Neuroscience 275 (2014) 81–88

LOW-GRADE INFLAMMATION DISRUPTS STRUCTURAL PLASTICITY IN THE HUMAN BRAIN

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Abstract—Increased low-grade inflammation is thought to be associated with several neuropsychiatric disorders characterized by decreased neuronal plasticity. The purpose of the present study was to investigate the relationship between structural changes in the human brain during cognitive training and the intensity of low-grade peripheral inflammation in healthy individuals (n = 56). A two-month training (30 min/day) with a platformer video game resulted in a significantly increased volume of the right hippocampal formation. The number of stressful life events experienced during the past year was associated with less pronounced enlargement of the hippocampus. However, the main predictor of hippocampal volume expansion was the relative peripheral expression of Nuclear Factor-κB (NF-κB), a transcription factor playing a central role in the effect of pro-inflammatory cytokines. Interleukin-6 (IL-6) and C-reactive protein levels were not related to hippocampal plasticity when NF-κB was taken into consideration. These results suggest that more intensive peripheral inflammation is associated with weaker neuronal plasticity during cognitive training.

Key words: inflammation, hippocampus, neuronal plasticity, cognitive training.

INTRODUCTION

Perhaps the pathophysiology of inflammation received the most intense attention during the past decades as a key factor in the genesis of degenerative, developmental, and stress-related disorders of the brain. The final common pathway disrupted by inflammation may be neuroplasticity subserving learning, memory, and cognitive/behavioral flexibility, which are severely impaired in numerous neurological and psychiatric disorder (e.g., Alzheimer's and Parkinson's disease, schizophrenia, and mood disorders) (Perry et al., 2007; Miller et al., 2009a,b; Schwartz and Shechter, 2010; Maes, 2011; Altamura et al., 2013; Nola et al., 2013).

However, neuroinflammation is not necessarily a pathological process and plays a remarkable role in the normal homeostasis of the brain. It has been postulated that psychological influences modulate immune mechanisms in the brain and peripheral blood, such as the production of inflammatory cytokines (interleukin [IL]-1, IL-6, Tumor Necrosis Factor-α [TNF-α]) and other mediators (e.g., arachidonic-acid derivates and various neurotrophins). The moderate and balanced production of these factors is vital in the promotion of neuronal plasticity, including hippocampal long-term potentiation and the formation of new cells and synapses, whereas their dysregulated overproduction may cause neurotoxicity and altered development (Yirmiya and Goshen, 2011; Schwartz et al., 2013; Xanthos and Sandkühler, 2014).

While experimental data from basic sciences provided multifaceted evidence, it has not been studied how low-grade inflammation affects human structural brain plasticity in real-life circumstances. It has been shown that acute peripheral inflammation impairs spatial memory by reducing glucose metabolism in the medial temporal lobe (Harrison et al., 2014), but the long-term structural consequences are less clear (Frodl and Amico, 2014).

What kind of evidence is available regarding training-related structural plasticity in the human brain? The first longitudinal study by Draganski et al. (2004) found that 3 months of juggling training was associated with increased gray matter volume in the mid-temporal area and intraparietal sulcus responsible for motion and spatial perception. Cross-sectional studies demonstrated that an extensive practice with commercially available video games induced gray matter expansion in various brain areas, including the hippocampal formation (Kühn et al., 2011; Kühn and Gallinat, 2013). Recently, researchers confirmed and extended these findings in a longitudinal study. Individuals who played a platformer game (Super Mario) for 2 months for at least 30 min/day displayed gray

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Abbreviations: ANOVA, analysis of variance; CRP, C-reactive protein; ICC, intraclass correlation coefficient; IL-6, interleukin-6; I-κB, inhibitors of κB; NF-κB, Nuclear Factor-κB; ROI, region-of-interest; SD, standard deviation.

http://dx.doi.org/10.1016/j.neuroscience.2014.06.002

matter increase in the right hippocampal formation and dorsolateral prefrontal cortex (Kühn et al., 2014). Moreover, increased hippocampal volume had a functional significance characterized by a shift from egocentric to allocentric spatial navigation strategy (Kühn et al., 2014; for a review of structural plasticity in other conditions, see Lövdén et al., 2013).

