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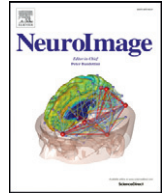
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## Structural neuroplasticity in expert pianists depends on the age of musical training onset



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### ABSTRACT

In the last decade, several studies have investigated the neuroplastic changes induced by long-term musical training. Here we investigated structural brain differences in expert pianists compared to non-musician controls, as well as the effect of the age of onset (AoO) of piano playing. Differences with non-musicians and the effect of sensitive periods in musicians have been studied previously, but importantly, this is the first time in which the age of onset of music-training was assessed in a group of musicians playing the same instrument, while controlling for the amount of practice. We recruited a homogeneous group of expert pianists who differed in their AoO but not in their lifetime or present amount of training, and compared them to an age-matched group of non-musicians. A subset of the pianists also completed a scale-playing task in order to control for performance skill level differences. Voxel-based morphometry analysis was used to examine gray-matter differences at the whole-brain level. Pianists showed greater gray matter (GM) volume in bilateral putamen (extending also to hippocampus and amygdala), right thalamus, bilateral lingual gyri and left superior temporal gyrus, but a GM volume shrinkage in the right supramarginal, right superior temporal and right postcentral gyri, when compared to non-musician controls. These results reveal a complex pattern of plastic effects due to sustained musical training: a network involved in reinforcement learning showed increased GM volume, while areas related to sensorimotor control, auditory processing and score-reading presented a reduction in the volume of GM. Behaviorally, early-onset pianists showed higher temporal precision in their piano performance than late-onset pianists, especially in the left hand. Furthermore, early onset of piano playing was associated with smaller GM volume in the right putamen and better piano performance (mainly in the left hand). Our results, therefore, reveal for the first time in a single large dataset of healthy pianists the link between onset of musical practice, behavioral performance, and putaminal gray matter structure. In summary, skill-related plastic adaptations may include decreases and increases in GM volume, dependent on an optimization of the system caused by an early start of musical training. We believe our findings enrich the plasticity discourse and shed light on the neural basis of expert skill acquisition.

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## Introduction

Professional musicians constitute an ideal group to study learning-related neuroplasticity (Schlaug et al., 1995; Münte et al., 2002; Gaser and Schlaug, 2003; Bengtsson et al., 2005; Bermudez et al., 2009; Imfeld et al., 2009) due to the intensity and scope of their training. Musical practice involves the development of fine motor skills, bimanual coordination, audio–motor integration, as well as cognitive processes, such as memory, attention and executive functions, all under the high motivational drive of the intrinsic emotional power of music (Schmithorst and Wilke, 2002; Zatorre et al., 2007; for a review see Jäncke, 2009 and Koelsch, 2010). Extensive musical practice during childhood and adolescence might have a strong effect on the development of brain structures. Importantly, this might be a bidirectional process: while music training promotes neuroplastic changes that enhance several underlying brain functions, this enhancement in brain structure and function might also improve music performance and learning (Pascual-Leone, 2001). Due to a high demand on bimanual dexterity, keyboard players have been a preferred group to study structural and functional brain changes (Amunts et al., 1997; Watson, 2006; Bangert et al., 2006). In a pioneering study, Schlaug et al. (1995) showed that professional musicians (pianists and string-players) had a larger middle section of the corpus callosum compared to a non-musician control group. Furthermore, those musicians who began their training before the age of 7 showed a larger anterior part of the corpus callosum compared to those with a late training onset. In a diffusion tensor imaging (DTI) study with pianists, Bengtsson et al. (2005) found that several white matter tracts correlated with the estimated amount of musical practice during childhood (e.g. posterior limb of internal capsule, the isthmus and the body of corpus callosum, and some fiber tracts in the frontal lobe), although the total number of practicing hours was lower in this period than the estimated hours in adolescence and adulthood. These results support the idea that the central nervous system exhibits greater plastic capacities during early stages of development and maturation periods, contrasting with its limited malleability during adulthood.

Previous studies have demonstrated the importance of the age of onset (AoO) of musical training in influencing brain plasticity. For instance, Amunts et al. (1997) affirmed that early musical training could lead to pronounced anatomical changes in the hand motor area. Similarly, a seminal magnetoencephalography (MEG) study (Pantev et al., 1998) showed that the dipole strength associated with piano tones was greater in the auditory network of those musicians who had begun practicing before the age of 9 years thus favoring the idea that the age of inception of musical training is important in determining the degree of cortical adaptation (Elbert et al., 1995; Amunts et al., 1997). The relevance of the AoO in relation to the performance level is generally confounded because early starters usually accumulate a larger amount of practice time. The relationship between sensitive periods and the level of expertise, and between these and the degree of anatomical predispositions or adaptations, is unclear at this point. Recent studies referring to one group of right handed early-onset and late-onset musicians show gray and white matter differences and enhanced timing skills in a finger tapping auditory–motor task in early-onset musicians. Via deformation-based morphometry, cortical gray matter differences in the right ventral premotor cortex were observed (Bailey et al., 2014), and using a novel multi-atlas automatic segmentation pipeline, smaller cerebellar gray matter volumes in the right lobule VI were shown (Baer et al., 2015). Using diffusion tensor imaging, Steele et al. (2013) found a higher fractional anisotropy in the isthmus of the corpus callosum. All of these morphological differences between the early- and late-onset groups correlated with their timing skills in an auditory–motor synchronization task using the right index finger: the earlier the start of music training, the better the performance in the synchronization task. In a recent study with selected highly trained pianists, Granert et al. (2011) measured the skill level of piano playing via the

temporal accuracy during a scale-playing task. These authors found that the higher the skill level of piano playing, the smaller the volume of gray matter in the right middle putamen.

Broadening the concept of expertise, Gaser and Schlaug (2003) compared professional keyboard players, amateur keyboard players and non-musicians and reported increased GM volume in primary motor, somatosensory, and premotor areas, among other regions in the musician groups. James et al. (2014) applied a regression analysis over a three-group population modeling expertise in the same way as Gaser and Schlaug (2003), trying to find the areas in which professional musicians > amateur musicians > non-musicians (or vice versa) differed, while controlling for training intensity. They found an intricate pattern of increased/decreased GM. In particular, musicians showed GM density increases in areas related to higher-order cognitive processes (such as the fusiform gyrus or the inferior frontal gyrus), whereas GM decreases were found in sensorimotor regions (as perirolandic and striatal areas). These reductions in GM were interpreted as reflecting a higher degree of automaticity of motor skills in more expert musicians (James et al., 2014).

With the present investigation, we aimed to examine brain differences between a homogeneous group of selected musicians and a control group of non-musicians. In order to avoid any confounds, we restricted our analysis to extremely skilled and highly performing, award-winning concert pianists from the Hannover University for Music, Drama and Media. This is the first time that the effects of musical training depending on the AoO are addressed in such a homogeneous cohort of expert pianists, taking into account both AoO and amount of practice. Although previous literature seems to point to an improved neural system in musicians with a higher level of expertise (acquired after long periods of training), the results of studies either focusing on gray (Han et al., 2009) or white-matter differences (Oechslin et al., 2010) as a function of AoO of musical training are not clear cut. Thus, we divided the musician sample in pianists who began to play piano before age 7 (early) and after or at age 7 (late). This cutoff is widely accepted among plasticity researchers as a crucial age for starting musical training (Schlaug et al., 1995; Bengtsson et al., 2005; Steele et al., 2013; Penhune and de Villers-Sidani, 2014; Bailey et al., 2014; Baer et al., 2015; see reviews by Wan and Schlaug, 2010, and Penhune, 2011). Thus, the main goal of our study was to examine the effect of music training and age of onset in the GM structure of expert pianists. Voxel-based morphometry (Ashburner and Friston, 2000) was used and, based on previous literature, GM differences in areas related with motor, auditory and emotional processing were expected (see Table 1 for a summary of previous studies on neuroplasticity in musicians). Moreover, a scale-playing task was administered to the pianists in order to control for differences in performance skill between the early- and late-onset groups. Playing a scale on the piano is a demanding task, and the subtle timing differences detectable using this task have previously been shown to be a reliable and highly relevant indicator of pianistic expertise (Jabusch et al., 2009; van Vugt et al., 2014).

