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Short-term plasticity following motor sequence learning revealed by diffusion magnetic resonance imaging

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Abstract

Current noninvasive methods to detect structural plasticity in humans are mainly used to study long-term changes. Diffusion magnetic resonance imaging (MRI) was recently proposed as a novel approach to reveal gray matter changes following spatial navigation learning and object-location memory tasks. In the present work, we used diffusion MRI to investigate the short-term neuroplasticity that accompanies motor sequence learning. Following a 45-min training session in which participants learned to accurately play a short sequence on a piano keyboard, changes in diffusion properties were revealed mainly in motor system regions such as the premotor cortex and cerebellum. In a second learning session taking place immediately afterward, feedback was given on the timing of key pressing instead of accuracy, while participants continued to learn. This second session induced a different plasticity pattern, demonstrating the dynamic nature of learning-induced plasticity, formerly thought to require months of training in order to be detectable. These results provide us with an important reminder that the brain is an extremely dynamic structure. Furthermore, diffusion MRI offers a novel measure to follow tissue plasticity particularly over short timescales, allowing new insights into the dynamics of structural brain plasticity.

KEYWORDS
diffusion MRI, learning, motor, neuroplasticity, piano

1 | INTRODUCTION

Neuroplasticity, the ability of the nervous system to adapt its organization according to the dynamic internal and external environment, has been extensively studied in recent decades. Numerous experiments have demonstrated neural plasticity throughout the brain, both functionally and structurally. However, structural plasticity was mainly investigated over long timescales such as months or weeks, using conventional anatomical magnetic resonance imaging (MRI; Draganski et al., 2004; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Zatorre, Fields, & Johansen-Berg, 2012).

Recently, diffusion-weighted (DW) MRI provided a new approach to explore short-term neuroplasticity in the human brain (Assaf, 2018; Blumenfeld-Katzir, Pasternak, Dagan, & Assaf, 2011; Brodt, Gais, Beck, Erb, & Scheffler, 2018; Hofstetter & Assaf, 2017; Hofstetter, Tavor, Tzur Moryosef, & Assaf, 2013; Sagi et al., 2012; Scholz et al., 2009; Tavor, Hofstetter, & Assaf, 2013). The mean diffusivity (MD) of water molecules, extracted from DW-MRI, has been shown to serve as a highly sensitive biomarker for microstructural changes associated with several types of learning: spatial navigation (Sagi et al., 2012; Tavor et al., 2013), phonological language learning (Hofstetter & Assaf, 2017), and object-location memory (Brodt et al., 2018).

Structural modifications were measured by a decrease in gray matter's MD and were detectable within hours of learning in brain regions that were relevant to the investigated cognitive domain (e.g., spatial navigation induced MD decrease in the hippocampus, reflecting microstructural changes). Animal studies have suggested that the neurobiological basis of the rapid microstructural changes that occur after experience-driven neuroplasticity (measured by MD) may be related to astrocyte remodeling (Assaf, 2018; Blumenfeld-Katzir et al., 2011; Sagi et al., 2012). For example, in a short-term water-maze study, MD decrease was found in the hippocampus of the learning rats compared with the control group, and a following histological analysis of their brains revealed increased levels of synaptophysin, glial fibrillary acidic protein, and brain-derived neurotrophic factor (BDNF; Sagi et al., 2012). These results suggest that within the regions of MD decrease there was an *increase* in the number of synaptic vesicles, astrocyte activation and BDNF expression, which may be indicative of long term potentiation (LTP). These studies in rats offer possible biological substrates underlying the change in diffusion properties, and provide further support for MD being highly sensitive to in vivo system-level neuroplasticity in humans. In the present study, we employed this novel approach to study short-term structural plasticity following a complex, multistep motor learning task.

The motor system has been the subject of many neural plasticity studies in recent years (Bezzola, Mérillat, Gaser, & Jäncke, 2011; Dayan & Cohen, 2011; Diedrichsen & Kornysheva, 2015; Doyon & Benali, 2005; Doyon, Gabitov, Vahdat, Lungu, & Boutin, 2018; Draganski et al., 2004; Herholz, Coffey, Pantev, & Zatorre, 2016; Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001; Sale et al., 2017; Sanes & Donoghue, 2000; Scholz et al., 2009; Zatorre, Carpentier, Segado, Wollman, & Penhune, 2018). Using various imaging techniques, it is possible to follow on both structural (Bezzola et al., 2011; Draganski et al., 2004; Rudebeck et al., 2009) and functional (Floyer-Lea & Matthews, 2005; Poldrack, 2000; Reithler, van Mier, & Goebel, 2010; Ungerleider, Doyon, & Karni, 2002; Zatorre et al., 2018) brain changes, mainly as a result of learning and memory of motor-related procedures. Different parts of the brain were found to be activated in early stages of learning as opposed to later stages (Dayan & Cohen, 2011; Diedrichsen & Kornysheva, 2015; Doyon et al., 2018; Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Lehéricy et al., 2005): Initial experience with a new motor learning task involves associative cerebellar and striatal regions, primary motor (M1), prefrontal and premotor cortices (Doyon et al., 2009; Doyon et al., 2018; Doyon & Benali, 2005; Verwey, Shea, & Wright, 2014), whereas continuous practice is associated with increased contribution of the sensorimotor regions of the striatum (e.g., the putamen; Coynel et al., 2010; Lehéricy et al., 2005) and motor cortical regions (Dayan & Cohen, 2011; Lohse, Wadden, Boyd, & Hodges, 2014; Penhune & Steele, 2012), as well as the cerebellar nuclei (Dayan & Cohen, 2011; Doyon et al., 2018; Doyon, Penhune, & Ungerleider, 2003).

