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Strong, Samantha L, Silson, Edward H, Gouws, Andre D et al. (2 more authors) (2017) Differential Processing of the Direction and Focus of Expansion of Optic Flow Stimuli in areas MST and V3A of the Human Visual Cortex. Journal of Neurophysiology. jn.00031.2017. ISSN 0022-3077

https://doi.org/10.1152/jn.00031.2017

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6	Differential Processing of the Direction and Focus of
7	Expansion of Optic Flow Stimuli in areas MST and V3A of
8 9 10	the Human Visual Contex.
11 12	RunningTitle: Cortical Analysis of Optic Flow Stimuli
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#### 48 Abstract

49 Human neuropsychological and neuroimaging studies have raised the possibility that 50 different attributes of optic flow stimuli, namely radial direction and the position of the focus 51 of expansion (FOE), are processed within separate cortical areas. In the human brain, visual 52 areas V5/MT+ and V3A have been proposed as integral to the analysis of these different 53 attributes of optic flow stimuli. In order to establish direct causal relationships between neural 54 activity in V5/MT+ and V3A and the perception of radial motion direction and FOE position, 55 we used Transcranial Magnetic Stimulation (TMS) to disrupt cortical activity in these areas 56 whilst participants performed behavioural tasks dependent on these different aspects of optic 57 flow stimuli. The cortical regions of interest were identified in seven human participants using 58 standard fMRI retinotopic mapping techniques and functional localisers. TMS to area V3A 59 was found to disrupt FOE positional judgements, but not radial direction discrimination, whilst 60 the application of TMS to an anterior sub-division of hV5/MT+, MST/TO-2, produced the 61 reverse effects, disrupting radial direction discrimination but eliciting no effect on the FOE 62 positional judgement task. This double dissociation demonstrates that FOE position and 63 radial direction of optic flow stimuli are signalled independently by neural activity in areas 64 hV5/MT+ and V3A.

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

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## 68 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.

#### 75 Introduction

76 When we move through our environment visual cues about the nature and direction of this 77 motion are provided by the changing pattern of images formed on our retinae - so called 78 optic flow. The ability of the human visual system to analyse optic flow is of crucial biological 79 significance as it provides key visual cues that can be used for the guidance of self-motion 80 and object avoidance (Gibson, 1950). Movement by an individual (typically forwards) 81 generates a focus of expansion (FOE) in optic flow from which all motion vectors expand and 82 this provides crucial information about heading direction (Warren & Hannon, 1988). Analysis 83 of the global nature and direction of radial motion, on the other hand, constitutes a very 84 different type of cue to that offered by the analysis of FOE position. The signalling of radial 85 motion provides information that can be used to globally subtract or parse flow motion, which 86 is essential for the tracking and avoidance of independently moving objects during self-87 motion (Warren & Rushton, 2009).

88

89 Visually presented moving stimuli elicit neural activity across an extensive network of human 90 brain areas including: V1, V2, V3, V3A, V3B, hV5/MT+, V6, IPS0-4 (Zeki et al., 1991; 91 Watson et al., 1993; Tootell et al., 1997; Smith et al., 1998; Culham et al., 2001; Claeys et 92 al., 2003; Sieffert et al., 2003; Pitzalis et al., 2010). In the human brain, two cortical areas 93 within this network exhibit a particularly high sensitivity to visual motion. The first of these is 94 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; 95 96 Culham et al., 2001). hV5/MT+ forms a complex comprising at least two, but possibly more 97 visual areas (see: Kolster et al., 2010). These subdivisions have been tentatively proposed 98 as human homologues of areas MT and MST, which form constituents of V5/MT+ in the 99 monkey brain (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 2009). In this study we 100 have adopted the terms MT/TO-1 for the posteriorly located area and MST/TO-2 for the 101 anterior sub-division. This nomenclature reflects the suggested functional homology with the 102 macaque as well their differentiation in the human brain on the basis of their retinotopic 103 characteristics (Amano et al., 2009). The other human visual area with a high degree of 104 motion selectivity is area V3A which contains a representation of the full contra-lateral visual 105 hemi-field and lies anterior and dorsal to area V3 in the occipito-parietal cortex. V3A is 106 second only to hV5/MT+ in terms of its sensitivity to motion stimuli (Tootell et al. 1997; Smith 107 et al., 1998; Vanduffel et al., 2002; Sieffert et al., 2003). This is in contrast to the monkey 108 brain where it is neurons in V3, rather than V3A, which are more responsive to motion stimuli 109 (Felleman & Van Essen, 1987).

