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General discussion
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As described in the general introduction (chapter 1), movement is the end-result of an ongoing interaction between sensory (perceptual), cognitive, and motor processes (Mulder et al., 2002). Under normal conditions, many activities are automated; that is, little or no attention is necessary for task performance. However, a (temporary) breakdown of automaticity – for example during motor fatigue – will increase the effort needed for the performance of these activities. Insights in the increase of the effort can be obtained using a dual-task paradigm. The topic of this study was: the (cognitive) control of movement during motor fatigue, while performing a concurrent cognitive task.

In all experiments we used a dual-task paradigm with an index finger abduction task (motor task) as the primary task and a two-choice reaction time task (cognitive task) as the secondary task.

Dual-task interference during demanding motor tasks

A previous study (using the same dual-task paradigm) showed that cognitive task performance deteriorated during motor fatigue; that is, there was an increase in reaction times and number of errors with time-on-task (Lorist et al., 2002). The decline in cognitive task performance was attributed to the increasing demands of the fatiguing motor task on central aspects of the motor control system (capacity interference). The increasing demands left less attention available for (secondary) cognitive task performance. During the fatiguing contractions, the maximal voluntary contraction force of the subjects declined, resulting in a relative increase in submaximal target force level. It was unknown whether the increase in demands on the central drive of the motor control system was due to motor fatigue or (only) due to this relative increase in target force level. Studies investigating dual-task performance showed that low-force contractions may have a facilitating effect on cognitive task performance, while high-force contractions may have a less facilitating effect or even a deteriorating effect (Bills, 1927; Bills and Stauffacher, 1937; Moran and Cleary, 1986, 1988; Parker, 1973; Pinneo, 2003). To reveal the origin of the increase in central drive, we used the same dual-task paradigm using short non-fatiguing contractions at two force levels, namely 30% MVC (the initial contraction force of the previous study) and 60% MVC (the relative contraction force at the end of the previous study). We showed that the contractions at a high force level (60% MVC) had a stronger deteriorating effect on cognitive task performance than contractions at a relatively lower force level (30% MVC; chapter 2). This suggests that the increase in central drive to the motor system in order to produce more force already
has an effect on the amount of attention that remains available for the performance of the cognitive task. However, the decrease in cognitive task performance was even stronger during motor fatigue, suggesting that the increase in central drive to the motor system is even larger during fatigue than during non-fatiguing contractions at high force levels, which corroborates the central effects of motor fatigue (for reviews see: Gandevia et al., 1995; Gandevia, 2001).

As motor fatigue has central aspects, the negative effects of motor fatigue might be diminished by caffeine. Caffeine is a well-known stimulant of the central nervous system, and it is known to improve cognitive performance (e.g., Brice and Smith, 2002; Ruijter et al., 1999; Warburton, 1995) and sometimes also motor performance (Jackman et al., 1996; Kalmar and Cafarelli, 1999; Plaskett and Cafarelli, 2001; for review see Graham, 2001). The effects of caffeine are most prevalent, when subjects perform under suboptimal conditions, such as during fatigue or boredom, or when tasks place a high demand on the information processing system (Lieberman et al., 1986; Lorist et al., 1994). Thus, caffeine or placebo was added to decaffeinated coffee and then administrated to the subjects (chapter 3). The amount of caffeine was an equivalent of two cups of coffee, a relatively low dose. Subsequently, the subjects performed a single cognitive task, the fatiguing motor task in combination with the cognitive task, and the single cognitive task again. Caffeine did not reduce motor fatigue or affect motor performance in any other way; however, caffeine indeed improved cognitive task performance. Furthermore, it partly prevented the decline in cognitive task performance during motor fatigue, probably by enhancing the availability of and/or by allocating the information processing capacity.

**Techniques**

To gain more insight in the central origin of the interaction between motor fatigue and cognitive task performance, we studied brain activation during dual-task performance, using functional magnetic resonance imaging (fMRI). However, due to the (magnetic) properties of the scanner, we had to adapt our experimental set-up to an MR environment. First, we developed an MR compatible force transducer (chapter 4). The transducer had to consist of non-ferro-magnetic materials, so that it would not be attracted to the scanner and/or affect the MR images. The system also had to be protected against the effects of the magnetic field and the changing magnetic gradients. In addition, the force transducer had to be adjustable to variable hand sizes, had to show a linear response to forces, and had to be able to measure fast force fluctuations.
Besides measuring force, we also wanted to measure muscle activity using electromyography (EMG). An MR compatible EMG system was developed by Brain Products; however, the EMG recordings were strongly affected by MR imaging. For that reason, we had to apply an MRI artifact correction method (chapter 5). After this artifact correction, it was possible to quantify the EMG recordings and to use these data in analyses of brain activation.