While a variety of studies focused on the functional aspects of motor plasticity, little is known about the structural remodeling of the tissue, particularly in the short-term. In this study, we used diffusion MRI to investigate the short-term neuroplasticity that accompanies motor sequence learning. Specifically, we set up a motor-sequence learning task using an electric piano keyboard. Thirty-two non-musician participants were scanned before and immediately after a 45-min training session in which they learned to play a short sequence based on Beethoven's Für Elise. Participants were instructed to repeat the sequence with an increasing number of notes and were given feedback on the accuracy of their key pressing. A subset of 15 participants continued on to a second learning session in which they received feedback on the rhythm, rather than accuracy, of key pressing (this second stage is only possible after reaching a sufficiently high accuracy level). Finally, these 15 participants were scanned for the third time. A preliminary cohort of eight professional pianists that were scanned before and after performing the same task was also acquired.

We hypothesized that a short-term motor-sequence learning task will induce structural brain changes, reflected as decreased MD within several motor system regions, and that these brain changes may vary following a second learning session. Furthermore, we hypothesized that the professional pianists' cohort will exhibit yet another pattern of brain changes associated with the same piano-learning task.

2 | MATERIAL AND METHODS

2.1 | Participants

Forty healthy volunteers participated in this study (mean age 25.7; *SD* 3.1, 20 males, all right-handed), with no history of neurological disease, psychological disorders, drug or alcohol abuse, or use of neuropsychiatric medication. The research protocol was approved by the Institutional Review Board of the Sourasky and Sheba Medical Centers. All participants signed an informed consent form. Out of the whole cohort, eight participants were professional pianists (with formal musical education and more than 8 years of experience). Out of the 32 naïve participants, 17 performed a single learning session, and 15 continued to a second learning session.

2.2 | Learning task

During the task participants learned to play a short sequence on an electric piano keyboard (MEDELI M10, Medeli Electronics Co.). The training sequence was the first 51 notes of the right-hand part of Beethoven's *Für Elise*. Using an in-house software, participants were presented with an increasing number of notes from 1 to the entire 51-note sequence (the number of notes added in each trial varied between 2 and 5 notes and was decided based on the structure of the musical piece). Each trial started with the presentation of a virtual keyboard on a screen placed in front of the participant. On this keyboard, notes to be played were shown in color simultaneously to their sound playing (i.e., simultaneous visual and auditory input). After viewing and listening to this combined visual–auditory presentation of the notes, participants were instructed to repeat the sequence they have just viewed on the electronic keyboard using their right hand. Participants heard their own playing and viewed their hand on the keyboard. After

playing, they were given feedback on their accuracy. In case they have made an error, the correct sequence was presented again with the note where error was made marked in red. The learning session included 63 trials and lasted approximately 45 min.

A subset of 15 participants continued to a second learning session. In order to participate in this second session subjects had to reach perfect accuracy performance (the performance of 12 out of 15 participants was at ceiling by the end of the first learning session, and the other three played 43–47 correct notes out of 51, yet reached perfection during the second session). In this second session, they played the entire 51-notes sequence over and over again and were given feedback on the rhythm of key pressing, rather than accuracy. Trials in which they made accuracy errors were stopped and excluded from further analysis. A key press was considered a rhythm error when it differed in time from the correct piece in more than an eighth of a beat. The second learning session included 21 successful trials (i.e., with no accuracy errors) and lasted approximately 40 min.

2.3 | MRI acquisition

MRI was performed using a GE Signa 3.0T scanner (GE, Milwaukee). Participants underwent two or three MRI scans, before and immediately after each learning session (see Section 2.2 above). Thus, the scans were approximately an hour apart. The MRI protocol of each of the two scans included diffusion tensor imaging (DTI) and conventional anatomical sequences for radiological screening, all acquired with an eight-channel head-coil.

2.3.1 | Conventional anatomical sequences

T1-weighted images were acquired with a three-dimensional spoiled gradient-recalled echo sequence with the following parameters: up to 160 axial slices (whole-brain coverage), TR/TE = 9/3 ms, resolution $1 \times 1 \times 1\ mm^3$, scan time 4 min. In addition to the T1-weighted scan, T2-weighted images (TR/TE = 6,500/85) and FLAIR images (TR/TE/TI = 9,000/140/2,100) were acquired. The entire anatomical data set was used for radiological screening.

2.3.2 | DTI protocol

Spin-echo diffusion weighted echo-planar imaging sequences were performed with up to 70 axial slices (to cover the whole brain) and resolution of $2.1 \times 2.1 \times 2.1\ mm^3$ reconstructed to $1.58 \times 1.58 \times 2.1\ mm^3$ (field of view is $202\ mm^2$ and acquisition matrix dimension is 96×96 reconstructed to 128×128). Diffusion parameters were: Δ/δ = 33/26 ms, b value of 1,000 s/mm^2 was acquired with 30 gradient directions and an additional image was obtained with no diffusion weighting (b_0 image).

2.4 | Behavioral data analysis

For each trial, two measurements were calculated to distinguish between two different learning aspects: (a) accuracy of key pressing was measured by the number of correct notes that were played in each trial and (b) accuracy of rhythm was measured by the average error in time (the distance between the original timing of each note and the time pressed by the participant) per note for each trial. It is noted that the first measurement is limited to the number of notes that are included in each trial. The second measurement is also influenced by the number of notes to be played in each trial (as the error in time is accumulating throughout the musical part). To prevent this from influencing our measure, timing was measured relatively to the previous note and averaged across all notes in a given trial.

2.5 | MRI data analysis

DW images were corrected for motion using a least-squares algorithm and six-parameter (rigid-body) transformations implemented in the SPM software. Then, DTI analysis was performed using an in-house software implemented in MATLAB 8.4.0 (Mathworks, Natick, MA), from which maps of MD were computed.

