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Stimulation of the Human Frontal Eye Fields Modulates Sensitivity of Extrastriate Visual Cortex

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Submitted 5 January 2006; accepted in final form 18 April 2006

Silvano, Juha, Nilli Lavie, and Vincent Walsh. Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. *J Neurophysiol* 96: 941–945, 2006; doi:10.1152/jn.00015.2006. The precise role of frontal eye fields (FEF) in vision independent of their role in eye movements remains a matter of debate. One proposal is that the FEF exert top-down influences on the extrastriate visual cortex prior to eye movement preparation. Here we establish, by use of transcranial magnetic stimulation (TMS), that activity in the human FEFs has a direct effect on the sensitivity of extrastriate visual area MT/V5, and that the spatial organization of this top-down effect is lateralized in the human brain. We show that phosphene threshold—the TMS intensity required to elicit a visual perception—for MT/V5 stimulation changes as a function of the delay between the application of TMS over FEF and MT/V5. The effects were specific to the location and time of stimulation. Stimulation of FEF 20–40 ms prior to stimulation of MT/V5 decreased the intensity of MT/V5 stimulation required to elicit phosphenes: TMS of the right FEF changed the sensitivity of left and right MT/V5 whereas TMS of the left FEF changed the sensitivity only of the left MT/V5. Thus, the sensitivity of human extrastriate cortex is modulated by activity in the FEF.

INTRODUCTION

The human frontal eye fields (FEFs) are part of a putative control network in which areas in the frontal and parietal lobes are thought to influence the sensitivity of neuronal responses in secondary visual areas (Gitelman et al. 1999; Hopfinger et al. 2000; Giesbrecht et al. 2003). Many studies have examined the parietal component of this network, but fewer have concentrated on the FEF. Early studies of the effects of lesions to the macaque FEF show that this area is required for normal performance on complex tasks such as visual search (Latto and Cowey 1971; Collin et al. 1982), and recording studies have subsequently demonstrated a role for the FEF in visual detection tasks. For example, Thompson and Schall (1999) recorded activity in monkey FEF neurons in a backward masking detection task. Activity of FEF neurons following the target presentation was greater for both hits and false alarms at late latencies, which indicates a role in motor decisions, but at short latencies (beginning around 40–60 ms), however, FEF activity was greater following the presentation of a target regardless of subjects' reports (i.e., for misses as well as hits), which indicates a role in visual registration.

Moore and Fallah (2001) found lower luminance detection thresholds following electric stimulation of monkey FEF neurons 50–175 ms before the onset of a visual stimulus in the motor receptive field of the FEF neuron. It is not clear,

however, whether the improvement in detection was mediated by a direct change in sensitivity of the FEF neuron or by FEF stimulation activating connecting neurons in other areas, such as extrastriate or parietal cortex. A follow-up study of FEF-V4 interactions (Moore and Armstrong 2003) showed that the sensitivity of neurons in extrastriate area V4 was increased if microstimulation was applied to the FEF if the endpoint of the saccade vector of the FEF neuron undergoing stimulation fell within the receptive field of the V4 neuron. This study has been interpreted as evidence of top-down modulation of V4 by FEF and also as supporting the premotor theory of attention (e.g., Smith et al. 2005) because it shows an association between eye movements and covert attention; however, microstimulation was applied for only 50 ms between 200 and 500 ms after visual stimulus onset. In other words, the stimulus had been in the vector field of the FEF neuron for a significant period during which the monkey was attending to the visual stimulus, covering the time period both of visual processing and saccade preparation. Further, the microstimulation was applied only during a period when the monkey was preparing an eye movement to the stimulus. These two aspects of the experiment preclude any dissociation of sensory modulation from eye movement preparation (Juan et al. 2004).

To examine the extent to which the findings from nonhuman primate physiology could be applied to the human cortex, Grosbras and Paus (2003), stimulated the human FEFs in a backward masking task and found that TMS applied 40 ms prior to the target onset improved detection sensitivity. As the authors note, however, it is possible that in this study the FEF were rendered more sensitive to incoming information rather than having an effect on the sensitivity of extrastriate visual areas. Moreover, the presentation of a visual stimulus to the retina—and therefore through the geniculostriate pathway—means that one cannot infer a specific effect of FEF stimulation on any particular visual area. More recently, Taylor et al. (2006) applied TMS over the FEF and simultaneously measured occipital visual-evoked potentials (ERPs) while subjects performed a covert orienting task. They recorded from electrodes placed on the same hemisphere as the TMS stimulation and observed that the FEF TMS changed the responses of the visual cortex. They concluded that the “FEF exerts a causal influence over activity in the visual cortex” during voluntary orienting of attention.