## Materials & methods

### Participants

Forty-one expert pianists and seventeen non-musicians participated in the study. All participants (both pianists and non-musicians) reported to be right-handed. Five participants from the pianists group were removed from the final analysis due to strong motion artifacts, thus leading to a final group of 36 musicians split into early (age of onset < 7 years;  $n = 21$ , 12 females; 15 caucasians, 6 asians) and late starters (age of onset  $\geq 7$  years;  $n = 15$ , 7 females; 12 caucasians, 3 asians). AoO of piano playing between early- and late-onset pianists was significantly different ( $p < .001$ ). On the one hand, musicians were either advanced master-class piano students or professional pianists having graduated with piano as a major from the Hannover

University of Music, Drama and Media. A comparable high level of musical proficiency and expertise was assured by the fact that the entrance examination is extremely competitive, with an admission rate for the piano-master program of 1% to 5% depending on the year. Furthermore, all but two of our pianists had won national youth awards (such as the “Jugend Musiziert” or the “Steinway Young Artists Award”), and 14 had won prestigious international piano awards (in competitions such as the Van Cliburn–U.S.A., the Busoni–Italy, the Chopin–Warsaw, or the Leeds Piano–UK). To further ensure a similar level of musical proficiency and expertise, pianists had to fill a self-report that allowed us to calculate: the total hours of lifetime practice, the mean hours of practice during the previous week as well as the number of hours of practice per week during the last year. These three parameters of practice were compared between groups and no significant differences were found (significance for the difference between early-onset and late-onset pianists groups was superior to  $p = .3$ ). On the other hand, non-musician controls were technical engineering and medicine students ( $n = 17$ , 7 females: all caucasians), and had no musical experience aside from the music lessons received in primary and secondary school. Further demographic and practice details are given in Table 2. The study was approved by the Ethics Committee of the MHH (Medical School of Hannover). All participants gave written informed consent, had no contraindications concerning an MRI scan (including seizure disorders, tinnitus, claustrophobia or hearing impairment) and reported no previous or current neurological or psychiatric disease.

#### *Imaging data acquisition & preprocessing*

Images were obtained with a 3-T magnetic resonance imaging (MRI) scanner (Siemens Allegra Magnetom Scanner, INI, Hannover, Germany). Conventional high resolution structural images [magnetization-prepared, rapid-acquired gradient echoes (MPRAGE) sequence, 192 slice sagittal, TR = 16 ms, TE = 4.9 ms, 1 mm thickness (isotropic voxels)].

#### *Voxel-based morphometry*

Voxel-based morphometry (VBM; Ashburner and Friston, 2000) was performed using MATLAB version 7.8.0 (The MathWorks Inc, Natick, Mass) and statistical parametric mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London). Specifically, the New Segment tool from SPM8 (an improved version of the ‘unified segmentation’ algorithm; Ashburner, 2012) was applied to the structural T1-weighted images to separate the different types of tissues. During this segmentation step, the ethnic differences of the participants were taken into account by specifying whether the affine regularization had to be done applying the values for the ICBM space template for East Asian brains or for European brains. After that, the resulting tissue probability maps (GM) were subjected to DARTEL (Ashburner, 2007) to achieve spatial normalization into MNI space. DARTEL normalization alternates between computing an average template of GM segmentation from all subjects and warping all the subjects’ GM tissue maps into a better alignment with the template created (Ashburner, 2009). Normalized images were modulated by their Jacobian determinants in order to identify regional differences in the volume or amount of GM; “modulation” is used in order to try to compensate for the effect of spatial normalization, Mechelli et al., 2005. These normalized and modulated images were smoothed by using an isotropic spatial filter (FWHM = 8 mm) to accommodate for residual inter-individual variability.

The individual smoothed GM images were entered into a second-level analysis employing a random effects analysis within the general linear model. In order to compare musicians and non-musicians, a two sample t-test was calculated. Total volume of GM was included as a nuisance variable to correct for global differences in GM (Buckner et al., 2004). Moreover, an implicit absolute masking with a threshold of 0.2 (i.e. only those voxels having a 20% probability of being GM are included) was also used (Ashburner, 2010) in order to select only the most homogeneous voxels and to avoid potential problems around the

boundaries between gray and white matter (James et al., 2014). Unless mentioned otherwise, contrasts are reported at whole-brain  $p < .05$  FWE corrected threshold at the voxel level with a cluster extent of more than 50 contiguous voxels, thus effectively controlling for multiple comparisons.

All the results will be referred as differences in volume or amount of GM, which are terms consistent with previous VBM literature using similar analyses of T1 images (in which GM and white-matter normalized images were modulated by the Jacobian determinants derived from the spatial normalization step. Ashburner, 2010). However, it is important to note that the terms “amount of GM” or “GM volume” are not referring to the actual volume of tissue or amount of neurons. The maps created by SPM during the segmentation process represent the probability of GM found in each voxel, and therefore our analysis focused on the differences in signal intensity across voxels. The authors of the present study are aware of this constraint but decided to use the classic VBM terminology in order to make our results more easily accessible to the VBM community.

#### *Correlation analysis*

After exploring the results between pianists and non-musicians, we decided to investigate potential differences among the pianists group depending on the AoO of musical practice. We applied two different approaches: (i) On the one hand, we performed a between-group analysis comparing early-trained and late-trained pianists at whole-brain level in the same fashion as the one applied to compare musicians and non-musicians (two sample t-test, adding total volume of GM as a nuisance variable, and using an implicit absolute mask thresholded at 0.2). (ii) On the other hand, we saved each individual cluster obtained in the comparison between pianists and non-musicians as a mask. Then, we calculated the mean GM value for each subject in every cluster-mask in order just to check (in a descriptive way) the mean GM distribution among the three groups of subjects: early-onset pianists, late-onset pianists and non-musicians. Only for some particular areas of interest (putamen, see the explanation in the Results section) Pearson’s correlations between mean GM volume within those particular structures and the AoO were computed. Unless mentioned otherwise, correlations are reported at an uncorrected  $p < .05$  threshold.

#### *Behavioral measurement of piano performance*

In order to obtain an objective measurement of the level of piano performance in our pianists, we assessed temporal precision during a scale-playing task. However, due to practical restrictions, not all the pianists in the VBM sample completed this task: only the data from 15 early-onset and 13 late-onset pianists was acquired.

Participants played on a Kawai MP9000 stage piano connected to a Pioneer A109 amplifier. The MIDI data was captured through an M-Audio MIDI-to-USB converter and fed in to a Linux-PC running a custom developed C program that captured the MIDI events. Before starting the task, the participants were invited to warm up and get used to the equipment by playing without guidance. After a few minutes, they began the scale exercises, which are explained in detail below. The exercises were presented visually as a musical score with indicated (standard) fingering. The pianists were asked to play as regularly as possible at a comfortable mezzo-forte loudness and in legato style. The entire procedure took about half an hour, and the pianists received a nominal financial compensation. Participants played two-octave piano scales accompanied by a metronome at 120 BPM. They played four notes within a metronome beat, i.e., eight keystrokes per second. They played blocks of approximately 30 alternating ascending and descending scales with a 9-note rest in between (to ensure alignment of the beginning of the scale with the metronome). The scales were played in the following blocks, separated by small breaks: (i) C-major scale with the right hand only, (ii) C-major with the left-hand, (iii) A-minor with the right hand, (iv) F#-major with the right hand, (v) C-major with both

**Table 1**

Summary of previous neuroplasticity studies with musicians. Techniques, participants and results are detailed.

Reference	Type of study	Subjects	More salient results
Schlaug et al. (1995)	MRI: morphometric analysis	Musicians ( $n = 30$ ) vs. non-musicians ( $n = 30$ ), & musicians between them	- Larger anterior CC in musicians compared to non-musicians, especially those who began musical training before age 7.
Amunts et al. (1997)	MRI: morphometric analysis (study of the depth and length of the central sulcus)	Musicians (keyboard students, $n = 21$ ) & non-musicians ( $n = 30$ )	- Greater symmetry of ILPG in musicians, due to greater ILPG in the right hemisphere.  - Strong negative correlation between the time at which musical training started and the right and left ILPG. - More symmetrical and superior distal finger performance (tapping) in musicians compared with controls.
Pantev et al. (1998)	MEG	Musicians with AP ( $n = 9$ ), musicians with RP ( $n = 11$ ) & non-musicians-controls ( $n = 13$ )	Strength of cortical activation higher in response to piano tones and in musicians who began practicing before the age of 9.
Pascual-Leone (2001)	TMS	Non-musicians	Cortical output maps showed an increased expansion during the beginning of a practice period in the contralateral M1 area ( <i>after musical training</i> ).
Schmithorst and Wilke (2002)	MRI-DTI	Musicians ( $n = 5$ ) vs. non-musicians ( $n = 6$ )	In musicians: Among several areas found, the FA values within the internal capsule were significantly smaller, while the FA values in the genu of the CC were significantly greater.
Schneider et al. (2002)	MEG & MRI	Non-musicians ( $n = 12$ ), professional ( $n = 12$ ) & amateur musicians ( $n = 13$ )	Greater GMV in the anterior-medial portion of Heschl's gyrus in musicians compared to non-musicians. GMV and signal amplitude in HG correlated positively with musical aptitude, and were higher in musicians.
Gaser and Schlaug (2003)	MRI-VBM (GM volume)	Professional ( $n = 20$ ) & amateur musicians ( $n = 20$ ) & non-musicians ( $n = 40$ )	GM highest in professional musicians, intermediate in amateurs musicians and lowest in controls. Areas related to musician status (professional musicians > amateurs > non-musicians): primary motor, premotor and somatosensory areas, ant. sup. parietal, inf. temporal gyrus, left cerebellum, left HG, and left inf. and right medial frontal gyrus.
Hutchinson et al. (2003)	MRI-VBM	Musicians, keyboard players ( $n = 60$ ) vs. non-musicians ( $n = 60$ )	Male musicians ( $n = 30$ ): Higher absolute and relative cerebellar volume; relative cerebellar volume correlated with intensity of practice. More GM in the right hemisphere in: frontal & prefrontal lobe, sup. temporal lobe, inf. & medial temporal gyrus, temporal pole, sup. pre- and postcentral gyrus, sup. & inf. parietal lobe, cuneus, cingulate and lingual gyrus.
Luders et al. (2004)	MRI-VBM	Musicians: non-AP ( $n = 40$ ) & with AP ( $n = 20$ )	More GM in the left hemisphere: sup. Temporal gyrus (HG), PT, inf. pre- & postcentral gyrus, mesial frontal lobe, thalamus, caudate and occipital pole. - <i>Childhood practicing</i> correlates positively with FA in: bilateral PLIC, CC, fiber tracts in sup. & inf. frontal lobe.
Bengtsson et al. (2005)	MRI-DTI	Musicians, pianists ( $n = 8$ ) vs. non-musicians ( $n = 8$ )	- <i>Adolescence practicing</i> corr. positively with FA in: the splenium and the body of CC.
Schneider et al. (2005b)	MEG-MRI	Musicians (professionals: $n = 51$ , amateur: $n = 16$ ) & non-musicians ( $n = 20$ )	- <i>Adult practicing</i> corr. positively with FA in: left ant. limb of the internal capsule, fiber bundle in right temporoparietal junction (arcuate fasciculus). Enhanced functional response and enlarged GM in the HG in professional musicians compared to non-musicians (corr. with musical aptitude). Structural and functional leftward lateralization for fundamental pitch listeners (as pianists or percussionists), rightward lateralization for spectral pitch listeners (as string players or singers).

