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Network connectivity of motor control in the ageing brain

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ABSTRACT

Older individuals typically display stronger regional brain activity than younger subjects during motor performance. However, knowledge regarding age-related changes of motor network interactions between brain regions remains scarce. We here investigated the impact of ageing on the interaction of cortical areas during movement selection and initiation using dynamic causal modelling (DCM). We found that age-related psychomotor slowing was accompanied by increases in both regional activity and effective connectivity, especially for 'core' motor coupling targeting primary motor cortex (M1). Interestingly, younger participants within the older group showed strongest connectivity targeting M1, which steadily decreased with advancing age. Conversely, prefrontal influences on the motor system increased with advancing age, and were inversely correlated with reduced parietal influences and core motor coupling. Interestingly, higher net coupling within the prefrontal-premotor-M1 axis predicted faster psychomotor speed in ageing. Hence, as opposed to a uniform age-related decline, our findings are compatible with the idea of different age-related compensatory mechanisms, with an important role of the prefrontal cortex compensating for reduced coupling within the core motor network.

1. Introduction

Ageing is associated with decline of various cognitive functions (Grady, 2012). Moreover, older people often display deterioration of motor performance such as psychomotor slowing or reduced fine motor skills (Salthouse, 2000; Seidler et al., 2010). One important factor contributing to age-related performance decline is neurodegeneration as represented by, e.g., grey matter atrophy (Draganski et al., 2013). However, functional neuroimaging studies revealed substantial evidence for adaptive plasticity paralleling structural decline.

Typically, older subjects display both enhanced and more widespread brain activation than their younger counterparts during motor performance (Mattay et al., 2002; Rowe et al., 2006). Notwithstanding, the exact functional role of increased regional brain activity for motor control in older individuals remains poorly understood. On the one hand, non-selective recruitment of brain activity could reflect a loss of neural specificity or efficiency in the ageing brain, i.e., dedifferentiation (Li and Lindenberger, 1999; Logan et al., 2002; Riecker et al., 2006). On the other hand, numerous studies point to a compensatory role in that stronger recruitment of brain activity is beneficial for motor performance in ageing (Mattay et al., 2002; Naccarato et al., 2006; Wu and Hallett, 2005). However, from a systems-level perspective, enhanced regional activity could as well depict a compensatory mechanism to account for age-related reduction in network connectivity, similar to what has been observed in neurodegenerative diseases such as Parkinson's disease or in stroke (Grefkes et al., 2008; Rowe et al., 2002). Here, studies of resting-state functional connectivity revealed that reduced motor performance in older individuals is associated with both increased and diminished interregional coupling within the motor network (Langan et al., 2010; Seidler et al., 2015; Solesio-Jofre et al., 2014). However, resting-state analyses do not allow direct conclusions about how brain areas interact during a given task, thereby limiting insights into the relationship between network changes underlying a specific behaviour and age-related performance decline (Rehme et al., 2013; Sala-Llonch et al., 2015). Nevertheless, the wealth of studies demonstrating age-related motor deficits is contrasted by the dearth of studies that addressed the question of how brain areas interact in the ageing brain during motor performance. The evidence thus far available

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from task-based studies suggests that interregional connectivity is enhanced in older as compared to young subjects, especially coupling among 'core' motor regions like premotor cortex and primary motor cortex (M1) (Boudrias et al., 2012; Heitger et al., 2013; Rowe et al., 2006). Furthermore, interindividual variability in premotor-M1 coupling has been shown to predict motor performance in older individuals (Stewart et al., 2014).

Nevertheless, motor actions do not only depend on such core motor regions, but also on activity in anterior/prefrontal and posterior/parietal brain regions, i.e., areas which typically show increased activity in older subjects even in simple motor tasks (Heuninckx et al., 2005, 2008; Mattay et al., 2002). Particularly enhanced prefrontal activity has consistently been shown in older subjects during motor performance (Heuninckx et al., 2005, 2008; Wu and Hallett, 2005). This is at first sight at odds with the frontal lobe hypothesis stating that age-related behavioural deficits are primarily due to the structural and functional deterioration of frontal parts of the ageing brain (Moscovitch and Winocur, 1992; West, 1996). Yet paradoxically, multiple neuroimaging studies have linked increased activity in anterior brain regions associated with higher-order cognitive demands to better behavioural performance in ageing individuals across multiple cognitive domains (Cabeza et al., 2002; Grady et al., 2005; Reuter-Lorenz et al., 2000). Intriguingly, this enhancement of top-down modulation seems to compensate for dysfunctional sensory-driven bottom-up processing in posterior brain regions of ageing individuals, a phenomenon termed the 'Posterior to Anterior Shift in Ageing' (PASA; Davis et al., 2008).

