Moduler la communication cérébrale au moyen de sons binauraux

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Section de médecine Clinique
Département des Neurosciences cliniques
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Thèse préparée sous la direction du Professeur Adrian G. Guggisberg

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" Moduler la communication cérébrale au moyen de sons binauraux "

Thèse
présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur en médecine
par

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TABLE DES MATIERES

RESUME

Les interactions entre nos neurones sont un élément déterminant dans le bon fonctionnement de notre cerveau. Il a récemment été possible de réparer certaines fonctions cérébrales en ciblant directement ces interactions neuronales. Dans ce travail, nous avons testé l'effet sur la connectivité cérébrale des sons binauraux, une illusion auditive qui pourrait synchroniser les ondes cérébrales. Nous avons observé une augmentation de la connectivité entre les deux cortex auditifs lors de la présentation de sons binauraux en comparaison à une condition contrôle. Dans une deuxième partie, nous avons cherché à savoir si les modifications électrophysiologiques observées s'accompagnaient de changements comportementaux. Aucune amélioration dans une tache de discrimination auditive n'a été mesurée.

Ce travail montre qu'il est possible de moduler la connectivité entre les cortex auditifs en utilisant un stimulus auditif externe. Toutefois, de nouvelles études sont nécessaires pour établir si un effet comportemental associé existe.

INTRODUCTION

Connectivité fonctionnelle

Notre cerveau est organisé en réseaux de neurones interconnectés qui nous permettent d'intégrer et de traiter des informations provenant de différentes modalités (Sporns, 2013). Le développement de nouvelles techniques de neuro-imagerie non invasives associé à de puissantes méthodes de modélisation du réseau neuronal ont récemment permis de développer des nouvelles mesures de ces interactions entre neurones. Une de ces méthodes est appelée connectivité fonctionnelle (functional connectivity, FC) et mesure la dépendance statistique entre des activités cérébrales de différentes régions (Friston, 2011). Ces dernières années, de nombreuses études portant sur FC ont permis d'améliorer non seulement nos connaissances sur le fonctionnement du cerveau sain mais également de mieux comprendre la pathophysiologie de certaines maladies (Bassett and Bullmore, 2009). Par exemple, on sait désormais que des anomalies de la connectivité neuronale sont impliquées dans les manifestations cliniques de nombreuses maladies comme la schizophrénie, la maladie d'Alzheimer ou encore la sclérose en plaques (Iturria-Medina, 2013).

En plus de son intérêt en pathophysiologie, l'étude de la connectivité inter-neuronale pourrait permettre le développement de nouvelles formes de traitements. Plusieurs études ont démontré que la performance dans un domaine (mémoire, fonction motrice, etc…) était directement corrélée à l'importance de la connectivité fonctionnelle du réseau correspondant (L. Wang et al., 2010; X. Wang et al., 2013; Hipp, Engel and Siegel, 2011; Fox et al., 2007; Koyama et al., 2011). Dès lors, certains scientifiques ont cherché à augmenter la connectivité fonctionnelle dans le réseau d'un système donné pour améliorer les fonctions dudit système et traiter certaines pathologies. Récemment, nous avons utilisé chez un patient hémiplégique un système de neurofeedback l'informant visuellement et en temps réel sur la connectivité fonctionnelle de son système moteur. Après 7 sessions d'entraînement durant lesquelles nous lui avons simplement demandé d'utiliser le feedback visuel pour augmenter sa connectivité, nous avons noté une amélioration motrice cliniquement significative qui a persisté dans le temps (**cf. Annexe 1;** Mottaz et al., 2015). Ainsi, augmenter la connectivité fonctionnelle peut s'avérer un outil thérapeutique efficace en neuroréhabilitation. Par ailleurs, cela pourrait également s'appliquer à d'autres pathologies (e.g. maladie d'Alzheimer, schizophrénie) ou même augmenter certaines performances chez les sujets sains.

Mesure de la connectivité fonctionnelle à l'électroencéphalographie (EEG)

L'électroencéphalographie (EEG) permet de mesurer l'activité électrique du cerveau de manière non invasive à la surface du crâne. Lorsque l'on enregistre un tracé EEG, on observe une activité neuronale rythmique et répétitive, déjà décrite en 1929 par Hans Berger (Berger, 1929). Ces oscillations s'observent dans différentes zones cérébrales à des fréquences et des phases d'oscillation qui peuvent être mesurées grâce à l'excellente résolution temporale de L'EEG. On appelle cohérence le coefficient de corrélation qui estime la consistance de la différence de phase entre différents signaux enregistrés (Nunez, 1995; Nunez and Srinivasan, 2006). De ce fait, la cohérence est élevée lorsque la différence de la phase d'oscillation entre deux régions cérébrales est constante. La cohérence reflète le lien qu'il existe entre le signal généré par différentes zones cérébrales et constitue par conséquent une mesure de la connectivité fonctionnelle.

