Structural Brain Alterations following 5 Days of Intervention: Dynamic Aspects of Neuroplasticity

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**Activation-dependent brain plasticity in humans on a structural level
has been demonstrated in adults after 3 months of training a visio-
motor skill. The exact timescale of usage-dependent structural
changes, whether days, months, or years, is, however, still de-
bated. A better understanding of the temporal parameters may help
elucidate to what extent this type of cortical plasticity contributes
to fast adapting cortical processes that may be relevant to learning
and effects of treatments. Using voxel-based morphometry, we are
able to show that repetitive transcranial magnetic stimulation de-
livered to the superior temporal cortex causes macroscopic cortical
changes in gray matter (GM) in the auditory cortex as early as
within 5 days of continuous intervention. These structural alter-
ations are mirrored by changes in cortical evoked potentials attrib-
uted to the GM changes and demonstrate the rapid dynamics of
these processes, which occur within a time range characteristic for
the onset of behavioral effects induced by a variety of treatment
methods for neuropsychiatric diseases. Our finding suggests that
cortical plasticity on a structural level in adult humans is already
detectable after 1 week, which provides support for fast adjusting
neuronal systems, such as spine and synapse turnover, and con-
tradicts slow evolving mechanisms, such as neuronal or glial cell
genesis.**

Keywords: auditory cortex, plasticity, rTMS, voxel-based morphometry

Introduction

Brain plasticity refers to the brain's ability to undergo functional
and structural alterations in response to internal and external
environmental changes. The actual underlying causes are attrib-
uted to a multitude of different mechanisms, which in the case
of structural plasticity may involve variance in spine density
(Grutzendler and others 2002; Trachtenberg and others 2002)
and glial- or possibly even neurogenesis (Kempermann and
others 1997). Animal models, however, suggest that the capac-
ity for adaptive change is limited. Whereas traditional research
has focused on functional forms of neuroplasticity, current
theoretically based concepts suggest structural types of cortical
plasticity in adult brains to play a crucial role in adaptation to
environmental changes and disease. Support for this hypothesis
comes from a recent study demonstrating activity-dependent
selective changes in gray matter (GM) induced in human adults
after 3 months of training (Draganski and others 2004), al-
though age may still limit the capacity for reorganization. As
activation-dependent brain plasticity in humans on a structural
level has to date only been demonstrated in younger adults after
3 months of training (Draganski and others 2004), further
studies are needed to establish an empirical understanding of
whether and to what extent the brain responds to environ-
mental demands in relationship to other parameters (i.e., age

and temporal parameters). Because the therapeutic effects of
centrally acting agents are often not instantaneous, but instead
emerge over an extended period of time from weeks to months,
longer duration changes such as functional or even structural
plasticity may be important in the mechanism of action of
centrally acting agents. Detailed knowledge about the temporal
parameters of structural neuroplasticity may help elucidate to
what extent this type of cortical plasticity is involved in
mediating short- and long-term clinical effects.

Focusing on the issue of whether structural neuroplasticity
may arise in a matter of days rather than months (Draganski and
others 2004), we used a double-blinded, placebo-controlled
study design with low-frequency repetitive transcranial mag-
netic stimulation (rTMS) in 2 homogenous groups of volunteers
who received either active or sham rTMS for 5 days. We used
rTMS as it has increasingly and successfully been used to ex-
plore the mechanisms and consequences of functional plasticity
in the human cortex (Bäumer and others 2003; Siebner and
Rothwell 2003). Depending on the stimulation frequency, rTMS
can induce neurobiological effects resembling direct electrical
stimulation, which has been shown to inducing neuroplasticity
in animals (Wang and others 1996; Post and others 1997). Con-
sequently, rTMS is not only used as a diagnostic tool but also to
treat specific symptoms. In humans, low-frequency 1-Hz rTMS
targeting the left temporoparietal cortex caused a remarkable
and sustained reduction of auditory hallucinations in schizo-
phrenia (Hoffman and Cavus 2002; Poulet and others 2005). In
addition, 1-Hz rTMS targeting of the auditory cortex is efficient
in reducing chronic tinnitus (Eichhammer and others 2003;
Plewnia and others 2003). In light of these observations, the
involvement of neuroplastic processes in mediating 1-Hz rTMS
effects has already been discussed (Chen and others 1996;
Langguth and others 2003). We therefore predicted that rTMS
of the left auditory cortex may alter the brain morphology in
this region, representing the structural counterpart of the above
mentioned functional neuroplasticity. In line with this hypoth-
esis, we decided to investigate healthy volunteers using a well-
controlled study design to avoid the possible pathophysiological
condition of patients suffering from tinnitus.