110

111 Human neuropsychological studies have raised the possibility that the analysis of FOE 112 position and radial motion direction of optic flow stimuli occurs within separate cortical areas. 113 Beardsley & Vaina (2005), for example, demonstrated that a patient with damage to 114 hV5/MT+ was impaired in terms of their ability to perceive radial motion direction but their 115 ability to detect FOE position remained intact. Neuroimaging data also point to a segregation 116 of function with regards to the analysis of the radial direction of optic flow and FOE position. 117 Consistent with the functional specialisations that have been reported for monkey MT and 118 MST (Saito et al., 1986; Mikami et al., 1986; Komatsu and Wurtz, 1988; Duffy and Wurtz, 119 1991a; b; Tanaka et al., 1993, Lagae et al., 1994; Eifuku and Wurtz, 1998; Duffy, 1998) the 120 anterior subdivision of hV5/MT+, MST/TO2, has been shown to be selectively responsive to 121 radial motion or optic flow stimuli. MST/TO-2 appears to be more specialised for encoding 122 the global flow properties of complex motion stimuli in comparison to its posterior counterpart 123 MT/TO-1 (Smith et al., 2006; Wall et al., 2008). In terms of the analysis of FOE position, 124 neural activity in area V3A has been identified as potentially important. Koyama et al. (2005) 125 in their fMRI experiments demonstrated that activity within human V3A is closely correlated 126 with the position of FOE. Cardin et al. (2012) have also demonstrated sensitivity in V3A to 127 FOE position.

128 Both neuropsychological and neuroimaging data have their limitations. In the case of the 129 former, lesions are rarely confined to discrete visual areas, whilst the latter provide only 130 correlative measures of brain function. As a result it is neither possible to ascertain from 131 these results whether the perception of FOE position is causally dependent on neural activity 132 in area V3A, nor whether a similar causal relationship exists between neural activity in 133 hV5/MT+ and the perception of radial direction in optic flow. Therefore the purpose of this 134 study was to test the hypothesis that human cortical areas hV5/MT+ (more specifically its 135 anterior sub-division, MST/TO-2) and V3A perform distinct and separable contributions to the 136 perception of radial motion direction and FOE position of optic flow stimuli. In order to 137 establish causal dependencies, we used repetitive Transcranial Magnetic Stimulation (rTMS) 138 to disrupt neural function within hV5/MT+ and V3A whilst participants performed behavioural 139 tasks that assessed the ability of human observers to discriminate the direction of radially 140 moving dots or changes in the position of FOE in optic flow stimuli. All cortical target sites 141 were identified in each of the participants using fMRI retinotopic mapping procedures 142 (Sereno et al., 1995; DeYeo et al., 1996; Engel et al., 1997) combined with functional 143 localisers (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 2009).

