Age-related changes in neural control of posture
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER 7

General discussion
1. GENERAL DISCUSSION

A review of the literature reveals that old compared with young adults exhibit differential modulation of spinal reflexes, higher brain activation, and lower cortical inhibition during voluntary manual tasks, suggesting a shift from spinal to supraspinal control. Although some studies indicate that this reorganization is also present during postural tasks, evidence is limited, and functional significance of such reorganization is unknown. The aim of this thesis was therefore to determine the age-related changes in neural control of posture, as quantified by measures of motor cortical excitability and brain activation, and how such changes affect body sway during standing. We conducted a series of experiments examining the influence of age and postural task difficulty on intracortical inhibition and facilitation. Figure 1 summarizes the main outcomes of these studies, demonstrating a down-modulation in intracortical inhibition with an increase in postural task difficulty and an age by condition interaction when comparing standing on a rigid platform with standing on foam. In a final study, we further increased postural task difficulty by adding a cognitive task and examined age-related changes in neural correlates of posture and dual-tasking using functional magnetic resonance imaging (fMRI). As expected, we found increased brain activation and greater dual-task costs in old compared with young adults. However, there were no correlations between the fMRI and behavioral measures. Below, I will discuss the main findings of this thesis in more detail.

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**Figure 1** | Overview of modulation in measures of intracortical inhibition in young and old adults as described in chapters 3 to 5. Arrows and equality signs indicate the modulation from supported to unsupported standing (upper line) and leaning (middle line), and from standing on a rigid platform to standing on foam (lower line). Task difficulty during leaning was adjusted to skill level by setting the leaning target to 75% of the maximum per participant. TA: tibialis anterior, SOL: soleus.
1.1. Cortical control of standing

This thesis adds to the body of literature supporting the involvement of cortical structures in postural control of standing [1-6]. Performing a simulated balance task activated cortical regions such as the premotor cortex, prefrontal cortex, inferior and middle frontal gyrus, SMA, visual cortex, insula, and inferior parietal areas (chapter 6). Brain regions that were also reported to be active during mental imagery and action observation of standing using fMRI [2] or actual standing using PET-scans [4]. A new aspect that is highlighted by this thesis is the role of intracortical inhibition in postural control, which was shown to modulate with postural task difficulty (chapters 3-5). Functional significance of this modulation was further supported by correlations between the amount of modulation and behavioral measures, such as center of pressure velocity (chapter 3) and forward lean (chapter 5). In young adults, the modulation was apparent only in the soleus, which is the main muscle controlling standing posture [7]. This is consistent with the view that the down-modulation in intracortical inhibition is targeted specifically to increase the excitability of corticospinal neurons projecting to motor neurons of the muscles that are involved in the task. In old adults, however, intracortical inhibition was modulated also in the tibialis anterior when standing on foam as compared with standing on a rigid surface. This may indicate an age-related increase in involvement of the tibialis anterior to control standing on an unstable surface, i.e., on foam, supported by higher levels of tibialis anterior activity. However, changes in intracortical inhibition did not correlate with changes in background EMG. Moreover, down-modulation in intracortical inhibition also occurred when background EMG was similar between conditions (chapter 5). Reducing intracortical inhibition is therefore probably not simply a mechanism to increase descending drive. It is speculated that it represents an increased readiness state of the motor cortex to prepare for potential perturbations.

1.2. Age-related changes in cortical control of standing

Old compared with young adults generally exhibit more brain activation and lower cortical inhibition when performing a voluntary manual task (chapter 2). This thesis shows that similar age-related changes are present during postural control of standing (chapters 3, 4 & 6). Additionally, it reveals an age effect on the modulation of intracortical inhibition between certain postural tasks (chapter 3).

We examined balance-related brain activation using fMRI during a simulated standing task. In this task, old compared with young adults exhibited more activation in motor (precentral and paracentral gyri) and sensory (cuneus and precuneus) brain areas (chapter 6). Although this is consistent with Zwergal et al. [8], who reported age-related increases in brain activation during imaginary standing, we note that simulating or imagining standing is quite different from actual standing. Technical advances allowing imaging of brain activation during upright standing are
required to properly address this issue.