2.6 | Image processing

Image processing including registration, spatial normalization, and spatial smoothing were done using SPM as described previously (Sagi et al., 2012; Tavor et al., 2013). Briefly, to ensure optimal alignment for voxel-based statistics, we used the fractional anisotropy (FA) maps in a two-step spatial registration routine, using an in-house template based on a single-subject FA image of an outgroup subject registered to the montreal neurological institute space. Nonlinear transformations were used for both within-subject and between-subject registration. Spatial smoothing was applied with a FWHM of 8 mm (See Sagi et al., 2012 for more details).

2.7 | Statistical analysis

Voxel-based statistics is used to detect regionally specific differences in brain tissue on a voxel-by-voxel basis. Statistical voxel-based analysis of MD maps was performed using MATLAB. Specifically, MD maps acquired before and after the learning task were compared in order to detect brain regions in which the MD decreased following the task, indicating a structural change. The decrease in MD was considered statistically significant in clusters that exceeded a threshold of $p < .005$ uncorrected and cluster size of 37 voxels, which is equivalent to a corrected threshold of $p < .05$ according to Monte Carlo simulation implemented in 3dClustSim program in the AFNI software package (i.e., the probability to find false positive clusters in this size is less than 5%; see *technical considerations* in Section 4). Clusters were labeled according to the anatomical automatic labeling atlas (Tzourio-Mazoyer et al., 2002). The exact location of the premotor cortex was further verified by the human motor area template atlas (Mayka, Corcos, Leurgans, & Vaillancourt, 2006).

3 | RESULTS

3.1 | Behavioral results

3.1.1 | First learning session

All participants improved their accuracy from trial to trial, as reflected by a significant linear effect across all trials (R^2 = .99) and across series of trials in which the number of notes to be played was fixed (median R^2 = .52, p < .00001). By the end of the first learning session, participants played 46.6 ± 1.49 (mean ± *SEM*) correct notes out of the total 51 notes (Figure 1). While improvement in accuracy was relatively high, during the first 24 trials there seemed to be a trade-off between accuracy and timing such that increase in accuracy level was paralleled by increase in timing errors (Figure 2a). By the 24th trial, the average error in time was approximately 150 ms per note and this did not change significantly during the rest of the task, even in trials in which the number of notes was fixed (Figure 2a). Specifically, paired t tests between each of the trials and the last trial did not yield significant results, and no significant linear effect across trials was found, both in the entire cohort and in the subset of 15 participants that continued to the second session (see Figure S1 for behavioral results of the subset of 15 participants separately). It should be noted that during the first learning session participants were only instructed to play the correct notes and were not given feedback on their timing. However, we

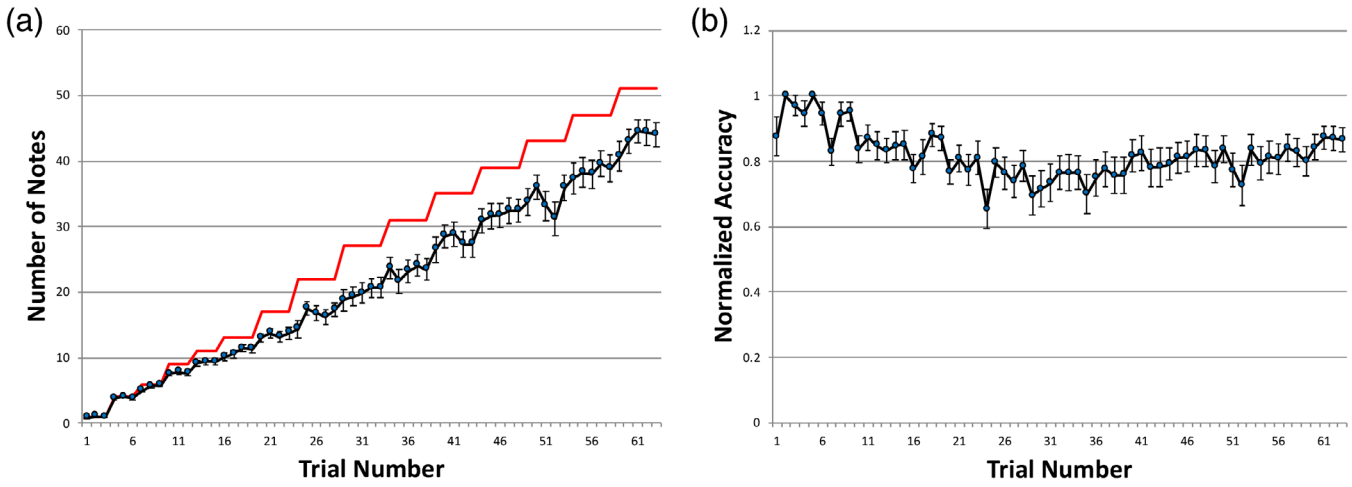

FIGURE 1 Performance in piano training (Session 1). Accuracy of key pressing during the first learning session is shown by the absolute number of correct notes (a) and the normalized accuracy levels (b). Blue circles represent the average number of correct notes played by participants in each trial. The number of notes that were presented to participants in each trial is shown in red. On average, the best performance participants achieved was 46.6 correct notes out of 51. Error bars depict *SEM*

