted significant differences between Baseline and V3A ($p = 0.005$), Control and V3A ($p = 0.019$), and MST/TO-2 and V3A ($p = 0.031$), highlighting the key role of V3A in FOE processing. No other comparisons were found to be significantly different (all other comparisons equated to $p = 1.00$) (see figure 3b).

Average response times are plotted in Figure 4 and were analysed to investigate for

potential differences between TMS conditions. Repeated-measures ANOVAs demonstrated no significant effects of TMS site on speed of response for experiment 1 ($F(3,18) = 0.80$, $p = 0.509$) or experiment 2 ($F(3,18) = 2.15$, $p = 0.129$). If subjects responded quickly at the cost of accuracy, this could have confounded our accuracy results. To investigate this, percent correct was correlated against response times (see Table 2). Evidence of a positive correlation would imply that a speed-accuracy trade-off may have been present, whereas evidence of a negative correlation would suggest that slow responses were potentially due to more difficult trials.

Figure 4 here *Table 2 here*

The data are plotted in figure 5 and Pearson's R analyses identified a moderate negative correlation between percent correct and response time for experiment 1 ($r = -0.36$, $n = 28$, $p = 0.061$) but no significant relationship for experiment 2 ($r = -0.20$, $n = 28$, $p = 0.305$). It is important to note that while one of the correlations is not significant and the other approaches significance, they are both negative indicating that if a relationship between the speed of response and accuracy exists, it is one that is in the opposite direction to a 'speed-accuracy' trade off. We are confident therefore that the results of our analysis of the accuracy data (above) are not confounded by reaction times as there is no evidence for faster response times resulting in poorer performance.

Figure 5 here

Discussion

In this study we have demonstrated that the perception of different attributes of optic flow stimuli, namely, radial direction and FOE position, are dependent upon neural activity within separate visual areas within the human cerebral cortex. We have established that there is a direct causal relationship between neural activity in area MST/TO-2, a sub-division of hV5/MT+ complex, and the perception of the direction of radial motion. In addition, a similar dependency exists between neural activity in area V3A and the perception of FOE position. Importantly, we have shown a double dissociation between the involvement of visual areas V3A and MST/TO-2 in the analysis of these different aspects of optic flow stimuli which indicates that the processing of FOE position and radial motion direction occur independently of one another within these separate cortical areas.

Expanding (radial) motion is naturally apparent when an individual moves forwards through space. This optic flow constitutes a rich source of visual cues that can facilitate navigation through external environments. In static environments analysis of the FOE can provide information about the direction in which the individual is travelling (Warren & Hannon, 1988). However, in more dynamic surroundings the importance of global directional properties of optic flow in the process of 'flow parsing' has also been highlighted (Warren & Rushton 2009). This process allows signals that are generated by self-movement to be discounted in order to identify the motion of objects within a scene that are moving independently. This complimentary visual information is essential for the tracking and avoidance of objects during self-motion. Appropriate interpretation of all these cues is essential for successful navigation of the external world. Of course in addition to visual, there are a number of other non-visual cues that also contribute to the perception of self-motion (Royden et al., 1992; Bradley et al. 1996; Gu et al., 2006; Fetsch et al., 2007; Cardin & Smith, 2010; Kaminiarz et al., 2014). But if we restrict our consideration to visual cues only, the importance of optic flow appears to be highlighted by the fact that many cortical areas are responsive to such stimuli. Human

neuroimaging studies have shown that hV5/MT+, V3A, V3B, V6, ventral intraparietal area (VIP) and the cingulate sulcus visual area (CSv) are all activated by optic flow (Smith et al., 2006; Cardin et al., 2012; Morrone et al., 2000; Wall & Smith, 2009; Pitzalis et al 2013a). The stimuli used in these and other behavioural (e.g. Warren & Hannon, 1988) and neurophysiological (e.g. Zang & Britten, 2010) studies into the mechanisms of self-motion guidance and perception have typically employed centrally viewed, large-field optic flow stimuli. In comparison, the stimuli used in this study are spatially constrained and, as a result, are unlikely to provide cues for the guidance of self-motion that are as powerful as those derived from more extensive optic flow fields. The small aperture stimuli lack the richness of all the visual as well as non-visual cues that are provided by optic flow stimuli observed under more naturalistic viewing conditions. For example, there is no sense of "vection", the perception of self-movement through space, generated by these small field stimuli. But despite their relative sparseness, the aperture stimuli used in these experiments are sufficient to reveal the existence of important functional differences between the earliest stages of this processing network, with areas MST/TO-2 and V3A playing different roles in the analysis of radial flow direction and FOE position, respectively. This functional segregation is important in that it may help to explain results from neuropsychological case studies. Beardsley and Vaina, for example, examined a patient (GZ) who suffered damage to her right hV5/MT+ complex. As a result of this lesion, GZ was impaired in her ability to discriminate the radial direction of optic flow stimuli, but her ability to determine the position of their FOE remained intact (Beardsley & Vaina, 2005). The results presented here raise the possibility that this preservation of function is due to the fact that the neural processing that underpins the perception of these different attributes of optic flow is localised within separate cortical locations. The preservation of FOE perception may be attributable to the fact that that if V3A remains intact in patient GZ, this would be sufficient to support the perception of FOE position, even in the absence of hV5/MT+.