Materials and Methods

Volunteers

We studied 36 healthy volunteers (27 females, 9 males; mean age, 24.8
years) and split them into 2 groups matched equally for sex and age:
receiving either active or sham rTMS (sham group: mean age = 23.5 ± 4
years, 15 females, 3 males; active group: mean age = 24.0 ± 5 years;
12 females, 6 males). None of the volunteers suffered from any diseases,
in particular, the neurological and otorhinolaryngological examination
were entirely normal. The subjects were recruited locally, and they
were informed that the purpose of the current study was to investigate

the central nervous system's adaptive behavior to repeated stimulation using rTMS.

The study was given ethical approval by the local ethics committee and written informed consent was obtained from all study participants prior to examination.

Repetitive Transcranial Magnetic Stimulation

The rTMS was administered both in the active as well as in the sham condition by means of a neuronavigational system, conventionally used in neurosurgery (Gumprecht and others 1999) and further developed and adopted for transcranial magnetic stimulation (TMS) (Vector-Vision, BrainLab AG, München-Heimstetten, Germany). This system allows real time stereotactic monitoring of coil location with respect to the individual cortex (Eichhammer and others 2003). Based on individual structural images acquired in our lab using T_1-weighted magnetic resonance (MR) scans, the left superior temporal gyrus (Brodmann area 41/42), corresponding to the primary auditory cortex, could be marked as the target for rTMS application (Schonfeldt-Lecuona and others 2004). As has been demonstrated recently, this procedure guarantees the placement of the TMS coil at a particular brain region with high precision and reliability (Herwig and others 2001).

The rTMS was administered by means of a Magstim Rapid stimulator (Magstim Co., Whiteland, Dyfed, UK) using a figure-of-eight coil. Stimulation was applied daily for 5 days, with 1 Hz stimulus frequency and at 110% motor threshold intensity. Because biological effects of TMS are known to be dose dependent, we chose suprathreshold intensity for stimulation, frequently used in treatment studies. Per session, 2000 stimuli were administered. For sham stimulation, a specific sham-coil system was used (Magstim Co., Whiteland, Dyfed, UK). The specifically designed sham coil does not induce a magnetic field but evokes an acoustic artifact comparable with the popping sound generated by the active coil.

VBM—Data Acquisition

Both groups received a T_1-weighted magnetic resonance imaging (MRI) scan on day 1 and on day 6, immediately following the intervention period. All volunteers were scanned again after a time period of 3 months without any intervention. MRI was performed on a Siemens Symphony scanner operating at 1.5 T. A 3-dimensional (3D) structural MRI was acquired for each subject using a T_1-weighted gradient echo magnetization prepared rapid gradient echo sequence (time repetition 11.08 ms, echo time 4 ms, time to inversion 300 ms, flip angle 15°, matrix size 256 × 192, field of view 256 × 192) yielding 150 sagittal slices with a defined voxel size of 1 × 1 × 1.08 mm. Conventional T_1 MRI showed no morphological abnormalities or artifacts in either the patient or the volunteer groups.

Voxel based morphometry (VBM) is based on high-resolution structural 3D MR images, transformed into a common stereotactic space and is designed to seek significant regional differences by applying voxelwise statistics in the context of Gaussian random fields (Friston and others 1999; Ashburner and Friston 2000). VBM has been cross validated with region-of-interest measurements and functional data in a number of studies (May and others 1999; Woermann and others 1999).

