Neural correlates of task-related changes in physiological tremor

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Laine CM, Negro F, Farina D. Neural correlates of task-related changes in physiological tremor. J Neurophysiol 110: 170–176, 2013. —Appropriate control of muscle contraction requires integration of command signals with sensory feedback. Sensorimotor integration is often studied under conditions in which muscle force is controlled with visual feedback. While it is known that alteration of visual feedback can influence task performance, the underlying changes in neural drive to the muscles are not well understood. In this study, we characterize the frequency content of force fluctuations and neural drive when production of muscle force is target guided versus self guided. In the self-guided condition, subjects performed isometric contractions of the first dorsal interosseous (FDI) muscle while slowly and randomly varying their force level. Subjects received visual feedback of their own force in order to keep contractions between 6% and 10% of maximum voluntary contraction (MVC). In the target-guided condition, subjects used a display of their previously generated force as a target to track over time. During target tracking, force tremor increased significantly in the 3–5 and 7–9 Hz ranges, compared with self-guided contractions. The underlying changes in neural drive were assessed by coherence analysis of FDI motor unit activity. During target-guided force production, pairs of simultaneously recorded motor units showed less coherent activity in the 3–5 Hz frequency range but greater coherence in the 7–9 Hz range than in the self-guided contractions. These results show that the frequency content of common synaptic input to motoneurons is altered when force production is visually guided. We propose that a change in stretch-reflex gain could provide a potential mechanism for the observed changes in force tremor and motor unit coherence.

coherence; tremor; motor units; EMG

IT HAS LONG BEEN APPRECIATED that human motor control involves continual adjustment of command signals using sensory feedback. In laboratory settings, subjects are often required to control muscle activation with visual feedback of force or position. In doing so, humans will always display some degree of tremor, the magnitude of which has some dependence on the details of the visuomotor task. For example, using visual feedback to guide muscle activity can increase tremor (Atheya et al. 2012; Baweja et al. 2009b; Davis 2007; Jordan and Newell 2004; Sutton and Sykes 1967; Vaillancourt and Russell 2002) to an extent partly determined by the visual scaling (gain) of the feedback signal (Baweja et al. 2009a; Hong and Newell 2008; Prodoehl and Vaillancourt 2010; Sosnoff et al. 2006; Stephens and Taylor 1974; Vaillancourt et al. 2006). In addition, effects may be frequency specific. For example, Sutton and Sykes (1967) found that a 7- to 9-Hz component of tremor disappeared upon removal of visual feedback, while Baweja et al. (2009a) found that increasing the gain of visual feedback reduced tremor in the 0–1 and 3–7 Hz ranges. To date, the neurophysiological mechanisms linking tremor with visual feedback are not known. Attempts to infer a mechanism from previous studies are made difficult by differences in the muscle(s) used, the experimental setup, and the techniques used to quantify tremor. Another complication is the fact that visual feedback is indirectly related to many other aspects of a task, such as its difficulty or the extent to which proprioceptive/tactile information is used. Finally, it is somewhat ambiguous whether or not the effects of visual feedback on tremor involve the visual system per se, or whether these changes depend more on the type of error correction required by a given task.

To clarify these issues, it is necessary to examine changes in tremor and neural drive to the muscle when the same mechanical action is performed under different task conditions. We therefore sought to characterize differences in neuromuscular control when force production is self guided (subject given visual force feedback without a target) versus target guided (where the subject’s own self-guided force trajectory is given as a target to track). We predicted that target tracking would elicit a greater degree of force tremor in the frequency range previously associated with the absence/presence of visual feedback (7–9 Hz; Sutton and Sykes 1967), provided that error correction, rather than visual feedback of force, is the more important factor. Assuming a central origin for this effect, we also predicted that changes in the frequency content of force fluctuations would be mirrored by changes in the frequency content of neural drive to the muscle. To test this, we recorded single-motor unit (MU) activity from the first dorsal interosseous (FDI) muscle of healthy volunteers while they performed slowly varying, isometric abduction of the index finger. Differences in force fluctuations were quantified by spectral analysis. The underlying changes in neural drive were investigated with coherence analysis of single-MU activity, which identifies the frequency content of common synaptic input to motoneurons (Farmer et al. 1993, 1997; Negro and Farina 2012; Rosenberg et al. 1989).

