Mémoire de Maîtrise en médecine

Hippocampus size predicts fluid intelligence in musically trained people

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Lausanne, décembre 2011

Summary

Introduction

Neurogenesis persists in the human adult hippocampus[1] and the survival of new progenitor cells is enhanced by learning activities[2]. Using the musician's brain as a model for cortical plasticity, musical training induced functional adaptations of the hippocampus have been demonstrated[3,4]. Furthermore, there is evidence for a positive correlation between hippocampus size and fluid intelligence[5], encompassing aspects of attention, working memory and executive functions[6]. Previous data strongly suggest that musical training impacts on such higher order cognitive functions[7,14]. Following these findings we hypothesize a linkage between hippocampus size and fluid intelligence in musically trained people.

Methods

Participants: Three groups – piano experts (E, n=20), piano amateurs (A, n=20) and non-musicians (N, n=19), matched by age and gender.

Task: short version of the Raven's Test, Advanced Progressive Matrices (time limit 15 minutes).

Structural MRI: manual segmentation[8,9,10,11,12] of left (LH) and right (RH) hippocampi done by a single investigator blinded for group belonging and ID of each subject, software MRIcroN[13] **(Fig. 1)**

Statistics: one-way ANOVAs on Raven performance and hippocampus volume; Fisher's r to z transformations; robust multiple regression models for each hemisphere: (i) to predict Raven performance by hippocampus volume and (ii) to test whether this prediction is modulated by the factor of musical training. Robust regression analysis (implemented by statistical software R) represents a valid alternative to least square regression analysis when data is potentially contaminated by single influential observations.

Results

One way ANOVAs with three levels of expertise: no main effects of Expertise neither in Raven's Test performance nor in

hippocampus volumes. No main effect of Lateralization (Fig. 2).

Pooling of musicians (M=A+E) justified as no difference in predictive power exists between A and E, neither in the left nor

in the right hemisphere. LH: z=0.84, p=0.401, RH: z=-0.45, p=0.623.

Robust multiple regression analysis testing the prediction of Raven's performance by hippocampus size, modulated by

musicianship (two levels: N, M(A+E)):

- **Left hemisphere:** Significant interaction (t=2.221, p=.030), revealing that prediction of Raven's performance by

hippocampus size is modulated by musical training: N (beta =.03) and M (beta =.46).

- **Right hemisphere:** Significant interaction (t=2.003, p=.050), revealing that prediction of Raven's performance by

hippocampus size is modulated by musical training: N (beta =.01) and M (beta =.38).

Conclusion

Hippocampus size significantly predicts fluid intelligence performance in musically experienced subjects but not in musically naïve ones. This result represents a striking additional corroboration of musicians' brain plasticity. It seems highly plausible that a long-lasting complex activity like musical instrumental training from childhood into adulthood induced an increase in hippocampus size associated with enhanced logical reasoning. Further research is needed to investigate cognitive functions favored by musical training and possible consequent impact on the development of peculiar brain structures.

NB: This research was performed within the framework of an ongoing research project performed by Clara James (principal investigator) and postdoc collaborator Mathias Oechslin entitled "Behavioral, neuro-functional and neuro-anatomical correlates of experience dependant music perception" (FNS 100014_125050). This research project investigates brain adaptations in correlation with changes of behavior in young adults with varying musical experience, anticipating gradual changes in behavior, brain functioning and brain structure with degree of musical aptitude. In this frame, I did the data collection of hippocampus volumes and analyzed the results in correlation with a literature research on the subject.

1. <u>Introduction</u>

The interest of the neurosciences for musical activities is constantly growing. Such complex activities, for instance mastering a musical instrument, entail a panoply of sensory-motor and cognitive functions. This in consequence appeals to scientific research on higher order cognitive and motor functioning that aims to deceiver the underlying brain networks involved and their possible experience-driven adaptations.

The current experiment, a comparative analysis of gray matter volume in the hippocampus, is part of a large research project investigating functional and structural cerebral plasticity in correlation with changes of behavior in young adults with varying musical expertise (James et al. in preparation, Oechslin et al. submitted[1]). Cerebral plasticity is the capacity of functional and structural reorganization of the cortex after a lesion, or induced by learning (Schlaug 2001). The mechanisms implicated are reinforcement of pre-existing synapses, the formation of new ones, the recruitment of task specific cerebral areas (Buonomano and Merzenich 1998) or a combination of these different mechanisms. Concerning complex motor learning *for example*, studies on the cerebellum showed an increased number of synapses per Purkinje cell (the only efferences of the cerebellar cortex), of glial cells per neuron and of capillaries in the cerebellar cortex (Black et al. 1990, Isaacs et al. 1992, Anderson et al. 1994 in Schlaug 2001).