The present study examined how different levels of low-grade systemic inflammation might affect structural brain plasticity in healthy individuals during cognitive training. To achieve this aim, we sought a possible relationship between hippocampal volume changes during video game training and pro-inflammatory markers.

We focused on three pro-inflammatory molecules (Murphy et al., 2013). One of the most frequently investigated marker is Nuclear Factor-κB (NF-κB), which is a transcription factor activated by various inflammatory stimuli, representing a ''hub'' in the pro-inflammatory intracellular network. Inactive NF-κB is sequestered in the cytoplasm by inhibitors of κB (I-κB) (Webster et al., 2002; Ghosh and Hayden, 2008). The stress hormone cortisol and catecholamines released from the sympathetic nervous system and adrenal gland have an impact on the expression of NF-κB and I-κB, and a higher NF-κB/I-κB ratio reflects more intense pro-inflammatory processes (Webster et al., 2002; Irwin and Cole, 2011).

The other two markers of systemic low-grade inflammation were IL-6 and C-reactive protein (CRP). IL-6 is a ubiquitous cytokine for systemic and neuronal inflammation produced by immune cells, muscle cells, and adipocytes; not surprisingly, IL-6 is supposed to be linked to several common diseases in which inflammation is implicated (neuropsychiatric disorders, cardiovascular diseases, autoimmune diseases, obesity, and cancer) (Rose-John, 2012; Ataie-Kachoie et al., 2013). CRP is an acute phase protein produced by liver cells in parallel with IL-6 (Bastard et al., 1999). This protein is an important marker of general systemic and neuroinflammation (Frodl and Amico, 2014; Lopresti et al., 2014), known for many decades (Powell, 1979).

The hypotheses of the present study were as follows: (1) Based on the results of Kühn et al. (2014), we expected increased hippocampal volume following video game training. To test the specificity of hippocampal changes, we also measured the volume of the caudate nucleus in which structural changes might reflect general improvements in motor skills. (2) We predicted a significant relationship between low-grade inflammation and structural brain changes. Specifically, we hypothesized that individuals with a higher level of low-grade inflammation would exhibit smaller volume expansion in the hippocampus (Frodl and Amico, 2014).

EXPERIMENTAL PROCEDURES

Participants

Fifty six healthy volunteers were recruited at the National institute of Psychiatry and Addictions, Budapest, via emails, social networks, and personal acquaintances. The subjects did not report any history of psychiatric and neurological disorders, and they did not suffer from known illnesses associated with inflammation. All participants received the following interviews and scales: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (First et al., 1996) to exclude mental disorders; Hollingshead Four Factor Index (Hollingshead, 1975) to describe the socioeconomic status; Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) to evaluate general cognitive functions; Brief Life Event Questionnaire (Brugha and Cragg, 1990) to assess stressful life events. Other factors influencing low-grade inflammation (smoking, alcohol consumption, use of oral contraceptives, visceral obesity) were also evaluated (Table 1). We asked the participants not to change their diet, sleep, and smoking/drinking habits during the experiment. All volunteers documented these habits, possible occurrences of major life events, and changes in mood and general health in a written daily diary. After a complete description of the study, all participants gave written informed consent. The study was approved by the institutional ethics board and was done in accordance with the Declaration of Helsinki.

Video game training

We followed the procedure of Kühn et al. (2014). Participants, who did not have extensive experience with video games, played with Super Mario 64 on a portable Nintendo Dual Screen (DS) XXL console for 30 min/day over a period of 2 months. In this platformer game, players move in the virtual environment and collect stars while exploring, solving puzzles, and defeating enemies. The environment is shown from two perspectives: on the top of the screen, players see a third-person perspective, and on the bottom of the screen the map is displayed from a bird's eyes view. At the end of the training procedure, participants received 5000 Hungarian Forints (15–20 Euros). Additionally, they rated on a seven-point scale how much fun, frustration, and desire to play they experienced during training. The stars collected were obtained from the video gaming console (Kühn et al., 2014).