METHODS

Experimental procedures were approved by the Universitätsmedizin Goettingen (approval no. 9/2/12), and informed consent was obtained from all subjects prior to testing. A group of 11 healthy right-handed (self reported) men (mean age = 30 yr, range 25–39 yr, SD = 4.9 yr) participated in the experiment. Muscle force recordings were obtained during fifty 2-min trials (25 trials for each of 2 experimental conditions).
Force and EMG Recordings

Subjects were seated upright in an adjustable chair with the right hand attached to a force measurement apparatus (Fig. 1, center). Nylon straps were used to prevent movement of the forearm and hand while subjects performed isometric abduction of the index finger against a force transducer (Interface, Scottsdale, AZ). The transducer output was amplified with an OT MISO-II amplifier (LISiN, Turin, Italy). Force measures were normalized to percent maximum voluntary contraction (MVC), which was assessed prior to experimental trials. Intramuscular EMG signals were recorded from the FDI muscle with pairs of Teflon-coated stainless steel wires (diameter 0.1 mm; A-M Systems, Carlsborg, WA). Two pairs of wires were inserted per subject with 25-gauge hypodermic needles, which were removed after insertion. Ground leads were placed at the right elbow. The signals were amplified and filtered (500–2,000 Hz) with CED 1902 amplifiers (Cambridge Electronic Design, Cambridge, UK). Both force and EMG signals were sampled at 10 kHz. Software for data acquisition and experimental control was custom written with MATLAB (The MathWorks, Natick, MA).

Experimental Tasks

Self-guided force production. In the first part of the experiment, subjects were asked to produce 2 min of slowly varying dynamic abduction force with their index finger. Force feedback was given in the form of a cursor that moved across a 56-cm computer screen from left to right over the course of 15 s before starting again at the left. The subjects controlled the vertical deflection of the cursor by applying force to the transducer. Subjects were shown two horizontal bars set at 6% and 10% of their MVC strength and instructed to keep the force cursor within these limits but to continually vary force so as to create a slow dynamic trajectory (~1–3 major fluctuations per 15 s; see Fig. 1). The monitor was placed ~1.5 m from the subject, making the vertical 6–10% MVC interval span roughly 4 degrees of visual angle (DVA) and the width of the screen span about 15 DVA.

Target-guided force production. After 4–5 min of rest the subjects were asked to complete the same task, but rather than viewing a force interval as a guide they were to follow a trace of their previously generated force trajectory. Subjects were instructed to follow the trace as closely as possible, ignoring any fast fluctuations that reflected unintentional twitches or tremors.

Data Analysis

Force analysis. The ability of the subjects to closely track their previously recorded force trajectories was quantified as the mean absolute difference between paired trials of self-guided and target-guided force production. Task-related differences in the frequency content of force fluctuations were evaluated by calculating the power spectrum density (PSD) of each force trajectory and comparing across conditions with a Wilcoxon rank sum test. Since target-guided contractions always followed self-guided contractions, we evaluated the possibility that changes in tremor over time (e.g., with fatigue) may have played a role. To do this, we used the same methods as previously described to compare the first and last 30 s of self-guided contractions. We also compared the last 30 s of the self-guided contractions (after 90 s of contraction) with the first 30 s of the target-guided contractions (after 4–5 min of rest).