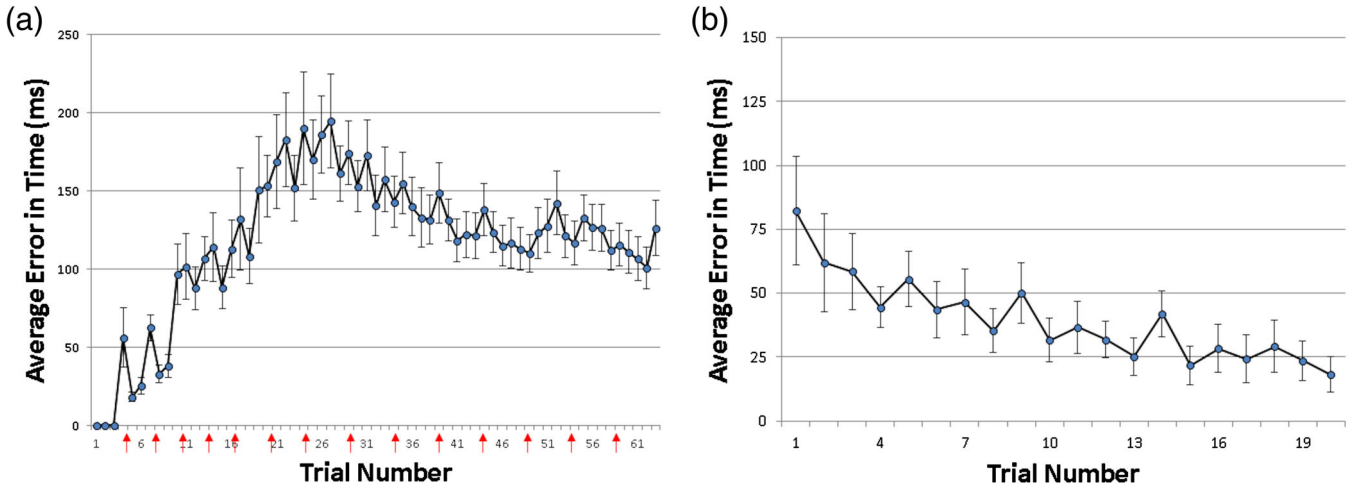

FIGURE 2 Performance in piano training (Session 2). Accuracy in the timing of key pressing during the first (a) and second (b) learning sessions is shown. Blue circles represent the average error in time per note for each trial. (a) During the first learning session, subjects did not show a decrease in their error rate. Red arrows indicate trials in which the number of notes increased. (b) During the second learning session, subjects' error rate decreased dramatically as they reached to an average error per note shorter than 20 ms. Error bars depict *SEM*

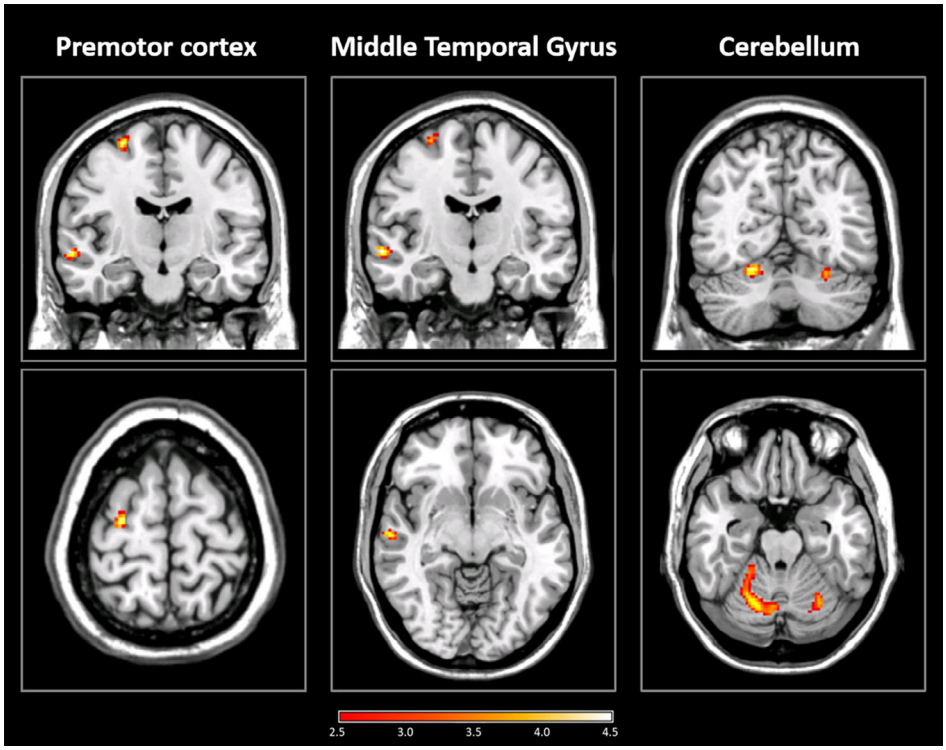

FIGURE 3 Reduction in mean diffusivity after piano training (Session 1). Structural remodeling of brain tissue, measured by DTI as a reduction in mean diffusivity (MD) after 45 min of training on a motor sequence learning task. A paired *t* test between the MD maps before and after the learning task (first session) was performed. The statistical parametric map is presented superimposed on coronal (upper row) and axial (lower row) slices of a single-subject T1 map. Significant clusters of MD decrease were found in the left premotor cortex, left middle temporal gyrus and the cerebellum ($p < .005$, cluster size >37, equivalent to $p < .05$, corrected for multiple comparisons). L indicates the left side of the brain; color bar represents the *T* value