Taken together, these lines of evidence (Moore and Fallah 2001; Moore and Armstrong 2003; Grosbras and Paus 2003; Smith et al. 2005; Taylor et al. 2006) suggest that visual cortex

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sensitivity is modulated by FEF. To demonstrate this directly in humans and to explore the hemispheric organization of FEF–sensory cortex interactions, we induced activity in the FEF via transcranial magnetic stimulation (TMS) and measured subjects' sensitivity to phosphenes induced by TMS over MT/V5. By locally inducing phosphenes with MT/V5 stimulation and hence bypassing the LGN and striate cortex, we were able to obtain a direct measure of the sensitivity of a specific extrastriate visual area – MT/V5. We show that stimulation of FEF 20–40 ms prior to stimulation of MT/V5 decreases the intensity of MT/V5 stimulation required to elicit a visual percept and therefore that the sensitivity of human MT/V5 is modulated by activity levels in the FEF. To control for site specificity, we also applied TMS to the vertex and MT/V5 at the same asynchronies as in the FEF condition, and to control for temporal specificity we applied TMS at seven different time points.

METHODS

Subjects

Nine subjects took part in the investigation, eight of whom were naïve to its purpose. Seven subjects were tested in each condition, with five subjects in taking part in both right and left FEF TMS sessions. The subject who was not naïve to purpose (J.S.) was naïve to the timing of the TMS pulses, as was the experimenter and all other subjects. The study was approved by the local ethics committee, and subjects gave informed consent. All subjects had previously participated in studies of phosphene perception, the advantage being that their phosphene thresholds (PTs) are stable.

TMS

TMS was administered with two Magstim Super Rapid stimulators (Magstim Company, Whitland, UK). The pulses were triggered remotely using a computer that controlled both stimulators, using E-Prime software. Fifty-millimeter figure-eight coils were used over both sites. The stimulation strength was always the same over FEF and Vertex, 65%, an intensity that has been used in many previous FEF studies (e.g., Muggleton et al. 2003; O'Shea et al. 2004) and is known to induce behavioral effects. Subjects were seated on a chair designed for massage so that the subject's head and body weight were forward and the head rested in a cushioned hole, which allowed the face to peer through. The head is more stable in this arrangement than in a conventional head and chin rest. The coils were fixed in place using "magic arm" (Manfrotto Bassano del Grappa, Italy) coil holders. The subjects' eyes were covered throughout the experiment, and they were instructed simply to report whether they had perceived a phosphene after each TMS pulse. All subjects reported phosphenes that were restricted to the visual field contralateral to stimulation of V5. To control for temporal specificity, we applied TMS at seven different time points. Specifically, TMS pulses were delivered at FEF/Vertex–MT/V5 stimulation asynchronies between –60 ms (FEF/Vertex TMS preceding MT/V5 TMS) and +60 ms (MT/V5 TMS preceding FEF/Vertex TMS) in 20-ms steps (Fig. 1C). After each TMS delivery, subjects reported verbally whether or not they had perceived a phosphene. To determine PTs for each TMS condition, the intensity of V5/MT pulse was varied according to a modified binary search (MOBS; Tirell and Owens 1988), an adaptive threshold-finding algorithm. The TMS intensity was increased or decreased according to the subject's report on the previous trial. The original upper boundary of the stimulation was 100% of stimulator output, and the lower limit 0%. The number of trials required for setting a threshold depends on the consistency of the subject's reports and in