VBM Protocol

Data preprocessing and analysis were performed with Statistical Parametric Mapping 2 (Welcome Department of Cognitive Neurology, London, UK) running under Matlab (Mathworks, Sherborn, MA, USA). Preprocessing of the data involved spatial normalization, segmentation, modulation, and spatial smoothing with a Gaussian kernel (Friston and others 1999; Ashburner and others 2000).

In order to reduce the scanner-specific bias, we created a customized GM anatomical template from the volunteers in this study. To facilitate optimal segmentation, we estimated normalization parameters while removing nonbrain voxels (skull, sinus) using an optimized protocol (Good and others 2001b). The optimized parameters, estimated while normalizing extracted GM images to the customized GM template, were reapplied to the original whole brain images. The images aligned with the stereotactic space defined by the Montreal Neurological Institute (International Consortium for Brain Mapping, http://www.loni.ucla.edu/ICBM/ [Evans and others 1994]) were corrected for nonuniform-

ities in signal intensity and partitioned into GM and WM, cerebrospinal fluid (CSF), and background using a modified mixture model cluster analysis. In addition, we performed a correction for volume changes (modulation) by modulating each voxel with the Jacobian determinants derived from the spatial normalization, allowing us to also test for regional differences in the absolute amount of GM (Ashburner and Friston 2000; Ashburner and others 2000). Subsequently, all images were smoothed by convolving them with an isotropic Gaussian kernel of 10 mm full-width at half maximum.

Statistical Analysis

Voxel-by-voxel t-tests using the general linear model were used to test for regionally specific GM and WM differences between the groups. The groups were closely matched for age and sex with no significant differences between the groups, and, therefore, no age or sex confounds were included. We used a time points (before intervention, after intervention) by group (TMS, sham) interaction analysis, testing for greater changes in the active rTMS group. The factor time points was modeled as a transient increase (increase from time point 1 to 2 then decrease again between time points 2 and 3 or vice versa). For the statistical analysis, we excluded all voxels with a GM or WM value below 0.2 (with a maximum value of 1) to avoid possible edge effects around the border between GM and WM and to include only voxels with sufficient GM proportion.

We hypothesized, based on the finding that induction of neuroplasticity may be a key consequence of 1-Hz rTMS (Chen and others 1996; Tergau and others 1999; Langguth and others 2003), that rTMS of the left auditory cortex may alter the brain morphology in this region. We applied a threshold of $P < 0.05$ (corrected across the whole brain for multiple comparisons). For regions for which we had an a priori hypothesis, a small volume correction (SVC), using a sphere of 6 mm radius in the left auditory cortex, was performed.

Auditory Measurement

All subjects obtained microscopic examination of the ear to exclude a tympanic membrane defect or middle ear effusion. The hearing status was confirmed on the basis of auditory tests. All auditory measurements were made before and after the stimulation period.

Normal middle ear status was demonstrated by tympanometry and the measurement of stapedius reflexes. "Normal hearing" was defined as pure tone thresholds of better than 20 dBHL in the frequency range of 0.25–8 KHz. The auditory threshold was determined by pure tone audiometry between 0.125 and 8 KHz.

Evoked potentials were collected in 8 out of 18 subjects of the verum group using Cz as the active electrode referenced to the contralateral mastoid. The ground electrode was placed on the forehead. The electroencephalography was sampled at 10 kHz (bandpass 1-500 Hz, ERA-System, ZLE Systemtechnik, Munich, Germany). The stimulus for cortical auditory evoked cotentials (CAEP) measurements was a 1-KHz tone burst of 400 ms plateau duration (2 cycles linear on- and offset). Each averaged waveform of 124 stimuli (interstimulus interval 1920 ms) was digitally low-pass filtered offline at 19 Hz (finite impulse response, zero phase shift) in order to enhance detection of the CAEP components, which were identified visually in the averaged data. P1 was defined as the first robust positive waveform. N1 was defined as the first negativity occurring after the P1 response and in the range of about 80–140 ms after stimulation. The P2 peak was determined as the most positive voltage reversal between 140 and 200 ms after stimulus onset. The N2 peak was determined separately as the most negative reversal occurring after P2.