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[1] **James**, C.E, Oechslin, M.S., Van De Ville, D., Lazeyras, F. & Hauert, C.-A. *Musical syntax processing as a function of musical expertise: spatio-temporal ERP analyses and source imaging* (in preparation).
Oechslin, M.S., Van De Ville, D., Lazeyras, F., Hauert, C.-A. & James, C.E. *Degree of musical expertise gradually modulates brain functioning* (submitted).

All this speaks for the hypothesis that one might also find a macroscopic size difference between musicians and non-musicians for structures engaged in music processing and performing. The pioneer paper on the subject of hippocampus plasticity was published by Maguire et al. (2000) and demonstrated a significantly enlarged posterior hippocampus in London taxi drivers compared with control subjects. A positive correlation with drivers' experience revealed a direct relationship between experience and hippocampus volume. This result is partially explained by the fact that neurogenesis persists in the human adult hippocampus (Eriksson et al. 1998) and that the survival of these new progenitor cells is increased thanks to learning activities, especially those involving the hippocampus (Gould et al. 1999). However we would like to mention here that not only neurogenesis can lead to an increase in the size of cerebral structures, but also a reorganization of the connections, knowing that every single new synapse sollicitates several astrocytes and oligodendrocytes to survive. This is why a mere volume measurement cannot be directly interpreted as the manifestation of an increased neurogenesis.

Given the fact that music is a widely spread activity, and that practically all levels of expertise exist in the population, from simple music-lovers to extensively trained professionals, it seems plausible to expect functional and structural differences between individuals with different levels of musical training. Gaser and Schlaug (2003) showed a strong correlation between musical status, the intensity of the training (non-musician, amateur or professional), and structural differences, particularly in the motor, auditory and visuo-spatial areas. Strikingly, the differences were proportional to the degree of expertise.

We can also evoke the famous and many times studied "Mozart effect". Rauscher et al. (1994) found improvement in spatio-temporal reasoning in subjects exposed to a Mozart piano sonata. Supporting the latter findings, Jausovec et al. (2006) more recently demonstrated that subjects exposed to Mozart's music performed better in a spatio-temporal rotation task. However the Mozart effect is transient, and only concerns specific spatio-temporal tasks that engage the right hemisphere, and may just represent a form of cognitive arousal (Steele et al., 1999). Nevertheless all these data suggest that merely listening to music but more strongly so playing a musical instrument may have important effects on cerebral function and structure. This can be explained by the fact that learning through active practice, via audio-motor feedback loops that compare current performance to an intended performance, may induce plasticity more strongly than mere exposure (James et al, 2008; James et al, 2011).

Music also entails important other cognitive aspects, such as memory, syntax processing and relevance detection (James et al. 2008, Koelsch et al. 2006, Tillmann et al. 2006). Musical notes are very transient stimuli, and short-term memory is thus essential to perceive music as a coherent sound stream. Music perception strongly relies on expectations based on the most common sequences and composition of notes and chords within music of a certain culture, in the framework of this research western tonal tradition (James et al. 2008, Koelsch et al. 2006, Tillmann et al. 2005). Long-term memory is obviously also necessary to remember all the musical pieces that we were exposed to, as well as their underlying structure, and particularly so for musicians, who logically have more occasions to memorize music. Memory networks that are known to be involved in music processing are situated in the frontal dorso-lateral and inferior areas, mostly in the right hemisphere (Griffiths et al. 1999, Zatorre et al. 1994 in Peretz et Zatorre 2005, Zatorre et al. 2002). The hippocampus is known to be engaged in memory performance, specifically in the formation of new memory traces, but also in delayed secondary memory (Gordon et al. 1994). Hanseeuw et al. (2011) recently indicated an atrophy of the subiculum and CA 2-3 in patients suffering from mild cognitive impairment, comforting the knowledge of the implication of the hippocampus also in other superior cognitive tasks, notably in the executive functions (Frodl et al. 2006).

Meng et al. (2009) showed an improvement of spatial learning capacities and of fear-motivated memory in mice exposed to classical music for a month as compared with non-exposed controls. Human subjects, when asked about the familiarity of different musical pieces, manifested activations of areas known to be associated with episodic, semantic and visuo-spatial memory, comprising the hippocampus. Activations were more largely distributed in musicians than in non-musicians (Groussard et al. 2010). As for more general aspects of auditory processing, Herdener et al. (2010) found an increase of hippocampus activation by temporal novelty in sounds in the left anterior hippocampus in professional musicians. This speaks for strong hippocampus activity in musicians during the processing of different aspects of musical listening and performance.

Moreover, the hippocampus may also be implicated in emotional aspects of music processing: Koelsch et al. (2006) showed hippocampus activation (among other areas) when subjects were exposed to unpleasant dissonant music contrasted with pleasant consonant music. In expert musicians hippocampus and adjacent amygdala activations occurred even when musical

incongruities were not sensorily unpleasant (dissonant), but only syntactically inappropriate (James et al., 2008).