144

### 145 Materials and Methods

#### 146 **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).

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#### Figure 1 here

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#### 156 Visual Stimuli

157 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: 158 4.69/deg<sup>2</sup>) within a 10° (diameter) circular aperture. The constituent dots moved at a speed 159 160 of 7°/s (with a flat speed gradient) and were presented for 200ms on each trial. In experiment 161 1, the radial motion stimuli comprised signal and noise dots. A percentage of the dots were 162 signal dots that moved coherently in a radial direction (expanding/contracting). The exact 163 percentage of signal dots was set (for each individual) at a level corresponding to the 75% 164 correct performance threshold for the radial direction discrimination task. This was 165 determined in preliminary psychophysical experiments. Across all the observers 75% correct 166 performance typically required relatively low percentages of signal dots (range: 10.1 -167 24.4%). The remaining (noise) dots moved in random directions and had a uniform density 168 across the stimulus aperture. In experiment 2 a similar radial motion aperture stimulus was 169 placed within a hemi-field of randomly moving dots and FOE position of this stimulus could 170 be moved upwards or downwards (see Figure 1). The magnitude of the FOE displacement 171 corresponded to 75% correct performance, which was also determined in preliminary 172 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 173 174 coherence level of 70% for the signal dots in the radial motion aperture stimulus was used. 175 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 176 177 and the background. To control for any potential cues arising from the difference in density of 178 the expanding dots at the FOE versus the periphery; 10% of the 70% coherent signal dots 179 were contracting towards a common focal point whilst the remainder were expanding in the 180 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.

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#### 189 fMRI Localisation of Cortical ROIs

190 All functional and structural magnetic resonance imaging scans were acquired using a GE 3-191 Tesla Sigma Excite HDX scanner. The multi-average, whole-head T1-weighted structural 192 scans for each participant encompassed 176 sagittal slices (repetition time (TR) = 7.8ms, 193 echo time (TE) = 3ms, inversion time (TI) = 450ms, field of view (FOV) = 290 x 290 x 276, 194 256 x 256 x 176 matrix, flip angle = 20°, 1.13 x 1.13 x 1.0mm<sup>3</sup>). The functional MRI scan 195 used a gradient recalled echo pulse sequences to measure T2 weighted images (TR = 196 3000ms, TE = 29ms, FOV = 192cm, 128x128 matrix, 39 contiguous slices, 1.5 x 1.5 x 1.5mm<sup>3</sup>, interleaved slice order with no gap). 197

198

199 Two sub-divisions of hV5/MT+ (MT/TO-1 and MST/TO-2) were identified using techniques 200 similar to those described previously (Dukelow et al., 2001; Huk et al., 2002; Amano et al., 201 2009). Briefly, localiser stimuli consisting of a 15° aperture of 300 moving white dots (8°/s) 202 were centrally displaced 17.5° relative to a central fixation target into either the left or right 203 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-204 205 1 was located by subtracting the anterior MST/TO-2 activity from the whole hV5/MT+ 206 complex activation found for contra-lateral stimulation (Dukelow et al., 2001; Huk et al., 207 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 208 209 resolution; viewing distance 57cm).

211 Standard retinotopic mapping techniques (Sereno et al., 1995; DeYeo et al., 1996; Engel et 212 al., 1997) using a 90° anti-clockwise rotating wedge (flicker rate 6Hz), and an expanding 213 annulus (≤15° radius), both lasting 36s per cycle, were used to identify area V3A and the 214 control site LO-1, in each participant. Area V3A, located in superior occipito-parietal cortex, 215 contains a complete hemi-field representation of the contra-lateral visual field. This 216 differentiates it from dorsal and ventral V2 and V3, which map only a guadrant of the contra-217 lateral field (Tootell et al., 1997). LO-1 lies ventral to V3A and contains a lower contra-lateral 218 visual field map posteriorly, and an upper contra-lateral visual field representation anteriorly 219 (see Figure 2). LO-1 was chosen as a control site because it lies in close proximity to areas 220 V3A and hV5/MT+, but unlike them, is largely unresponsive to visual motion (Larsson & 221 Heeger, 2006) and exhibits only weak activation in response to moving stimuli (Bartels et al., 222 2008). Brainvoyager QX (Brain Innovation, Maastricht) was used to analyse the fMRI data 223 and to identify target sites for the TMS, which were selected as centre-of-mass co-ordinates 224 for identified ROIs. Table 1 provides Talairach co-ordinates for each of the target sites (right 225 hemisphere only) in all 7 participants.