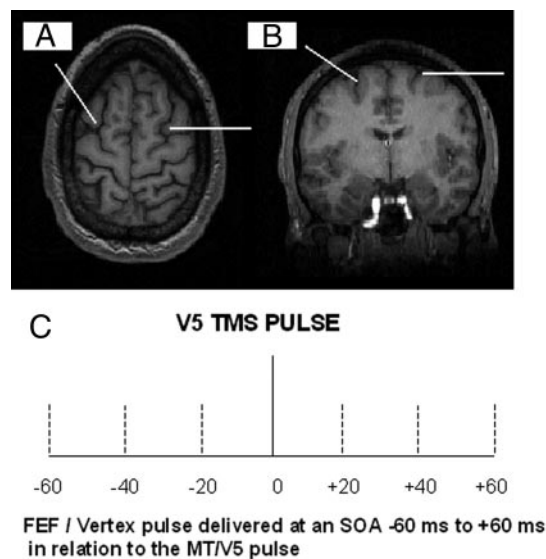


FIG. 1. A and B: transverse and coronal views indicating the location of the left and right FEFs in one subject. C: timeline of an experimental trial. On all trials, a TMS pulse was applied over MT/V5. A second pulse of TMS was applied, depending on the experimental condition, over either FEF or vertex at an SOA between –60 ms (stimulation preceding the MT/V5 pulse) and +60 ms (stimulation postdating the MT/V5 pulse). A trial with a particular combination of stimulation site (FEF; vertex) and SOA (–60 ms; –40 ms; –20 ms; 0 ms; +20 ms; +40 ms; +60 ms) was repeated until the PT had been successfully determined for that condition using a modified binary search paradigm. This required between 6 and 15 trials. FEF and vertex were always stimulated with an intensity of 65% of the maximum output of the stimulator.

this experiment was between 6 and 20 trials. Intertrial interval was determined by the subject's speed of response and was approximately 5 s per trial.

TMS localization

TMS was applied over locations that corresponded with the anatomical delineation of left and right FEF (Fig. 1) and left and right MT/V5 (Dumoulin et al. 2000; Watson et al. 1993) by structural magnetic resonance imaging (MRI) in each subject (see Muggleton et al. 2003 and O'Shea et al. 2004 for details). For MT/V5 an additional criterion was the induction of moving phosphenes (Stewart et al. 1999). Vertex was used as an additional control stimulation site to control nonspecific effects of TMS. The stimulation sites were identified on each subject's T1-weighted MRI scan and coregistered with scalp coordinates. FEF was determined anatomically as lying over the posterior middle frontal gyrus, rostral of the junction of the precentral sulcus, and the superior frontal sulcus (Blanke et al. 2000; Paus 1996). In terms of scalp measurements, the average position of stimulation was 5 cm lateral of the sagittal midline and 3–4 cm anterior of the hand area. This site corresponds well with our previous studies (Muggleton et al. 2003; O'Shea et al. 2004) and those of others (Leff et al. 2001; Muri et al. 1991). Mean Talairach coordinates were 32, –2, 47 for the right FEF and –32, –2, 46 for the left FEF (Talairach and Tournoux 1988; Paus 1996). V5 can be accurately determined from the production of moving phosphenes (Stewart et al. 1999), and we also determined this usingBrainsight coregistration (following Campana et al. 2002, 2005).

Procedure

The order of the TMS conditions was intermixed pseudo-randomly, so that a condition in which FEF TMS preceded or followed MT/V5 TMS by a given time window was followed by a condition in which vertex TMS preceded or followed MT/V5 TMS in the same time

window, and vice versa. There were three experimental sessions and in each session two conditions were carried out: One session consisted of right FEF–right V5 and vertex–right V5 conditions, another consisted of right FEF–left V5 and vertex–left V5, and another consisted of left FEF–right V5 and left FEF–left V5 conditions. Within and between each session the order of TMS conditions was randomized. The structure of each session was 1) an SOA selected randomly by the software; 2) PTs measured for this SOA for both experimental conditions in that particular session (e.g., right FEF–right V5 and vertex–right V5); 3) the next SOA selected randomly; and 4) again, PTs measured for both experimental conditions for this SOA. The condition that was carried out second for the previous SOA is now carried out first. Whether a given timing started with an FEF–MT/V5 or vertex–MT/V5 condition was counterbalanced. In each condition, the PT was determined once using the binary search paradigm, which takes 6–20 trials. Because there were seven SOAs (–60, –40, –20, 0, 20, 40, 50) and six experimental conditions (right FEF–right V5; vertex–right V5; right FEF–left V5; vertex–left V5; left FEF–right V5; left FEF–left V5), the PT was measured a total of 42 times (14 times in each session), with an average of 12 trials required for each threshold. In addition, the baseline threshold (in which TMS was applied only over left or right MT/V5) was measured a total of 16 times (8 times for each V5). Baseline thresholds were measured at the beginning and the end of each session, as well as after the fifth and ninth TMS/vertex conditions (as mentioned above, there were 14 threshold conditions in each session). The mean values of the baseline thresholds were 60% and 65% of the maximum stimulator output for left and right MT/V5, respectively. Stimulations of left and right MT/V5 were carried out on separate days. No vertex condition was run in comparison with the left FEF condition based on the prediction from Grosbras and Paus (2003) that there would be left-right field differences in the effects of left FEF stimulation (specifically a null prediction for the left FEF stimulation) and our previous evidence that right and left FEF TMS have different effects on visual processing in the two visual fields (Muggleton et al. 2003).