Statistical Analyses

The effects of active and sham stimulation as well as stimulated versus unstimulated side on amplitude differences P1–N1, P2–N2, N1–P2 were evaluated by nonparametric Wilcoxon matched pairs test. All probabilities are 2-tailed.

Results

Based on the results using VBM, the group comparison at the beginning (baseline) demonstrated no significant regional

difference in GM between the active and sham treated groups, whereas comparison at the end of the treatment period revealed differences between the groups. Volunteers treated with active rTMS showed a significant transient increase exclusively in GM in the left superior temporal area (which was targeted by the TMS coil) between the 1st and the 2nd scan ($x = -62$, $y = -3$, $z = 1$; $t = 3.36$), which again decreased toward the 3rd scan (Z interaction $P < 0.05$ small volume corrected; Fig. 1). No white matter (WM) changes were detected. The dynamic pattern of the GM changes was specific to the active rTMS, as the sham group revealed no GM changes during the same period of time. Pure tone audiometry could not detect significant differences between both groups after TMS treatment, whereas in CAEP, a significant ($P = 0.002$) increase in P2–N2 amplitude could be found, indicating alterations in auditory processing between active and sham treated volunteers.

Additionally, we also found a transient increase and decrease of GM in the superior temporal area contralateral to the site of stimulation and bilaterally in the thalamus ($P < 0.001$, uncorrected; see Fig. 2). However, we had no a priori hypothesis for these regions and consequently did not perform any SVCs. Because these findings did not survive correction for multiple comparisons, we only report them as trends. A boxplot showing the mean, standard deviation, and range for each time point (Fig. 3), as well as a table showing changes in specific brain regions (Table 1) are included in the supplementary material.

Regarding the auditory measurements, in the active group, the amplitude difference P2–N2 was significantly larger (Wilcoxon test, $P = 0.008$) compared with the change in amplitude of P2–N2 after sham stimulation (Wilcoxon test, $P = 0.461$). The amplitude difference in P2–N2 before and after the stimulation procedure of the unstimulated left ear, in contrast, did not differ significantly in either group (Wilcoxon test, $P = 0.313$ vs. $P = 0.383$). Our model of the potential influence of plasticity on CAEP generators included the a priori hypothesis that only the amplitudes of the CAEP are influenced. We solely considered amplitude, as we were using VBM to look for GM changes, and any changes as a consequence of repeated TMS could only influence the amplitudes of CAEP. Neither latencies nor other amplitude differences were significantly different at all after the stimulation procedure in both groups and both ears. Because the auditory measurements were only done in 8 subjects, we have not correlated the amplitude difference P2–N2 and the amount of change in GM because statistically more subjects are necessary to detect possible significant changes.

Discussion

Our results suggest that dynamic alterations in GM can occur very rapidly and at least within a time range of 1 week. This period of time corresponds to the onset of therapeutic effects in neuropsychiatric diseases initiated by TMS (Tergau and others 1999) and antipsychotic agents (Stahl and others 2001), indicating that cortical plasticity at a structural level may be involved in mediating sustained clinical improvement.