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#### 229 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

Figure 2 here

Table 1 here

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

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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.

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## 247 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.

254

255 In the combined behavioural/TMS experiments we employed a 2-AFC procedure and the 256 order of conditions (each comprising 100 trials) was counter-balanced across participants 257 and TMS was applied single-blind. In experiment 1, participants indicated whether the dots 258 were moving inwards (contracting) or outwards (expanding). In experiment 2, participants 259 viewed a reference stimulus comprising a similar aperture of radially expanding dots placed 260 within a field of random dots (see figure paradigm). The FOE was level with fixation but was 261 displaced in the left visual field. In a second presentation (test stimulus) the FOE was 262 displaced either up or down at a distance set to threshold (75%) performance. Participants 263 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.

267

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 ( $\epsilon$ ) was reported as less than 0.75, and Huynh-Feldt correction when sphericity exceeded 0.75.

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#### 276 **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.

283

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. 291

## Figure 3 here

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294 In order to examine the main effect of TMS site on performance for each task separately, 295 repeated-measures ANOVAs were also used. For the radial motion direction discrimination, 296 a significant effect of TMS condition on task performance was found (F(3,18) = 13.55, p < 297 0.001). Pair-wise comparisons (Bonferroni-corrected) for this task indicated that this effect 298 was due to significant differences existing between Baseline and MST/TO-2 (p = 0.018), 299 Control and MST/TO-2 (p = 0.012), and, crucially, V3A and MST/TO-2 (p = 0.015). All other 300 comparisons failed to demonstrate any significant differences (Baseline versus Control, p = 301 0.448; all other comparisons, p = 1.00) (see figure 3a). These results demonstrate that 302 neural processing in area MST/TO-2 appears to be essential for normal levels of 303 performance for the radial motion direction discrimination task. Conversely, disruption to 304 neural activity in area V3A has no effect on performance levels for this task.

305

306 Similar analyses applied to the data obtained in the FOE displacement experiment 307 demonstrated show the opposite effects for areas MST/TO-2 and V3A. There is a significant 308 main effect of TMS site on performance on the FOE task (F(3,18) = 15.36, p < 0.001). 309 Subsequent pair-wise comparisons (Bonferroni-corrected) highlighted significant differences 310 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 311 312 were found to be significantly different (all other comparisons equated to p = 1.00) (see 313 figure 3b).

314

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

316 potential differences between TMS conditions. Repeated-measures ANOVAs demonstrated 317 no significant effects of TMS site on speed of response for experiment 1 (F(3,18) = 0.80, p = 318 0.509) or experiment 2 (F(3,18) = 2.15, p = 0.129). If subjects responded quickly at the cost 319 of accuracy, this could have confounded our accuracy results. To investigate this, percent 320 correct was correlated against response times (see Table 2). Evidence of a positive 321 correlation would imply that a speed-accuracy trade-off may have been present, whereas 322 evidence of a negative correlation would suggest that slow responses were potentially due to 323 more difficult trials.

324

325

#### Figure 4 here Table 2 here

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327 The data are plotted in figure 5 and Pearson's R analyses identified a moderate negative 328 correlation between percent correct and response time for experiment 1 (r = -0.36, n = 28, p 329 = 0.061) but no significant relationship for experiment 2 (r = -0.20, n = 28, p = 0.305). It is 330 important to note that while one of the correlations is not significant and the other 331 approaches significance, they are both negative indicating that if a relationship between the 332 speed of response and accuracy exists, it is one that is in the opposite direction to a 'speedaccuracy' trade off. We are confident therefore that the results of our analysis of the 333 accuracy data (above) are not confounded by reaction times as there is no evidence for 334 335 faster response times resulting in poorer performance.