RESULTS

The subjects' PTs in each condition were measured as a percentage of the maximum output of the stimulator unit. To obtain a relative measure of the PTs, the subjects' absolute thresholds in the FEF and vertex condition were normalized relative to the baseline threshold level in that session.

TMS over right FEF

The application of TMS to right hemisphere FEF decreased PTs in both right and left MT/V5. Figure 2A shows normalized PTs of right MT/V5 TMS as a function of each TMS condition. For the right MT/V5 TMS, a within-subjects ANOVA with stimulation site (FEF, vertex) and stimulation onset asynchrony (–60, –40, –20, 0, +20, +40, +60) as factors indicated a significant interaction between stimulation site and timing ($F[1,6] = 3.549$; $P = 0.007$; mean square of error [MSE] = 0.0026). A paired-sample t -test revealed that FEF stimulation applied 20 ms before the MT/V5 pulse significantly lowered the PT in comparison to vertex stimulation at the same time window ($t[6] = 5.012$; $P = 0.002$; SD = 0.069; SE = 0.026). In contrast, there was no statistically significant difference between the FEF and vertex conditions when their stimulation postdated the MT/V5 pulse by 20 ms ($t[6] = 0.323$; $P = 0.390$; SD = 0.105; SE = 0.023).

The normalized PTs of left MT/V5 as a function of each right FEF and vertex TMS condition, averaged across the

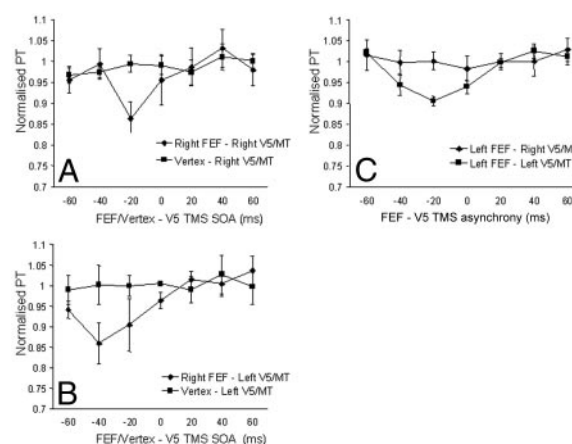


FIG. 2. Mean of normalized PTs ($n = 7$) of MT/V5 in each experimental condition. All error bars indicate ± 1 SE. *A*: effects of rFEF TMS on the sensitivity of ipsilateral visual cortex: TMS of the right FEFs (diamond symbols) lowered the PT of ipsilateral MT/V5, with the peak of this effect occurring when TMS was applied over the FEF 20 ms before MT/V5 was stimulated. TMS over vertex (squares) had no effect. *B*: effects of rFEF TMS on the sensitivity of contralateral visual cortex: TMS of the right FEFs (diamond symbols) lowered the PT of contralateral MT/V5, with the peak of this effect occurring when TMS was applied over the FEF 40 ms before MT/V5 was stimulated. TMS over Vertex (squares) had no effect. *C*: Ipsilateral but not contralateral effects of IFEF TMS on cortical sensitivity: TMS applied over the left FEF lowered the PT of the ipsilateral MT/V5 (squares) but not contralateral visual cortex (diamonds).