**Brain activation**

**Motor control**

To be able to reveal the areas in the brain that are involved in the complex interaction between motor fatigue and cognitive task performance, we first wanted to perform some baseline experiments on brain activation during motor control and motor fatigue. In the first fMRI study (chapter 6), we looked at the relationship between force, muscle activity (EMG), and brain activation during short isometric contractions at different force levels (5%, 15%, 30%, 50%, and 70% MVC). It is known that there is more or less a linear relationship between force and muscle activity during short submaximal contractions (Lippold, 1952; Bigland and Lippold, 1954). Indeed, we found a strong linear correlation between force and EMG amplitude during the contractions. Furthermore, several studies already showed a correlation between the amount of brain activation and different force levels (Dai et al., 2001; Dettmers et al., 1995; Thickbroom et al., 1998; Ward and Frackowiak, 2003). However, we investigated whether brain activation was directly correlated with muscle activity, and whether there were differences between brain areas in their relation to muscle activity. To study this, we used the mean EMG amplitude per scan as a regressor in the analysis of the fMRI data. In this analysis, we also added a second regressor (‘on/off’) that revealed activation in brain areas that were involved in task performance *per se*, independently of the amount of force that was produced. Activation that correlated with muscle activity mainly revealed known ‘motor areas’, such as the contralateral primary sensorimotor cortex, premotor areas, the supplementary motor area, and the ipsilateral cerebellum. Areas in which the activation was more determined by task performance *per se* were the inferior part of the right precentral sulcus, bilateral parietal areas, bilateral putamen, and insular cortex. The fact that some areas showed activation that correlated stronger with task performance per se than with the amount of force suggested that these areas were more involved in higher-order motor processes, such as preparatory processes or monitoring feedback mechanisms.
A separate region of interest analysis revealed that the amount of activity in the first ('motor') areas indeed strongly correlated with the EMG amplitude, both at group and at subject level, while activity in the other areas did not. Now we knew that the amount of activation in the motor areas correlated with the amount of muscle activity, so the amount of brain activation resembled the central drive, just as Logothetis and colleagues showed that the amount of brain activity correlated with the local field potential in monkeys (Logothetis et al., 2001). Chapter 2 showed that the changes in central drive during motor fatigue differed from the changes in central drive during different force levels, as was shown by the differences in secondary task performance. We wanted to know whether these differences in central drive were also visible in the brain activation.

**Motor fatigue**

In a second fMRI study (chapter 7), we studied the effects of motor fatigue on brain activation. We focused on changes both during and after fatigue. Subjects performed again short submaximal contractions at different force levels (10%, 30%, and 70% MVC) and sustained submaximal contractions at a non-fatiguing (5% MVC) and a fatiguing (30% MVC) force level. Again, mean EMG amplitude per scan was used as a regressor to reveal brain activation. The short submaximal contractions induced activation in the same brain areas as in the previous study, and so did the sustained contractions. However, the activation during the fatiguing contractions was less pronounced than during the short submaximal contractions, especially in the cerebellum. We also analyzed the brain activation during the sustained contractions with another model to study the effects of time. This analysis revealed an increase in the activation of several motor areas with time on task during the fatiguing contractions, predominantly in the contralateral sensorimotor cortex (SMC) and the supplementary motor area (SMA). Furthermore, this analysis revealed activation of a middle frontal area. This suggests that the increase in central drive to the motor system due to motor fatigue is visible in the amount of brain activation.

We also investigated whether there were changes in brain activation after fatigue (also chapter 7), as Benwell and colleagues (2005, 2006) showed a decrease in brain activation after fatigue. For this purpose, subjects performed maximal voluntary contractions (MVCs, a simple motor task) and two reaction time tasks before and after the fatiguing task. During MVC performance, we found the most pronounced effect in the SMA. In this area, activity was decreased after fatigue. On the other hand, during
reaction time task performance, we found an increase in activity after fatigue in the orbitofrontal cortex. This suggests that both the SMA and frontal areas are sensitive to effects of fatigue, as these areas show both changes during and after fatigue.

_Dual-task interference_

Finally, we studied brain activation during dual-task performance (_chapter 8_). In this study, the same tasks were used as in the previous study; that is, the MVCs and reaction time tasks before and after fatigue, the short submaximal contractions and the sustained submaximal contractions. However, in this experiment were the sustained contractions combined with a secondary cognitive task. Functional MRI studies on dual-task performance showed either an increase in brain activation during dual-task performance compared to single task performance (Adcock et al., 2000; D’Esposito et al., 1995; Herath et al., 2001) or a decrease (Johansen-Berg and Matthews, 2002; Just et al., 2001; Newman et al., 2006). Based on the results of our previous studies, we expected to find a decrease in secondary task performance as a result of an increased central drive to the motor task. We expected to find this increase in central drive to the motor task as an increase in brain activation in the areas that were involved in (primary) motor task performance. Furthermore, we expected that this increase would result in a decrease in brain activation that correlated with (secondary) cognitive task performance, which would be reflected in the decrease in cognitive task performance. Indeed, we found a decrease in cognitive task performance with increasing motor fatigue. However, the changes in brain activation were more complicated. Contrary to our previous findings of increased brain activation with increasing motor fatigue during a single motor task (_chapter 7_), in the dual task we did not find an increase but a decrease in brain activation in areas related with motor task performance. This indicates that the combination of the motor task with the choice reaction time task affected the brain activation during motor fatigue.

_Conclusions_

In conclusion, motor fatigue increases the demands of the motor system on the central drive to activate fatigued muscles. The increase in central drive to motor task performance can be measured as a decrease in secondary cognitive task performance. We showed that the increase in central drive due to the increase in force is less than the increase in central drive due to motor fatigue. We also showed that caffeine, a well-known stimulant of the central nervous system, can partly prevent the deterioration in
secondary task performance. Furthermore, we showed that the increase in central drive can be found in the brain as an increase in brain activation, both during increasing force levels and during motor fatigue, although there are subtle differences. However, the changes in brain activation in a fatiguing dual-task paradigm are much more complex.