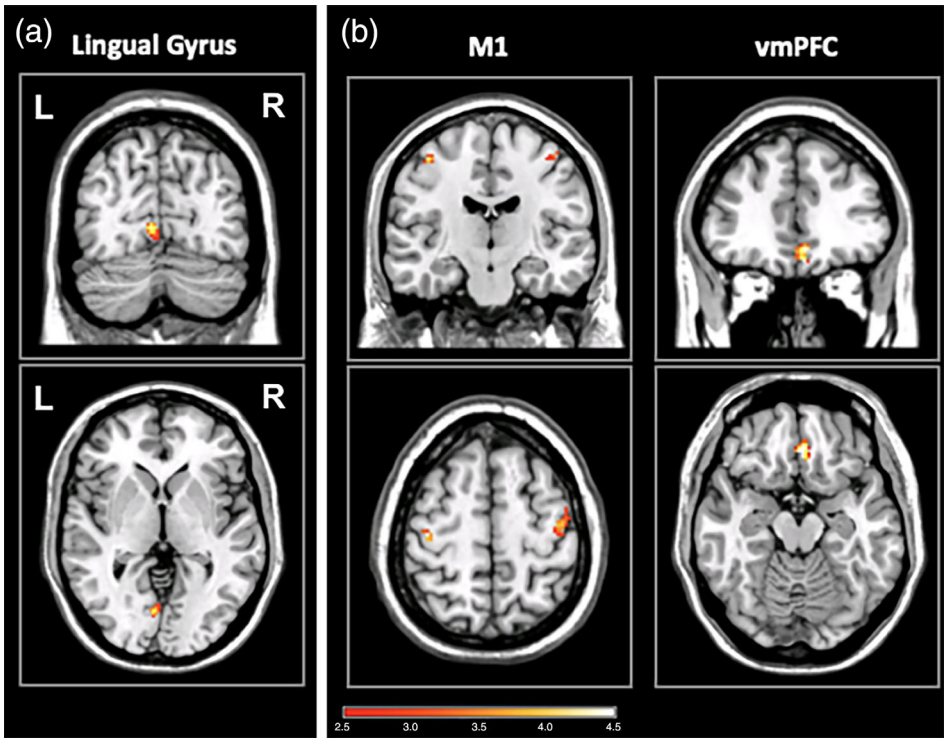

FIGURE 4 Reduction in mean diffusivity (a) after piano training (Session 2) and (b) after professional pianists' exposure to the task. Structural remodeling of brain tissue, measured by DTI as a reduction in mean diffusivity (MD) after 45 min of training on a motor sequence learning task. (a) In a second training session in the naïve participants feedback was given on the timing of key pressing. Analysis of variance (ANOVA) of the MD maps before and after each learning task was performed, and post hoc analysis revealed a significant cluster in the left lingual gyrus ($p < .005$, cluster size >37, equivalent to $p < .05$, corrected for multiple comparisons) in which the effect was a result of a reduction in MD after the second learning session. (b) Professional pianists experienced a piano-playing session similar to the first session in the naïve participants. A paired *t* test between the MD maps before and after the session was performed. Significant clusters of MD decrease were found in the primary motor cortex bilaterally and in the ventromedial prefrontal cortex (vmPFC). $p < .005$, cluster size >37, equivalent to $p < .05$, corrected for multiple comparisons. The statistical parametric maps are presented superimposed on coronal (upper row) and axial (lower row) slices of a single-subject T1 map. L indicates the left side of the brain; color bar represents the statistic (*F* or *T*) value

cannot exclude possible interdependence between accuracy and timing learning.

3.1.2 | Second learning session

Participants that continued on to a second learning session, in which they were given feedback on the timing of key pressing, improved their timing performance dramatically: the average error per note decreased from trial to trial and by the 20th trial the deviation from the correct timing was less than 20 ms per note (Figure 2b). Participants were at ceiling with regards to accuracy performance (see Section 2); therefore, we did not collect behavioral measurements of accuracy in this second learning session. Still, we cannot rule out the possibility of additional gain in performance due to off-line learning (between the two sessions) or to additional experience with the musical piece during the second session (see Section 4 for further elaboration on this methodological limitation).

3.2 | MRI results

3.2.1 | Changes in diffusion properties following the first learning session

We performed a paired *t* test on the prelearning and postlearning MD images of all 32 nonmusician participants in order to detect regions of learning-related MD decrease. We found a significant MD reduction in several brain regions, including the left premotor cortex and the superior part of the cerebellum, in both right and left hemispheres. In addition to evidence of structural plasticity in these motor system regions, MD reduction was also observed in the left middle temporal gyrus (Figure 3). The reduction in MD was about 2–3% in all regions (described in Figure 5). Additional smaller clusters in the right supplementary motor area and the posterior part of the right cerebellum ($p < .005$, cluster size >15 voxels, Figure S2) did not exceed the corrected threshold but are shown nevertheless due to the relevance of these regions to the task.

3.2.2 | Changes in diffusion properties following the second learning session

We performed a repeated-measures analysis of variance (ANOVA) on the MD images of the 15 participants that performed two learning sessions and were scanned three times, in order to detect differences in structural plasticity as a result of different stages of motor sequence learning. Post hoc analysis revealed two types of clusters: regions that showed decreased MD in the second scan compared to the first, but less so in the third scan; and regions in which there was no significant change between the first and second scans yet a significant reduction in MD was observed in the third scan, indicating that different stages of learning may induce different patterns of structural plasticity.

