Journal Club

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Pulse-Pattern Sensitivity in the Frontal Eye Field of the Macaque Monkey

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Review of Kimmel and Moore (http://www.jneurosci.org/cgi/content/full/27/29/7619)

Electrical microstimulation is widely used to examine causal links between the activity of specific brain areas and behavioral function, as well as in treatment for neurodegenerative diseases such as Parkinson's. Experimentally, microstimulation is often considered as mimicking natural activity (Tehovnik et al., 2006). For example, in area MT, the volume of stimulated tissue correlates with the fidelity of the motion signal. In the parietal cortex, the rate of microstimulation has been linked to the perceived frequency of tactile vibration. In the superior colliculus, the phase of simultaneous microstimulation trains has been associated with the summing or averaging of saccadic vectors. Microstimulation has also been used to study higher cognitive functions such as executive control, decision making, and spatial attention. Such studies typically use a constant interpulse interval (IPI), which does not fully mimic the biological signal because the average change of the interspike interval (ISI) is associated with sensory and motor events (Bruce and Goldberg, 1985; Hanes and Schall, 1996). In their recent article in *The Journal of Neuroscience*, Kimmel and Moore (2007) asked whether the temporal pattern of microstimulation affects behavioral responses. To examine this question, the authors tested the sensitivity of the oculomotor system to specific microstimulation pulse patterns. Microstimulation was applied to the frontal eye field (FEF), an area of the frontal cortex that encodes saccadic eye movements evoked by fixed patterns of microstimulation (Bruce et al., 1985). Kimmel and Moore (2007) compared five patterns of biphasic pulses of 0.25 ms width per phase. For "FIXED," the IPI was constant at 5 ms throughout the train; " DECEL" had increasing IPIs within each trial, from 2 to 8 ms, in steps of 1 ms; "ACCEL" had the same IPIs as the DECEL pattern in decreasing order, from 8 to 2 ms. Two random patterns were also used: random order, in which the order of IPIs used in ACCEL and DECEL were randomly shuffled, and random interval (RI), in which the eight pulses were assigned randomly to 2-ms-wide bins with 1 pulse per bin. The average IPI was 5 ms for all pulse patterns except the RI pattern.

For the same current, saccades were less likely to be evoked with DECEL and more likely to be evoked with the ACCEL pattern compared with the FIXED and random patterns [Kimmel and Moore (2007), their Fig. 2 (http://www.jneurosci.org/cgi/content/full/27/29/7619/F2)]. Because the DECEL and ACCEL patterns consisted of the same IPIs in reversed order, the results convincingly demonstrated that the recent history of pulses determined the effectiveness in eliciting a saccade. Moreover, a saccade-triggered average of random pulse trains [Kimmel and Moore (2007), Fig. 5 (http://www.jneurosci.org/cgi/content/full/27/29/7619/F5)] showed that the saccade-evoking trains were accelerating on average, whereas the nonevoking trains were decelerating. Saccades evoked with DECEL, although less common on average, tended to have shorter latencies, larger amplitudes, faster peak velocities, and longer durations than saccades evoked with equal probability by all other patterns, with the reverse being true of ACCEL saccades as a whole [Kimmel and Moore (2007), Table S2B (http://www.jneurosci.org/cgi/data/27/29/7619/DC1/1)]. When comparing saccades of the same latencies, ACCEL pattern saccades had the largest amplitudes and DECEL saccades had the smallest amplitudes.

The authors interpreted these results within a broad theoretical framework in which the saccade-generating signal consists of three phases. In the first "primer" stage, constant or gradually increasing low-frequency activity increases the probability of a saccade in a certain direction. Next, a "trigger" initiates the saccade with a high-frequency burst. Finally, the "driver" influences the movement itself, supported by previous evidence of lengthening of saccades resulting from contin-

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ued microstimulation after saccade onset. Within this interpretation, priming preceding the high-frequency portion of the ACCEL pattern renders it more effective as a saccade trigger, although it is reached later during the trial, resulting in longer latencies of evoked saccades. Similarly, the reverse would be true for the DECEL pattern. However, the authors did not mention whether the magnitude of the saccadic latency differences matched the putative high-frequency trigger latency differences between pulse trains, which would corroborate their model. Moreover, they only report log normalized values of the latencies for the entire population, making it difficult to determine the overall latency difference magnitudes. In the framework of the model, the data demonstrate that trials that occur with both less priming activity and more driving activity are larger in amplitude and duration, although the authors ascribe the amplitude effects solely to the driving activity. The authors show that this last result is consistent with existing work, and indeed it may be correct. However, the data in this paper alone cannot discriminate whether the priming or driving stages lead to the effects on saccade amplitude. Additional experiments in which one stage was held constant while varying the other would be needed to support this claim.

The authors discuss several hypotheses to explain the mechanism and location of the pulse-pattern sensitivity. For example, they propose that recruitment of interneurons would provide feedback inhibition. In terms of the relevant site, given that stimulation thresholds in FEF are known to be much lower (10–15 microamps) when the electrode tip is located in layer V, and that the threshold can become miniscule (<5 μA) in locations where large movement neurons that are likely to project to SC and the brainstem can be recorded, we prefer the view that FEF movement neurons are directly stimulated by each microstimulation pulse, eventually leading to a saccade. This is further supported by the short latencies of evoked saccades with respect to stimulation onset, which in their Figure 1 (http://www.jneurosci.org/cgi/content/full/27/29/7619/F1) were as low as 40 ms after stimulation onset for a representative site. To evoke a saccade in FEF, the stimulation train must be longer than 25 ms (Tehovnik and Sommer, 1997). In other words, the saccade-triggering threshold in FEF is not reached until 25 ms or longer after stimulation onset. Given the additional and uncompressible efferent delay of 10–15 ms between threshold crossing of FEF movement neurons and the actual movement of the eyes, most saccades evoked with latencies as low as 40 ms after stimulation onset are likely to reflect a direct stimulation of movement neurons and not slower polysynaptic effects within FEF.

This article improves understanding of how saccades are initiated and controlled in FEF while examining an important question concerning the use of microstimulation experimentally or clinically, most notably with deep brain stimulation. The authors show that the temporal order of interpulse intervals affects the effectiveness of microstimulation, and that accelerating activity in FEF, likely in movement neurons, is particularly effective at eliciting a saccade. They present a plausible three-stage primer–trigger–driver model of the initiation of saccades and the modulation of several saccade parameters in FEF.

References

Bruce CJ, Goldberg ME (1985) Primate frontal eye fields. I. Single neurons discharging before saccades. J Neurophysiol 53:603–635.

Hanes DP, Schall JD (1996) Neural control of voluntary movement initiation. Science 274:427–430.

Kimmel DL, Moore T (2007) Temporal patterning of saccadic eye movement signals. J Neurosci 27:7619–7630.

Tehovnik EJ, Sommer MA (1997) Electrically evoked saccades from the dorsomedial frontal cortex and frontal eye fields: a parametric evaluation reveals differences between areas. Exp Brain Res 117:369–378.

Tehovnik EJ, Tolias AS, Sultan F, Slocum WM, Logothetis NK (2006) Direct and indirect activation of cortical neurons by electrical microstimulation. J Neurophysiol 96:512–521.