As the hippocampus is importantly implied in many aspects of music processing, particularly sensitive to training-related neuroplasticity (Herdener et al. 2010) and thus "subject to beneficial modification (neurogenesis and synaptogenesis) from engagement in new learning activites" (Sullivan et al. 2001), it seems reasonable to expect a structural difference relative to musical experience. The question of possible lateralization of hippocampal functions remains unclear. The right hippocampus seems involved in the retrieval accuracy of musical memory, the left side more in verbal memory (Watanabe et al. 2007). A case study found indications that hippocampus activation on the left side is modulated by musical dissonances and on the right side by higher-order pitch processing (Wieser et Mazzola 1986 in James et al. 2008). Luders et al. (2004) showed numerous inter-hemispheric asymmetries in musicians and pointed out that the medial part of the superior temporal lobe, the posterior parts of the inferior and medial gyrus and the temporal pole were larger on the right side, with other parts of the superior temporal gyrus found larger on the left side. Groussard et al. (2010) demonstrated with voxel-based-morphometry (VBM) an increase of grey matter density in the hippocampal head on the left side in musicians (Groussard et al. 2010). The left hippocampus was also shown to be implicated in subjective memory rather than in objective or contextual memory. This could be explained by the fact that musicians do less easily associate their musical memories to autobiographic events as their musical experiences are repetitive and thus not linked to a unique life-event (Spaniol et al. 2009 in Groussard 2010). Note that musical memory is composed of both objective (rhythm, melody, harmony etc.) and subjective (emotions, evoked images like when one sees a landscape when hearing a certain music, etc.) elements. The latter study also showed an activation of the visual primary cortex, bilateral orbito-medial frontal gyri, middle cingulated cortex and bilateral superior temporal areas, that are known to be engaged in a more contextual memory.

Our principal interest was to study the relationship between hippocampal volume and fluid intelligence. We would first like to briefly explain the concept of fluid intelligence, based on Blair's review about fluid cognition and general intelligence (2006). There is a growing belief that fluid intelligence is a total different entity than general intelligence. It comprises notably attention processes, working memory and executive functions and is also known as performance IQ. It is described as distinct from "crystallized intelligence", which rather refers

to cognitive processes involving previously learned material; in other words "fluid intelligence represent skills through which crystallized knowledge was acquired in the past and further knowledge would be acquired in the future" (Blair, 2006). Raven's progressive Matrices Test, which was used in the present study, is believed to be the most representative test to examine fluid cognition. There is growing evidence that fluid intelligence can be considerably influenced by environment and concern areas of the prefrontal cortex and the limbic system; hippocampus is also involved in cognitive functions requiring attention, information maintenance, spatio-temporal context and emotional aspects. The parallel with music, being complex as we previously evoked, thus appealing to a lot of cognitive processes, is here easily drawn.

Andreasen et al. (1993) found whole cerebral volume to be positively correlated with general intelligence (full-scale IQ, tested with Wechsler Adult Intelligence Scale--Revised). This correlation could be attributed in particular to prefrontal cortex size (Reiss et al. 1996, Langer et al. 2011), but also to temporal cortex (Flashmann et al. 1998). Full-scale, verbal and performance IQ scores are also correlated to increased size of sensorimotor and mid-temporal brain areas (Peterson et al. 2011). And the hippocampus may also be particularly implicated in fluid intelligence; Raz et al. (2008) for instance demonstrated lower levels of fluid intelligence significantly correlated with smaller prefrontal and hippocampal volumes.

As for the musical aspect, a behavioral study by Moreno et al. (2011) demonstrated an improvement in verbal intelligence tests after 20 days of musical training, and Schellenberg (2004) found that children taking music lessons reached higher full-scale IQ scores than controls after only 36 weeks of training.

Concerning the link between the hippocampus and fluid intelligence, the literature is by now rather contradictory. Amat et al. (2007) found a significant negative correlation between hippocampal volumes and full-scale IQ: higher IQ was associated with decrease of the anteromedial hippocampus bilaterally. They also revealed that the left hippocampus correlated more with verbal IQ and the right one with performance IQ (see also Toulopoulou et al. 2004). We should here notice that they didn't use Raven's Matrices to measure fluid intelligence, which is still considered as the gold standard, and that they looked at subregions, which cannot be compared with a segmentation of the whole volumes. On the other hand, Andreasen et al. (1993), followed by Schumann et al. (2007) demonstrated that there was a

positive relationship between brain size and IQ and that it principally concerned the bilateral hippocampi, which were significantly correlated with full scale and verbal IQ, but not with performance IQ; it should be mentionned that they also didn't use Raven's Matrices to measure fluid intelligence. Recently, in a more prospective way, Reuben et al. (2010) found a significant correlation between hippocampal atrophy and increasing age relative to the decrease of fluid intelligence, tested among others with the Matrix Reasoning Test of Raven. The conclusions to be drawn remain thus rather unclear concerning the increasing or decreasing of the hippocampal volume in correlation with fluid intelligence.