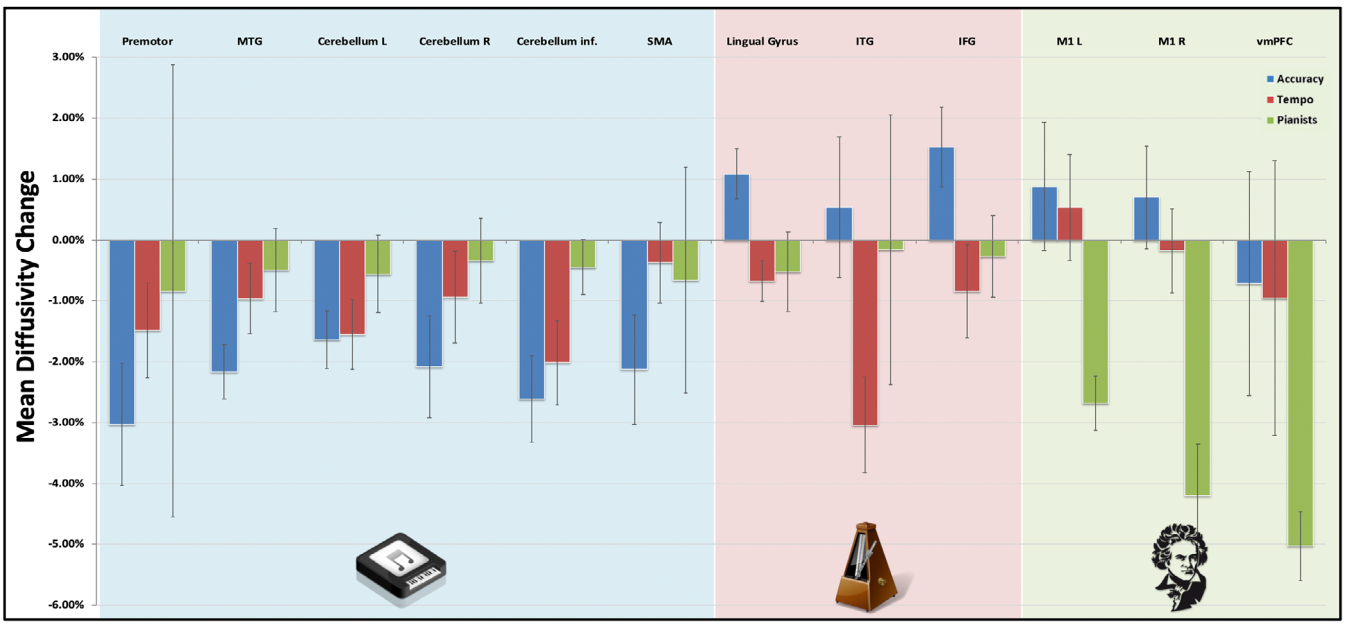

FIGURE 5 Specificity of brain networks plasticity to the learning procedure. Significant reduction in mean diffusivity was found in different brain regions for different stages of learning. Regions that underwent significant change after the first training session, in which feedback was given on accuracy, are presented on the left; regions of significant change after the second training session, in which feedback was given on timing, are presented in the middle; regions that were found in professional pianists are presented on the right. For each of these regions, the percentage reduction in mean diffusivity ([MD after–MD before]/MD before) is shown for three conditions: accuracy and timing training of naïve subjects (blue and red bars, respectively) and training of the professional pianists (green bar). The first scan was used as baseline for all conditions. The values presented refer to the MD decrease within the significant clusters. Error bars depict the *SEM*

The comparison between the first and second scans, taken before and after the first learning session in which emphasis was put on the accuracy of key pressing, revealed evidence of structural plasticity in some of the regions that were already found in the whole cohort (see Section 3.2 above): the left premotor cortex ($F_{(2,\ 28)} = 7.64$, $p < .005$), the left middle temporal gyrus ($F_{(2,\ 28)} = 8.68$, $p < .005$), and the cerebellum ($F_{(2,\ 28)} = 7.26$, $p < .005$). The comparison between the second and third scans, taken before and after the second learning session in which emphasis was put on the timing of key pressing, revealed evidence of structural plasticity in the left lingual gyrus ($F_{(2,\ 28)} = 8.87$, $p < .005$, Figure 4a). Additional smaller clusters were revealed in the anterior part of the right inferior temporal gyrus (ITG) and the left inferior frontal gyrus (IFG), but these did not exceed the corrected threshold of 37 voxels ($p < .005$, cluster size >15 voxels, Figure S3). We also performed an analysis of covariance (ANCOVA) to examine whether the behavioral changes in the first learning session may partially account for the modifications in MD values after the second learning session and found no significant effect (see Figure S4 for more details).

3.2.3 | Changes in diffusion properties in professional pianists

A comparison of the MD images acquired before and after professional pianists participated in the task was conducted. We detected a bilateral significant MD reduction in the primary motor cortex (M1) and the ventromedial prefrontal cortex (vmPFC; $p < .05$, corrected, see Figure 4b). Visual inspection of the professional as opposed to naïve participants statistical maps revealed relatively different patterns of MD change: naïve participants exhibited significant clusters in the premotor cortex and cerebellum, while professional pianists showed significant clusters in M1 and vmPFC. To directly test the hypothesis of different patterns of brain changes, we also conducted a group (naïve/pianists) by time (pre/post exposure to the task) ANOVA and found similar clusters (Figure S5). These clusters did not exceed the cluster size threshold for multiple comparison correction, possibly due to the difference in sample size of the two groups.

A summary of the results in all experimental groups, as well as the mean percentage change in MD values in each one of the detected brain regions, is shown in Figure 5. Clusters size and coordinates are summarized in Table S1. Absolute MD values are presented in Figure S6. For the behavioral performance of the professional pianists (see Figure S7).

4 | DISCUSSION

In this work, we demonstrate that diffusion MRI can be used to detect rapid structural modifications in the motor system following a motor learning task. These structural modifications occur in a multiregional fashion and at different timescales, depending on the focus of the task. Importantly, structural modifications were observed within regions of the motor system almost exclusively, although the statistical analysis was done on the whole brain, demonstrating the specificity of the plasticity process.

First, we detected a decrease in MD in 32 nonmusician participants that performed a short (~45 min) piano sequence learning task, focused on accuracy of key pressing. The decreased MD suggests structural tissue changes related to the learning procedure. Next, we found that a second learning session, taking place immediately afterward in which feedback was given on rhythm rather than accuracy, induced a different pattern of structural changes. Finally, professional pianists were exposed to the same piano-playing task and our results suggest a possible difference in task-related changes in the brains of these experts compared to the nonmusician participants. These results are further discussed below.

4.1 | The location of brain structural plasticity

Most of the regions that were found to be changed are parts of the motor system, meaning that learning processes in a specific cognitive domain involve short-term structural modifications in the relevant brain regions.