Sons binauraux

Lorsque deux sons de fréquence légèrement différente sont présentés simultanément, nous percevons un seul son de fréquence égale à la moyenne des deux fréquences jouées et oscillant en amplitude avec une périodicité égale à leur différence. Par exemple, si deux sons respectivement de 395Hz et de 405Hz sont mélangés, nous percevons un seul son ayant une fréquence de 400Hz et dont l'amplitude oscille à une fréquence de 10Hz (405Hz-395Hz). Ce phénomène purement physique s'explique par l'addition mathématique des deux ondes sonores (Moore, 2012). Cependant, lorsque deux sons sont présentés indépendamment l'un de l'autre dans chaque oreille, le sujet perçoit, dans cette situation aussi, un seul son dont la fréquence correspond à la moyenne des deux sons présentés et oscillant en amplitude avec une périodicité égale à leur différence de fréquence. Ce phénomène est une illusion auditive appelée son binaural car le son perçu n'existe pas physiquement mais est recréé au niveau cortical à partir de l'information reçue par chaque oreille (Oster, 1973). Certains scientifiques ont suggéré que les sons binauraux pourraient être utilisés comme stimulus externe rythmique pour moduler les oscillations neuronales (Atwater, 2004). Dans ce cas, les ondes cérébrales se synchroniseraient à la fréquence du son binaural ce qui entrainerait une augmentation de la synchronisation entre les hémisphères (Vernon, 2009). Deux études ont récemment observés des modifications de la synchronisation du signal cérébral mesuré à la surface du cerveau (entre pairs d'électrodes) durant la présentation de sons binauraux (Gao et al., 2014; Becher et al., 2015). Cependant, il est également possible de reconstruire à partir du signal enregistré en surface les oscillations neuronales qui ont lieu dans le cortex et ainsi de calculer la cohérence entre des régions cérébrales définies. Cependant, des analyses de cohérence inter-hémisphérique lors de la présentation de sons binauraux n'ont à ce jour pas été publiées. Cette approche permettrait d'apprécier la connectivité fonctionnelle entre des régions d'intérêt et de comparer directement l'interaction entre les deux hémisphères.

Si l'analyse de la connectivité fonctionnelle nous semble intéressante avec les sons binauraux c'est également parce que plusieurs études ont démontré certains effets comportementaux lorsque ces sons sont écoutés. Ainsi, il a déjà été prouvé qu'ils peuvent être bénéfiques pour traiter la douleur (Wilson, 1990; Rhodes, 1993), améliorer la vigilance (Lane et al., 1998) ou réduire l’anxiété (Le Scouarnec et al., 2001; Padmanabhan et al., 2005). Toutefois, aucune étude n’a directement testé si les potentielles modulations de la connectivité étaient directement reliées à des changements comportementaux du système concerné.

Objectifs de l’étude

Dans cette étude nous avons étudié la relation entre les sons binauraux, la cohérence inter-hémisphérique et le comportement. Dans une première partie, nous avons mesuré l’effet de sons binauraux de différentes fréquences sur l’oscillation neuronale. Comme nous avons observé une augmentation de la cohérence inter-hémisphérique entre les cortex auditifs lors de ces stimulations auditives, nous avons recherché lors d’une deuxième expérience si l’exposition aux sons binauraux améliorait la discrimination auditive.

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Binaural beats increase interhemispheric alpha-band coherence between auditory cortices

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Running title: EEG Coherence & Binaural Beats

Abstract

Binaural beats (BBs) are an auditory illusion occurring when two tones of slightly different frequency are presented separately to each ear. BBs have been suggested to alter physiological and cognitive processes through synchronization of the brain hemispheres. To test this, we recorded electroencephalograms (EEG) at rest and while participants listened to BBs or a monaural control condition during which both tones were presented to both ears. We calculated for each condition the interhemispheric coherence, which expressed the synchrony between neural oscillations of both hemispheres. Compared to monaural beats and resting state, BBs enhanced interhemispheric coherence between the auditory cortices. Beat frequencies in the alpha (10 Hz) and theta (4 Hz) frequency range both increased interhemispheric coherence selectively at alpha frequencies. In a second experiment, we evaluated whether this coherence increase has a behavioral aftereffect on binaural listening. No effects were observed in a dichotic digit task performed immediately after BBs presentation. Our results suggest that BBs enhance alpha-band oscillation synchrony between the auditory cortices during auditory stimulation. This effect seems to reflect binaural integration rather than entrainment.

Keywords: Functional connectivity, alpha band, EEG, phase synchrony, dichotic digit test, Interhemispheric synchronization

1. Introduction

Human brain function crucially depends on interregional neural communication (Varela et al., 2001). Such interactions are thought to be accompanied by a synchronization of oscillations between different brain regions (Aertsen et al., 1989; Gray and Singer, 1989; Engel et al., 1992; Fries, 2005). Interregional synchronization can be quantified with the concept of functional connectivity (FC), which is a measure of the statistical dependency between activities in different brain regions. Interestingly, FC has been shown to linearly correlate with behavioral performance in a variety of cognitive and motor functions. In other words, the more synchronous neural oscillations are between nodes of a given network, the better is the behavioral performance in tasks relying on that network (Hummel and Gerloff 2005a; Fox et al., 2007; Guggisberg et al., 2015). Therefore, interventions leading to modulation of FC should have beneficial behavioral effects and could lead to new applications and therapies.