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Figure 5 here

#### 341 **Discussion**

342 In this study we have demonstrated that the perception of different attributes of optic flow 343 stimuli, namely, radial direction and FOE position, are dependent upon neural activity within 344 separate visual areas within the human cerebral cortex. We have established that there is a 345 direct causal relationship between neural activity in area MST/TO-2, a sub-division of 346 hV5/MT+ complex, and the perception of the direction of radial motion. In addition, a similar 347 dependency exists between neural activity in area V3A and the perception of FOE position. 348 Importantly, we have shown a double dissociation between the involvement of visual areas 349 V3A and MST/TO-2 in the analysis of these different aspects of optic flow stimuli which 350 indicates that the processing of FOE position and radial motion direction occur independently 351 of one another within these separate cortical areas.

352

Expanding (radial) motion is naturally apparent when an individual moves forwards through 353 354 space. This optic flow constitutes a rich source of visual cues that can facilitate navigation 355 through external environments. In static environments analysis of the FOE can provide 356 information about the direction in which the individual is travelling (Warren & Hannon, 1988). 357 However, in more dynamic surroundings the importance of global directional properties of 358 optic flow in the process of 'flow parsing' has also been highlighted (Warren & Rushton 359 2009). This process allows signals that are generated by self-movement to be discounted in 360 order to identify the motion of objects within a scene that are moving independently. This 361 complimentary visual information is essential for the tracking and avoidance of objects during 362 self-motion. Appropriate interpretation of all these cues is essential for successful navigation 363 of the external world. Of course in addition to visual, there are a number of other non-visual 364 cues that also contribute to the perception of self-motion (Royden et al., 1992; Bradley et al. 365 1996; Gu et al., 2006; Fetsch et al., 2007; Cardin & Smith, 2010; Kaminiarz et al., 2014). But 366 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 367

368 neuroimaging studies have shown that hV5/MT+, V3A, V3B, V6, ventral intraparietal area 369 (VIP) and the cingulate sulcus visual area (CSv) are all activated by optic flow (Smith et al., 370 2006; Cardin et al., 2012; Morrone et al., 2000; Wall & Smith, 2009; Pitzalis et al 2013a). The 371 stimuli used in these and other behavioural (e.g. Warren & Hannon, 1988) and 372 neurophysiological (e.g. Zang & Britten, 2010) studies into the mechanisms of self-motion 373 guidance and perception have typically employed centrally viewed, large-field optic flow 374 stimuli. In comparison, the stimuli used in this study are spatially constrained and, as a 375 result, are unlikely to provide cues for the guidance of self-motion that are as powerful as 376 those derived from more extensive optic flow fields. The small aperture stimuli lack the 377 richness of all the visual as well as non-visual cues that are provided by optic flow stimuli 378 observed under more naturalistic viewing conditions. For example, there is no sense of 379 "vection", the perception of self-movement through space, generated by these small field 380 stimuli. But despite their relative sparseness, the aperture stimuli used in these experiments 381 are sufficient to reveal the existence of important functional differences between the earliest 382 stages of this processing network, with areas MST/TO-2 and V3A playing different roles in 383 the analysis of radial flow direction and FOE position, respectively. This functional 384 segregation is important in that it may help to explain results from neuropsychological case 385 studies. Beardsley and Vaina, for example, examined a patient (GZ) who suffered damage to 386 her right hV5/MT+ complex. As a result of this lesion, GZ was impaired in her ability to 387 discriminate the radial direction of optic flow stimuli, but her ability to determine the position 388 of their FOE remained intact (Beardsley & Vaina, 2005). The results presented here raise the 389 possibility that this preservation of function is due to the fact that the neural processing that 390 underpins the perception of these different attributes of optic flow is localised within separate 391 cortical locations. The preservation of FOE perception may be attributable to the fact that 392 that if V3A remains intact in patient GZ, this would be sufficient to support the perception of 393 FOE position, even in the absence of hV5/MT+.