seven participants, are shown in Fig. 2B. For the left MT/V5 TMS a within-subjects ANOVA with stimulation site (FEF, vertex) and stimulation onset asynchrony as factors indicated a significant interaction between stimulation site and time window ($F[1,6] = 3.305$; $P = 0.017$, MSE = 0.0047). Pairwise comparisons revealed that FEF stimulation preceding the MT/V5 pulse by 40 ms significantly lowered subjects' PTs in comparison to vertex stimulation in this time window ($t[6] = 3.01$; $P = 0.024$; SD = 0.126; SE = 0.048). In contrast, the difference between the two conditions was not statistically significant when their stimulation postdated the MT/V5 pulse by 40 ms ($t[6] = 0.795$; $P = 0.457$; SD = 0.076; SE = 0.029). It is apparent in Fig. 2B that the facilitatory effect of right FEF TMS on the activity of left MT/V5 is moderately present at SOAs that precede and postdate the time window of the strongest effect. At these time windows, however, the difference between the FEF and vertex conditions was not statistically significant for (20 ms: ($t[6] = 1.752$; $P = 0.130$; SD = 0.143; SE = 0.054; 60 ms: $t[6] = 1.774$; $P = 0.126$; SD = 0.072; SE = 0.027).

TMS over left FEF

Figure 2C shows normalized PTs of right and left MT/V5 TMS as a function of each FEF TMS condition. The application of TMS to left FEF decreased PTs in left but not in right MT/V5. A within-subjects ANOVA with phosphene stimulation site (left vs. right MT/V5 TMS) and FEF stimulation onset asynchrony as factors indicated a significant interaction between phosphene stimulation site and SOA ($F[1,6] = 3.402$; $P = 0.009$; MSE = 0.0018). A paired-sample t -test revealed that FEF stimulation applied 20 ms before the left MT/V5 pulse significantly lowered the PT in comparison to right MT/V5 TMS at the same time window ($t[6] = 6.148$; $P =$

0.001; SD = 0.0387; SE = 0.0146). In contrast, there was no statistically significant difference between the right MT/V5 and left MT/V5 conditions when their stimulation postdated the MT/V5 pulse by 20 ms ($t[6] = 0.832$; $P = 0.437$; SD = 0.10; SE = 0.376).

Again, a moderate facilitatory effect of left FEF TMS on the activity of left MT/V5 is present at stimulation onset asynchronies (SOAs) that precede and postdate the time window of the strongest effect. At these time windows, however, the difference between the FEF and right MT/V5 condition was not statistically significant for the left MT/V5 condition (-40 ms: $t[6] = 2.126$; $P = 0.078$; SD = 0.103; SE = 0.039; 0 ms: $t[6] = 2.088$; $P = 0.082$; SD = 0.094; SE = 0.036).

DISCUSSION

Our results clearly show that activity in the human FEF modulates the excitability of extrastriate visual cortex. Together with the findings of Grosbras and Paus (2003), Taylor et al. (2006), Smith et al. (2005), Thompson and Schall (1999), and Bullier (2001), our data suggest that one of the saccade-independent functions of FEF is to exert top-down modulation over extrastriate visual cortex. Several studies have now shown that some FEF responses are independent of saccade command signals, and it is these visual rather than motor FEF neurons that have been associated with top-down control and attention. The content of the top-down control may be either spatial or feature-related. Thompson et al. (2005), for example, have identified spatially selective enhanced activity in visual FEF neurons during a covert spatial attention task and a concurrent suppression of activity in FEF movement neurons. They concluded that "selective activity in FEF visually responsive neurons corresponds to the mental spotlight of attention via modulation of ongoing visual processing." Other recording studies have shown that some visual FEF neurons' responses are correlated with the identity of the target, and it is therefore possible that FEF visual neurons are involved in both spatial and object-related processes in selective attention tasks. Bar et al. (2005) have also presented evidence from magnetoencephalography and functional MRI studies for an early top-down role for FEF in visual object processing. Greater activation in FEF was seen when subjects were presented with objects they successfully recognized than for object they did not. This activity preceded activity in visual object recognition areas by 30 ms (O'Shea et al. 2004; O'Shea and Walsh 2006). Whether this early FEF activity in reflects top-down control processes dedicated to space, object features or both remains to be determined. With regards to how FEF exerts top-down control, it is possible that FEF activity occurs prior to sensory stimulation as opposed to rapid responses to visual stimuli (contrast a possible role for FEF neurons in visual priming: Bichot and Schall 2002). It is important to note that the term "top-down" is used in the temporal context of FEF receiving visual information prior to the extrastriate areas, but it remains entirely possible that top-down processes are mediated by a feed forward anatomical connection from, say, FEF to V4 (e.g., Barone et al. 2000).