In chapters 3 to 5, intracortical inhibition was assessed using paired pulse and subthreshold TMS during postural tasks of varying difficulty. Age-related decreases in intracortical inhibition were found in the tibialis anterior (chapters 3 & 4) but not in the soleus (chapters 4 & 5). As is evident from figure 1, there was an age by task difficulty interaction in intracortical inhibition when young and old adults had to perform the same difficult postural task, i.e. standing on foam. As age-related sensory and motor deficits complicate postural control [9-16], standing on foam can be considered a more challenging task for old than for young adults. Therefore, the age-related difference in modulation of intracortical inhibition may have been due to the relatively higher postural challenge. This is supported by the fact that young and old adults showed similar modulation of intracortical inhibition when the postural tasks were relatively easy (normal standing) or when the difficult task was adjusted to skill level (forward leaning to 75% of your maximum) even though maximum forward lean was significantly lower in old adults. Moreover, greater reductions in intracortical inhibition were related to greater instability when standing on foam (chapter 3) and to leaning closer to the maximum during unsupported leaning (chapter 5). Together, these results imply that postural challenge is the main factor influencing intracortical inhibition and that age does not affect the motor control strategy of reducing intracortical inhibition with increasing postural challenge. However, as a similar task can be more challenging for old compared with young adults, the threshold for down-modulation decreases with aging.

1.3. Age-related changes in intracortical inhibition are muscle specific

As briefly mentioned in the previous paragraph, old compared with young adults consistently exhibited lower intracortical inhibition in the tibialis anterior (chapters 3 and 4), but similar intracortical inhibition in the soleus (chapters 4 and 5). This muscle specificity may be explained by differences in corticospinal projections, which are much stronger in the tibialis anterior than in the soleus [17-20]. Also in the upper extremity, intracortical inhibition is lower [21-23] or similar [24-27] in old compared with young adults when examined in muscles with strong corticospinal projections (hand muscles), and higher when examined in muscles with weaker corticospinal projections (wrist flexors and extensors) [28,29]. Together, these data suggest that the influence of age on intracortical inhibition is dependent on the examined muscle and its corticospinal projections.

The question arises what the underlying causes are for such muscle specificity. One reason could be that it reflects a compensatory mechanism to the varying effects of aging on different muscles [30,31]. Histochemical data indeed indicate greater age-related changes in the extensor digitorum brevis, a small hand muscle, than in more proximal arm muscles [30]. To our knowledge, there is no data available for such comparisons between the tibialis anterior and the soleus. However, muscle strength actually seems more preserved in the tibialis anterior than in the sole-
Therefore, the age-related changes in intracortical inhibition do not seem to be related to the effect of age on the muscle. An alternative explanation could be that the muscle specificity is related to the different muscle functions. Monosynaptic corticospinal connections are thought to be evolved in primates to allow skilled precision control [34]. The muscle specificity may therefore reflect a mechanism of the aging nervous system to maximize corticospinal input to specific muscles favoring fine over gross motor control. In the case of the tibialis anterior this may be particularly important because of its role in toe clearance during erect walking, which requires extreme precision control [35,36] and flexibility to avoid obstacles [20,37].

1.4. No age- or task-related changes in intracortical facilitation

Besides intracortical inhibition, we also examined intracortical facilitation. Our finding of no age-related changes in intracortical facilitation (chapters 3 and 4) agrees with the majority of previous studies [25,38,39], although others reported decreased intracortical facilitation in old compared with young adults [40,41]. As our measurements were taken during standing, our finding is also consistent with McGinley et al. [42], who reported no difference in intracortical facilitation between age groups during a weak isometric muscle contraction. Our second finding was that there was no modulation between postural tasks (chapters 3 and 4). Great inconsistency exists in the literature regarding modulation of intracortical facilitation between postures, with reports of reduced [43], similar [44], and increased [45] intracortical facilitation during standing as compared with sitting. These inconsistencies may be caused by methodological differences like the examined muscle, stimulation intensity and interstimulus interval, and/or reflect the high between-subject variability of this measure. This thesis is the first to examine intracortical circuits between various task difficulty situations of standing and suggests that during standing motor cortical excitability is modulated through intracortical inhibition and not facilitation.