EMG analysis and statistics. Intramuscular EMG signals were decomposed to obtain single-MU activity with EMGLAB (McGill et al. 2005). Each MU spike train was manually edited by an experienced operator to correct any discrimination errors. In the event that a single MU was discriminated from both intramuscular signals, the more noisy/less reliable discrimination was discarded. Synchronized firing activity between pairs of simultaneously recorded single MUs can reflect various aspects of their shared neural input. We assessed the frequency content of shared input by coherence analysis. For each subject with 25-gauge hypodermic needles, which were removed after insertion. Ground leads were placed at the right elbow. The signals were amplified and filtered (500–2,000 Hz) with CED 1902 amplifiers (Cambridge Electronic Design, Cambridge, UK). Both force and EMG signals were sampled at 10 kHz. Software for data acquisition and experimental control was custom written with MATLAB (The MathWorks, Natick, MA).

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frequency, coherence analysis produces a coefficient ranging from 0 to 1, with 0 indicating no correlation between signals and 1 representing perfect linear correlation. To carry out the analysis, spike times for each MU were converted to binary impulse trains with a sampling frequency of 10 kHz. The impulse trains from each pair of MUs were then tested for coherence with the mcohere function in MATLAB, specifying 2-s, nonweighted, nonoverlapping segmentation of the data. Prior to statistical analysis, coherence values (C) were converted to Fisher’s z (FZ) values with the equation $FZ = \frac{1}{2} \ln\left(\frac{C + 1}{1 - C}\right)$. The individual FZ values calculated at each frequency for a given MU pair were then converted to standard Z scores with the equation $Z = FZ_1/\sqrt{1/(2L)}$, where $L$ is the number of time segments used to calculate the coherence. We then subtracted an inherent bias from each coherence profile, which we determined empirically as the mean value between 100 and 250 Hz, since this range can be assumed not to contain any significant correlated activity (Baker et al. 2003). A composite coherence profile could then be calculated for each condition with Stouffer’s Z score method. A sign test was used to determine whether task-related changes in coherence were directionally consistent across the population of MU pairs. Effect magnitude was analyzed with a standard difference of coherence test. For a given frequency, two FZ values calculated over equal numbers of time segments can be tested against the null hypothesis of equal coherence with the equation $Z = (FZ_1 - FZ_2)/\sqrt{1/(2L)}$, where $Z$ is a standard Z score (Rosenberg et al. 1989). In this way, a composite difference of coherence was calculated across all MU pairs at each frequency, again with Stouffer’s method. Finally, the coherence profile of each MU pair was integrated to obtain an index of total shared input over all frequencies. A signed-rank test was then used to determine whether integrated coherence values were affected by task.

RESULTS

Force

Subjects were able to accurately copy self-guided muscle activity using a visual target. The mean (SD) force recorded for self-guided contractions was 8.10 (0.48) %MVC and 8.07 (0.057) %MVC for target-guided trials. These were not significantly different ($P = 0.84$, signed-rank test). In addition, the mean (SD) absolute difference between self-guided and target-guided trials was only 0.56 (0.19) %MVC. Figure 1A displays a 30-s epoch of self-guided and target-guided force production for a single subject. Differences in force dynamics between self-guided and target-guided contractions were then compared in the frequency domain. Figure 1B depicts a frequency-domain comparison of the same force trajectories shown in Fig. 1A (but over the entire 2-min trial). This example shows an increase in tremor during target-guided contractions, with a higher frequency peak of force at 7.5 Hz. The average PSD obtained across all self-guided and target-guided force trajectories is shown in Fig. 2A. In general, visually guided contractions contained higher power at frequencies up to $\sim 12$ Hz. The strongest and most consistent effects fell within the 2–4.5 and 7–11 Hz frequency bands. The results of a rank sum test on each frequency are shown in Fig. 2A, bottom.

Since fatigue might influence force tremor, we used the same analysis to compare the first and last 30 s of self-guided contractions (Fig. 2B). No statistical differences were seen at any frequency (Fig. 2B, bottom). To rule out potential effects of fatigue that may have occurred late in the second trial, we compared the last 30 s of self-guided contractions (after 90 s of contraction) with the first 30 s of target-guided contractions (after 4 min of rest). We found clear differences up to $\sim 12$ Hz (Fig. 2C), similar to those shown in Fig. 2A.