One intervention that has been suggested to provide such modulation of neural oscillation synchrony is the binaural presentation of tones with slightly different frequencies (Atwater, 2004). If two sinusoidal tones with slightly different frequencies are played simultaneously, one perceives a tone with their average frequency plus a so-called beat, i.e., a modulation of the amplitude at a rate equal to the difference between them. For instance, a tone of 395 Hz presented together with a tone of 405 Hz will produce a perceived frequency of 400 Hz, which modulates in amplitude with a frequency of 10 Hz (Moore, 2012). If the two tones are presented separately to each ear, a similar beat is perceived by the subject although no such physical sound exists (Oster, 1973). This auditory illusion is known as BBs and has been interpreted as arising from the convergence of phase preserved neural activity from the two ears in binaurally sensitive neurons within the medial superior olivary nucleus (Wernick and Starr, 1968; Kuwada et al., 1979).

A common assumption of binaural beats is that they can elicit an entrainment effect of neural oscillation at their proper frequency (Vernon, 2009). Many electrophysiological studies have explored the effect of BBs on oscillatory amplitude with contradictory results. Some authors have reported increases in amplitude following exposure to binaural beats compared to resting state (Karino, 2004; Schwarz and Taylor, 2005; Karino et al., 2006; Draganova et al., 2008; Pratt et al., 2009; Pratt et al., 2010; Grose and Mamo, 2012) whilst others have failed to find evidence of such a change (Wahbeh et al., 2007; Goodin et al., 2012; Vernon et al., 2014). However, it seems that when BBs increase power, it is always in smaller amplitude than the modulation occurring under the corresponding monaural beats (MBs) condition (Schwarz and Taylor 2005; Draganova et al., 2008; Pratt et al., 2010).

It has further been argued that BBs enhance the synchrony of neural activity between the two brain hemispheres (Atwater, 1997; Atwater, 2004). Recently, two studies have tested the effect of BBs on FC. Gao and colleagues quantified frequency-specific synchronization between pairs of scalp electrodes (Gao et al. 2014). They detected both increases and decreases in FC during BBs stimulation compared to a resting state without stimulation, depending on oscillation frequencies and electrode location. In another study, Becher and colleagues (Becher et al., 2014) measured phase synchronization between channel pairs using intracranial signals mainly in the temporo-lateral and temporo-basal area. Synchronization increases were essentially found for stimulation with monaural 10-Hz beats at medio-temporal sites and for stimulation with binaural 5-Hz beats at temporo-lateral sites.

These two recent studies suggest that BBs could modulate oscillation synchrony. However, it remains unclear whether these changes occur in the BBs frequency, which brain structures are concerned and if they are associated with behavioral changes.

This last point is of particular interest because BBs have been praised for supposedly beneficial behavioral effects, such as relaxation, pain reduction, and other mental states (Wilson, 1990; Rhodes, 1993). Several studies have demonstrated specific behavioral changes following BBs such as improvement of vigilance (Lane et al., 1998), increase in hypnotic susceptibility (Brady and Stevens 2000), reduction of self-reported anxiety (Le Scouarnec et al., 2001; Padmanabhan et al., 2005), or increase in some forms of creativity (Reedijk et al., 2013), although their robustness remains to be demonstrated. Given the assumed positive effect of BBs on synchronization between hemispheres, it would be particularly interesting to test whether such improved interhemipheric integration can be measured on the behavioral level. However, no study has probed the effect of BBs on tasks specifically requiring the collaboration between cerebral hemispheres in general or between both auditory cortices in particular.

The purpose of this study was therefore to directly test the hypothesis that BBs synchronize activity between hemispheres both at the neural and at the behavioral level. Experiment 1 examined the effect of BBs on interhemispheric oscillation synchrony in the auditory cortex using high-density scalp EEG and advanced source localization. Experiment 2 probed behavioral effects in a task requiring binaural listening. A dichotic listening task was used to assess the ability of participants to discriminate numbers presented simultaneously to different ears. This task has been validated for behavioral assessment of information exchange between the hemispheres across the corpus callosum (Musiek, 1983; Bellis and Wilber 2001; Westerhausen and Hugdahl 2008). We therefore used it to examine whether BBs improve the ability to exchange information between the auditory cortices even after stimulation.

2. Materials and Methods

The University Hospital of Geneva Ethics Committee approved all procedures and all subjects gave informed written consent for their participation to the study.

2.1. Experiment 1

2.1.1. Data acquisition

Sinusoidal tones of 395 Hz and 405 Hz (producing a beat of 10 Hz), as well as 398 Hz and 402 Hz (producing a beat of 4 Hz) were created using Matlab® (The MathWorks Inc., Natick, USA). These pairs of tones were presented with stereo headphones in two different conditions. In the monaural beats (MBs) condition, which was used as control, both tones were played to both ears (i.e. the beat is a purely physical phenomenon perceived by each ear). In the binaural beat condition, which was of interest here, each tone was played to separate ears (i.e. the beat is created by binaural integration and doesn’t exist at the single ear level). Sound intensity was determined for each subject to be comfortably loud but small enough to avoid bone conduction and kept constant between conditions.