Table 1. Demographic characteristics and markers of low-grade peripheral inflammation

Age (years)	36.8 (10.3)
Gender (male/female)	30/26
Education (years)	13.7 (4.1)
IQ	109.5 (10.2)
Socioeconomic status	39.2 (8.2)
Stressful life events (past 1 year)	2.1 (1.9)
Smoking (cigarettes/week)	3.5 (8.4)
Alcohol use (number of drinks/week)	2.9 (7.7)
Waist-to-hip ratio	0.78 (0.07)
Number of individuals using oral contraceptives	12
CRP (mg/L)	0.94 (0.81)
IL-6 (pg/mL)	0.64 (0.80)
NF-κβ	7.8 (2.2)
I-κβ	6.3 (1.2)
NF-κβ/I-κβ	1.2 (0.2)

Data are mean (standard deviation) with the exception of gender ratio and the number of individuals using oral contraceptives. NF-κβ and I-κβ are relative expression values of RNAs normalized to β-actin.

Structural brain imaging

We used the FreeSurfer protocol as described in the manual and previous studies (Martinos Center for Biomedical Imaging, Boston, MA, USA; http://surfer.nmr.mgh.harvard.edu; version: v5.1.0, Dell XPS workstation, Linux system) (Desikan et al., 2006; Fischl et al., 2002, 2004). A multiecho FLASH sequence with 1-mm^3 isotropic resolution was applied (Siemens Trio 3T scanner; 256 × 256 matrix, 176 sagittal slices with a thickness of 1 mm, TR 2530 ms, TI 1100 ms, TE 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz, non-selective excitation at 7°). We measured the volume of the hippocampi and the caudate nucleus. FreeSurfer regions-of-interest (ROIs) were visually inspected before the analysis, but no manual correction was necessary. In a pilot study, two independent experts performed the manual parcellation of the hippocampal region and the caudate nucleus in 20 healthy control subjects. The intraclass correlation coefficients (ICCs) for FreeSurfer and manual parcellation methods were high (ICCs > 0.8). Hippocampal and caudate volumes were normalized to total intracranial volume (ICV), which was also measured with FreeSurfer (Whitwell et al., 2001).

Characterization of low-grade inflammation

We used the procedure of Murphy et al. (2013) as a standard protocol to characterize the level of low-grade inflammation in healthy individuals for social and neurosciences. In the quantitative real-time polymerase chain reaction (qPCR) procedure, the methodological recommendations of Baine et al. (2013) were taken into consideration. We isolated peripheral blood mononuclear cells from fresh blood samples using Ficoll-Hypaque density-gradient centrifugation. We used the QIAshredder cell lysis kit and the Qiagen RNeasy RNA extraction kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The Superscript III Reverse Transcriptase system (Invitrogen, Carlsbad, CA, USA) was used for the reverse transcription of RNA. The AB 7500 Fast System and the QuantiTect SYBR Green PCR kit (Applied Biosystems, Foster City, CA, USA) were applied for the complete analysis. NF-κβ and I-κβ RNAs were measured as described by Rohleder et al. (2009) and Murphy et al. (2013). Data were normalized to β-actin.

CRP was measured using high-sensitivity chemiluminescence (IMMULITE 2000, detection threshold: 0.20 mg/L; interassay coefficient of variation: 2.2%) (Diagnostic Products Corporation, Los Angeles, CA, USA). IL-6 was measured using high-sensitivity enzyme-linked immunosorbent assay kits (HS600B; R&D Systems, Minneapolis, MN, USA; detection threshold: 0.039 pg/mL and interassay variability: < 10%).

Each parameter of low-grade inflammation (NF-κβ and I-κβ RNA, CRP, IL-6) was measured twice from two different blood samples. The first measurement was performed at the beginning of the training period, whereas the second measurement was performed 2 months later. All measures showed less than 10% changes across the two measurements. We also determined the composition of the circulating leukocyte pool and found no relevant changes (< 10%). In the statistical analysis, we included the data from the first measurement.