These contradictory results could be interpreted as caused by different imaging methods, different fluid intelligence tests, different population's characteristics, etc. However these reports lead us to hypothesize that a link may exist between hippocampus size and intelligence scores or even particularly fluid intelligence.

To our knowledge, this issue has not been examined within the context of musical experience, another candidate for hippocampal plasticity. Therefore we studied here the correlation between hippocampus volume and intelligence as a function of musical expertise. Our second aim was to verify a difference in hippocampus size on both sides of the brain as a function of musical expertise.

2. <u>Methods</u>

2.1. Participants

We recruited 20 expert pianists (E: mean age=24.5 (SD=4.5), 10f/10m, start of musical training at mean age=6.2 (SD=1.9), mean training duration (in years)=18 (SD=4.2)), 20 amateur pianists (A: mean age=22.2 (SD=3.1), 10f/10m, start of musical training at mean age=7.0 (SD=1.4), mean training duration (in years)=14.4 (SD=4)) and 20 non-musicians (N: mean age=24.3 (SD=4.4), 10f/10m) matched by gender and age (one-way ANOVA on age, $F_{2,56}$= 2.013, p=0.143). One non-musician was excluded from the analysis, since structural data acquisition was corrupted. All subjects were positively tested for right-handedness (*Edinburgh Inventory* (*1*)) and reported normal hearing. E and A samples did not significantly differ for the age of start of musical training. We defined inclusion criteria for N to have no

extracurricular musical education. The criterion for being part of group A was defined as being still musically active at the moment of participating this study, however, musical practice should have never exceeded 10 hours per week.

2.2. Test for fluid intelligence: Raven's Progressive Matrices

Participants were asked to perform a short version of the Raven's Test with a time limit at 15 minutes. Raven's progressive Matrices Test is believed to be the most representative test to examine fluid cognition.

"Developed by British psychologist J. C. Raven and first published in 1938, the progressive matrices (PM) tests measure the ability to deduce relationships within geometric patterns or among figural elements contained in a matrix. Items employ either a complete pattern from which a piece has been removed, or figural elements placed in discrete rows and columns, with one element missing. The missing element must be selected from six or eight answer choices presented. These tests reportedly assess the ability to impose meaning on confusion, to formulate nonverbal constructs to explain complex relationships, and to minimize the influences of verbal communication and past experience" (J. Raven, J. C. Raven, & Court 1998 in Robertson 2010).

2.3 Hippocampus segmentation

The decision to perform a manual segmentation rather than an automated one is justified by the fact that the manual method is still proven to be the gold standard for the most accurate volumetric measurement, although automated methods could bring less interrater variability (Tae et al. 2008). We thus tried to reduce this variability by defining precise and invariable borders for the segmentation. The determination of the borders of the hippocampus used here relies on several papers describing protocols for the most precise segmentation of this area (Watson et al. 1992, Insausti et al. 1998, McHugh et al. 2007, Pruessner et al. 2000 and 2002). The analyses were done by a single investigator, blinded for group belonging and ID of each subject, in order to avoid possible bias relative to our hypothesis.
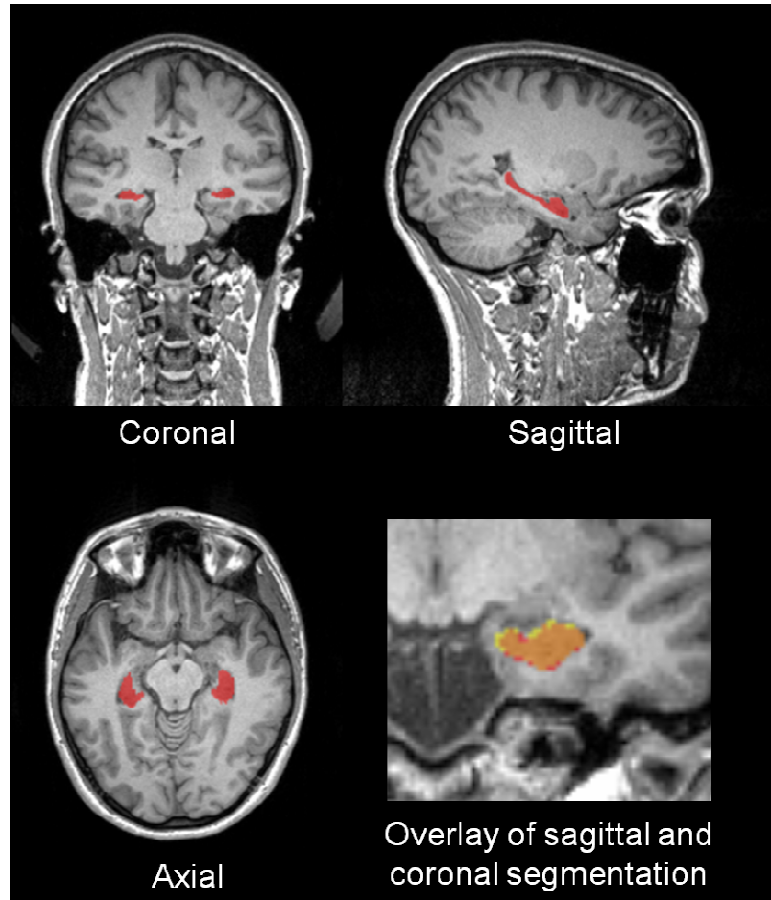
Figure 1