(continued on next page)

Table 1 (continued)

Reference	Type of study	Subjects	More salient results
Bangert et al. (2006)	fMRI (task: listening/pressing piano keys)	Musicians, pianists ( $n = 7$ ) vs. non-musicians ( $n = 7$ )	<ul style="list-style-type: none"> <li>- <i>Acoustic task</i>—higher activity in: right SMA, left precentral, bilat. middle temporal gyrus, left STG, left Broca's area &amp; left inf. parietal lobule.</li> <li>- <i>Motion-related task</i>: bilateral prefrontal &amp; precentral gyrus, right SMA, right middle temporal, right HPC &amp; left PHPC, right supramarginal, right cingulate, left STG &amp; Broca's area.</li> <li>- <i>Conjunction</i>: Left-hemisphere network in musicians (involving frontal, temporal, parietal areas, &amp; language regions of the cerebral cortex).</li> </ul>
Bermudez et al. (2009)	MRI-VBM & cortical thickness	Musicians ( $n = 71$ , 27 of them with AP) vs. non-musicians ( $n = 64$ )	<ul style="list-style-type: none"> <li>- <i>Musicians vs. controls</i> (areas of convergence among methods: VBM &amp; Cortical thickness): greater GM and thickness in superior temporal (more on the right); greater cortical thickness in BA 44/45 and 47; greater GM and thickness in sup. central sulcus.</li> </ul>
Han et al. (2009)	MRI-VBM (GM Density) & DTI	Musicians-pianists ( $n = 18$ ) vs. non-musicians ( $n = 21$ )	<ul style="list-style-type: none"> <li>- Musicians &gt; non-musicians: <i>GM density</i>: higher in left sensorimotor cortex and right cerebellum; lower in right OFG and left ant. cingulate cortex. <i>FA</i>: higher in the right PLIC and midbrain, &amp; left inf. frontal gyrus.</li> <li>- Lower mean FA values in left and right CST for musicians.</li> </ul>
Imfeld et al. (2009)	MRI-DTI (study of CST)	Musicians ( $n = 26$ , 13 of them with AP & 13 without AP) vs. non-musician controls ( $n = 13$ )	<ul style="list-style-type: none"> <li>- Mean diffusivity values correlated with onset of musical training in the CST, and other fiber structures (higher diffusivity for earlier onset).</li> <li>- Left-greater-than-right lateralization in FA values in AP-musicians.</li> </ul>
Oechslin et al. (2010)	MRI-DTI (study of SLF)	Professional musicians with AP ( $n = 13$ ), professional musicians without AP ( $n = 13$ ) & non-musician controls ( $n = 13$ )	<ul style="list-style-type: none"> <li>- High performance in the AP-test correlates with low mean FA values.</li> <li>- But no significant lateralization effect as a function of musical expertise.</li> </ul>
Steele et al. (2013)	MRI-DTI + TMST	Early-trained musicians ( $n = 18$ , AoO: before age 7), late-trained musicians ( $n = 18$ , AoO: after age 7), & non-musicians ( $n = 17$ )	<ul style="list-style-type: none"> <li>- Synchronization and performance of TMST was better in ET, intermediate in LT and lower in NM. Synchronization of the TSMT was correlated with FA in the left temporal lobe, extending to posterior limb of internal and external capsules.</li> <li>- ET showed greater FA than LT in posterior midbody / isthmus of CC.</li> <li>- AoO significantly correlated positively with FA (in the CC and temporal regions) and negatively with RD (in temporal regions).</li> <li>- <i>RST</i>: ET outperformed NM, but not LT in performance measures. In ITI deviation, ET outperformed LT, and both groups outperformed the NM.</li> </ul>
Bailey et al. (2014)	MRI: morphometrical analyses (VBM, DBM & cortical thickness) + rhythm synchronization task (RST)	Early-trained ( $n = 15$ , AoO: before age 7), late-trained musicians ( $n = 15$ , AoO: after age 7) & non-musicians ( $n = 20$ )	<ul style="list-style-type: none"> <li>- <i>VBM &amp; DBM overlapping results</i>: ET showed more GM and more deformation in right vPMC, compared to LT.</li> <li>- Deformation values from right vPMC correlated with AoO and performance in RST.</li> <li>- <i>GMD increases with expertise in</i>: right fusiform gyrus, right mid orbital gyrus, left inf. frontal gyrus, left intraparietal sulcus, bilateral cerebellar Crus II &amp; left HG.</li> <li>- <i>GMD decreases with expertise in</i>: bilateral perirolandic and striatal areas.</li> <li>- GMD in the right mid orbital area and the IFG predicted accuracy in detecting fine-grained incongruities in tonal music.</li> </ul>
James et al. (2014)	MRI: morphometrical analysis (VBM: relation with expertise)	Professional ( $n = 20$ ) & amateur pianists ( $n = 20$ ), & non-musicians ( $n = 19$ )	<ul style="list-style-type: none"> <li>- ET showed reduced WM volume bilaterally compared to LT.</li> <li>- ET showed reduced WM volume in lobules IV, V and VI compared to LT.</li> <li>- Better timing performance, greater musical experience and earlier age of start were associated with smaller cerebellar volumes.</li> <li>- Better timing performance was associated with smaller WM volumes of the right lobule VI.</li> </ul>
Baer et al. (2015)	MRI (multi-atlas segmentation pipeline)	Musicians ( $n = 38$ ) & non-musicians ( $n = 20$ )	<ul style="list-style-type: none"> <li>- ET showed reduced WM volume bilaterally compared to LT.</li> <li>- ET showed reduced WM volume in lobules IV, V and VI compared to LT.</li> <li>- Better timing performance, greater musical experience and earlier age of start were associated with smaller cerebellar volumes.</li> <li>- Better timing performance was associated with smaller WM volumes of the right lobule VI.</li> </ul>

Summary of some previous findings in musicians. Abbreviations: *Techniques and parameters*: MRI: magnetic resonance imaging, MEG: magnetoencephalography, DTI: diffusion tensor imaging, fMRI: functional MRI, FA: fractional anisotropy, VBM: voxel-based morphometry, GM: gray matter, GMD: gray matter density, GMV: gray matter volume, WM: white matter, RST: rhythm synchronization task, ITI: inter-tap interval, TMST: temporal motor sequencing task, corr.: statistically correlated/correlating. *Musicians' traits*: AP: absolute pitch, RP: relative pitch or non-AP, ET: early-trained musicians, LT: late-trained musicians, NM: non-musicians. *Areas*: CC: corpus callosum, ILPG: intrasulcal length of the precentral gyrus, HG: Heschl's gyrus, PLIC: posterior limb of internal capsule, SMA: supplementary motor area, BA: Brodman's area, PT: planum temporale, OFG: orbitofrontal gyrus, CST: corticospinal tract, SLF: superior longitudinal fasciculus, vPMC: ventral premotor cortex, HPC: hippocampus, PHPC: parahippocampus, sup.: superior, inf.: inferior, mid.: middle, ant.: anterior, post.: posterior.

**Table 2**

Main characteristics of the sample (musicians and non-musicians). Mean and s.d. (standard deviation) are shown.