Data analysis

The STATISTICA 11 software (StatSoft, Inc., Tulsa, USA) was used for data analysis. A repeated measures analysis of variance (ANOVA) was used to examine potential changes in brain structures during training. Multiple regression analysis was used to determine the predictors of volume changes. Partial correlation analysis was applied to follow-up the results from the regression analyses. The level of statistical significance was $\alpha < 0.05$.

RESULTS

Changes in brain volumes

The brain volumes are depicted in Table 2 and Fig. 1. An ANOVA conducted on the corrected hippocampal volumes indicated a significant interaction between sessions (before and after video game training) and laterality (right vs. left hippocampus) (F (1,110) = 80.93, $p < 0.001$, partial $\eta^2 = 0.42$, power: 1.0). Planned comparisons with F-tests indicated a significant volume expansion in the right hippocampus (F (1,110) = 4.60, $p < 0.05$, partial $\eta^2 = 0.04$, power: 0.57), but not in the left hippocampus ($p > 0.5$) (Fig. 1). A separate ANOVA indicated no significant changes in the volume of the caudate nucleus ($p > 0.5$) (Table 2).

Predictors of hippocampal volume changes

The dependent variable was the volume change of the right hippocampus (after training minus before training), which was significant in the previous analysis. In the first forward stepwise linear regression analysis, we included demographic parameters (age, gender, education, IQ, socioeconomic status, number of stressful life events, smoking, alcohol use, oral contraceptives, waist-to-hip ratio) (Table 1), but not the inflammatory markers, as potential predictors of volume changes. There was a single significant negative predictor: the number of stressful life events ($b^* = –0.31$, t (54) = –2.46, $p < 0.05$, $R^2 = 0.08$).

In the second forward stepwise linear regression analysis, inflammatory markers were added to the model. Results revealed a two-factor solution, with NF-κβ as a significant predictor ($b^* = –0.51$, t (53) = –4.33,

Table 2. Absolute volumes (mm^3) of the hippocampal formation and caudate nucleus before and after training on *Super Mario 64*

	Before training	After training
Left hippocampus	4114.4 (510.6)	4108.4 (509.4)
Right hippocampus*	4203.4 (507.1)	4468.2 (445.7)
Caudate nucleus	6754.6 (329.8)	6749.8 (350.0)

Data are mean (standard deviation). Absolute volumes were corrected by dividing with the intracranial volume (ICV) (mean: 1.6×10^6 mm^3, SD = 0.2).

* F-tests, $p < 0.05$.