The local changes mirroring structural neuroplasticity are in line with current studies, demonstrating that low-frequency rTMS is able to produce powerful and widespread changes in
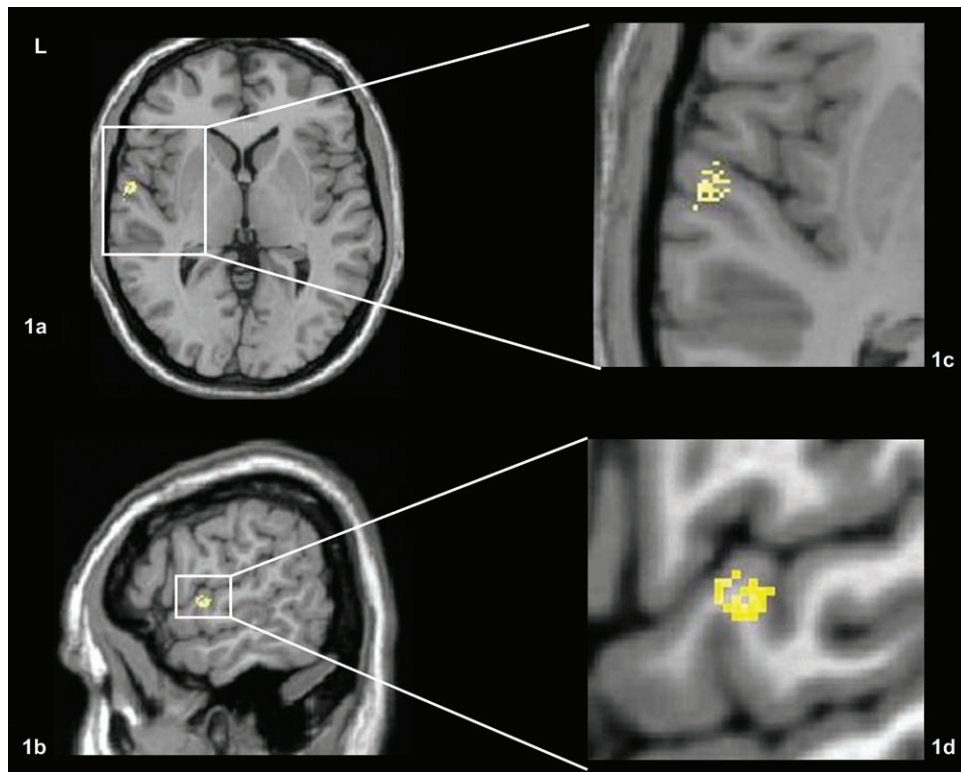
Figure 1. "Time points by group interaction analysis": statistical parametric maps demonstrating the structural difference in GM in the active group, following 1 week of 1-Hz low-frequency rTMS, delivered to the left auditory cortex. Significant GM increase ($P < 0.05$, SVC) is superimposed in color on a normalized image of a healthy control subject. The left side of the picture is the left side of the brain (L). (a, b) "statistical parametric maps" of the changes in brain structure induced by rTMS. (a) axial; (b) sagital view. Exclusively in the active group, a significant increase in GM (Brodmann area 22; $x = -62$, $y = -3$, $z = 1$) was detected on the side of rTMS (left side in all volunteers). (c, d) magnifies the same axial and sagittal view as (a) and (b), to better visualize the finding.
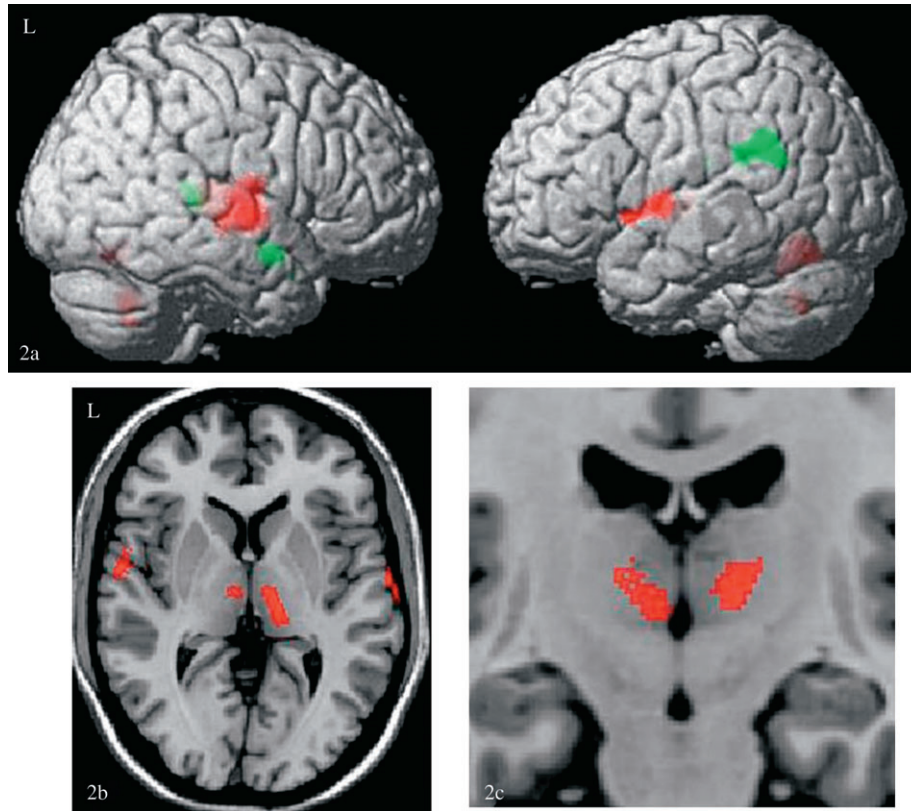
Figure 2. "Simple main effects analysis" (time for verum group): statistical parametric maps demonstrating the structural difference in GM in the active group, following 1 week of 1-Hz low-frequency rTMS, delivered to the left auditory cortex. Significant GM increases and decreases ($P < 0.0015$, uncorrected) are superimposed in color (red color for increase and green color for decrease of GM) on a normalized image of a healthy control subject. The left side of the picture is the left side of the brain (L).