Characteristics	Early-onset pianists	Late-onset pianists	Control subjects
N	21	15	17
Mean age	24.90 (s.d. 4.89)	23.60 (s.d. 3.62)	24.06 (s.d. 4.39)
Ethnicity	15 caucasians, 6 asians	12 caucasians, 3 asians	17 caucasians
Gender	12 females, 9 males	7 females, 8 males	7 females, 10 males
Mean age of musical exposure	5.19 (s.d. 0.69)	8.33 (s.d. 1.98)	---
Total hours of practice	14853.48 (s.d. 9294.13)	12366.67 (s.d. 7668.25)	---
Mean hours of practice last week	14.26 (s.d. 9.31)	15.49 (s.d. 11.18)	---
Hours of practice last year	19.92 (s.d. 12.27)	19.13 (s.d. 14.91)	---

Summary of the demographical traits of the sample. There was no significant difference in age between the three groups (significance for the difference between the three groups regarding age was superior to  $p = .3$ ). Age of onset between early- and late-onset pianists were significantly different ( $p < .001$ ). However, there were no significant differences in the amount of practice between both groups of pianists: Total hours of practice:  $p = .387$ ; Mean hours of practice per week:  $p = .720$ ; Hours of practice last year:  $p = .864$ .

hands. In the current study, we only analyzed the C-major scales for left and right hand (condition i and ii). The collected dataset was also included in a previously published study (van Vugt et al, 2012).

We then proceeded to calculate the temporal unevenness of the key-strokes by taking the SD of the inter-keystroke-intervals (medianSD-IOI in milliseconds) in each scale run and then averaged for all runs in each playing direction (ascending, descending). The higher this value, the more irregular the timing of the keystrokes, indicating poorer timing control. The medianSD-IOI has been employed previously (Wagner, 1971; MacKenzie and van Eerd, 1990; van Vugt et al, 2012).

After obtaining timing unevenness measures for each hand, 4 different analyses were performed: (i) a between-group comparison in order to check for potential differences in timing unevenness between the early-onset and the late-onset groups of pianists; (ii) Pearson's correlations between timing unevenness in each hand and the AoO (2 correlations); (iii) using the same masks applied for the correlation between GM volume and AoO, Pearson's correlations between the GM values inside these masks (i.e., bilateral putamen) and the timing unevenness for each hand (4 correlations); (iv) we repeated the correlation between the GM volume inside each VBM mask (right and left putamen) and the AoO, but this time controlling for the timing unevenness in each hand (4 partial correlations). Unless mentioned otherwise, correlations are reported at an uncorrected  $p < .05$  threshold.

## Results

### Between-group comparison: pianists vs. non-musicians

The between-group analysis showed that musicians presented greater GM volume than non-musicians in the basal ganglia, specifically

**Table 3**

Areas showing differences in the VBM analysis (gray matter volume) between the whole group of musicians and the non-musician control group.

Area	Hemisphere	Cluster size (mm <sup>3</sup> )	T value	Peak coordinates		
				x	y	z
<i>Pianists &gt; non-musicians</i>						
HPC–Putamen	L	849	8.25	−29	−10	−12
Amygdala	L			−18	−3	−14
Calcarine sulcus	R	1716	7.79	6	−88	−0
Lingual gyrus	R			6	−78	−11
Putamen	R	815	6.78	29	2	−3
Thalamus	R	341	6.48	14	−25	−3
STG	L	60	5.86	−47	−1	−11
<i>Pianists &lt; non-musicians</i>						
Supramarginal	R	1813	7.67	66	−21	19
STG	R			63	−24	3
PCG	R			69	−13	39

Results of the VBM analyses of T1 images (gray matter volume). Table shows the areas that show differences in both directions, pianists > non-musicians and pianists < non-musicians, at a whole-brain FWE corrected  $p < 0.05$  with 50 clusters of spatial extent. Peaks coordinates are given following the MNI system. Abbreviations: HPC, hippocampus; STG, superior temporal gyrus; PCG, postcentral gyrus; L, left hemisphere; R, right hemisphere.

in the putamen bilaterally, extending to part of the anterior hippocampus, the pallidum and the amygdala—specifically the superficial and medial nuclei, the central nuclei and the laterobasal amygdala (identification based on descriptions by Snell, 2001; and Koelsch, 2014; and using the WFU–Pickatlas software, ANSIR—Advanced Neuroscience Imaging Research Laboratory, Department of Radiology of Wake Forest University School of Medicine, Winston, Salem, NC; Maldjian et al., 2003, 2004; Lancaster et al., 1997, 2000; Tzourio-Mazoyer et al., 2002) and in the right thalamus (particularly, in the ventral posterolateral and lateral posterior nuclei, as well as in parts of the dorsomedial and the pulvinar regions; based on Behrens et al. (2003) and Johansen-Berg et al. (2005)), as well as in the bilateral lingual gyri and the left superior temporal gyrus. In addition, pianists showed a reduction in GM volume in the right supramarginal, right postcentral and right superior temporal gyri as compared to non-musicians (see Table 3 and Fig. 1A and C).

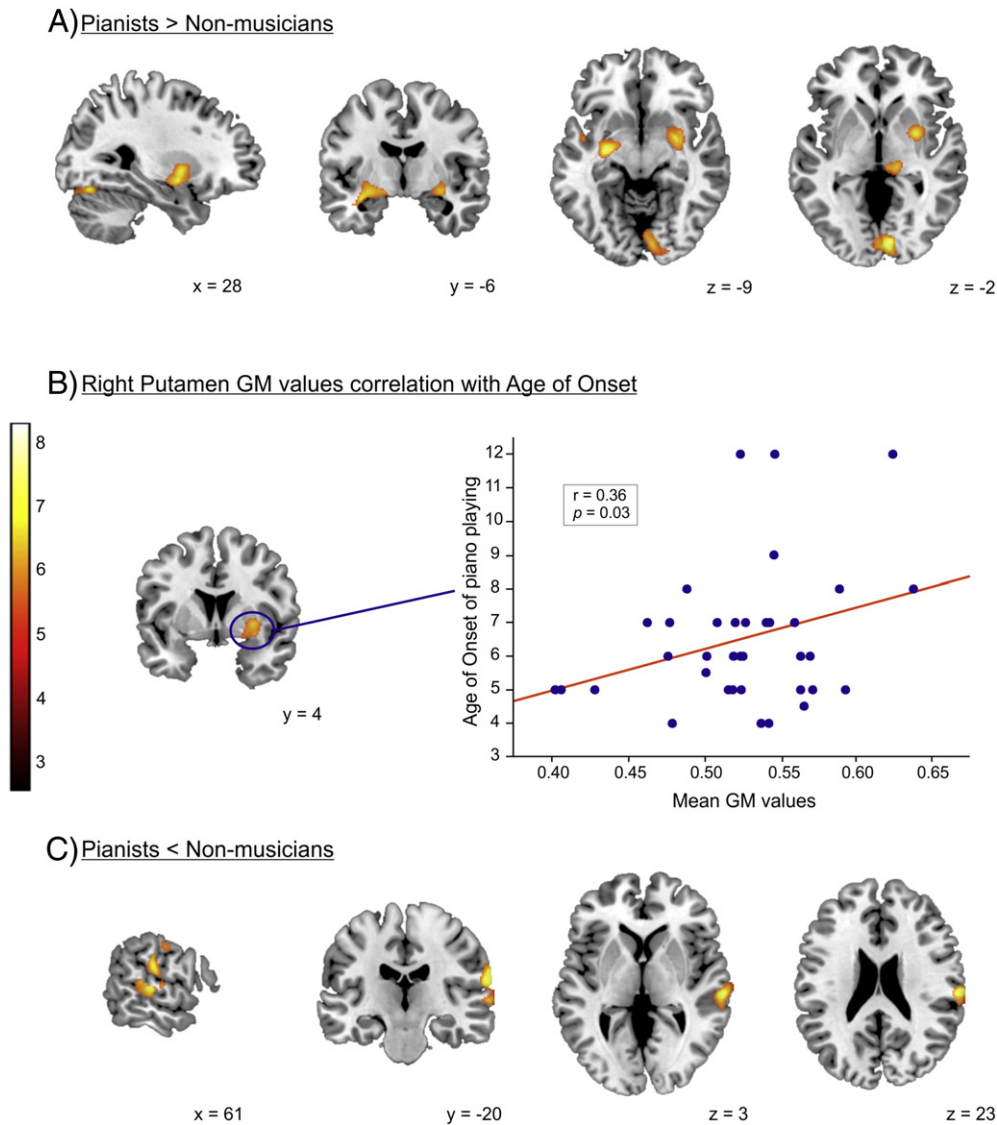
### Exploring differences depending on the age of onset of piano playing

#### Between-group comparison: early-onset vs. late-onset pianists

A between-group analysis comparing early-trained and late-trained pianists at whole-brain level was performed in the same fashion as the one carried out to compare musicians and non-musicians. However, no significant differences were found between the two groups of pianists at a whole-brain level, with a  $p$ -value  $< .05$  FWE corrected threshold at the voxel level, with a cluster extent of more than 50 contiguous voxels.