Nine normal-hearing subjects (6 females, mean age of 28 years ranging from 25 to 34 years old) were asked to listen to 10Hz BBs and 10Hz MBs. Five participants were also exposed to 4 Hz BBs and the corresponding MBs. Each sound was presented continuously for 4 minutes in a counterbalanced order while a continuous EEG was recorded at a sampling rate of 1024 Hz using a 128-channel Biosemi Active Two EEG system (Biosemi B.V., Amsterdam, Netherlands). The participants were asked to listen to the sound. A resting state condition was also recorded before any auditory stimulation. All conditions were recorded with the eyes closed. Vigilance was checked by monitoring the EEG signal for signs of drowsiness or sleep and by asking the subjects whether they had fallen asleep after each condition. Artifacts like eye movements, muscular contractions and electrode artifacts were excluded by visual inspection. About three minutes of clean data were retained for each condition and each subject. Channels containing artifacts over prolonged periods were completely excluded from further analyses.

2.1.2. Analysis

Analyses were performed in Matlab with NUTMEG (http://nutmeg.berkeley.edu) (Dalal et al., 2011) and its FCM toolbox (Guggisberg et al., 2011).

We divided the three minutes artifact-free data into non-overlapping segments of one-second duration. Recordings were bandpass filtered between 1 and 20 Hz. A spherical model with anatomical constraints (SMAC) (Spinelli et al., 2000) was created from the individual coregistered magnetic resonance image of the head and used to compute the lead potential. The signal was then projected to grey matter voxels with an adaptive spatial filter (scalar minimum variance beamformer) (Sekihara et al., 2004).

The Heschl Gyrus was defined as region of interest (ROI) using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) since we expected changes in the primary auditory cortex during auditory stimulation.

Power spectrogram was computed using Fourier transformation. The difference in power between resting state, MBs and BBs conditions was compared in the Heschl Gyrus and tested against the null-hypothesis of zero change using two-tailed paired *t*-test.

The detailed steps of FC analysis and their validation have been described previously (Guggisberg et al., 2008; Guggisberg et al., 2011). We calculated the imaginary component of coherence (IC) (Nolte et al., 2004) between each voxel and its homologous contralateral region during the entire auditory stimulus, hence resulting in a measure of interhemispheric coherence or interhemispheric oscillation synchrony. We calculated the spectrum of interhemispheric coherence between 1 and 20 Hz in the Heschl Gyrus by averaging across its voxels. Differences between rest, MBs and BBs conditions were specifically tested in alpha and theta band given the auditory stimulation that we used, using a two-tailed paired *t*-test.

Finally, to ensure not to miss coherence changes in other brain areas, we created an interhemispheric FC map of the whole brain in a voxel-wise manner. Differences between rest, MBs and BBs conditions were tested with statistical non-parametric mapping for the voxel-wise map.

2.2. Experiment 2

We created two sets of a dichotic digit task to assess if BBs could increase binaural auditory discriminability. Each set contained 20 trials, composed of numbers ranging from 1 to 12 spoken by a male native French speaker. Four different numbers were simultaneously presented to both ears, two per ear, and the participants were instructed to recognize the four different numbers of each trial. One set of the test was presented before and after having listened to three minutes of a 10Hz BBs (395 Hz and 405 Hz tones) and the other set before and after the corresponding MBs. Sounds and tests were presented in counterbalanced order.

Eighteen healthy subjects participated (10 females, mean age of 26 years ranging from 21 to 32 years old). Performance was quantified by calculating the number of correct answers out of the 80 total heard numbers (20 trials with 4 digits each). Improvement was computed for each condition by subtracting the number of correct answers after the auditory stimulation from the number of correct answers before stimulation. Differences in improvement between BBs and MBs conditions were tested for significance with a two-tailed paired *t*-test. We then confirm null effects using JZS Bayes factor tests with default prior scales (Morey and Rouder, 2011) so that a Bayes factor (B) <0.33 implies substantial evidence for the null hypothesis. Analyses were performed with R (R Development Core Team, 2013) including the BayesFactor package (Morey and Rouder, 2015).

3. Results

3.1. Experiment 1

No significant differences were found in oscillation power in the auditory cortices between BBs, MBs and resting state conditions during 4Hz and 10Hz beats (minimal voxel value in 9-11Hz band: $p>0.26$ and $p>0.39$ respectively)

Conversely, interhemispheric coherence between the Heschl gyri was significantly greater in the alpha band (9-11Hz) during 10Hz BBs stimulation compared to a 10Hz MB condition ($t_8=3.24$; $p=0.012$) (Figure 1A) and resting state ($t_8=3.83$; $p=.005$). A similar coherence spectrogram pattern was found during 4Hz BBs stimulation compared to 4Hz MB (Figure 1A & Figure 1B), with a significant increase in interhemispheric coherence at 9Hz ($t_4=3.87$; $p=0.018$) and no significant difference observed around 4Hz (minimal p value found at 3Hz = 0.17) (Figure 1B).

A voxel-wise analysis of interhemispheric coherence showed that this increase during the BBs condition was relatively specific to the primary auditory cortex, although changes were also observed in frontal and occipital areas (Figure 1C).

3.2. Experiment 2

We observed an improvement in the dichotic digit test in both conditions (BBs $t_{17}=5.55$, $p<.001$; MBs $t_{17}=2.64$, $p=.02$) but no statistically significant difference between conditions ($t_{17}=.268$; $p=.79$) (Figure 2). Bayes factor confirmed the null effect showing that Ho was around 5 times more likely then the alternative hypothesis (B= 0.18). Complementary statistical analysis revealed that the performance achieved before the auditory stimulus (i.e. baseline score) was negatively correlated to the improvement after exposition to BBs ($r = -.576$; $p=.01$). Conversely no similar correlation was observed with improvement under MBs ($r = -.11$; $p=.65$).