regional synaptic activity within cortical and subcortical structures (Bäumer and others 2003; Siebner and others 2003; Li and others 2004). The significant increase in GM in the superior temporal area contralateral to the site of stimulation reflects close functional connectivity between both auditory cortices (Read and others 2002). Moreover, the increase in GM in the thalamus suggests reciprocal interconnections between this brain structure and the temporal cortex (Nolte 2001). Both in vivo electrical stimulation of the cortex and low-frequency rTMS in patients with depression have been shown to produce neurobiological effects in a variety of thalamic nuclei, including the mediodorsal nucleus and the pulvinar (Destexhe and others 1998; Li and others 2004). The fact that unilateral rTMS leads to bilateral changes on a functional level was demonstrated in previous studies using functional imaging and may reflect close connectivity between directly stimulated brain regions and remote areas in both brain hemispheres (Siebner and others 2003).

Although the sham coil which we used in our study is the best available sham condition for rTMS studies, one could argue that active and sham rTMS are still different in the acoustical sensation and that any changes in GM reflect auditory stimulation rather than the effects of the magnetic field. Although we cannot entirely deny that subtle differences between active and sham rTMS in terms of acoustic artifacts exist, there is no literature based on precise acoustic measurements supporting this argumentation. Considering the critical impact of acoustic stimuli alone on brain plasticity, the sham-rTMS–treated group (which were also subject to repetitive acoustic stimuli) should

have demonstrated changes in the auditory cortex, too. On the other hand, subtle differences in sound compete with a multitude of different acoustic stimuli that our subjects are exposed to during non-TMS. Moreover, the majority of our volunteers was not aware of any difference, including the loudness, between active and sham stimulation, and the main finding of our study—changes in GM as early as 5 days of intervention—is valuable, even if the sound rather than the magnetic input is the source of the changes.

Using the very conservative approach of an interaction analysis, the changes in GM are exclusively seen in the active group. It is tempting to argue in favor of a direct effect of rTMS on brain plasticity. The crucial question regarding the mechanisms of rTMS is whether these changes are due to the direct impact of magnetic waves versus sound or possibly even sensory input due to stimulation of the underlying scalp muscles. As our study aimed at understanding the temporal effects of structural plasticity rather than understanding the mechanisms of rTMS, our model is not valuable regarding the latter.