#### Correlation analysis

In order to investigate potential individual differences among the pianist groups using another analysis, we obtained a mask for every significant cluster of the between-group comparison between pianists and non-musicians. We then calculated the mean GM value for each subject in every cluster-mask to check the distribution among the three groups of subjects: early-onset pianists, late-onset pianists and non-musician. As a merely descriptive measure and only for visualization purposes, the distribution by group for each significant cluster is depicted in Fig. 2 and the mean GM volume values for every cluster are detailed in Table 4. The mean GM values in the two clusters in the putamen (from the contrast pianists > non-musicians) showed the largest difference in plain sight between the two groups of pianists (*mean GMV in the left putamen*: early-onset pianists = 0.454, late-onset pianists = 0.473, and non-musicians = 0.425; *mean GMV in the right putamen*: early-onset pianists = 0.515, late-onset pianists = 0.539, and non-musicians = 0.478). These clusters were qualitatively selected: no between-group comparison or statistical analysis was performed. Thus, a Pearson's correlation analysis was calculated between the AoO of piano playing and the mean GM value for each musician solely inside right and left putamen cluster-masks. Only the mean GM volume in the right putamen showed a significant positive correlation with the AoO of piano playing ( $r = 0.36$ ,  $p = 0.03$ ). Meaning that the later the age of



**Fig. 1.** VBM results: Between-group comparison and correlation with age of onset. A. Pianists > non-musicians: compared to non-musicians, musicians presented greater GM volume in basal ganglia, specifically in the putamen bilaterally (extending also into hippocampus, pallidum and amygdala, among other near-by structures) and in the right thalamus, as well as in the bilateral lingual gyri and the left superior temporal gyrus. B. Right putamen GM values correlation with age of onset: the right putamen was the only area that correlated significantly with the AoO of piano playing. This positive correlation means that the later the age of start of piano playing, the greater the GM volume in the right putamen. C. Pianists < non-musicians: pianists showed less GM volume in the right supramarginal, postcentral and superior temporal gyri as compared to non-musicians. Abbreviations: VBM: voxel-based morphometry; AoO: age of onset of piano playing; GM: gray matter.

start of piano playing, the greater the GM volume in the right putamen (see Fig. 1B).

#### Piano playing performance

From the scale playing recordings, we discarded scales that were played incorrectly (2.44% of the recorded material) and analyzed the remaining 31.0 (SD = 1.9) scale runs.

#### Between-group comparison: early-onset vs. late-onset pianists

A between-group comparison for the scale-playing timing unevenness (medianSD-IOI) in each hand was carried out in order to check for behavioral differences in piano playing between early-onset and late-onset pianists. We performed an ANOVA with timing unevenness (medianSD-IOI) as dependent variable and within-subjects factor hand (left/right) and between-subjects factor age of onset (early/late). We found a main effect of hand ( $F(1,31) = 20.83, p < .0001$ ) indicating that right hand scales were played more evenly. The main effect of AoO was significant ( $F(1,31) = 7.11, p = .01$ ) indicating that early onset

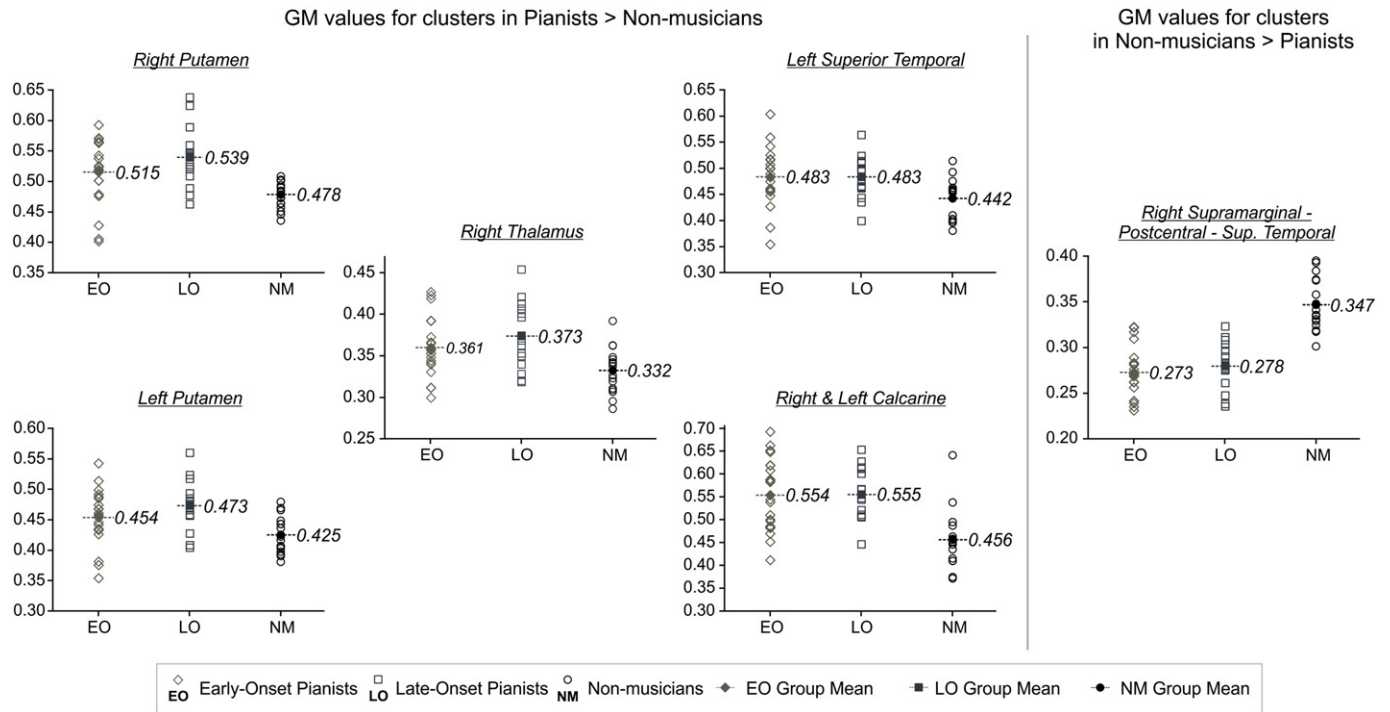
pianists played more evenly (mean = 10.35, SD = 2.19 ms) than late onset pianists (mean = 12.69, SD = 3.60 ms) (see Table 5).

#### Correlation analyses

**Correlation between performance and age of onset.** A positive significant (Pearson's) correlation was found between the timing unevenness of the left hand performance values and the AoO ( $r = 0.40, p = 0.03$ ; see Table 5). This means that the later the onset of piano playing, the greater the temporal variability in scale-playing in the left hand.

**Correlation with the GM volume in the putamen.** We performed Pearson's correlations between the GM volume inside the putamen masks (left and right) obtained from the musicians vs. non-musicians VBM comparison (the same ones applied for the correlation between GM volume and AoO), and the measurements of performance for each hand. No significant results were found for the left- or the right-hand temporal variability measurements.





**Fig. 2.** Distribution of GM values by group and cluster. Distribution of GM values for each group (early-onset pianists, late-onset pianists and non-musicians) in each significant cluster obtained in the VBM analysis for the between-group comparison. Abbreviations: VBM: voxel-based morphometry; GM: gray matter.

*Partial correlation between GM volume in the putamen and AoO, controlling for performance.* In order to ensure that the positive correlation found between GM volume in the right putamen and the AoO could not be explained by the differences in performance found between early-onset and late-onset pianists, partial correlations between the GM volume inside each VBM mask (right and left putamen) and the AoO, controlling separately for left-hand and right-hand timing variability values, was carried out. We found that the significant positive correlation between AoO and the GM volume in the right putamen was still significant only when controlling for the timing variability in the left hand ( $r = 0.39, p = 0.04$ ).

**Discussion**

The present study addressed brain structural effects of musicianship by comparing a highly select group of expert pianists with a non-musician control group. Taking into account that each instrument involves different muscles and techniques (eliciting plastic effects in different brain areas) and that previous studies have shown an influence of the type of instrument played on neuropsychological (Tervaniemi, 2009) and neurophysiological measures (Margulis et al., 2009; Gebel

et al., 2013), we decided to include only expert pianists. To the best of our knowledge, this is the first time that the differences between musicians and non-musicians were studied in such a homogeneous sample (only expert pianists), taking into account both age of onset (AoO) and amount of practice, and also including a very precise and musically relevant behavioral test (i.e., scale-playing task) to assess performance level directly at their chosen instrument. The cutoff for the AoO was 7 years old (early-onset < 7 years, late onset  $\geq$  7 years) and there were no significant differences in the amount of hours of practice between early- and late-onset pianists. Our results will be discussed within the framework of plasticity effects induced by sustained and repetitive practice, considering also how neural efficiency due to intensive and long-term skill training could take place in the brain at different age periods.