In the monkey brain, investigation of the physiological substrates of self-motion perception has centred on area MST (Britten 2008). Neurons in the dorsal region of MST (MSTd) are tuned to complex patterns of optic flow that result from self-motion (Saito et al., 1986; Tanaka et al 1986; 1989; Duffy & Wurtz, 1991; 1995). Importantly, a causal dependency has been firmly established between neural activity in this area and the perception of heading direction in monkeys (Britten & Van Wezel, 1998; 2002; Gu et al., 2006; 2007; 2008; 2012; Yu et al., 2017). The lack of any disruption to FOE positional judgments when the human homolog of MST is disrupted by TMS therefore presents something of an inconsistency between human and monkey data. A possible explanation for the lack of effect reported here might lie in our fMRI localizer paradigms for MST/TO-2. It is conceivable that whilst neurons in MST/TO-2 are activated by ipsi-lateral stimuli, some will have much stronger response biases to contra-lateral stimuli. This potentially might lead to some voxels which are genuinely part of MST/TO-2 being misclassified as falling within the MT/TO-1 sub-division of hV5/MT+. This could feasibly lead to an under-estimation of the extent of MST/TO-2 and failure to localize it properly. However, we consider this unlikely for a number of reasons. Firstly, previous studies have demonstrated a high degree of correspondence between functional data and population receptive field maps (Amano et al., 2009), which gives us confidence that the localiser used here is an appropriate method for identifying MT/TO-1 and MST/TO-2. Secondly, the Talairach co-ordinates from our centre-of-mass target points for MT/TO-1 and MST/TO-2 are similar to those previously reported for these regions (Dukelow et al., 2001; Kolster et al., 2010). Finally, the use of the current fMRI localisers has previously enabled successful functional differentiation between MT/TO-1 and MST/TO-2 where selective effects have been demonstrated for radial motion direction discrimination tasks following the application of TMS to these regions (Strong et al., 2016).

The lack of any effect of disruption to MST/TO-2 of FOE positional judgements would appear to suggest that human MST/TO-2 may not be critical for the perception of the direction of

self-motion. This is in agreement with studies that have shown human MST/TO-2 to be responsive to optic flow stimuli regardless of whether they were compatible with the perception of self-motion or not (Wall & Smith, 2008). However, an alternative explanation for the apparent lack of involvement of human MST/TO-2 in FOE judgements might lie in the fact that the task in experiment 2 requires the detection of a change in FOE position. In the macaque, MSTd neurons are insensitive to temporal changes in heading direction signaled by FOE positional shifts (Paolini et al 2000). Human MST/TO-2, whilst clearly being responsive to optic flow stimuli (Smith et al., 2006; Wall et al., 2008; Strong et al., 2016), shows a similar lack of sensitivity to changes in FOE position (Furlan et al. 2014). The detection of such changes are important in that they signal shifts in heading direction as opposed to providing information relating to instantaneous heading direction (Furlan et al., 2014). Results from this study implicate V3A as an area that is critical for signaling these transient changes in FOE position. This is consistent with previous findings. For example, studies by Koyama et al. (2005) and Cardin et al. (2012) have both shown that fMRI signal increases in V3A are elicited by changes in position of the FOE. Furthermore, this function may form part of a wider role in the analysis and prediction of the position of moving objects that has been proposed for area V3A (Maus et al., 2010).

V3A has been given relatively little consideration in the context of self-motion perception in the monkey brain (see: Britten, 2008). This may be due to differences in the role of area V3A across the species (Gaska et al., 1988; Girard et al., 1991; Galletti et al., 1990; Tootell et al., 1997; Orban et al., 2003; Tsao et al., 2003; Anzai et al., 2011). In humans, area V3A has been shown to be highly responsive to moving stimuli forming a much more prominent constituent of the cortical network that exists for motion processing (Tootell et al., 1997; McKeefry et al., 2008; 2010). Nonetheless, V3A is still considered sub-ordinate to area hV5/MT+ in this motion processing hierarchy (see: Felleman & Van Essen 1991; Britten 2008). However, the results presented here challenge this strict hierarchy by showing that

neural activity in V3A can support the perception of specific attributes of moving stimuli, even in the absence of a normally functioning hV5/MT+. The analysis of optic flow does not simply occur in a serial fashion with information passing from V3A to hV5/MT+ for further processing. Instead, our results, consistent with neuropsychological reports, point to the existence of parallel processing pathways for radial direction and FOE positional change. MST/TO-2 and V3A would appear to form important initial stages in the processing of these two key attributes of optic flow stimuli that can ultimately be used in flow parsing and signal heading direction, both of which make important contributions to the guidance of self-movement.