We used the software MRIcroN (free on http://www.cabiatl.com/mricro/mricron/install.html) that allows a 3D view (**figure 1**), important for a more accurate detection of the hippocampus boundaries. Frequent verifications were performed in the other plans while drawing the regions in each plan, to help clarify the boundaries, because evidence exists that "with 3D visualization, the irregularly shaped hippocampus can be reliably and precisely segmented" (Pruessner et al. 2000).

We performed the segmentation in both the coronal and the sagittal plans to improve the accuracy of the segmentation, with a satisfactory mean difference of 4% between the volume measurements in the two plans.

The segmentation of the hippocampal cortex that we adopted here included the hippocampus proper, the gyrus dentatus and the subiculum and was performed from a rostral to caudal direction with a track-ball mouse. Anteriorly, to make the difference between the hippocampus and the amygdale, we used the alveus, particularly well visible in the sagittal plan (Hasboun et al. 1996 in Tae et al. 2008), and the uncal recess of the inferior horn of the lateral ventricle (Watson et al. 1992, Pruessner et al. 2000). The hippocampal fissure (choroid fissure) was used to determine the border with the entorhinal cortex along the coronal slices (Insausti et al. 1998).

The lateral and medial borders where more easy to define, as bordered either by the cerebral spinal fluid in the lateral ventricle, or by white matter of the temporal cortex. Some studies used the crus of the fornix as the most posterior border of the hippocampus tail, but evidence exists that this approach left 5 to 10% of the hippocampal cortex aside (Watson et al. 1992). We thus chose to delineate the tail completely, helped by the sagittal plan that allows to see more clearly the hippocampus tail as surrounded by white matter (Duvernoy 1988 in McHugh et al.
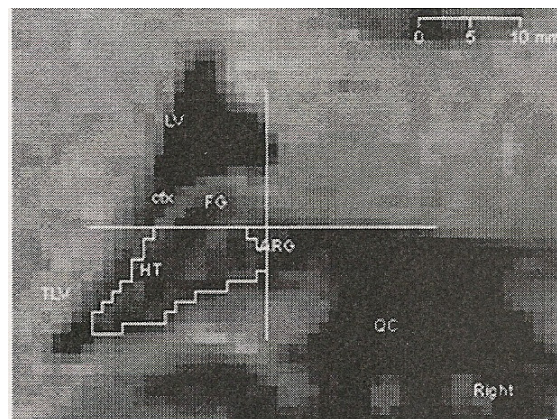

Figure 2   (Pruessner et al. 2000)
Arbitrary differenciation between fasciolar gyrus and hippocampus tail
ARG: andreas retzius gyrus, cfx: crus of the fornix, FG: fasciolar gyrus, HT: hippocampus tail, LV: lateral ventricle, QC: quadrigeminal cistern, TLV: trigone of lateral ventricle

2007), that means inferomedially to the trigone of the lateral ventricle (Pruessner et al. 2000). We followed the guidelines described in the paper of Pruessner et al. (2000) **(figure 2)** to discriminate the hippocampus tail from fasciolar gyrus: we drew a vertical line from the medial end of the trigone of the lateral ventricle down to the parahippocampal gyrus and a horizontal line along the superior border of the quadrigeminal cistern of the lateral ventricle. We then correlated the hippocampal volume measurements, that we first averaged per group of expertise level and for all participants, with the results of the Raven's progressice Matrices tests.

3. <u>Results</u>

Group	Performance Raven's Test	Left Hippocampus	Right Hippocampus
N (n=19)	18.263 ± 5.674	2972 ± 246	2972 ± 395
A (n=20)	20.650 ± 5.274	3045 ± 319	2985 ± 351
E (n=20)	19.400 ± 3.235	2954 ± 340	2865 ± 398

Table 1: Group values (mean ± SD) for performance in Raven's Test and Number of voxels in left and right hippocampus.

An overall analysis (n=59) resulted in a general effect showing that hippocampus size of left and right hemispheres are highly correlated (r=0.834, p<0.0001).

A one way ANOVA with three levels of expertise revealed no main effect of *Expertise* for Raven's Test performance ($F_{2,58}$=1.191, p=0.311).