Motor Unit Coherence

Intramuscular EMG recordings were accurately decomposed from a subset of five subjects. This yielded 66 pairs of MUs whose activities could be followed across both conditions. The number of MU pairs recorded from each subject was 10, 12, 28, 10, and 6 for subjects 1–5, respectively. MUs showed a mean (SD) discharge rate of 11.86 (2.20) Hz during self-guided contractions and 11.62 (2.22) Hz during target-guided contractions. Their discharge rates did not change significantly between conditions ($P = 0.21$, signed-rank test). Similarly, MU discharge profiles showed no condition-related change in coefficient of variation ($P = 0.11$, signed-rank test). The consistency of discharge properties across MUs and conditions adds validity to the analysis of coherence, since the sensitivity of the measure depends on the relationship between discharge frequencies and the frequency content of common input (Negro and Farina 2012). Figure 1D shows an example of how coher-
ence between a single pair of MUs changed between the two conditions. The MU pair was recorded during the same contraction as the force traces in Fig. 1A. The composite coherence of all MU pairs in each condition is shown in Fig. 3A. MU pairs showed greater coherence at 3–5 Hz during self-guided contractions and greater coherence in the 7–9 Hz band during target-guided contractions. A sign test was used to confirm that the apparent effects occurred in a significant proportion of MU pairs (Fig. 3A, bottom), and a composite Z score of pairwise differences in coherence was used to evaluate the statistical magnitude of the effects as a group (Fig. 3B). The statistical tests confirmed that the largest and most consistent effects of task on coherence occurred in the 3–5 and 7–9 Hz bands. The per-subject averages shown in Fig. 3C indicate that effects on MU-MU coherence (Fig. 3C, left) and force PSD (Fig. 3C, right) occurred in four of five subjects, for both frequency bands. Although a portion of MU pairs in each condition did show coherence at beta and gamma band frequencies (≥15 Hz), we did not observe any reliable differences across conditions in this frequency band. Finally, the total (integrated) coherence between MU pairs did not change across tasks (P = 0.9 signed-rank test).

**DISCUSSION**

In this study, we compared neuromotor control of self-guided versus target-guided force production. We assessed differences in the frequency content of force fluctuations as well as differences in the frequency content of neural drive to the muscle.

We observed an increase in <5-Hz force tremor when subjects followed a target compared with self-guided force production. Tremor in this band is thought to reflect the frequency content of voluntary error corrections and fluctuations of the net drive to a motor pool, with a peak frequency between 1 and 2 Hz (Allum et al. 1978; Miall et al. 1993; Slifkin et al. 2000; Squeri et al. 2010; Sutton and Sykes 1967). MU discharge rates showed coherent activity in this frequency range under both conditions. It is known that MUs exhibit concurrent fluctuations in their discharge rates, a phenomenon originally referred to as “common drive” (De Luca et al. 1982) and analogous to coherence at frequencies <5 Hz (Myers et al. 2004; Negro and Farina 2012; Negro et al. 2009). Although it is possible that voluntary error corrections could influence common drive to some degree, common drive has been measured in muscles that are tonically active without voluntary control (Laine and Bailey 2011; Mochizuki et al. 2006). We found that MUs showed less 3–5 Hz coherence during target tracking, while at the same time force fluctuations in the 3–5 Hz range increased. One explanation comes from the findings of De Luca at al. (2008), who reported that increased afferent feedback, such as occurs with MU recruitment, tends to decrease common drive among previously active MUs. They found this to be true regardless of whether force production was static or dynamic, especially for those muscles with higher spindle densities. We would therefore expect that an increase in afferent gain during a dynamic contraction would lower the magnitude of common drive, and this was indeed what our results indicated. Of course, a change in the pattern of MU discharge rates could also account for the observed changes in coherence.
recruitment or afferent feedback may also have contributed to the effect.