The largest reduction in MD was found in the cerebellum, as bilateral significant clusters were detected in the superior part of the cerebellar posterior hemispheres (Figure 3). A third (uncorrected for multiple comparisons) cluster was observed in inferior part of the cerebellar right hemisphere (Figure S2). The involvement of the cerebellum in motor learning is well documented (Doyon et al., 2003; Herholz & Zatorre, 2012; Hikosaka et al., 2002; Penhune & Steele, 2012). The cerebellum, and especially its lateral parts, is considered to be essential for error-correction and error-based learning (Doya, 2000; Hikosaka et al., 2002). In a recently proposed model for motor sequence learning, the cerebellum is further suggested to be responsible for adjusting movements according to sensory inputs and for acquiring an optimal internal model for performing a sequence of movements (Penhune & Steele, 2012). Such processes are crucial for succeeding in our piano learning task. In addition, the short timescales of cerebellar modifications reported in here are also in line with previously reported evidence for rapid response of the cerebellum to explicit motor learning (Penhune & Steele, 2012), as opposed to other motor-system regions such as the putamen and primary motor cortex, that react during later stages of learning.

In addition to the cerebellum, evidence for brain plasticity was also found in the premotor cortex (Figure 3), and presumably, in a lesser extent, within the supplementary motor area (Figure S2). These regions are known to be involved in the planning of movement and were previously reported to have a role in musical training (Chen, Rae, & Watkins, 2012; Lahav, Saltzman, & Schlaug, 2007). More specifically, the dorsal premotor cortex is considered to play a role in linking between auditory pitch information and its related key press (Chen et al., 2012; Herholz & Zatorre, 2012). The premotor cortex was found to be activated during listening to melodies that participants were previously trained to play (Lahav et al., 2007), and is considered to be involved in the integration of sensory information with motor actions (Chen et al., 2012). Taken together, our results in the

cerebellum and premotor cortex demonstrate the ability of the motor system to undergo rapid structural remodeling in response to a short learning task.

Structural modifications following our motor sequence learning task were also found in the middle temporal gyrus (Figure 3), which is not a motor area per se. The temporal lobes are known to be involved in auditory perception, thus it is reasonable to assume that the middle temporal gyrus is involved in the auditory aspects of the task. The middle temporal gyrus was previously found to be sensitive to music structure (Fedorenko, McDermott, Norman-Haignere, & Kanwisher, 2012) and is considered to be part of an auditory-motor network (Bangert et al., 2006), which is required for musical abilities. In sum, learning to play music is a multisensory assignment and it is not surprising to find learning related changes in auditory regions alongside motor regions, especially regions surrounding the superior temporal sulcus that are considered to be involved in sound-action interaction (Zimmerman & Lahav, 2012). Notably, despite their well-established role in early stages of learning (Doyon et al., 2009) we found no structural modifications in the striatum or the hippocampus, possibly due to the specific nature of the motor learning task.

4.2 | Different stages of the task involve different brain regions

One of the novelties of this study is the inclusion of two additional learning routines: (a) Nonmusician participants underwent a second learning session, focusing on a different performance aspect—rhythm rather than accuracy. We compared the scans acquired before and after this second learning session to explore the dynamics of structural plasticity, namely, changes in the patterns of plasticity that may be associated with the rhythm training or with delayed effects of the accuracy training; (b) a preliminary cohort of professional pianists performed the first session of the piano task that focused on accuracy, similar to the naïve group. We compared the pretask and posttask scans to explore the patterns of structural plasticity in the professional pianists. Figure 5 summarizes the different regions that were involved in different aspects of the task. Interestingly, the patterns of brain plasticity following the second training session were different than those observed following the first session, and the plasticity patterns in the pianists' group were different than those observed in the naïve group. These changes in the pattern of brain plasticity when the focus of learners was shifted or when learners were highly trained, highlight the dynamic nature of this phenomenon, formerly thought to require months of training in order to be detectable.

While the first learning session which focused on accuracy training resulted in MD reduction mainly in motor system regions (premotor cortex and the cerebellum), the second session induced neuroplasticity in different locations (Figure 4a). The main change in MD was found in the lingual gyrus, a region usually associated with high-level visual processing, rather than the motor or auditory processes. The simplest explanation to this finding may involve the visual aspect of the task, in which a keyboard was presented on the screen, correct notes in a sequence were presented in blue and feedback about errors was presented to the participant in red (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Tricomi, Delgado, & Fiez, 2004). The visual processing of this information is relevant to accuracy training as much as for timing\rhythm training, but it is possible that the complexity of the second training might have increased the importance of the visual input and therefore the involvement of this region. Alternatively, there is also evidence supporting the involvement of the lingual gyrus in motor (Müller, Kleinhans, Pierce, Kemmotsu, & Courchesne, 2002; Parsons, Sergent, Hodges, & Fox, 2005) or auditory (Bengtsson et al., 2009; Janata et al., 2002; Schmithorst & Holland, 2003) aspects of the task directly.

Smaller clusters of plasticity following the second learning session were found in the left IFG and the right ITG (Figure S3). While there is an extensive literature about the involvement of these regions in musical processes (Gaser & Schlaug, 2003; Penhune & Steele, 2012; Tillmann, Janata, & Bharucha, 2003; Watanabe, Yagishita, & Kikyo, 2008), conclusions about them from the current work should be done carefully as the small size of these clusters prevent them from exceeding the statistical threshold after correction for multiple comparisons. Nevertheless, the fact that only three regions showed a reduction in MD after the second training, while values in regions that were changed after the first training almost returned to baseline (see Figure 5), highlights the rapid and dynamic nature of learning-induced structural remodeling, as measured by MD reduction. These results may suggest that shifting the focus of the task to a different aspect of learning (accuracy vs. timing/rhythm) result in a different pattern of brain plasticity. Alternatively, the different patterns of plasticity following the second learning session may reflect transient and/or delayed effects triggered by the first learning session (see Section 4.4 below).