The notion of multiple motion processing pathways emanating from early visual areas is compatible with previous studies (Pitzalis et al., 2010; 2013b,c, 2015) but carries with it the implication that signals from these pathways must be combined at some later stage. In both humans and monkeys other 'higher' brain areas have been identified as possible subsequent stages in the perception of self-motion. One such area is V6, which is found in the medial parieto-occipital sulcus and is thought to be involved in the analysis of self-motion relative to object motion in dynamic environments (Galletti et al., 1990; 2001; Shipp et al., 1998; Pitzalis et al., 2010; 2013a,b,c, 2015; Cardin & Smith, 2011; Fischer et al., 2012; Cardin et al., 2012; Fan et al., 2015). V6 does not appear to exhibit sensitivity to changes in FOE position (Cardin et al., 2012; Furlan et al., 2014) and as a result is considered more important in flow parsing for the purposes of object avoidance during self-motion, rather than heading direction analysis per se (Cardin et al., 2012). Another key region is the polysensory ventral intraparietal area (VIP). In monkeys, VIP contains neurons that have very similar response properties to those found in MSTd and are important in the encoding of heading direction (Schaafsma & Duysens, 1996; Bremmer et al., 2002; Zhang & Britten, 2010, 2011). The putative human homologue of VIP has also been shown to be responsive to egomotion compatible optic flow and changes in FOE position (Wall & Smith 2008; Furlan et al, 2014).

In the human brain, VIP along with another cortical region found on the cingulate gyrus, CSv, have been identified as key areas in a pathway involved in the analysis of instantaneous changes in FOE position as a means of computing heading direction (Furlan et al., 2014). The extent to which neural activity in these higher human cortical areas can be causally related to flow parsing mechanisms or to the perception of heading direction remains to be determined. But results from this study would suggest that at a relatively early stage there is evidence of segregated processing for FOE position and radial motion direction in optic flow stimuli. This segregation may persist in areas V6, VIP and CSv as a means to support the different requirements for the analysis and guidance of self-motion.

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Tables

		x	y	z
MST/TO-2	*This Study (n=7)*	42 ± 5	-69 ± 9	0 ± 9
	Dukelow et al., 2001 (n=8)	45 ± 3	-60 ± 5	5 ± 4
	Kolster et al., 2010 (n=11)	44	-70	5
V3A	*This Study (n=7)*	17 ± 6	-93 ± 5	15 ± 8
	Tootell et al., 1997 (n=5)	29	-86	19
LO-1	*This Study (n=7)*	27 ± 6	-89 ± 2	1 ± 3
	Larsson and Heeger, 2006 (n=15)	32 ± 4	-89 ± 5	3 ± 7

Table 1. *Average Talairach co-ordinates for centre of target TMS sites (MST/TO-2, V3A, LO-1) in right hemisphere (RH) ± standard deviation (where available). Results from the current study are compared with previous data as cited in the table.*

	Mean	**Std. Deviation**
Experiment 1 (Radial)		
Percent Correct (%)	76.86	8.15
Response Times (s)	0.73	0.28
Experiment 2 (FOE)		
Percent Correct (%)	73.25	7.32
Response Times (s)	0.65	0.20

Table 2. *Means and standard deviations for percent correct and response times for the correlational analysis.*

Figure Legends

Figure 1. *TMS/Behavioural Paradigms. Experiment 1: radial motion stimuli (expanding or contracting) were presented in a circular aperture displaced 15° to the left of a fixation cross. The onset of a repetitive train of 5 TMS pulses was coincident and coextensive with the onset of this stimulus. Following stimulus offset the participants reported the perceived direction of the motion (in or out) by a key press. Experiment 2: each test sequence began with the onset of a reference stimulus (200 ms) comprising a circular aperture of radially expanding dots embedded in a background of randomly moving noise dots. After a 2000 ms delay a test stimulus was presented, in which the FOE of the radial motion was displaced either upwards or downwards. The delivery of the TMS pulse train was coincident with the onset of the test stimulus. Following test offset participants reported the perceived direction of FOE displacement (up or down) by a key press.*

Figure 2*. Location of main cortical ROI target sites for TMS. Inflated right hemispheres for two subjects (S3 and S7) with overlaid positions of TMS target sites used in experiment 1 and experiment 2. The bottom figure shows a magnified view of the posterior section of the hemisphere. The representation of the visual field in each area is denoted with a symbol ('+' / '-'). A '+' indicates representation of the superior contra-lateral visual field; whilst '-' indicates the inferior contra-lateral visual field. These markings are absent from the representations of MST/TO-2 as the retinotopic mapping did not produce reliable maps within these regions.*

Figure 3. *Average Percent Correct Data from Experiment 1 and Experiment 2. Bar charts showing average percent correct (%) across experiment 1 (a) and experiment 2 (b). Error bars represent S.E.M. Asterisks represent significance at p<0.05 (*) and p<0.01 (**).*

Figure 4. *Average Response Time Data from Experiment 1 and Experiment 2. Bar charts showing average response time (s) across experiment 1 (a) and experiment 2 (b). Error bars represent S.E.M.*

Figure 5. *Correlational Data for Percent Correct and Response Time from Experiment 1 and Experiment 2. A scatter plot showing relationship between percent correct and response time across experiment 1 (Radial) and experiment 2 (FOE). Error bars represent S.E.M. Asterisks represent significance at p<0.05 (*).*