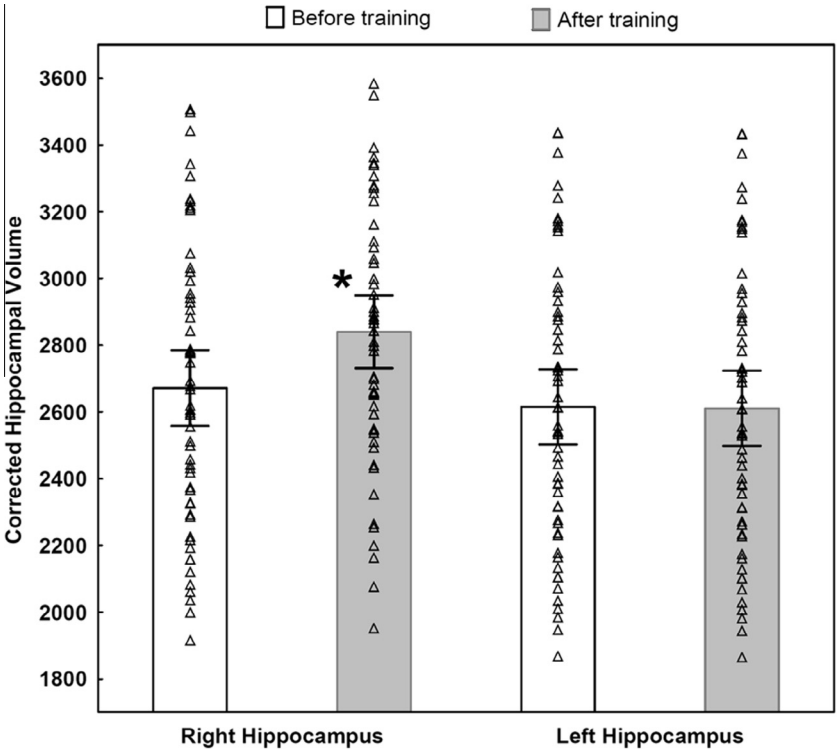

Fig. 1. Corrected mean hippocampal volumes (mm^3) and raw data before and after video game training. Error bars indicate 95% confidence intervals. $^*p < 0.05$ (after > before, right hippocampus).

$p < 0.001$, R^2-change = 0.35). CRP also appeared in the final solution of the regression model (R^2-change = 0.03, $p = 0.1$).

To follow-up and confirm the results from the regression analyses, we conducted partial correlations including changes in right hippocampal volume, number of stressful life events, and NF-κβ. There were significant negative correlations between changes in right hippocampal volume and NF-κβ ($r = –0.59$, $p < 0.01$) and between changes in right hippocampal volume and stressful life events ($r = –0.32$, $p < 0.05$) (Fig. 2). However, when the relationship between hippocampal change and stressful life events was corrected for NF-κβ, the correlation did not reach the level of statistical significance (r [corrected] = –0.19, n.s.).

It is important to note that the correlation plot between hippocampal volume change and stressful life events suggested that the few individuals with the highest number of stressful life events had very small changes. When these individuals (number of stressful life events > 5) were excluded from the analysis, the same trend for negative correlation was seen, but it did not reach the level of significance ($r = –0.26$, $p = 0.06$).

Behavioral measures

Participants obtained an average of 82.6 stars (standard deviation (SD) = 25.4) on the video game. Rating scales (scores: 1–7) showed the following values: desire to play: 4.3 (SD = 3.7); frustration: 1.3 (SD = 0.9); fun: 5.2 (SD = 2.6). These behavioral measures did not correlate with changes in right hippocampal volume ($–0.1 < r < 0.1$, $p > 0.1$) with the exception of desire to play ($r = 0.39$, $p < 0.05$). When this score was included in the regression models described above, the results did not change.

DISCUSSION

The results of the present study confirmed our hypotheses. As expected, video game training was associated with a selectively increased right hippocampal volume, which is consistent with the results of Kühn et al. (2014). The importance of this replication is that we were able to show this effect by using a different methodology (ROI-based FreeSurfer versus voxel-based morphometry). We did not find changes in the caudate volume. Kühn et al. (2011) reported increased striatal volume in frequent video game players, but it was not revealed in a later longitudinal study (Kühn et al., 2014). Moreover, we included the dorsal striatum, whereas the positive finding of Kühn et al. (2011) was confined to more ventral regions.

Kühn et al. (2014) demonstrated a significant positive relationship between desire to play the game and changes in right hippocampal gray matter probability. We replicated this finding and excluded the possibility that stressful life events were associated with decreased desire to play in our participants. Similarly, written diaries did not indicate changes in lifestyle, major life events, and general health that might have confounded the results.

The novel finding of the study was that low-grade systemic inflammation predicted the extent of the