Last, although measured in a small group of participants, results from the professional pianists provide further support for our claim that different training procedures involve different brain networks and influence brain tissue in different locations. While the professional pianists performed the same accuracy task, their cognitive requirements were somewhat different. They already knew the sequence and their accuracy performance showed no improvement as their level reached perfection already in the first trial and stayed the same throughout the experiment. The location of brain plasticity in these participants was very homogenous, showing no reduction in MD in any of the aforementioned brain regions but a bilateral substantial MD reduction in the primary motor cortex (M1, Figure 4b). The fundamental role of this area is to control voluntary movements, and it also has a role in motor learning (Penhune & Steele, 2012; Sanes & Donoghue, 2000). Moreover, M1 is thought to store the representation of learned sequences, of which performance is highly skilled and even automatic (Penhune & Steele, 2012). Indeed, the sequence used in our study was already known to the professional pianists, as reflected by the bilateral M1 changes, possibly indicating that participants also have a representation of the left-hand movements of the musical piece. Decreased MD in the professional pianists was also found in the vmPFC which might reflect changes due to automatic (Ashby, Turner, & Horvitz, 2010) or habitual performance of a task (Coutureau & Killcross, 2003; de Wit, Corlett, Aitken,

Dickinson, & Fletcher, 2009). While separate statistical comparison of the pre/postlearning scans revealed different statistical maps for each group, future studies should directly compare the two groups with comparable group sizes.

4.3 | The temporal dynamics of neuroplasticity

The fact that different plasticity patterns were observed following different stages of learning reflects an important implication for the study of neuroplasticity, namely, the sensitivity of diffusion MRI to dynamic, flexible brain modifications in very short timescales. While learning-related brain changes were previously observed a week after a first learning procedure (Tavor et al., 2013), here we demonstrate a shift from one pattern of plasticity to another (i.e., different brain areas demonstrated MD reduction following different learning routines) within no more than an hour. This rapid decrease in MD values may influence the way we refer to structural brain plasticity. Obviously, interpretations of volumetric structural brain changes reported in voxel-based morphometry studies after months or years of training cannot explain the diffusion MRI changes reported here, and different biological substrates should be examined. The rapid modification of astrocytes structures, described previously (Johansen-Berg, Baptista, & Thomas, 2012; Sagi et al., 2012; Tavor et al., 2013), may fit the timescale reported in the present study.

4.4 | Technical considerations

The current study design includes several limitations that should be noted. First, defining control conditions to the different aspects of the learning task is challenging. To overcome that, data were collected from a cohort of participants at three time-points, making it possible to analyze as an internal control condition, as performed by Thomas and colleagues (Thomas et al., 2009). Such a within-subject design with several time-points can be more powerful than a comparison between experimental groups (Thomas & Baker, 2013). Still, this experimental design does not allow a clear dissociation between timing-related effects and delayed accuracy effects. In other words, while the two stages of learning induced distinct patterns of brain plasticity, those changes cannot be unequivocally attributed to accuracy as opposed to rhythm learning. They may alternatively reflect delayed or transient effects of the first (accuracy) learning session, or additional "offline" learning between the two sessions. Whether emerging from rhythm learning or from prolonged effects of accuracy learning, these different plasticity patterns demonstrate the highly dynamic nature of learning-induced micro-structural modulations.

Second, in a pre/postlearning experimental design, effects of learning may be partially confounded with an effect of the time-of-day, since a postlearning scan is inherently always later than the prelearning scan. There is evidence for time-of-day effects on MD values in temporal and occipital brain regions (Jiang et al., 2014); however, it should be noted that the prelearning and postlearning scans in the present study were only 2 hr apart, and not 12 hr as in Jiang et al. Moreover, if the time-of-day would have caused a reduction in MD independently of learning, we would expect additional MD decrease in the subset of participants who underwent a third MRI scan. Rather than that we found that in brain areas where MD was reduced following the first learning session, there was no further decrease in MD values following the second learning session, while MD in other areas decreased (see Figure 5 and Figure S6). Thus, we argue that learning and not time-of-day accounts for the reported MD decrease.

Third, the complexity of the task makes it impossible to design an equivalent animal study, as was done in a spatial learning experiment described previously (Sagi et al., 2012). This makes it harder to interpret the MRI observations and find their biological correlates. However, given the similarity of the MRI findings reported in the present study and those of Sagi et al. (i.e., MD reduction), together with the timescale of the structural changes we observed, it is reasonable to assume that the biological substrates suggested by Sagi et al. (2012) are related to the MRI changes found in here as well.

Last, the statistical analysis performed in this experiment included a correction for multiple comparisons based on the combination of p value threshold and cluster size. The routine in which the problem of multiple comparisons should be corrected is debatable, and more strict ways to control the false-discovery-rate are sometimes expected (Bennett, Wolford, & Miller, 2009). However, it is important to mention that the cluster size threshold used in this study was not arbitrary, but calculated specifically for our data using Monte-Carlo simulation provided by the AFNI software. That way we could calculate the probability of getting a noise-only cluster and make sure the chance of it is less than 5%. The failures recently addressed by Eklund, Nichols, and Knutsson (2016) are taken into consideration in this work, in aspects of cluster forming threshold and the way we estimate the smoothness of the data. Moreover, the fact that clusters were found mainly within the motor system, although statistical analysis was performed on the entire brain, strengths our confidence that these clusters reflect true task-related brain changes rather than statistical false-positives.

5 | CONCLUSIONS

The results reported in this work expand and elaborate our knowledge about diffusion MRI-sensitive structural brain modifications. First, we demonstrate that rapid changes in diffusion properties, indicating microstructure tissue remodeling, extend beyond traditional learning regions such as the hippocampus and occur in the neocortex and the cerebellum. Second, we show that behavioral modifications are accompanied by congruous changes to brain networks. Acquiring a new skill, specialization in a newly learned skill or practicing a well-established ability, each has its own related brain regions that undergo modifications when necessary. Last, we show that these modifications are very flexible and can be altered within a few hours. Most importantly, the current study together with previous ones demonstrate the great potential of diffusion MRI for studying the dynamic nature of the adult human brain in different cognitive domains and brain systems.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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