1.5. Age-related functional changes: deterioration or compensation?

We proposed a classification model of the different domains of age-related changes in the neuromotor system; structural, functional, and behavioral changes (chapter 2, figure 1). Functional changes were subdivided into deterioration (as a direct result of the structural changes) and compensation (changes in function to counteract the deterioration). As the subsequent chapters described several age-related functional changes, an interesting and important topic of discussion is whether these changes are due to deterioration or compensation. For example, in chapter 3 we reported that old but not young adults down-modulate intracortical inhibition when standing on foam as compared to a rigid surface. Greater down-modulation was correlated with greater increases in center of pressure velocity (i.e. worse performance). One interpretation of this finding is that increases in center of pressure velocity were caused by the down-modulation in intracortical inhibition, suggesting a functional deterioration. Alternatively, old adults with higher center of
pressure velocity had a greater need to adjust intracortical inhibition, as a compensation for the greater instability. The latter explanation was supported by chapter 5, where task difficulty was adjusted to individual skill level, and modulation of EMG suppression, presumably representing intracortical inhibition, was similar between young and old adults. Moreover, leaning closer to the maximum was correlated with greater reductions in EMG suppression; again suggesting that intracortical inhibition decreases in unstable situations. Therefore, assuming that both chapters measured similar inhibitory mechanisms, the different modulation in old adults reported in chapter 3 was most likely a compensatory mechanism.

Another age-related functional change reported in this thesis (chapter 6) and previous studies [8,46-53] is an age-related increase in brain activation during motor and cognitive tasks. Although this finding is consistent among studies, there is no consensus yet on its functional meaning. Both positive [49,54-58] and negative [48,50,53,59] correlations with behavioral performance have been reported, suggesting that the functional meaning may be dependent on the task and the involved brain structures. We found no correlations between brain activation in the “over-activated” areas and performance on a calculation and visuomotor balance simulation task. Van Impe et al. [60] used comparable tasks (calculation and visuomotor drawing), reported similar brain areas with higher activation in old adults (precentral gyrus, paracentral lobule, precuneus), and also no correlation with performance. Therefore, it seems that at least in such tasks a functional deterioration occurs with an age-related spreading of brain activity without functional meaning.

1.6. Motor cortical control is similar for postural and non-postural contractions

Voluntary and postural contractions are often considered distinct entities even though little is known about the underlying neural mechanisms. Neural control of voluntary and postural contractions has been investigated by comparing muscle contractions during sitting or lying with standing [43,61-65]. An important limitation of these studies is that conditions did not only differ in the aim of the contraction (postural or non-postural), but also in posture (sitting or lying vs. standing) and postural challenge. In chapter 5 we aimed to dissociate how these different factors affect TMS-induced EMG suppression by comparing sitting, supported leaning, and unsupported leaning. EMG suppression decreased during unsupported leaning, probably reflecting a reduction in intracortical inhibition. There was no difference in EMG suppression between sitting and supported leaning. We concluded that postural challenge, which was high during unsupported leaning and low during sitting and supported leaning, was the main factor affecting intracortical inhibition. The aim of the contraction, postural or non-postural, did not seem to influence intracortical inhibition. This supports the idea that, as long as postural challenge is unchanged, there is no difference in neural control of postural and non-postural contractions. This idea is further supported by the fact that the age-related changes in motor cortical control of posture described
in chapters 3 to 6, i.e. reduced intracortical inhibition and increased cortical activation, were similar to those previously reported in voluntary manual tasks (chapter 2). However, other inhibitory and excitatory circuits within the brain that we did not measure may still be involved differently in postural and non-postural contractions.

