



White matter integrity of motor connections related to training gains in healthy aging

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ABSTRACT

Impaired motor skill acquisition is a feature of older age. Acquisition of new motor skills requires the interplay between different cortical motor areas. Using diffusion tensor imaging we reconstructed cortico-cortical connections between the primary motor cortex (M1) and secondary motor areas in 11 older and 11 young participants who took part in a motor skill acquisition paradigm with the nondominant left hand. Examining the extent to which tract-related integrity correlated with training gains we found that white matter integrity of fibers connecting contralateral M1 with both contralateral ($r = 0.85$) and ipsilateral supplementary motor areas ($r = 0.92$) were positively associated in old participants. Also, fibers connecting contralateral M1 with ipsilateral dorsal premotor ($r = 0.82$) and fibers connecting ipsilateral dorsal premotor and supplementary motor area ($r = 0.88$) were positively related to skill acquisition (all $p < 0.05$). A similar structure-behavior relationship was not present in the young control subjects suggesting a critical role of brain structural integrity for motor learning in healthy aging.

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1. Introduction

Impaired acquisition of novel motor skills is a feature of older age which has a critical impact on activities of daily living, on independence, and integration in modern society (Seidler et al., 2010). The question is whether there are specific alterations in the motor system underlying this deficit or whether it is caused by rather unspecific, more general alterations in the aging brain?

Skill acquisition such as motor sequence learning requires the interplay between cortical and subcortical brain regions (Doyon et al., 2003; Halsband and Lange, 2006; Kantak et al., 2012). Aside from cortico-subcortical and cortico-cerebellar circuits involved in different stages throughout the learning process (Doyon et al., 2003), cortico-cortical interactions between primary (M1) and secondary motor areas, such as the dorsal (PMd) and ventral (PMv) premotor cortex (Kantak et al., 2012; Sanes, 2003) as well as the supplementary (SMA) and the pre-supplementary motor area

(Nachev et al., 2008) also play a relevant role. Hereby, M1 and SMA have been particularly found to show both a dynamic modulation in regional activity and time-dependent changes in inter-regional coupling (Ma et al., 2010). Moreover, in healthy aged participants, M1 and SMA have shown an increased activation already in simple movements (Hutchinson et al., 2002; Inuggi et al., 2011).

The structural integrity of the underlying network pathways is an important basis for neuronal information throughput and explains at least some of the behavioral variance between young healthy participants during skill acquisition. For instance, training gains in a visuomotor tracking task have been associated with the micro-structural integrity of cerebellar and precentral white matter (WM) (Tomassini et al., 2011). Improvement in visuomotor adaptation learning has been correlated with WM integrity of the cerebellum, its outflow tract and regions within posterior parietal brain regions (Della-Maggiore et al., 2009). Recently, it has also been shown that the level of synchronization reached after days of rhythmic finger tapping training correlated with the integrity of long association fibers such as the longitudinal fascicle underlying the sensorimotor cortices as M1 and the primary sensory cortex (Steele et al., 2012).

In healthy aging, numerous studies have demonstrated age-dependent structural alterations of the brain (Giorgio et al., 2010; Sullivan and Pfefferbaum, 2006) affecting neural networks in the

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cognitive and motor domain (Sullivan et al., 2010; Voineskos et al., 2012; Zahr et al., 2009). However, learning related structure-behavior relationships have only been addressed for a few subcortico-cortical connections in old participants: the microstructural integrity of specific thalamo-cortico-striatal connections has been associated with gains in probabilistic reward learning (Samanez-Larkin et al., 2012). The integrity of prefrontal-subcortical fibers has predicted the success in implicit motor sequence learning (Bennett et al., 2011). We hypothesized that such a positive structure-behavior relationship would also hold true for a limited number of specific cortico-cortical connections in explicit motor sequence learning, expecting the connection between SMA and M1 to be of particular importance in regard of skill acquisition in healthy old adults. The task used was a well-established skill acquisition task in which the participants had to perform sequential finger tapping with 4 fingers according to a training sequence. It engages activity in a distributed motor network including primary and secondary motor areas (Orban et al., 2011). We also aimed to investigate whether young and old participants depend on the integrity of similar cortico-cortical pathways. Whether both groups call similar networks remains unclear: previous functional (Aizenstein et al., 2006; Daselaar et al., 2003) and structural imaging studies (Bennett et al., 2011) have reported inconsistent findings, which makes it difficult to draw strict conclusions. Additionally, we hypothesized that these specific tract-behavior associations affect specific cortico-cortical tracts of interest in old adults compared with young participants and are not the result of not rather unspecific general reduction of WM integrity in old participants.

For these aims, we used diffusion tensor imaging to reconstruct all 28 intra- and interhemispheric pathways connecting primary and 3 secondary motor areas that are PMd, PMv, and SMA in groups of young and old participants. Estimating the microstructural integrity of each individual tract we sought to examine the extent to which tract-related WM integrity correlated with training gains in the sequential finger tapping task in young and healthy aged adults.