The FEFs are part of the frontoparietal network involved in many aspect of vision, but, as we noted in the introduction, the role of the FEF has not received the same attention as that of the PPC. To understand the function of the FEF within this network, however, requires a description of the similarities and differences between these two major nodes. One aspect of our

findings reflects the well-established hemispheric asymmetry in attentional functions in humans, namely, that the right hemisphere is more commonly concerned with processing information in both visual fields, whereas the left hemisphere appears to be concerned only with the right visual field (e.g., Mesulam 1981). That right FEF TMS decreased PTs in both visual fields whereas left FEF TMS only decreased PTs in the right visual field is consistent with this and adds to the many examples of similarities between the organization of FEF and PPC in vision and attention. For example, frontal and parietal areas have both been shown to produce neglect when damaged (Keating and Gooley 1988; Mesulam 1999); have both been shown to be important in detecting abrupt changes in the visual field (Beck et al. 2001, 2005; Turatto et al. 2004) and have been shown to be important in visual search (Donner et al. 2000; Nobre et al. 2003).

Demonstrating differences between the two nodes, however, is a less common finding, and our result may have implications in this regard. We interpret the effects of FEF TMS on extrastriate activity to be evidence of a top-down role for FEF because it is consistent with a role for the early visual activity of FEF visual neurons (Murthy et al. 2001). An area involved in control would be expected to be active early and by responding to target features, the FEF could increase the sensitivity of extrastriate neurons to task relevant parameters (e.g., Moore and Armstrong 2003 Moore and Fallah 2001). Our finding may also help to understand why a recent TMS study obtained only equivocal evidence of a role for the PPC in top-down control (Hung et al. 2005): damage to the frontoparietal network may only result in a disruption of top-down modulation if the early input to the FEF is disrupted. Both frontal and parietal nodes may be important for aspects of visual orienting and awareness, and there are reports of early visual responses, attributed to attentional processes in both. Bisley et al. (2005) for example, recently reported rapid responses to visual stimuli of neurons in lateral intraparietal cortex, and Fuggetta et al. (2006) reported that TMS over the PPC after onset of a visual search display can eliminate the N2pc component associated with target detection. This was interpreted as evidence of TMS interfering with spatial processes in the search task. Both FEF and PPC, then, have been associated with spatial top-down processing, but a major difference between them seems to be that the FEFs have also been associated with feature processes. Some physiological properties of the FEF may make it well placed to exert feature-related top-down influence: the FEF responds to visual stimuli very rapidly and is part of what has been called "the fast brain" (Bullier 2001; O'Shea et al. 2004); the organization of FEF-visual cortex connections is retinotopic (Schall et al. 1995); FEF neurons show distinct feature-related activity (Thompson and Schall 1999) and a preference for stimuli that are relevant as targets (Schall and Hanes 1993); and preactivation of the FEF improves visual detection with the same spatial pattern of hemispheric specialization as found in the current study (Grosbras and Paus 2003) and influences attention-related activity in the visual cortex (Taylor et al. 2006). Further, comparison of the effects of FEF versus PPC stimulation using a partial report task designed to probe top-down control has shown that human FEF is important for target rather than distractor processing (Hung 2005). The pattern of hemispheric asymmetries is an important component of interpreting the role of the FEF in humans and our effects show that

the right FEF needs approximately 20 ms longer to influence the contralateral than the ipsilateral visual cortex, presumably due to callosal transmission time.

In summary, these findings extend and complement the microstimulation studies of nonhuman primate FEF (Moore and Fallah 2001; Moore and Armstrong 2003) and the magnetic stimulation study of Grosbras and Paus (2003) in showing that FEF activity modulates the responses of visual cortex in a manner consistent with a role in top-down control of visual processing.

ACKNOWLEDGMENTS

This work was supported by a scholarship from the University College London Graduate School and grants from the United Kingdom Medical Research Council and the Wellcome Trust. V.Walsh. is supported by the Royal Society.

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