*Structural effects of musicianship: Enlargements in GM volume*

Current understanding of brain plasticity effects elicited by early training or early and intense lifetime experiences (either in form of enlargements or reductions of GM), as well as “normal” neural maturation, is still provisional and incomplete (Tau and Peterson, 2010; Zatorre, 2013). In the present study, highly skilled pianists showed greater GM volume in bilateral putamen compared to non-musicians, a part of the striatum that has been classically related to motor control and more recently to implicit sequence learning, reinforcement learning and memory-related processes (Packard and Knowlton, 2002; Graybiel, 2005; Carlson, 2012; Wilkinson and Jahanshahi, 2007). Basal ganglia is a region in which GM and white matter structural experience-related effects have been previously described in studies with other kind of experts (i.e., chess players: Hänggi et al., 2014; golfers: Jäncke et al., 2009). The effects observed in the basal ganglia in the present investigation might be surprising in comparison with those found in Granert et al. (2011) and James et al.’s (2014) studies, in which reductions of GM were found as a function of accurate performance and expertise. In the present study, however, we found an increase in GM volume in this structure in pianists compared to non-musicians. This effect could be explained by the fewer amount of hours practiced by our pianists

**Table 4**  
Mean GM values for the significant clusters obtained in the VBM comparison between pianists and non-musician controls.

	Early-onset pianists	Late-onset pianists	Control subjects
<i>Contrast pianists &gt; non-musicians</i>			
Right putamen	0.515	0.539	0.478
Left putamen	0.454	0.473	0.425
Right thalamus	0.359	0.374	0.332
Left STG	0.483	0.483	0.442
Bilateral lingual gyrus–Calcarine	0.554	0.555	0.456
<i>Contrast pianists &lt; non-musicians</i>			
Right Supramarginal–Postcentral – STG	0.273	0.278	0.347

Abbreviations: GM: gray matter; VBM: voxel-based morphometry; STG: superior temporal gyrus.

**Table 5**  
Values of the measurements of scale-playing timing unevenness (medianSD-IOI in ms) by hand. Between-group comparison and correlation of the complete pianists group with the AoO.

Between-group comparison of timing unevenness					
	Early-onset pianists ( <i>n</i> = 15)	Late-onset pianists ( <i>n</i> = 13)	<i>T</i> -value	Degrees of freedom	Significance ( <i>p</i> -value)
Left hand unevenness	10.82 ± 2.17	13.82 ± 3.85	2.59	26.00	0.016*
Right hand unevenness	9.47 ± 1.36	11.85 ± 3.05	2.60	16.07	0.019*
Correlation between timing unevenness and AoO					
	Mean (pianist whole group, <i>n</i> = 28)				Significance ( <i>p</i> -value)
Left hand unevenness	12.21 ± 3.37				0.034*
Right hand unevenness	10.57 ± 2.56				0.115

Abbreviations: MedianSD-IOI: median standard deviation of the inter-onset interval; AoO: age of onset (of piano playing).

\* Significant at an uncorrected *p*-value < .05.

compared to these previous investigations (present study's mean total life hours of practice: 13817.31 ± 8627.13, versus Granert et al.'s (2011) mean total life hours of practice: 36708 in dystonia patients/41684 in healthy pianists, although the pianists in the study were significantly older; the present study's mean hours per week in the last year: 19.59 ± 13.23, versus James et al.'s (2014) mean hours per week in the last age period measured for the expert musicians: 30.7 ± 8.5). As Poldrack et al. (2005) described, the basal ganglia (and the putamen in particular) is a structure related to motor skill automaticity, resulting from sequence motor training. Practice allows performance of well-known motor sequences as a single unit of activity, and this process causes a decrease (chunking) in activation in the areas related with sequence motor execution and knowledge. Previous studies (such as Granert et al., 2011, and James et al., 2014) showed a reduction of GM in striatal regions as a result of expertise, while here we found more GM in the putamen for the general comparison between musicians and non-musicians, but less GM as a result of an early onset of training among the pianists. It could be the case that the pianists in the present cohort presented a smaller degree of automaticity compared to pianists in previous studies, leading to this apparent discrepancy in the results. However, it is important to note that the present and previous research show a similar effect: the higher the motor efficiency in pianists (i.e., the smaller the temporal variability during playing), the smaller is the GM volume in the putamen, probably due to optimization processes such as pruning or more concise synapsing as a result of extensive practice during sensitive periods.

Significant differences were also found in other regions such as the hippocampus and amygdala, important structures relevant for emotional learning and memory consolidation (Blair et al., 2001; Maren, 1999; Amunts et al., 2005; Graybiel, 2000). More specifically, we found some significant voxels covering the anterior portion of the hippocampus. The anterior hippocampus has been related to novelty detection and associative learning (Mayes et al., 2007; Schinazi et al., 2013; Simó et al., 2015) and, interestingly, also to movement-related responses, reward or goal-directed functions and emotional memory (Strange et al., 2014). Important for the present results is also the involvement of the anterior hippocampus in the auditory domain, specifically in pitch processing and consonance/dissonance detection (Wieser and Mazzola, 1986; James et al., 2008). Finally, effects of musical expertise and auditory-specific training have been also found in the anterior hippocampus, both in musicians (James et al., 2008; Groussard et al., 2014) and in piano-tuners (Teki et al., 2012). In addition, we found differences in the superficial, medial, central and laterobasal nuclei of the amygdala. These nuclei are closely connected with the hippocampus, the dorsolateral thalamus and several cortical areas, such as the auditory cortices (Koelsch et al., 2008). The relationship between the amygdala and the auditory system has been highlighted in expert pianists performing a music expectation violation task (James et al., 2008), as well as in animal

studies of fear conditioning and learning (Armony et al., 1998; Maren, 1999). Human studies suggest that the amygdala is not restricted to the processing of emotional or fear-related stimuli, but that it has a broader role in the detection of relevant stimuli (Sander et al., 2003), which might be important during the music-learning process. A circuit involving cortical structures, the amygdala, the hippocampus and the basal ganglia, has been associated with processing of emotional musical content (Koelsch, 2014). In addition, musical performance is associated with emotional and rewarding experiences (Zatorre et al., 2007) and it has been suggested that musicians construct particular memories relating to their musical experiences in a more detailed, emotional and vivid way than non-musicians (Groussard et al., 2014). Thus, based on previous studies, it is expected that other functions carried out by these regions, such as associative learning (Mayes et al., 2007; Schinazi et al., 2013; Simó et al., 2015), emotional memory (Strange et al., 2014) and pitch and auditory-expectancy discrimination (James et al., 2008; Teki et al., 2012; Groussard et al., 2014), might have been of great importance during the training of our expert pianists and, as a consequence, they could also explain the experience-dependent differences observed in musicians in comparison with non-musicians.

Enlargements in the volume of GM were also observed in the right thalamus, specifically in the ventral posterolateral and lateral posterior nuclei, and in parts of the dorsomedial and pulvinar regions. The thalamus acts as a crucial cortical-subcortical interconnectivity hub (Sherman, 2006); for example, the ventral posterolateral nucleus sends projections to primary somatosensory areas (Snell, 2001; see also Behrens et al., 2003; Johansen-Berg et al., 2005), relaying common sensations to consciousness. The dorsomedial nucleus has been associated with the integration of somatic information and subjective emotional states. Finally, the functional role of the lateral posterior and pulvinar nuclei is less clear, connecting with areas of the cerebral cortex such as premotor, primary and secondary somatosensory and temporal cortices.

Furthermore, greater GM volume was found in bilateral lingual gyri, a region linked to visual processing, dreaming (Bogousslavsky et al., 1987), visuo-spatial transformations of visual stimuli (Jackson et al., 2006) and word processing during reading (Price et al., 1997). Regarding the latter, the lingual gyrus is engaged in global shape processing and its activation is related to the length and visual complexity of the stimulus (not being specific to word processing; see Mechelli et al., 2000). Based on these evidences we suggest that this area might be involved in music-score reading and/or the visuo-spatial transformations needed to locate the read notes into the keyboard.

The last area found to be larger in pianists compared to non-musician controls was the left superior temporal gyrus, a cortical region containing the primary auditory area. Left auditory cortex has been discussed to have more precision than the right auditory area in processing rapid temporal changes (Zatorre, 2013; Schneider et al.,

2005b). Although musical and fine grained pitch processing have been attributed to the right auditory cortex (Zatorre et al., 2002) and the only significant results we found in auditory regions were located at the left superior temporal gyrus, this left-hemispheric finding may be explained by the percussive character of piano sounds. Schneider et al. (2005a,b) found that fundamental pitch listeners – those who mainly decode the keynote or fundamental pitch of the stimuli (Schneider et al., 2005a) – present both greater GM volume and enhanced functional MEG activity in the left lateral Heschl's gyrus and showed a preference toward percussive or high-pitch instruments (such as piano, percussion instruments or guitar) compared to spectral pitch listeners. In addition, these authors also showed that 65% of the pianists in their sample were fundamental pitch listeners (Schneider et al., 2005b). Furthermore, effects of music practice were previously found in the left auditory cortex (Gaser and Schlaug, 2003; James et al., 2014).