1.7. Neural correlates of dual-tasking

In addition to changing sensory input or support, postural task difficulty can also be modified by adding a cognitive task. Especially old adults generally have difficulty with performing two tasks simultaneously and show greater dual-task costs than young adults [66-68]. We hypothesized that this age-related deficit in dual-task performance may be related to the increased cortical activation when performing a motor or cognitive task (chapter 2). In chapter 6, this was tested using fMRI during a simulated balance task combined with a mental arithmetic task. Although age-related increases in brain activation and dual-task costs were found, there were no correlations between the behavioral and fMRI measures, contradicting our hypothesis. It therefore seems that, at least in these tasks, the increased brain activation did not affect dual-tasking. It remains to be explored what did cause the reduced dual-tasking performance in old adults. One alternative theory is that there is a central bottleneck that can perform certain processes only sequentially, resulting in serial queuing and time delays [69]. Future research using high-temporal resolution measures such as time-resolved fMRI [70] will test this hypothesis.

1.8. Limitations and future recommendations

This thesis has several limitations. First, the currently available measures for intracortical inhibition are not perfect. Although there is quite convincing evidence that the subthreshold TMS pulse stimulates intracortical inhibitory neurons [71-73]; background EMG [43,74,75]; stimulation intensity [76], cortical facilitatory circuits, and the extent of cortical involvement in the ongoing EMG [77] can also affect the outcome. Second, as motor threshold and stimulation hotspot slightly differ between the soleus and tibialis anterior, it is difficult to acquire reliable data from both muscles in one experiment. Therefore, in our first study comparing easy and difficult postural tasks, we focused on the tibialis anterior. Future research is needed to ascertain that the age by task difficulty interaction in intracortical inhibition also occurs when examining the soleus muscle. A third limitation is that the simulated balance task in chapter 6 differs from actual balance in several ways, e.g., different sensory input from the vestibular system, no real threat of falling, and no weight-bearing. Although torque variability during a plantar flexion torque-matching task correlated with torque variability during actual standing [78,79] and the simulated balance task activated brain regions supposed to be involved in balance (chapter 6), caution is still required with regard to the external validity of the task. Technical advances are needed to provide means to properly examine neural correlates of standing in the future.
1.9. Clinical implications

A better understanding of the age-related differences in neural control of posture is essential for the development of fall prevention and intervention programs for old adults. This thesis provides evidence that the ability to adjust motor cortical excitability to different environments is unaffected by age (chapters 4 and 5). Balance training should therefore focus on other aspects of postural control, such as sensory input [80] and muscle power [12,81]. This thesis also confirms previous reports that old compared with young adults have more difficulty with performing a cognitive and balance task simultaneously [66-68] (chapter 6). Another important aspect of balance training in old adults should thus be to practice such dual-task situations [12]. Lastly, as age-related differences in neural measures were found only during difficult balance tasks (chapter 3), this thesis underpins that including relatively difficult balance exercises may be essential in order to cause neural adaptations [82]. Future work is needed to verify this suggestion and examine changes in motor cortical excitability that are induced by balance training in old adults.

1.10. Conclusions

The aim of this thesis was to determine the age-related changes in neural control of posture, as quantified by measures of motor cortical excitability and brain activation, and how such changes affect body sway during standing. The results show an age-related muscle-specific reduction in intracortical inhibition and increase in cortical activation during postural tasks, suggesting a similar neural reorganization with age as during manual tasks. Age-related increases in brain activation did not correlate with single- or dual-task performance, favoring the theory of de-differentiation over compensation. Modulation of intracortical inhibition between postural tasks differed between age groups when comparing an easy with a difficult task, but was similar when adjusting task difficulty to the individual skill level. This implies that the ability to modulate intracortical inhibition by postural challenge is unaffected by age, but the threshold for down-modulation is lower in old as compared with young adults. Functional significance of the task-related modulation in intracortical inhibition was supported by correlations with behavioral measures.

REFERENCES

5. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of
General discussion