2. Methods

2.1. Participants

Eleven healthy old (aged 73.1 ± 1.9 , range 65–83 years, 7 women) and young (aged 23.6 ± 0.6 , range 20–27 years, 7 women) volunteers participated in a skill acquisition task based on the training of sequential finger movements (explicit) of the left, nondominant hand over 5 consecutive days. All participants were right-handed, as assessed by the Edinburgh handedness inventory (Oldfield, 1971) and none of them reported any history of serious medical, neurologic, or psychiatric diseases. In all participants, the Mini-Mental State Examination (Folstein et al., 1975) score was $\geq 28/30$. Subjects were naive to the experimental purpose and none of them were professional piano players or trained as a typist. Furthermore, none of the participants were taking any central nervous system-active medication. The study design was approved by the local institutional ethics committee. All participants gave their written informed consent according to the ethical Declaration of Helsinki.

2.2. Learning paradigm

The task required the participants to perform sequential finger tapping with 4 fingers on a 4-button electronic keyboard according to one visually guided 9-element constant training sequence T, that is, 2-3-5-4-2-5-4-3-4 (numbers 2–5 indicating index- to small finger, for more description about the task please see Walker et al.,

2003, Fig. 1A). Aside from the training sequence, 5 different additional random sequences R_1 – R_5 of the same complexity (assessed by Kolmogorov Index, Lempel and Ziv, 1976) were interleaved, one on each training day, and served as a measure of general motor performance. In the beginning of the training, participants had to play a first baseline (random) sequence for familiarization. Daily training (duration 20 minutes) consisted of 7 blocks (90 seconds each) of which 6 included the training sequence T (same for all days) adapted to a previous study (Karni et al., 1995). One of the 5 random sequences R_1 – R_5 was pseudo-randomly assigned to one of the blocks 3–5 separately for each day (Fig. 1A). Participants were instructed to play the sequences as accurate and fast as possible. A personal computer with Presentation 0.61 (Neurobehavioral Systems, Albany, CA, USA) was used to present the instructions. It was also used to display the numeric sequence at all times to exclude any working memory component. A white dot, jumping from number to number, indicated the actual position (advancing clue, Fig. 1A) within the sequence without any other feedback. Key presses were recorded and analyzed offline using an in-house Matlab script (The MathWorks, Natick, MA, USA).

Motor sequence learning is defined as the process by which simple, stereotyped movement elements come to be performed effortlessly as a unitary well rehearsed sequence (Doyon and Benali, 2005). We hypothesized that in the present explicit learning paradigm participants would increase the velocity of their finger movements and decrease the interval between successive key presses along the training period, resulting in a reduction of the duration to complete a correct sequence (a measure of speed) and the number of errors made (a measure of accuracy). Learning was assessed by the number of correctly played training sequences per block (normalized to the average number of the correctly played random sequences over all 5 days, Fig. 1B, R_1 – R_5). This allows the assessment of the improvement in the execution of the training sequence in relation to the individual stable performance level for the present task (Krakauer and Shadmehr, 2006), particularly in the light of differences in motor performance between young and old participants (Seidler et al., 2010). The total amount of learning was calculated as the absolute difference between the first and last block of training (Fig. 1C).

2.3. Brain imaging

A 3T Siemens Skyra MRI scanner (Erlangen, Germany) was used to acquire diffusion- (repetition time = 9000 ms, echo time = 82 ms, 75 axial slices, 2 mm^3 isotropic, acquisition matrix of 128×104 , covering the whole brain with gradients $b = 1500 \text{ mm}^2/\text{s}$ applied along 64 non-collinear directions) and T1- weighted images (MPRage, echo time = 2.12 ms, repetition time = 2500 ms, $0.8 \times 0.8 \times 0.9 \text{ mm}^3$, acquisition matrix of 208×256 , field-of-view = 256 mm) 9 months after the training. The image analysis was conducted using the FSL 4.1.9 software package (<http://www.fmrib.ox.ac.uk/fsl>). Images were corrected for Eddy-currents and head motion applying a 3D affine registration (Jenkinson et al., 2002). After brain extraction (Smith, 2002) local diffusion directions were estimated for each voxel using Markov Chain Monte Carlo sampling (Behrens et al., 2007). Fractional anisotropy (FA) maps were also calculated fitting the diffusion tensor model at each voxel. These individual FA maps were registered nonlinearly to the Montreal Neurological Institute standard space using the available FA template. Anatomic images were also normalized. Proper registration was checked in every subject by visual inspection before further statistical analysis.

The following methodology was used to define cortical seed regions. First, brain segmentation into WM and gray matter (GM) with subsequent cortical anatomic parcellation was conducted in

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