#### *Structural effects of musicianship: Reductions of GM volume*

Pianists also presented some regions with a decreased GM volume compared to non-musician controls. Specifically, we found a reduced rightward cluster at the supramarginal gyrus, extending as well to the postcentral and superior temporal gyri. Several previous studies have shown that musical practice induces brain plasticity changes in the sensorimotor cortices (Elbert and Rockstroh, 2004; Jäncke, 2009). Hence, the postcentral gyrus, involved in the control of sensorimotor information (Kaas, 2004), is an area expected to show plastic effects due to the enormous tactile and motor stimulation that highly skilled pianists receive during their daily practice. This finding confirms a recent study (James et al., 2014), in which three groups of participants differing in their level of musical expertise showed reductions of GM density associated with greater expertise in the right postcentral gyrus. The right superior temporal gyrus, another area covered by this rightward cluster of reduced GM, contains the primary auditory cortex, but this hemisphere has been reported to be more sensitive to changes in fine grained pitch than its left homologue, causing an advantage for tonal functions (Zatorre et al., 2007). Consequently, it is generally assumed that the right auditory cortex is more involved in musical abilities and processing (Zatorre et al., 2002).

The supramarginal gyrus is part of the somatosensory associative cortex and has an important role in multisensory integration, body ownership and the location of the limbs in space (Carlson, 2012; Reed and Caselli, 1994; Berlucchi and Aglioti, 1997). Furthermore, this region has been related to language processing (Catani and Mesulam, 2008) and, interestingly for the present study, to music-score reading (Besson and Schön, 2001). In a PET study of sight-reading (reading and listening to a score simultaneously) Sergent et al. (1992) showed that the supramarginal gyrus, which was found active in both hemispheres, was involved in a visual-auditory mapping process. However, Stewart et al. (2003) and Stewart (2005) found activation in the left supramarginal gyrus after 3 months of musical training (score reading and piano playing) only when reading the scores, with no auditory stimuli. These authors attributed this activation to an automatic, learned association between the musical notation and the learned motor response (Stewart et al., 2003). In line with this interpretation, McDonald (2006) reported several problems in reading music scores and playing the piano after a stroke involving the right angular and supramarginal gyri. Some of the reported deficits were difficulties in reading the score when the notes were not assigned with their alphabetical name and incorrect placement of the notes on the keyboard. This evidence support the role of the supramarginal gyrus in music-score reading and, probably, in the motor preparation of the learned piano-playing response.

When one starts to play an instrument, visual, proprioceptive and auditory feedbacks are crucial; however, once the skill is acquired and one starts to master the instrument, neural systems may undergo a reorganization following the principles of economy (Krings et al., 2000;

James et al., 2014), meaning that fewer neurons are recruited for the same processes. As Rypma and Prabhakaran (2009) proposed, when fewer nodes (individual neurons or functionally connected cell-assemblies) need to be crossed, the processing paths are more direct, the neural activity is reduced and the information processing is faster. As commented before, Poldrack et al. (2005) showed a reduction in activity associated with experience and training and proposed a chunking in the resources that leads to automaticity. These reductions in activity and tissue, such as the smaller volume found in our pianists, could be the result of an improved efficiency on the multi-sensory-motor pathways involved in long-term music training.

#### *Behavioral relationship with scale-playing performance*

We measured piano performance via a scale-playing task, calculating the timing unevenness (medianSD-IOI) for each hand during this task. We found a significant difference between early-onset and late-onset groups of musicians, evidencing that late-onset pianists present more timing variability during scale-playing. This is in line with previous reports, which have found better musical performance in early-trained musicians compared to late-trained musicians (Granert et al., 2011; Bailey and Penhune, 2012, 2013). In addition, and in line with this first result, we found a significant positive correlation between the performance of the left hand and the AoO of piano playing: the earlier the start of piano training, the better the performance of the left hand (the smaller the timing variability). We did not find any significant direct correlation between the GM volume in the putamen and the medianSD-IOI values, probably due to the small subsample of pianists that completed the scale-playing task. However, taking into account that both the GM in the right putamen and the performance of the left hand correlated positively with the AoO, our results might support previous findings (Granert et al., 2011). Granert et al. (2011) showed that early-onset pianists have both smaller volume of GM in the right putamen and higher skill-level of piano playing.

The link between our results regarding GM volume, the AoO and the performance values of the left hand, could suggest that the correlation found between AoO and GM volume in the right putamen might be explained by the differences in performance between early-onset and late-onset musicians. In order to rule out this option, we repeated the correlation between GM values in bilateral putamen and the AoO, but this time controlling for the performance in both hands (separately). We found that the correlation between GM volume in the right putamen and the AoO was still significant when controlling for the performance of the left hand, thus ensuring that the effects shown in the right putamen are due to the AoO of piano training and not to differences in skill level. We think that this correlation with GM in the right putamen only holds when controlling for the performance in the contralateral hand because this structure seems to be involved in motor control of the contralateral limbs, although there is still some debate regarding this laterality (Granert et al., 2011). Moreover, plastic effects in right motor-related structures as a consequence of improvement in left-hand motor performance have been previously reported after musical training (Hyde et al., 2009). These effects probably provide evidence that the left hand is the one which right-handed pianists have to practice more in order to control their performance, and the earlier they start to practice, the greater structural differences and the better overall control over their timing variability they accomplish.

#### *Brain structural effects of age of onset of piano playing*

All the pianists in our sample were highly skilled and currently practicing musicians, with a similar level of musical proficiency. However, as it has been discussed for language learning, similar proficiency levels do not directly inform about the implication of the same cognitive resources (Rodríguez-Fornells et al., 2009). Thus, we decided to investigate potential differences among the pianists group depending on the

age of onset of musical practice, applying two different approaches. First, we performed a between-group analysis comparing early-trained and late-trained pianists at whole-brain level in the same fashion than the one applied to compare musicians and non-musicians. There were no significant differences between early- and late-onset pianists at a whole-brain  $p$ -value  $< .05$  FWE corrected threshold at the voxel level, with a cluster extent of more than 50 contiguous voxels. The lack of significant results in this analysis could be explained by the small sample size of each group (early-onset pianists'  $n = 21$ , late-onset pianists'  $n = 15$ ). Another possible explanation is that, since the two groups are highly skilled pianists, the differences could be too subtle to be detected at a whole-brain level.

Secondly, we carried out a Pearson's correlation between the AoO and the mean GM values of the right and the left putamen (those clusters from the comparison pianists > non-musicians which showed a qualitative higher difference between early- and late-onset pianists). A significant correlation was found at the right putamen: the later the onset of piano playing, the greater the volume of GM in this subcortical structure. Granert et al. (2011) recently reported that a low temporal precision (more temporal variability) in scale playing in professional piano players was associated with a larger volume of GM in the putamen. Previous reports show that early-onset musicians have better performance in musical-ability tasks (such as rhythm-learning tests: Bailey and Penhune, 2012, 2013) and motor-learning tasks (Watanabe et al., 2007) compared to late-onset musicians. This is also the case for the present study, at least for the subsample of pianists with measures of scale-playing performance.

The putamen has been reported to be crucial for the long-term storage of learned motor skills (Lehéricy et al., 2005), and it has been also related with temporal precision during piano playing and musical proficiency (Granert et al., 2011). Higher GM volume in the putamen of musicians could be interpreted as an index of better storage capacity for learned motor skills compared to non-musicians, although it should be kept in mind that music practice involves not only motor but an interaction of multi-sensorimotor and higher-cognitive functions (Jäncke, 2009; Herholz and Zatorre, 2012). Functions in the putamen could be refined when the training starts at an early age and would be demonstrated by a shrinkage in GM volume, which might explain the higher musical performance exhibited by early-onset musicians in previous reports (Granert et al., 2011; Bailey and Penhune, 2012, 2013) and in the present cohort. Moreover, less GM or white matter in the region of the basal ganglia in relation with greater experience, has been also described in other kind of experts after long-term training (chess players: Hänggi et al., 2014; golfers: Jäncke et al., 2009).

Late-onset pianists had to practice a large amount of hours in a reduced time window in order to obtain the same degree of proficiency as early-onset musicians; this intensive practice could have led to different patterns of brain reorganization as a function of the AoO. For instance, Sampaio-Baptista et al. (2014) observed that in a low-intensity group of juggling training, the performance was negatively associated with changes in GM volume in motor areas and the dorsolateral prefrontal cortex between a baseline MRI-scan and a second scan performed after 6 weeks of training. However, high-intensity jugglers showed a positive correlation between the pre- and post-training differences of GM volume in these areas and their juggling performance. This means that only high-practice elicited some plastic effects in direct positive relation with the achieved performance. Sampaio-Baptista et al. (2014) stated that, despite the fact that both groups presented the same level of performance, high- and low-intensity participants could be experiencing different stages of learning at the moment of the evaluation. Following this idea, the greater GM volume showed in the putamen by the late-onset pianist in our cohort could be interpreted as a consequence of an enormous practice in less time than the early-onset musicians. As mentioned above, our findings and previous reports together point out that early-onset pianists have both better motor skills

and less volume in the putamen (Granert et al., 2011). Hence, the greater GM volume that the late-onset pianists present in this region may be taken as a 'predictor' for the lower skill-level of piano playing that they displayed behaviorally (see Results for the scale-playing test).