4. Discussion

In this study we found that, compared to MBs and resting state, BBs increased interhemispheric coherence between the auditory cortices. Moreover, both 10 Hz and 4 Hz beats increased coherence selectively in the alpha band. These changes in oscillation synchrony were not associated with changes in amplitude. Despite these electrophysiological findings, no corresponding behavioral effect could be demonstrated after the stimulation.

Our study provides the first evidence for the long suspected increased interhemispheric synchrony under BBs and insights into underlying mechanisms. Our observation is comparable to previous reports that cognitive tasks can modify alpha-band coherence. For example, increased alpha oscillation synchrony has been reported during object recognition (Mima et al., 2001), spatial attention (Doesburg et al., 2009), error processing (van Driel et al., 2012), mental calculation (Palva, Palva et Kaila 2005) or memory tasks (Haegens et al., 2010). We consider BBs as a challenging listening situation with a binaural perceptual conflict that the auditory system solves by increasing communication between both auditory cortices. This in turns leads to an increase in phase locked synchrony among neurons oscillating in alpha band. Hence, we surmise that the increase in the alpha-band coherence observed here reflects binaural integration.

One might be surprised by the selective effect in alpha frequencies only. Neurons preferably oscillate at certain frequencies that are typically biologically important (Herrmann, 2001). As for several other sensory modalities, alpha oscillations are the predominant frequency in the auditory cortex and can be modulated by auditory stimuli (Hartmann et al., 2012; Strauß et al., 2014). We postulate that BBs effect on interhemispheric communications is restricted to the alpha band because it is the main spontaneous oscillation band and is involved in most of the interactions between cortical areas (von Stein et al., 2000).

Conversely, we didn’t find an increase in power during 10Hz and 4Hz BBs compared to rest or the corresponding MBs. The absence of alpha power modulation during 10Hz BBs is consistent with previous studies (Goodin et al. 2012; Vernon et al., 2014). Regarding the lack of modulation of theta power during 4Hz BBs, both similar (Wahbeh et al., 2007) and opposite results (Brady and Stevens, 2000; Karino et al., 2006; Pratt et al., 2010) have been reported in the literature. These studies have different designs in terms of recording device (EEG vs MEG) or exposition time (from 2 s up to 20 minutes) that could account for these discrepancies. In any case, consistent with our findings, increase in alpha oscillation synchrony has already been reported several times without corresponding modification of oscillation power (Mima et al. 2001; Vanni, Revonsuo et Hari 1997).

Some authors have hypothesized that EEG changes observed under BBs are elicited through an entertainment effect (Vernon, 2009), but our findings cannot be explained by this mechanism. We found that BBs stimulation with 4 Hz beats increases interhemispheric coherence in non-harmonic alpha frequencies, which is difficult to bring in line with entrainment. Moreover, in our study coherence increased independently of power changes whereas synchronization of neuron's firing to the frequency of the beating stimulus would theoretically lead to an amplitude increase of the corresponding EEG frequency. On the basis of these findings, we assume that the increase in the interhemispheric coherence observed here could not be explained by synchronization to the external rhythmic force.

Given the observed electrophysiological effect, we tried to improve binaural auditory discrimination abilities using BBs in healthy subject. However, no significant effect was observed compared to a monaural control condition. One possible explanation for this finding is that our behavioral task was not sufficiently sensitive to reveal an improvement in auditory function. However, dichotic digit tests have been successfully used to assess interhemispheric integration (Musiek 1983; Bellis and Wilber 2001; Westerhausen and Hugdahl 2008). A more likely explanation is that the increase in interhemispheric collaboration was limited to the simulation period and not associated with a corresponding aftereffect at the time at which we performed our dichotic digit task. It would have been interesting to record EEG not only during, but also after auditory stimulation in order to confirm the lack of aftereffect also on the neural level.

Our study does not exclude that repetitive BBs stimulation over several days would eventually result in measurable aftereffects. However, there is currently no evidence for this possibility. Finally, we found that the less the subjects were able to distinguish binaurally presented numbers at baseline, the more BBs increased their performance. Since no such correlation was found for MBs, we might speculate that BBs could be more beneficial for patients with impairment in interhemispheric interaction. This is consistent with previous observations on BBs behavioral effect. For instance, Brady and Steven found that hypnotic susceptibility increased only among low and medium-susceptible subjects (Brady and Stevens, 2000). However, this will need to be confirmed by more robust evidence.

In conclusion, this study demonstrates for the first time a modulation of interhemispheric coherence by BBs. However, a single session of BBs does not seem to result in corresponding behavioral aftereffects of improved interhemispheric communication.