The possibility of an increase in afferent feedback may be particularly relevant because we observed an influence of task on force fluctuations and MU-MU coherence in the 7–9 Hz range. Tremor in this frequency band is associated with the activity of the stretch reflex loop (Christakos et al. 2006; Erimaki and Christakos 1999, 2008; Hagbarth and Young 1979; Lippold 1970). Deafferentation can eliminate this tremor (Halliday and Redfearn 1958; Sanes 1985), as can limb ischemia (Erimaki and Christakos 2008); cooling or heating of the forearm changes its frequency, consistent with an influence on conduction delay (Lippold 1970); and common manipulations of stretch-reflex gain change its amplitude (Young and Hagbarth 1980). We found that target-guided contractions produced more 7–9 Hz coherence among MUs than self-guided contractions, which is consistent with the predicted effects of an increase in the magnitude or gain of afferent feedback. Such a change in afferent feedback and/or fusimotor activity might have stemmed from changes in the cognitive aspects of the task (Hospod et al. 2007; Ribot et al. 1986; Ribot-Ciscar et al. 2000, 2009), changes in sympathetic drive (Abila et al. 1985), or the change in force dynamics associated with error correction (Marsden et al. 1970). Our results suggest that the absence/presence of a target underlies changes in tremor previously associated with the general absence/presence of visual feedback. It may even be the case that continuous error feedback of any kind (e.g., tactile) would produce effects similar to those of visual error feedback. To our knowledge, this study provides the first neural support for the early speculation (Sutton and Sykes 1967) that changes in afferent feedback mechanistically link visual feedback to 7–9 Hz tremor. We should note, however, that the initial generation of 7–9 Hz tremor is probably multifactorial (McAuley and Marsden 2000), allowing many possible explanations for a change in tremor amplitude. For example, Keogh et al. (2004) suggested that the twitches of newly recruited MUs might explain why 8- to 12-Hz upper limb tremor increased during a pointing task when target size was reduced. While certainly possible, their speculation was based on an observed increase in surface EMG amplitude during the higher-precision task rather than on MU recordings. It seems unlikely that subjects in our study attempted to gain a higher degree of force control through increased muscle activity, since we did not observe an increase in MU firing rates and the FDI is the only muscle that abducts the index finger. That said, antagonist activity may still have occurred on a shorter timescale, when error corrections required reduction of abduction force. Overall, task-related changes in antagonist muscle activity and FDI MU recruitment would not clearly explain our findings of altered 7–9 Hz coherence among already-active MUs. In contrast, a change in ongoing afferent feedback would provide an explanation for our results, since 7- to 9-Hz force tremor has been associated with reflex-loop activity and MU-MU coherence in the same range (Elble and Randall 1976; Erimaki and Christakos 2008; Lippold 1970).

The idea that feedback could influence both the magnitude of force tremor and the synchronization of MUs is also supported by the findings of Sowman et al. (2006, 2007), where anesthetization of periodontal mechanoreceptors reduced 8-Hz bite force tremor and masseter MU-MU coherence. In line with their findings, we suggest afferent feedback as a common factor influencing both force tremor and MU-MU synchronization. We found no evidence to suggest that force tremor and MU-MU synchronization were causally linked. Indeed, coherence in the 3–5 Hz range decreased when force tremor increased. According to study of De Luca et al. (2008), pulses of afferent feedback arising from MU recruitment are a major factor in desynchronizing MU activity in the “common drive” range (<5 Hz). A recruitment-related effect would clearly be of higher impact during a dynamic task compared with a static task. This may be relevant for the interpretation of studies that relied on single measures of MU synchrony. For example, Schmied et al. (2000) showed that common input strength increases in a target-guided force holding task when the task is made more difficult by manipulating the visual gain of force feedback. Although our study also introduced higher demands on accuracy and error correction, we found no increase in the overall strength of common input (integrated coherence). Since our task was dynamic, the increased MU synchrony in the 7–9 Hz range was averaged out by the recruitment-related decrease in 3–5 Hz MU synchrony. Had we relied on a single measure of common input strength, it is possible that no task-related effects would have been detected. This emphasizes a major advantage in using frequency-domain measures of common input strength.