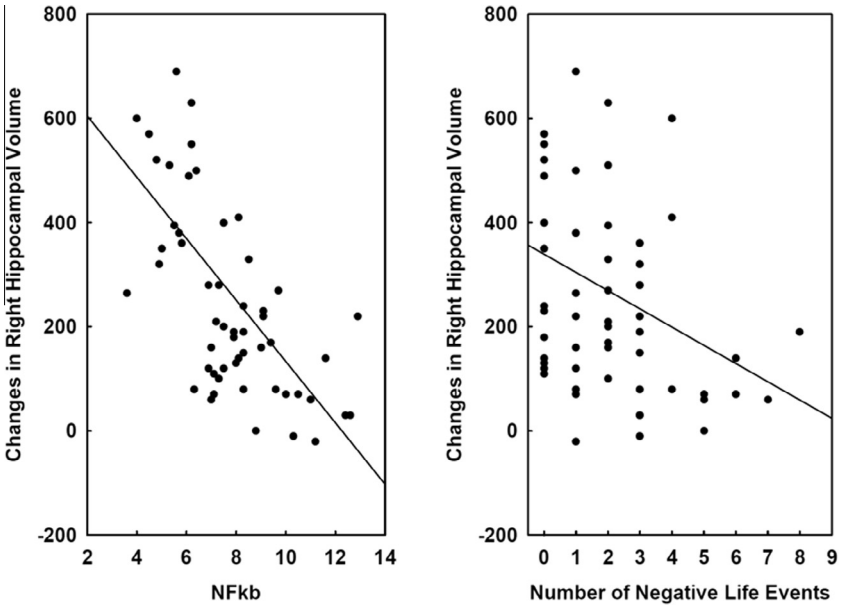

Fig. 2. Correlations between changes in the right hippocampal volume (mm^3, after training minus before training), the relative expression of NF-κB ($r = –0.59$, $p < 0.01$), and the number of stressful life events ($r = –0.32$, $p < 0.05$). Partial correlation analyses revealed that the correlation with stressful life events did not retain significance when it was corrected for NF-κB ($r = –0.19$).

training-related right hippocampal enlargement. Specifically, NF-κβ was a robust predictor accounting for more than 30% of the variance in the hippocampal enlargement. Studies using various methodological approaches suggest that our key finding regarding NF-κβ is not a false-positive result. This transcription factor is an important convergence point for several signal transduction pathways that are essential in inflammation (Koo et al., 2010; Hoesel and Schmid, 2013). From a neuroanatomical point of view, it is especially critical in the homeostatic regulation of neurons in the hippocampal formation, which is sensitive for systemic inflammation (e.g., Marsland et al., 2008; Satizabal et al., 2012; Liu et al., 2012; Järlestedt et al., 2013). Koo et al. (2010) demonstrated that stress activated NF-κβ signaling and decreased cell division in the hippocampus, which was blocked by an inhibitor of NF-κβ. Moreover, NF-κβ mediated the relationship between depressive behavior and chronic stress (Koo et al., 2010). Mice exposed to constant darkness, a robust environmental stress, also displayed depressive behavior and enhanced NF-κβ acidity in the hippocampus (Monje et al., 2011). NF-κβ plays an important role in hippocampal neurogenesis, neuronal growth, and learning and memory (Crampton and O'Keeffe, 2013), which might be affected in stress and depression (Danzer, 2012). These results may explain why the negative relationship between hippocampal enlargement and stressful life events disappeared when NF-κβ was included in the regression model (note that the negative correlation between hippocampal volume change and stressful life events was driven by a few cases with the highest number of stressful events).

Human studies also support the role of NF-κβ in stress response and neuronal plasticity. There are several psychosocial stressors that activate pro-inflammatory cytokines and NF-κβ at the intracellular level. These factors include social rejection (Dickerson et al., 2009; Slavich et al., 2010; Murphy et al., 2013), childhood abuse (Pace et al., 2012), interpersonal conflict with spouses and friends (Kiecolt-Glaser et al., 2005; Fuligni et al., 2009; Miller et al., 2009a,b), providing care for individuals with severe illness (Rohleder et al., 2009), low socioeconomic status (Jousilahti et al., 2003; Owen et al., 2003; Nazmi and Victora, 2007), and social isolation and loneliness (Cacioppo et al., 2003; Steptoe et al., 2004; Eisenberger et al., 2010; Hackett et al., 2012) (for reviews, see Hänsel et al., 2010; Chen and Miller, 2013). It has been demonstrated that stressful life events have a negative impact on human brain structure even without clinically relevant psychopathology (Cohen et al., 2006; Gianaros et al., 2007; Ganzel et al., 2008; Papagni et al., 2011).