A 2-way ANOVA (*Expertise* x *Hemisphere*) for repeated measures revealed no expertise dependent lateralization of hippocampus volumes (interaction *Expertise* x *Hemisphere*: $F_{2,56}$= 0.908, p=0.409). Main effects *Expertise* and *Hemisphere* did not reach level of significance (Expertise, $F_{2,56}$=0.518, p=0.599; Hemisphere, $F_{1,56}$=3.287, p=0.075). See Table 2 for detailed group values (mean Performance Raven's Test and left/right hippocampus size).

For further analyses A and E were pooled together into a musicians group (M, n=39), since correlations between Raven performance and hippocampus size did not significantly differ between these groups – neither for the left (LH) nor right (RH) hemisphere. Fisher's r to z transformations revealed that correlations between Raven's test performance and hippocampus size do not differ between the two groups of musicians (A vs E), neither in LH nor RH. Correlations: Raven vs. LH: A (r=0.700, p=0.005), E (r=0.521, p=0.019); Raven vs. RH: A (r=0.590, p=0.006), E (r=0.479, p=0.033); Fisher's r to z transformation: LH: z=0.158, p=0.437; RH: z=-0.295, p=0.382.

We performed robust multiple regression models for each hemisphere (scatter plots and fitted regression in Figure 1): (i) to predict Raven performance by hippocampus volume and (ii) to test whether this prediction is modulated by the factor of musical training. Robust regression analysis (implemented by statistical software R) represents a valid alternative to least square regression analysis when results are potentially contaminated by single influential observations: LH: significant interaction (t=2.221, p=0.030), showed that prediction of Raven's performance by hippocampus size is modulated by musical training, N (beta =0.03)

and M (beta =0.46); RH: Significant interaction (t=2.003, p=0.050), demonstrated that prediction of Raven's performance by hippocampus size is modulated by musical training, N (beta =0.01) and M (beta =0.38).
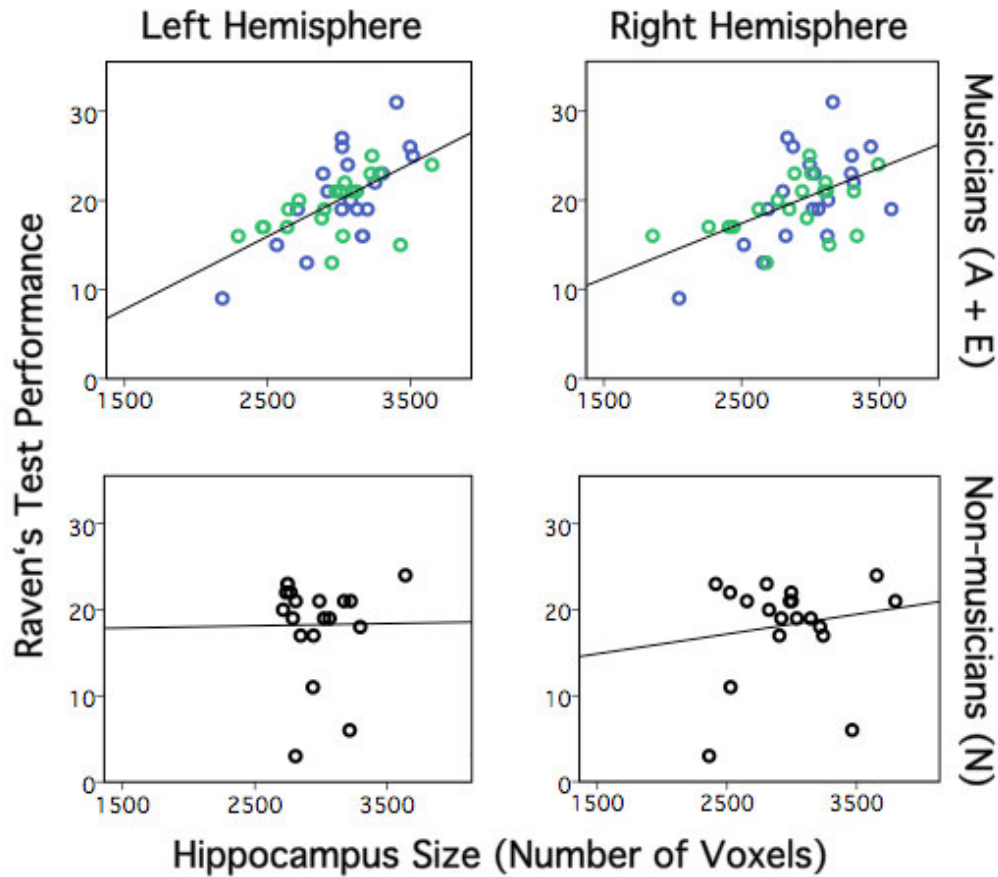