5. Acknowledgments

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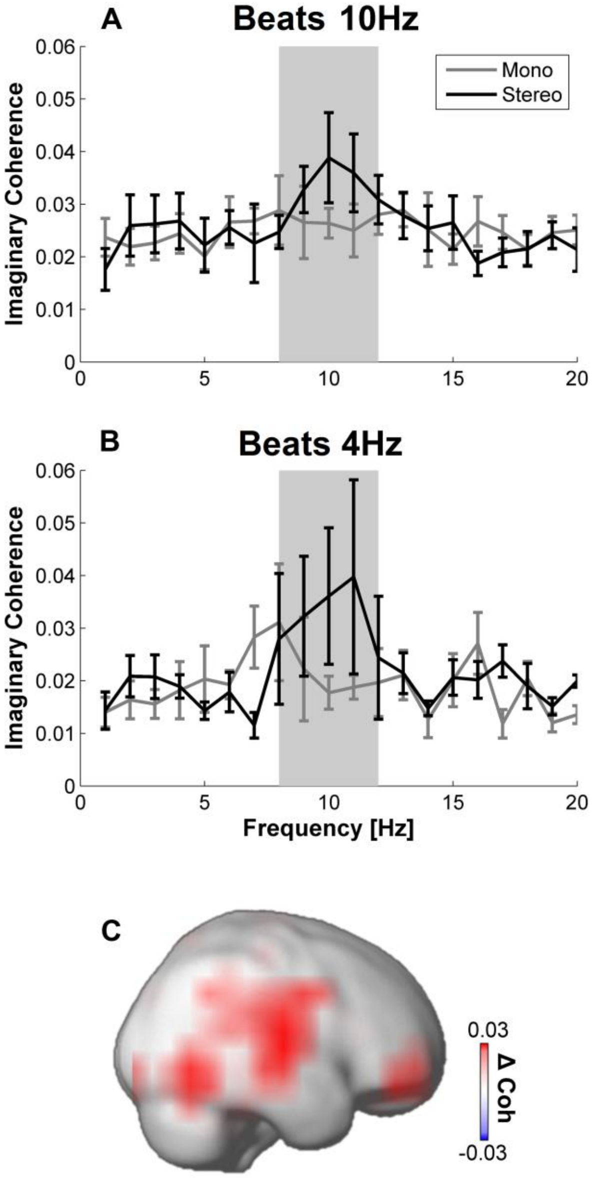
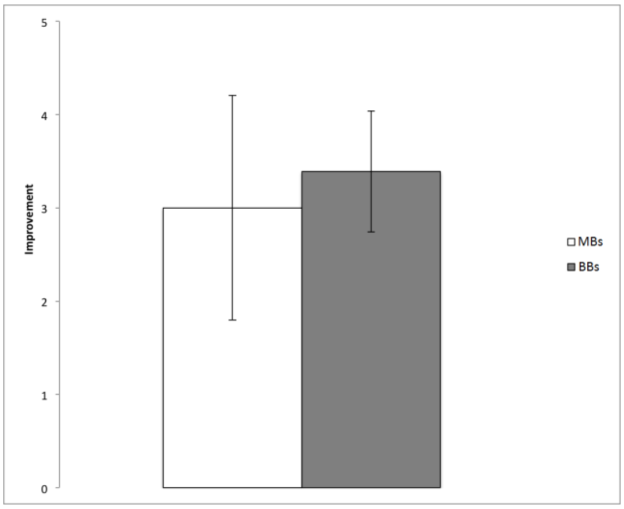
6. Legends to Tables and Figures

Figure 1: *Effect of BBs on interhemispheric coherence*



Both (A) 10Hz BBs and (B) 4Hz BBs produced a significant increase in interhemispheric coherence between the primary auditory cortices compared to MBs in alpha frequencies (9-11Hz). Note the similarity of the patterns of the two graphs. (C) Subtraction of FC map during BBs from the FC map during MBs shows a significant increase in interhemispheric alpha-band coherence in fronto-temporo-parietal areas around the auditory cortex ($p<0.05$ uncorrected).

Figure 2: Behavioral performance in dichotic digit test.



Subjects improved after both stimulation conditions, but no statistically significant difference between BBs and MBs was found (p=.79)

DISCUSSION GENERALE

Dans cette étude nous avons mis en évidence une augmentation de la cohérence interhémisphérique durant la présentation de sons binauraux en comparaison à une condition contrôle où les deux mêmes sons étaient présentés dans chaque oreille. Il est important de noter que ces changements de cohérence ont été exclusivement observés dans la bande alpha (8-12Hz), et ce, quelle que soit la fréquence du son binaural utilisée. De plus, nous n'avons pas mesuré d'augmentation globale des oscillations cérébrales (i.e. power) lors de l'une ou l'autre des stimulations auditives.

Contrairement à ce qui avait été suggéré par certains auteurs précédemment (Vernon, 2009; Atwater, 2004), nos résultats ne sont pas compatibles avec une synchronisation des ondes cérébrales avec le stimulus auditif externe. Effectivement, dans ce cas nous aurions alors mesuré une augmentation de la puissance de la bande alpha et la synchronisation des oscillations aurait été sélective à la fréquence des stimulis auditifs présentés.