To date, it remains, however, to be elucidated how the PASA theory relates to motor network connectivity, i.e., how anterior and posterior brain regions change their influence on the core motor system. It is currently poorly understood how the balance between top-down influences from regions anterior to and bottom-up influences from regions posterior to core motor regions affects motor performance in ageing individuals. To address this question, we assessed effective connectivity in an extended cortical motor network underlying psychomotor processes in young and older subjects using functional magnetic resonance imaging (fMRI) and dynamic causal modelling (DCM; Friston et al., 2003). We used a reaction paradigm that enabled us to study the neural mechanisms of both basic motor aspects such as movement initiation as well as higher-order movement preparation, selection and visuomotor integration within the same experimental setting (Hoffstaedter et al., 2013; Michely et al., 2015). Moreover, such psychomotor processes, that are typically slowed in ageing individuals, strongly rely on the integrity of neural coupling between both top-down modulation from anterior/prefrontal and bottom-up modulation from posterior/parietal brain regions onto the core motor system (Berchicci et al., 2012; Stewart et al., 2014; Vallesi et al., 2011). We expected that ageing is associated not only with changes in interregional coupling within the core motor network, but also with differences in the influence that prefrontal and parietal areas exert onto (pre)motor regions. In line with the PASA theory, we hypothesized that age-related reduction in bottom-up modulation from posterior/parietal regions might be compensated by increasing top-down modulation from anterior/prefrontal regions onto the core motor system. Finally, in order to address this compensation theory, we tested whether age-related coupling changes related to the PASA theory are linked to behavioural parameters of psychomotor speed in ageing individuals.

2. Materials and methods

2.1. Subjects

Twenty-four healthy male subjects participated in the study after providing informed written consent (12 younger subjects, mean age 27.4 ± 4.2, range 21–35; 12 older subjects, mean age 62.1 ± 6.3, range 52–74). The underlying rationale for the inclusion of subjects with this particular age range was two-fold: First, we wanted to assess general ageing effects by comparing two distinct age groups, i.e., young and older subjects. Second, we aimed to characterize how changes in neural coupling relate to progressive structural atrophy and behavioural performance in advancing age, i.e., within our older subgroup between 52 and 74 years of age.

All participants underwent a comprehensive clinical interview to exclude a history of any neurological or psychiatric disease or other chronic disabling medical problem. According to the Edinburg handedness inventory (Oldfield, 1971), all subjects were right-handed (mean 81.0 ± 20.2). In order to exclude cognitive deficits in older participants, subjects were additionally tested by the means of a comprehensive cognitive test battery, assessing executive functions, working memory, attention, and visuospatial functions, i.e., the Parkinson Neuropsychometric Dementia Assessment (Kalbe et al., 2008). Importantly, all subjects scored well above the cut-off score for cognitive impairment, hence, there was no indication of cognitive impairment in our older participants (mean score 25.6 ± 3.7, range 20–30, cut-off score < 18). FMRI data of the older subjects was previously used as healthy control data in a study on Parkinson's disease (Michely et al., 2015). However, all analyses, models and results in the present study are new, hence, there is no overlap with previously presented results. The study was in accordance with the Declaration of Helsinki and approved by the local ethics committee.

2.2. FMRI paradigm

The experimental paradigm (Fig. 1) was equivalent to our previous studies on motor control in healthy subjects (Hoffstaedter et al., 2013), patients suffering from Parkinson's disease (Michely et al., 2012, 2015) and major depression (Hoffstaedter et al., 2012). The task comprised three conditions and an imbedded functional localizer. Subjects responded via button presses on a MRI compatible response device using the right or left index finger. Visual stimuli were generated using the 'Presentation' software package (Version 10.3, Neurobehavioral Systems Inc., Albany, CA). Each condition was presented in blocks of 20 s duration separated by resting baselines of 16 s during which subjects watched a blank screen. Each block was introduced by a one-word instruction presented for 2.5 s, informing the subject about which of the four conditions followed next.

2.2.1. Condition 'Free': self-timed movement selection

In the 'Free'- condition, subjects were instructed to press either the left or right button at any self-chosen time. Hence, subjects were free in terms of both movement lateralization and timing. Every response was followed by an immediate visual feedback consisting of an arrow pointing to the side of the button-press (duration: 400 ms; Fig. 1). By providing a feedback arrow, we kept this condition comparable to the reactive ones in terms of visual input and display delays. Moreover, during feedback, no further response was allowed to prevent repetitive finger tapping. Since subjects were not allowed to press any button whilst the feedback arrow was presented, response times in the 'Free'-condition reflect the interval between the end of the presentation of the feedback arrow and the next self-initiated button press. Subjects were instructed to roughly balance between left and right button presses, and to avoid extensive periods of rest between button presses.

2.2.2. Condition 'Intern': reaction to a non-informative cue

Subjects were asked to respond to a double-headed arrow, i.e., non-informative cue (displayed for 400 ms; Fig. 1) with a button press of either their left or right index finger. Since subjects were prompted to press the right *or* left button as fast as possible, they were restricted with regard to the timing of movement execution, but free in terms of