Figure 3: This figure displays the relationship between hippocampus size and fluid intelligence (Raven's Matrix Reasoning Test, Set 2). Robust multiple regression analyses revealed that hippocampus size in both hemispheres predict test performance in musicians (upper row, A=blue, E=green) but not in non-musicians (lower row, N=black).
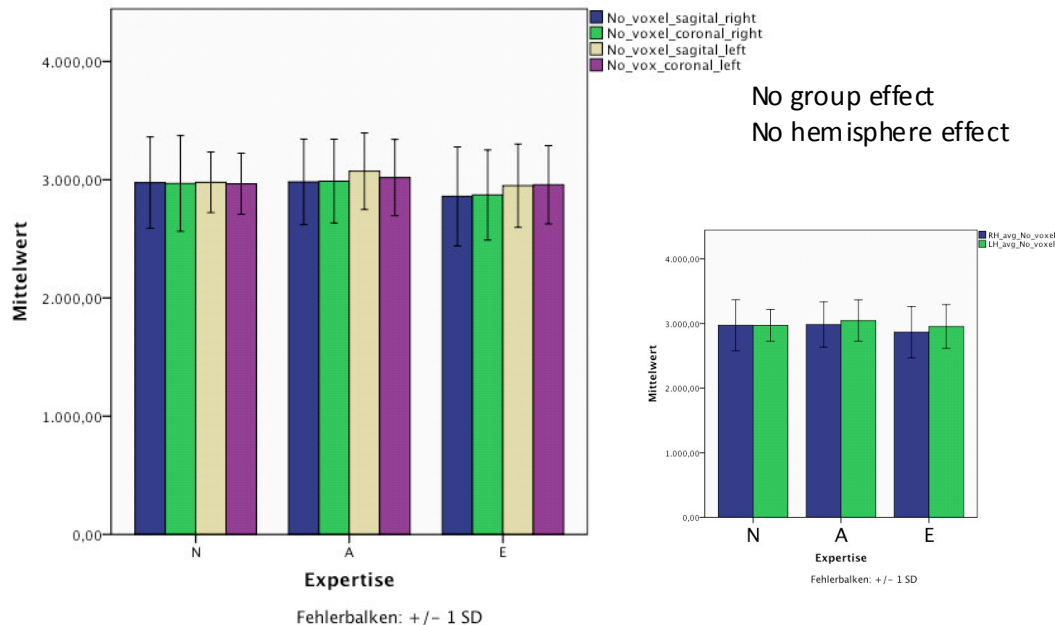
Hippocampus Volumina

Figure 3 No significant difference of the hippocampus size between non-musicians, amateur and professional musicians.

4. Discussion

We already detailed the concept of fluid intelligence in the introduction, comprising attention processes, working memory and executive functions. Several studies have demonstrated existence of a significant correlation between IQ and general or localized brain volume, like Haier et al. (2004) who found a link between a large amount of Brodmann areas, including some situated in the temporal lobe (namely BA 21: middle temporal, BA 37: occipito-temporal, BA 22: superior temporal, BA 42: primary auditory cortex), and general IQ scores, or Reiss et al. (1996) who found a positive correlation between total cerebral volume and full-scale IQ. Flashman et al. (1998) established a relationship of full-scale IQ with frontal and temporal brain regions, which could comfort the hypothesis that the hippocampus among others may be linked in some way with intelligence measures.

As for fluid intelligence specifically, its putative sources in the brain are for now quite unclear. Gong et al. (2004) found more gray matter in the medial prefrontal cortex in subjects with better performances on measures of fluid intelligence. On the other hand, there is evidence that general intelligence is rather associated with frontal regions (Haier et al. 2004, Gray et al. 2003, Reiss et al. 1996) and that performance subtests, like Picture Completion, Picture Arrangement and Block Design may rather be linked with the temporal lobe. The discrepancy between these study results can be partially explained by the use of different tests to estimate fluid intelligence; a greater consistency would allow better comparison. Gogtay et al. (2006) found no significant correlation between full-scale (=general) IQ and hippocampal volume. However Raz et al. (2007) then demonstrated that lower fluid intelligence is correlated with smaller hippocampal and prefrontal volumes, speaking for an implication of the hippocampus rather regarding fluid intelligence than general intelligence. As for the functional aspect, fluid intelligence specifically tested with Raven's Progressive Matrices test, that we also used, significantly correlated with cerebral activity in the lateral prefrontal cortex, dorsal anterior cingulated, lateral cerebellum, parietal but also temporal cortex (Gray et al. 2003). Blair, in his review about fluid intelligence (2006), mentioned that a link between fluid cognitive deficits and early hippocampal pathology has already been demonstrated (Lipska and Weinberger 2000 and Lipska et al. 2002 in Blair 2006). Our results are consistent with the latter, speaking for a direct implication of the hippocampus in fluid intelligence, with a positive correlation between hippocampal volume and the results of Raven's Progressive Matrices test for all participants (groups collapsed), as a measure of performance IQ.