#### *Plasticity and efficiency in music learning*

Musicians have to practice accurate sequences of movements during a large period of time, in a training that implies integration of cognitive resources as well as a great amount of motivation. This daily routine might modify the synaptic efficacy and induce cortical and subcortical reorganization. In the present study we encountered greater GM volume in expert pianists in a network that might be involved in the learning and memorizing of auditory-motor material in presence of a high emotional content. On the other hand, we observed less GM volume in pianists in the right hemisphere in regions related to auditory-motor processing and practice, as well as with music-score reading. This decrease of GM could be interpreted as a sign of refined efficiency in a highly skilled and trained system. As it has been showed previously in animal studies (Kleim et al., 2004; Xu et al., 2009; Yang et al., 2009), dendritic spine refinement and circuit pruning are crucial processes in plastic phenomena. The present GM results could be puzzling and difficult to interpret, since all the areas found seem to be part of the same network or at least work together to accomplish functions that are involved in music training and piano practicing (Elbert and Rockstroh, 2004; Zatorre et al., 2007; Jäncke, 2009; Granert et al., 2011; James et al., 2014; Koelsch et al., 2008; Koelsch, 2014). However, we hypothesize that this pattern of increased GM volume in subcortical structures and decreased GM volume in cortical areas could be due to a balance-maintenance operation of the neural system: if some regions gain in volume or amount of GM, the same circuit should suffer a shrinkage in other regions to compensate and maintain the global volume of the network. Previous studies in literacy acquisition (Dehaene et al., 2015) have shown this kind of 'recycling' phenomena in some brain areas: after learning to read, the boundary between the left fusiform face area (FFA) and the visual word form area (VWFA) seems to shift, allowing more "space" for the VWFA (that is now needed for the new learnt skill); moreover, as literacy increases, the activity in the left FFA becomes smaller and seems to shift to the right hemisphere. Thus, in order to maintain the global balance of the visual system, the brain changes the structure and reorients some of its functions to preserve some of the old activities (i.e., face recognition) but allowing the new skill (reading) to take place and be stored in the brain. We suggest that a similar process could be taking place in this network involved in motor and emotional-reinforcement learning in our pianists. Moreover, we hypothesize that the AoO of piano playing could also influence how these plasticity effects get instantiated in the brain, leading to an even more efficient system in those pianists who started earlier in life.

The current most accepted hypotheses state that plasticity decreases with aging (Hallett, 1995), with several examples in the literature emphasizing the importance of plasticity during the first years of life (Schlaug et al., 1995; Amunts et al., 1997; Hyde et al., 2009; Imfeld et al., 2009). However, our knowledge regarding brain plasticity has been broadened in the last decades. Several examples in the literature showed reorganization of neural systems in different fields of expertise (i.e., musicians: Haslinger et al., 2004, athletes: Del Percio et al., 2009, chess-players: Hänggi et al., 2014, golfers: Jäncke et al., 2009), following a specific training (Maguire et al., 1997; Draganski et al., 2004; Poldrack et al., 2005), and also plastic adaptations as a consequence of a pathological state. For example, blind people (who are a good model of pathological reorganization due to the lack of sensory inputs in the visual modality) generally show shorter latencies of event-related potentials for auditory and somatosensory stimulations (Niemyer and Starlinger, 1981; Röder et al., 2000). Furthermore, a recent fMRI investigation by Stevens and Weaver (2009) has highlighted the importance of critical

periods in this population. In this experiment, [Stevens and Weaver \(2009\)](#) found that across all tonal stimuli (pure tones and frequency modulated ones) and comparing responses to silence, early-blind individuals showed substantially less signal in the auditory cortex, fewer active voxels, than late-blind and sight control participants. These authors argued that the decreased signal could be reflecting a greater processing efficiency. As they also remark, this hypothesis is supported by previous electrophysiological studies showing shorter latencies of early evoked potentials originated in the auditory cortex in early-blind individuals ([Röder et al., 1996](#); [Naveen et al., 1997](#), [1998](#); [Manjunath et al., 1998](#)), as well as the reduced metabolic responsiveness in a PET study of auditory localization with monkeys ([Recanzone et al., 1993](#)).

Functional neuroimaging studies have also revealed decreased cortical activation after long-term piano training, which has been taken as evidence for increased efficiency of the motor system and the need for a smaller number of active neurons to perform a determined set of movements ([Krings et al., 2000](#); [Jäncke et al., 2000](#); [Haslinger et al., 2004](#)). [Ragert et al. \(2003\)](#) conducted a tactile discrimination study in pianists in which they argued that metaplasticity processes (a higher-order form of plasticity related to the phenomenon of “learning to learn”) are the substrate for the changes in neuronal efficacy induced by repetitive practice. Thus, it seems that sustained practice of a skill helps developing a state in which metaplasticity processes could enhance the learning induced plastic phenomena. Practicing routines in pianists could have helped developing this metaplastic state in neural networks, facilitating potential brain changes and promoting an altered efficiency of the sensorimotor, auditory and associative system. Furthermore, the existence of a sensitive period ([Huttenlocher, 2003](#); [Hensch, 2005](#)) for music-skills acquisition has been proposed ([Penhune et al., 2005](#); [Bailey and Penhune, 2010](#)) and has been supported by several morphometric studies ([Steele et al., 2013](#); [Bailey et al., 2014](#)). Evidence for a critical period have been not only reported for the primary sensory systems (as the visual domain with experiments of monocular deprivation; [Hubel et al., 1976](#); [Shatz and Stryker, 1978](#)), but also for language acquisition ([Lenneberg, 1967](#)). Although nowadays we probably describe this window of time, that extends from early infancy to puberty, as a sensitive period ([Penhune, 2011](#)), the concepts of neural plasticity, neurogenesis and brain repair have been redefined during the last years and the current picture of the adult learning brain is more dynamic ([DeFelipe, 2006](#)). All this information sheds some doubts on a rigid interpretation of the sensitive window hypothesis, even in language and music learning in adults ([Rodríguez-Fornells et al., 2009](#); [Penhune, 2011](#)). However, starting to play an instrument early in life seems to have an advantage for auditory, motor, cognitive and associative systems. This advantage is probably due to the fact that training during sensitive periods (in which developmental plastic phenomena are taking place) may induce changes in the brain that might serve as a scaffold on which later training can build, enhancing the system ([Steele et al., 2013](#)).

### Limitations

The present investigation may comprise some limitations, mainly associated with the structural neuroimaging analysis selected. VBM analysis presents several limitations that could affect the results and should be considered. First of all, during the segmentation process: on the one hand, because the model assumes that all voxels contains only one type of tissue, those voxels in the border and/or with a mixture of tissues may not be modeled correctly; on the other hand, tissue maps are created based on ‘a priori’ probability images, thus if a brain (due to its own special traits) cannot be adequately registered with the probability images, the segmentation will not be perfectly accurate ([Ashburner and Friston, 2000](#)). Secondly, in VBM various preprocessing steps (such as spatial normalization and smoothing of the images) are performed before any statistical comparison is carried out; the aim of these preprocessing steps is to make each brain more comparable to

the rest of the group, but they should be done carefully in order to avoid losing the individual characteristics of each subject. Third, the threshold for the Gaussian kernel applied during the smoothing is inconsistent among different VBM studies, and it could affect the results ([Ashburner and Friston, 2000](#)). Fourth, as stated in the [Materials and methods](#) section, it is important to note as well that, although the terminology GM density and volume has been classically used to refer to VBM results, it should not be confused with actual measurements of cell packing density or volume of neurons that could be obtained via cellular or molecular techniques; one should keep in mind that VBM is only measuring voxel intensities ([Ashburner and Friston, 2000](#)), even though one uses the classic term ‘GM volume’ to explain the results, as in the present study. Fifth, great differences in the results could be obtained depending on the type of nuisance covariates used and the specifications applied to include them ([Ashburner, 2010](#)). Finally, [Ashburner and Friston \(Ashburner and Friston, 2000\)](#) stated that even with many hundreds of subjects in a database with controls, VBM may not be powerful enough to detect subtle differences among individuals. Furthermore, we think that depending on the amount and distribution of early- and late-onset participants in the sample of a study, different kind of findings could be obtained (for example, in the present study it would have been interesting to include more pianists in the range of age of onset between 9 and 12 years).

### Conclusion

In the present investigation we found a complex pattern of increases and decreases in GM volume in several cortical and subcortical regions associated with musical practice (in line with previous findings: [Stewart et al., 2003](#); [Zatorre et al., 2007](#); [Jäncke, 2009](#); [Granert et al., 2011](#); [James et al., 2014](#)). Moreover, we found a significant positive correlation between the GM volume in the right putamen and the AoO of piano playing, even when controlling for the level of performance. We also found differences in the performance of piano practice between early-onset and late-onset pianists, and a significant correlation between performance of the left hand and the AoO. All these results indicate that the earlier the onset, the better the piano performance and the smaller the GM volume in the right putamen. The present results confirm some of the previous reports regarding plasticity effects induced by sustained and repetitive music practice (effects in somatosensory, motor, auditory, association and limbic regions). Moreover, we observed that neural efficiency due to intensive and long-term skill training seems to be determined by the age of commencement of musical practice.

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## Conflict of interest

None declared.

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