394

395 In the monkey brain, investigation of the physiological substrates of self-motion perception 396 has centred on area MST (Britten 2008). Neurons in the dorsal region of MST (MSTd) are 397 tuned to complex patterns of optic flow that result from self-motion (Saito et al., 1986; 398 Tanaka et al 1986; 1989; Duffy & Wurtz, 1991; 1995). Importantly, a causal dependency has 399 been firmly established between neural activity in this area and the perception of heading 400 direction in monkeys (Britten & Van Wezel, 1998; 2002; Gu et al., 2006; 2007; 2008; 2012; 401 Yu et al., 2017). The lack of any disruption to FOE positional judgments when the human 402 homolog of MST is disrupted by TMS therefore presents something of an inconsistency 403 between human and monkey data. A possible explanation for the lack of effect reported here 404 might lie in our fMRI localizer paradigms for MST/TO-2. It is conceivable that whilst neurons 405 in MST/TO-2 are activated by ipsi-lateral stimuli, some will have much stronger response 406 biases to contra-lateral stimuli. This potentially might lead to some voxels which are 407 genuinely part of MST/TO-2 being misclassified as falling within the MT/TO-1 sub-division of 408 hV5/MT+. This could feasibly lead to an under-estimation of the extent of MST/TO-2 and 409 failure to localize it properly. However, we consider this unlikely for a number of reasons. 410 Firstly, previous studies have demonstrated a high degree of correspondence between 411 functional data and population receptive field maps (Amano et al., 2009), which gives us 412 confidence that the localiser used here is an appropriate method for identifying MT/TO-1 and 413 MST/TO-2. Secondly, the Talairach co-ordinates from our centre-of-mass target points for 414 MT/TO-1 and MST/TO-2 are similar to those previously reported for these regions (Dukelow 415 et al., 2001; Kolster et al., 2010). Finally, the use of the current fMRI localisers has 416 previously enabled successful functional differentiation between MT/TO-1 and MST/TO-2 417 where selective effects have been demonstrated for radial motion direction discrimination 418 tasks following the application of TMS to these regions (Strong et al., 2016).

419

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

422 self-motion. This is in agreement with studies that have shown human MST/TO-2 to be 423 responsive to optic flow stimuli regardless of whether they were compatible with the 424 perception of self-motion or not (Wall & Smith, 2008). However, an alternative explanation 425 for the apparent lack of involvement of human MST/TO-2 in FOE judgements might lie in the 426 fact that the task in experiment 2 requires the detection of a change in FOE position. In the 427 macaque, MSTd neurons are insensitive to temporal changes in heading direction signaled 428 by FOE positional shifts (Paolini et al 2000). Human MST/TO-2, whilst clearly being 429 responsive to optic flow stimuli (Smith et al., 2006; Wall et al., 2008; Strong et al., 2016), 430 shows a similar lack of sensitivity to changes in FOE position (Furlan et al. 2014). The 431 detection of such changes are important in that they signal shifts in heading direction as 432 opposed to providing information relating to instantaneous heading direction (Furlan et al., 433 2014). Results from this study implicate V3A as an area that is critical for signaling these 434 transient changes in FOE position. This is consistent with previous findings. For example, 435 studies by Koyama et al. (2005) and Cardin et al. (2012) have both shown that fMRI signal 436 increases in V3A are elicited by changes in position of the FOE. Furthermore, this function 437 may form part of a wider role in the analysis and prediction of the position of moving objects 438 that has been proposed for area V3A (Maus et al., 2010).

439

440 V3A has been given relatively little consideration in the context of self-motion perception in 441 the monkey brain (see: Britten, 2008). This may be due to differences in the role of area V3A 442 across the species (Gaska et al., 1988; Girard et al., 1991; Galletti et al., 1990; Tootell et al., 443 1997; Orban et al., 2003; Tsao et al., 2003; Anzai et al., 2011). In humans, area V3A has 444 been shown to be highly responsive to moving stimuli forming a much more prominent 445 constituent of the cortical network that exists for motion processing (Tootell et al., 1997; 446 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 447 2008). However, the results presented here challenge this strict hierarchy by showing that 448