There is evidence that an enriched environment can specifically lead to an increase in hippocampus size in rats, more precisely to an increase of the number of progenitor cells in their dentate gyrus, and this could be associated to better results on spatial learning tasks (Nilsson et al. 1999). The same was demonstrated in mice, showing the same pattern of changes (Kempermann et al. 1997). Knowing that the enriched environment included diverse toys to play with, regularly renewed and thus allowing to discover and practice diverse activities, one can imagine playing a music instrument can be described in the same way, and may lead to similar changes in brain structure. The novelty brought by the present study is a link between Raven's test and the hippocampal size, exclusively in musicians, showing that larger hippocampus positively correlates, only in musicians, with results in fluid intelligence tests. We would like to emphasize the fact that we specifically chose pianists in our musician

populations because playing the piano particularly requires complex problem solving in the motor and in the cognitive domain compared to other instruments. Playing the piano and reading piano scores is highly complex, as it appeals to very elaborated harmonic and rhythmic rules, with its playing with both hands several notes or chords at the same time , its parallel use of distinct melodic lines and of chords that have to pass together, its rhythm that can also be different for each hand, etc. The choice of pianists may thus have helped us to find an association between musical expertise and intelligence.

We saw previously that the hippocampus is functionally and structurally related to diverse intelligence performances (Flashman et al. 1998, Gogtay et al. 2006, Raz et al. 2007, Gray et al. 2003, Nilsson et al. 1999, Kempermann et al. 1997). And we also quoted some studies that demonstrated a role of musical training in developing certain aspects of intelligence (Moreno et al. 2011, Schellenberg et al. 2004, Jausovec et al. 2006, Rauscher et al. 1994). Putting it together, while knowing that musicians also showed functional and structural plasticity, particularly in the hippocampus (Groussard et al. 2010, Herdener et al. 2010), leads us to conclude that it is likely that hippocampus size could be related to musical abilities regarding intelligence performances, evocating a possible direct link between musical experience and some forms of intelligence. Our interpretation is that musicians may, through intense and early musical practice, prepare their brain through cerebral plasticity for significative volume increasing, whereas their intelligence develops, revealing that the musician's brain may have the potential of a singular brain plasticity.

As for our second question, there is some evidence that the hippocampus grows little after having achieved its maximum size at the age of 2 to 3 years (Giedd et al. 1996, Giedd, Jeffries et al. 1999, Klekamp, Riedel, Harper and Kretschmann 1991, Kretschmann, Krammradt, Krauthausen and Wingert 1986, Pfluger et al. 1999, Utsunomiya, Takano, Okazaki and Mistudome 1999, Yurgelun-Todd, Killgore and Cintron 2003 in Van Petten 2004, Gogtay et al. 2006). But several studies demonstrated significant differences in hippocampus size linked to different environmental conditions (Maguire et al. 2000, Gogtay et al. 2006) and to different cognitive status, as for example in patients suffering from Alzheimer's disease or Mild Cognitive Impairment, who exhibit smaller hippocampal volumes than matched control groups (Chetelat and Baron 2003, Kantarci et al. 2002, Wolf et al. 2003 in Van Petten 2004). Our finding of no significative difference in hippocampus size between non-musicians, amateur and professional musicians may reflect the fact that musical training doesn't

influence the global hippocampus size strongly enough for a difference to be detectable, but we would like to keep in mind that our results could have been influenced by the relative small number of subjects included and also by the fact that we chose to measure only the total volume of the hippocampus, and not subregions that might have shown finer differences.

As for the small, unsignificative difference that could be seen between the hippocampus size on both sides in expert, the right hippocampus being smaller than the left (see figure 3 page …), we searched for a possible explanation in the literature. It is indeed known that musicians have more grey matter density in the head of their left hippocampus (Spaniol et al. 2009 in Groussard et al. 2010) but their right hippocampus seems to be more strongly actiavated during retrieval success in musical memory tasks. There is thus no clear explanation for this slight but questioning difference, that could possibly be investigated in further studies.

5. <u>Conclusion</u>

Our finding that the hippocampus is significantly larger on both sides of the brain exclusively in musicians with higher fluid intelligence scores suggests that its size may be positively influenced by musical training and that its function might play a role in certain aspects of fluid intelligence. That musical experience may enhance fluid intelligence seems plausible, but this assumption demands further investigation to better understand the possible link that we raised up in these pages. We suggest that the latter hypothesis should be examined in further studies, maybe in a more mature population, in order to examine subjects with longer exposition to musical training and performance. Although there are some discrepancies in studies concerning hippocampus growth throughout life, based on the increasing knowledge of brain and specifically hippocampus plasticity we believe that its size can be significantly influenced by experience, intensive musical training over time being a perfect way to examine this. This field of research could eventually lead to better understanding of the concept of intelligence and the precise influence environment and experience exercise on it. We revealed here one more of the many ways musical activities can positively act upon our brains.

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