Although changes in GM further underline the potential of rTMS to interfere actively with cortical plasticity in humans (Siebner and Rothwell 2003), the neurobiological basis of these structural alterations on a microscopic level is not well defined. VBM detects changes in GM concentration per voxel as well as changes in the classification of individual voxels, for example, from WM to GM (Good and others 2001a) and probably a combination of both. In general, an increase in GM could be due to an increase in cell size, neural or glial cell genesis, spine density, or even changes in blood flow or interstitial fluid. The

latter possibility (increased interstitial fluid due to some sort of "injury") is unlikely as animal data show no such lesion (Okada and others 2002; Liebetanz and others 2003) and 2 weeks of repeated rTMS to the prefrontal cortex does not alter T_2-weighted MRI in humans (Nahas and others 2000). Although the changes in GM that we observed may reflect alterations in cell genesis, the time course of our data suggest fast adjusting neuronal systems, such as spine and synapse turnover (Trachtenberg and others 2002), rather than such slow evolving mechanisms as neuronal or glial cell genesis (Kempermann and others 1997). Further work is needed to clarify whether vascular changes due to increased cerebral blood volume and/or cerebral blood flow may have additional effects to the observed changes (Swain and others 2003).

Independent of the precise histological nature of these structural alterations, our results support theoretical considerations stressing structural forms of neuroplasticity to be important in processing the information in dynamic networks according to novel informational demands (Chambers and others 2004). Based on our results, functional and structural cortical changes may not differ substantially with regard to onset. Rather the occurrence of dynamic structural alterations mirrored by changes in functional processing, such as in our study, exemplifies structural neuroplasticity as a counterpart of function. The obvious benefit of the central nervous system's capacity to change is the acquisition of new skills. In the process of learning, the brain has to change to be able to encode and appropriately implement new knowledge. It is reasonable to assume that plasticity is a characteristic of the nervous system that evolved for coping with changes in the environment. The challenge we face is to unravel the exact nature of the dynamic structural alterations and ultimately to be able to adapt and modulate this knowledge for disease management. Understanding normative changes in brain structure as a result of environmental changes and demands is pivotal to understanding the characteristic ability of the brain to adapt.

Ethical Considerations

As we have shown structural brain changes as a consequence of rTMS, some ethical considerations need to be addressed. When we first discussed this study with the local ethics committee, it was already known that rTMS does induce functional changes in humans (Bäumer and others 2003; Siebner and others 2003; Li and others 2004) and that rTMS can induce neurobiological effects resembling direct electrical stimulation producing neuroplasticity in animals (Wang and others 1996; Post and others 1997). However, as it was not clear whether we would find any possible structural changes, so we agreed to use the term "investigation of neuroplastic changes" on the consent form. Using the results of our study, one could argue that structural changes, that is, impact on cell structure, may reflect potential risks for the patients and that rTMS, at least if administered therapeutically, may therefore be harmful. None of our volunteers reported any side effects from either active or sham stimulation, and it needs to be pointed out that the changes in GM were transient and decreased again when the stimulation stopped.

Viewing our data in the context of a recent study demonstrating activity-dependent selective changes in GM induced in human adults after 3 months of training (Draganski and others 2004), we would rather suggest that any significant environmental change that requires specific functions, including learning specific tasks, has the potential to change brain structure. Our results certainly support theoretical considerations stressing structural forms of neuroplasticity to be important for processing information in dynamic networks according to novel informational demands (Chambers and others 2004). In future studies using rTMS as a therapeutical tool, we suggest that the possibility of functional along with structural brain changes as an eventual consequence to be included in the written informed consent form. Although 2 weeks of repeated rTMS to the prefrontal cortex does not alter T_2-weighted MRI (Nahas and others 2000), animal studies are certainly mandatory to understand the mechanisms underlying VBM changes.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

Notes

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