neural activity in V3A can support the perception of specific attributes of moving stimuli, even 449 450 in the absence of a normally functioning hV5/MT+. The analysis of optic flow does not simply 451 occur in a serial fashion with information passing from V3A to hV5/MT+ for further 452 processing. Instead, our results, consistent with neuropsychological reports, point to the 453 existence of parallel processing pathways for radial direction and FOE positional change. 454 MST/TO-2 and V3A would appear to form important initial stages in the processing of these 455 two key attributes of optic flow stimuli that can ultimately be used in flow parsing and signal 456 heading direction, both of which make important contributions to the guidance of self-457 movement.

458

459 The notion of multiple motion processing pathways emanating from early visual areas is 460 compatible with previous studies (Pitzalis et al., 2010; 2013b,c, 2015) but carries with it the 461 implication that signals from these pathways must be combined at some later stage. In both 462 humans and monkeys other 'higher' brain areas have been identified as possible subsequent 463 stages in the perception of self-motion. One such area is V6, which is found in the medial 464 parieto-occipital sulcus and is thought to be involved in the analysis of self-motion relative to 465 object motion in dynamic environments (Galletti et al., 1990; 2001; Shipp et al., 1998; Pitzalis 466 et al., 2010; 2013a,b,c, 2015; Cardin & Smith, 2011; Fischer et al., 2012; Cardin et al., 2012; 467 Fan et al., 2015). V6 does not appear to exhibit sensitivity to changes in FOE position 468 (Cardin et al., 2012; Furlan et al., 2014) and as a result is considered more important in flow 469 parsing for the purposes of object avoidance during self-motion, rather than heading 470 direction analysis per se (Cardin et al., 2012). Another key region is the polysensory ventral 471 intraparietal area (VIP). In monkeys, VIP contains neurons that have very similar response 472 properties to those found in MSTd and are important in the encoding of heading direction 473 (Schaafsma & Duysens, 1996; Bremmer et al., 2002; Zhang & Britten, 2010, 2011). The 474 putative human homologue of VIP has also been shown to be responsive to egomotion 475 compatible optic flow and changes in FOE position (Wall & Smith 2008; Furlan et al, 2014).

476 In the human brain, VIP along with another cortical region found on the cingulate gyrus, CSv, 477 have been identified as key areas in a pathway involved in the analysis of instantaneous 478 changes in FOE position as a means of computing heading direction (Furlan et al., 2014). 479 The extent to which neural activity in these higher human cortical areas can be causally 480 related to flow parsing mechanisms or to the perception of heading direction remains to be 481 determined. But results from this study would suggest that at a relatively early stage there is 482 evidence of segregated processing for FOE position and radial motion direction in optic flow 483 stimuli. This segregation may persist in areas V6, VIP and CSv as a means to support the 484 different requirements for the analysis and guidance of self-motion.

485

## 486 Acknowledgements

This work was funded by the BBSRC (grant B/N003012/1). We thank William McIlhagga for
comments on previous versions of this paper.

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# 705 Tables

		x	У	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.

# 719 Figure Legends

720 Figure 1. TMS/Behavioural Paradigms. Experiment 1: radial motion stimuli (expanding or contracting) 721 were presented in a circular aperture displaced 15° to the left of a fixation cross. The onset of a 722 repetitive train of 5 TMS pulses was coincident and coextensive with the onset of this stimulus. 723 Following stimulus offset the participants reported the perceived direction of the motion (in or out) by a 724 key press. Experiment 2: each test sequence began with the onset of a reference stimulus (200 ms) 725 comprising a circular aperture of radially expanding dots embedded in a background of randomly 726 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 727 728 coincident with the onset of the test stimulus. Following test offset participants reported the perceived 729 direction of FOE displacement (up or down) by a key press.

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**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.

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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 (\*\*).</li>

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**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.

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**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 (\*).







Exp. 2 - FOE



Exp. 1 - Radial



TMS Condition



Exp. 1 - Radial