En conséquence, nous pensons que l'effet électrophysiologique que nous observons est secondaire à l'intégration inter auriculaire nécessaire à la perception d'un son binaural. Cette hypothèse se base sur plusieurs travaux ayant suggéré qu'une tâche cognitive complexe peut moduler la cohérence du système concerné (e.g. Mima et al., 2001; Palva, Palva and Kaila, 2005; Driel, Ridderinkhof and Cohen, 2012). Lors de la présentation d'un son binaural, le cerveau crée à partir des deux sons perçus séparément un son identique à celui qui aurait été entendu si les deux sons avaient été combinés dans l'environnement extérieur. Nous pensons que c'est l'intégration entre les cortex auditifs de chaque hémisphère nécessaire à la création de ce son unique qui est à l'origine de l'augmentation de la communication inter-hémisphérique que nous avons observée.

Malgré ces effets sur la cohérence et le lien qu'il existe entre FC et comportement (Hummel et Gerloff, 2005; Fox et al., 2007; Guggisberg et al., 2015), nous n'avons pas pu mettre en évidence d'effet comportemental dans ce travail. La tâche de discrimination auditive que nous avons employée est considérée comme un outil fiable dans la mesure de l'intégration auditive inter-hémisphérique (Musiek, 1983; Bellis and Wilber, 2001; Westerhausen and Hugdahl, 2008) et nous pensons que son choix est pertinent compte tenu de nos résultats électro-physiologiques révélant une augmentation de la FC entre les deux cortex auditifs. Un élément qui pourrait expliquer l'absence d'amélioration auditive est l'effet potentiellement limité dans le temps des sons binauraux. En effet, dans cette étude, la cohérence a été mesurée durant la stimulation auditive alors que la performance auditive a été évaluée après la stimulation. Comme nous n'avons pas d'indication sur la durée des changements de la cohérence, il est possible que celle-ci soit limitée à la période de stimulation auditive et par conséquence sans effet sur la tâche comportementale. Une nouvelle étude mesurant la FC après stimulation permettrait d'établir si les sons binauraux ont un effet prolongé sur la cohérence et ainsi définir leur potentiel intérêt clinique. En analysant les résultats, nous avons remarqué que plus les sujets avaient une capacité de discrimination auditive faible (i.e. performance basse avant stimulation), plus ils s'amélioraient après l'écoute du son binaural sans qu'une corrélation semblable ait été observée lors de la stimulation contrôle. Ce dernier élément suggère que les sons binauraux pourraient être bénéfiques chez des patients ayant une communication interhemisphérique diminuée mais cette hypothèse devrait être formellement testée.

Nous avons récemment montré que la cohérence pouvait être ciblée par un système de neurofeedback et utilisée pour améliorer la fonction motrice chez des patients hémiplégiques (cf. Annexe 1, Mottaz et al., 2014). Parvenir à moduler la connectivité fonctionnelle pourrait donc conduire au développement de nouvelles thérapies en réhabilitation mais également en psychiatrie où plusieurs anomalies de la FC ont été décrite (Iturria-Medina, 2013). Ce travail montre qu’il est possible de moduler la FC en utilisant un simple stimulus auditif externe, même si d’autres études sont nécessaires pour établir s’il existe un effet comportemental associé qui pourrait être utilisé à des fins thérapeutiques.

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ANNEXE

ARTICLE ORIGINAL:

Neurofeedback training of alpha-band coherence enhances motor performance

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Highlights

- New brain–computer interface approach with training of coherence between target areas.
- Healthy subjects and stroke patients can learn to enhance coherence.
- Training of alpha-band coherence between motor cortex and rest of brain leads to improved motor performance after stroke.

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- Training of alpha-band coherence between motor cortex and rest of brain leads to improved motor performance after stroke.

ABSTRACT

Objective: Neurofeedback training of motor cortex activations with brain–computer interface systems can enhance recovery in stroke patients. Here we propose a new approach which trains resting-state functional connectivity associated with motor performance instead of activations related to movements.
Methods: Ten healthy subjects and one stroke patient trained alpha-band coherence between their hand motor area and the rest of the brain using neurofeedback with source functional connectivity analysis and visual feedback.
Results: Seven out of ten healthy subjects were able to increase alpha-band coherence between the hand motor cortex and the rest of the brain in a single session. The patient with chronic stroke learned to enhance alpha-band coherence of his affected primary motor cortex in 7 neurofeedback sessions applied over one month. Coherence increased specifically in the targeted motor cortex and in alpha frequencies. This increase was associated with clinically meaningful and lasting improvement of motor function after stroke.
Conclusions: These results provide proof of concept that neurofeedback training of alpha-band coherence is feasible and behaviorally useful.
Significance: The study presents evidence for a role of alpha-band coherence in motor learning and may lead to new strategies for rehabilitation.

1. Introduction

The technology of brain–computer interfaces (BCI) enables the monitoring of brain activity and the generation of a real-time output about specific changes in activity patterns. The recorded subject receives a feedback about the neural activity associated with his/her efforts and can thus learn to voluntarily modulate brain activity (Kamiya, 1969). This has been shown in particular for the sensorimotor rhythm (SMR). The SMR corresponds to activity of neuronal groups in the sensorimotor cortex in alpha and beta frequencies (~8–30 Hz), which is suppressed by real or imagined movements (Arroyo et al., 1993; Pfurtscheller et al., 2006). The ability of humans to voluntarily modulate the SMR has led to the development of BCI for motor substitution, i.e., for controlling prosthetic and robotic devices (Galan et al., 2008; McFarland et al., 2008). A more recent application of BCI technology consists in training brain patterns with feedback. In neurorehabilitation, the interest of neurofeedback lies mainly in its potential for improving recovery of patients with brain lesions (Birbaumer et al., 2007; Daly et al., 2008). Neurofeedback for motor rehabilitation mostly aims to train SMR modulation (Buch et al., 2008; Broetz et al., 2010; Caria et al., 2011; Ramos-Murguialday et al., 2013) and thus can be seen as a support for motor imagery training (Mattia et al., 2012).