Coherence among MUs at higher frequencies (16–32 Hz) is typically associated with direct cortical drive to alpha motorneurons (Farmer et al. 1997) but is not reflected in force fluctuations due to the low-pass filtering effects of the muscle. Although the present study is focused on neural drive associated with tremor, it is worth mentioning that high-frequency corticomuscular coupling may also have a dependence on afferent feedback (Baker 2007). For example, deafferentation reduces EEG-EMG coherence in the 15–30 Hz range (Kilner et al. 2004) and prevents the shift toward higher-frequency coherence (Patino et al. 2008) normally associated with an increase in the dynamic content of isometric force production (Omlor et al. 2007). It has also been suggested that force dynamics and/or afferent feedback may be important considerations when attention or task precision is manipulated (Kristeva-Feige et al. 2002). Consistent with our results, these studies suggest afferent feedback as a potential mechanism for task-related effects on neuromotor control. While we did not find consistent effects of task on MU-MU coherence at high frequencies, coherence between EEG and EMG signals may be the more appropriate measure for a direct evaluation of corticomuscular coupling. The general practice of quantifying coherence between pairs of MUs is a well-established standard in the field but has known sensitivity issues when evaluating the very high-frequency common input expected of cortical drive (Laine and Bailey 2011; Laine et al. 2012; Negro and Farina 2011, 2012). In addition to the analysis of frequency-specific corticomuscular coupling, global changes in cortical drive could be evaluated with TMS. This would avoid the need to equate the magnitude of drive with the statistical strength of synchronization.

Overall, our study is unique in that we have directly measured neural and mechanical changes elicited by production of the same dynamic force with and without a visual target. We suggest that the requirement of error correction leads to an increase in afferent feedback (or its effective gain), causing enhancement of 7–9 Hz physiological tremor. A change in
stretch-reflex gain is suggested by the observed reduction in low-frequency coherence among MUs (De Luca et al. 2008), as well as the increase in 7–9 Hz force tremor and MU-MU coherence, which are associated with reflex-loop activity (Erimaki and Christakos 2008; Lippold 1970). Compared with self-guided force production, the use of a target introduces many new demands on a subject. The task becomes more difficult, requires more attention and greater precision, involves the perception and correction of small errors, etc. While experimental manipulation of such factors is known to influence force control and muscle activity, the results of our study suggest a possible mechanism involving effects on afferent activity and/or fusimotor drive. Further research will be needed to fully understand the effects of task on neural input to muscles. Our study demonstrates one experimental framework in which this can be evaluated. For example, we would predict that task-related effects on tremor would be more pronounced in muscles with higher spindle densities and weaker under conditions in whichafferent feedback might be reduced. Furthermore, if task-related effects stemmed from changes in afferent feedback, it would be important to evaluate any dependence on mean force level or fatigue, as these would likely influence ongoing spindle activity as well as the size of newly recruited MUs. In addition, direct evaluation of reflex gain through electrical stimulation and quantification of the H reflex would also be possible within the experimental framework of this study. Finally, the results of this study emphasize the potential for cognitive/psychological differences between tasks to alter neuromotor control through indirect effects on peripheral mechanisms. A better understanding of these mechanisms may provide new strategies for optimizing performance or rehabilitation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: C.M.L., F.N., and D.F. conception and design of research; C.M.L., performed experiments; C.M.L., F.N., and D.F. analyzed data; C.M.L., F.N., and D.F. interpreted results of experiments; C.M.L. prepared figures; C.M.L., F.N., and D.F. drafted manuscript; C.M.L., F.N., and D.F. edited and revised manuscript; C.M.L., F.N., and D.F. approved final version of manuscript.

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