Bierhaus et al. (2003) showed that NF-κβ is important in the responsiveness of mononuclear blood cells to psychosocial stress. The authors demonstrated that NF-κβ rapidly increased during stress exposure together with plasma levels of catecholamines and cortisol (Bierhaus et al., 2003). Powell et al. (2013) demonstrated that sympathetic nervous system-induced up-regulation of myelopoiesis during chronic psychosocial stress was associated with the pro-inflammatory component of the leukocyte transcription response, including NF-κβ.

There is accumulating evidence that low-grade systemic inflammation is influenced by a multitude of environmental factors in addition to stressful life events. These factors include abdominal obesity, smoking, alcohol consumption, oral contraceptives, diet, exercise, sleep, factors influencing gut permeability, atopic disorders, periodontal diseases, and vitamin D intake (Imhof et al., 2001; Pirkola et al., 2010; Berk et al., 2013; Murphy et al., 2013). In aged rats, Barrientos et al. (2011) found that physical exercise reversed inflammation-induced impairments in hippocampus-dependent long-term memory, normalized Brain-Derived Neurotro-

phic Factor (BDNF) expression in the hippocampus, and prevented age-related microglial sensitization.

Of course, these factors display complex interactions and covariances; when controlled in our analysis, only NF-κβ remained a significant predictor of decreased hippocampal plasticity. Similarly, pro-inflammatory factors (IL-6, CRP, and NF-κβ) also co-vary with each other. One may suggest that NF-κβ mediated the relationship between stress and decreased hippocampal plasticity. However, in light of complex covariances among psychosocial and physiological factors with dubious functional and causal relevance (Chen and Miller, 2013), this assumption may be an over-simplification. This complexity is illustrated by the study of Frodl et al. (2012) who showed that in patients with major depressive disorder childhood maltreatment was associated with increased CRP. Patients also displayed high levels of IL-6 and less expression of glucocorticoid-inducible genes. The regression analysis conducted by Frodl et al. (2012) indicated a significant positive effect of glucocorticoid-inducible gene expression and an inverse effect of IL-6 level on hippocampal volumes. Therefore, taking into account the complex and less-defined relationships of these factors, we did not conduct a formal mediation or moderator analysis including stressful life events and NF-κβ.

Another limitation of the present study was that we did not assess changes in the volume of the dorsolateral prefrontal cortex, despite the fact that Kühn et al. (2014) showed significantly increased gray matter volume in this cortical area. We omitted this cortical region because we were not able to gain acceptable test–retest reliability using the FreeSurfer ROI-based approach in groups of healthy individuals without any intervention, whereas in the case of hippocampus, repeated measurements provided highly reproducible results (Levy-Gigi et al., 2013; Molnár and Kéri, 2014).

It must also be mentioned that the magnitude of hippocampal volume expansion was small, which casts doubts on the biological reliability of the findings. However, we found a significant interaction between training and laterality (left vs. right hippocampus), with the expected volume expansion in the case of the right but not left hippocampus. A change of raw 264.8 mm^3 (6.3%) is not unreliably small if we consider the findings of the literature. For example, Draganski et al. (2004) found 3–4% of gray matter expansion in the sensory cortex after an extensive visuomotor training.

We did not correct our analyses for multiple comparisons, because we used a hypothesis-driven approach when corrections are not needed (Saville, 1990). Critically, the two key findings (interaction between training and laterality and the relationship between hippocampal volume changes and NF-κβ) were robust.

In conclusion, these results lend further credence to the concept that cognitive training is capable of changing brain structure in humans. Notably, we provided evidence that this plasticity is influenced by the level of low-grade inflammation, that is, a higher activity of pro-inflammatory processes was associated with a smaller increment of hippocampal volume. Future studies should investigate the relevance of these findings in neuropsychiatric disorders, as well as potentially different vulnerabilities of subfields in the medial temporal lobe (Wang et al., 2010; Teicher et al., 2012; Huang et al., 2013).

Acknowledgements—This research was supported by the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP-4.2.4.A/2-11/1-2012-0001 'National Excellence Program'. The authors declare no conflict of interest.

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(Accepted 3 June 2014)
(Available online 11 June 2014)