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Here, we propose a new approach for enhancing motor performance with neurofeedback, which does not target circumscribed neural activations related to movements. Instead it is based on a resting-state network correlate of motor performance.

The brain is a complex network of dynamic systems with abundant functional interactions between local and more remote brain areas (Varela et al., 2001). Interregional neural communication is thought to be accompanied by a synchronization of oscillations between different brain regions (Fries, 2005). This interregional synchronization can be quantified with the concept of *functional connectivity* (FC) which is a measure of the statistical dependency between activity in different brain regions.

Synchronization has also been observed in the resting brain with different imaging techniques including fMRI (Greicius et al., 2003), magnetoencephalography (He et al., 2008; Brookes et al., 2011), and electroencephalography (EEG) (Guggisberg et al., 2011; Guggisberg et al., 2014). Moreover, a linear correlation has been described between FC at rest and performance in motor and cognitive tasks, in healthy people (Fox et al., 2007; Wang et al., 2010; Hipp et al., 2011; Koyama et al., 2011; Schlee et al., 2012; Wang et al., 2013) and in stroke patients (He et al., 2007; Carter et al., 2010). Particularly, FC in the EEG alpha band (8–12 Hz) between a brain area and the rest of the brain was significantly correlated with performance in tasks depending on this area. For instance, the more the primary motor cortex of stroke patients was functionally connected to the rest of the brain in the alpha band, the better patients were able to perform motor tasks (Dubovik et al., 2012; Dubovik et al., 2013). Based on this observation, we hypothesized that a treatment capable of increasing alpha-band FC between the motor cortex and the rest of the brain should have beneficial effects on motor performance. Recent studies have indeed shown that traditional neurofeedback training of SMR modulation improves motor cortex FC as a marker of recovery (Várkuti et al., 2013; Sugata et al., 2014). Here, we developed a neurofeedback system where EEG FC is trained directly (Sacchet et al., 2012). This study aimed to provide proof of principle that such a network variant of neurofeedback training is feasible and that it is behaviorally useful.

As training FC may require different mental efforts than activations of the motor cortex, we first tested whether healthy participants need particular instructions to be able to modulate cortical FC. In a second experiment, we demonstrated that most healthy subjects can voluntarily enhance alpha-band FC of their motor cortex in a single session of neurofeedback. In the third experiment, a patient with chronic stroke learned to enhance alpha-band FC of his affected primary motor cortex in 7 neurofeedback sessions applied over one month. This was associated with clinically meaningful improvement of his motor function.

2. Methods

All procedures were approved by the University Hospital of Geneva Ethics Committee and subjects gave informed written consent for their participation in the study. Healthy subjects were paid for participation.

2.1. Experiment 1

The purpose of this experiment was to test whether particular instructions can facilitate the voluntary modulation of FC.

2.1.1. Participants

Seven healthy subjects participated. Data from two subjects were excluded because of abundant EEG artifacts. The participants had a mean age of 28 years ranging from 26 to 33 years old, five were females, and two subjects were left-handed.

2.1.2. Task

Three different mental imagery tasks were performed by the subjects, and each was repeated once for the left side and once for the right side. They were chosen based on previous work suggesting that they might be associated with modulations of alpha-band coherence. In the first task, the subjects had to imagine the space or distance separating the fingers of their hand. Mental imagery of space was reported to induce a consistent increase in alpha-band coherence in pioneering studies on neurofeedback (Fehmi, online article). In the second task, the subjects had to imagine a movement of their hand without actually moving it (Andrew et al., 1996). In the third task, the subjects simply received the instruction to increase the neural synchrony in their brain hemisphere.

Before these tasks, subjects were recorded during a resting-state condition of the same duration.

2.1.3. Data acquisition

EEG was recorded with a 128-channel Biosemi ActiveTwo EEG-system (Biosemi B.V., Amsterdam, Netherlands) at a sampling rate of 512 Hz. Artifacts like eye movements, muscular contractions and electrode artifacts were excluded by visual inspection of the data leaving between one and three minutes of clean data for each condition. Channels containing artifacts over prolonged periods were completely excluded from further analyses.

2.1.4. Functional connectivity analysis

The detailed procedures for EEG source connectivity analyses have been described previously (Guggisberg et al., 2011). Artifact-free data was divided into segments of 1 s duration, re-referenced against the average of all included electrodes, and bandpass filtered between 1 and 20 Hz. A spherical head model with anatomical constraints (SMAC) with 10 mm grid spacing (~1000 solution points) (Spinelli et al., 2000) was created based on the Montreal Neurological Institute (MNI) standard brain (Mazziotta et al., 2001). An adaptive spatial filter (scalar minimum variance beamformer) was used to estimate grey matter source time series from the sensor data (Sekihara et al., 2004). Computation of the spatial filter $\mathbf{w}$ used a lead-potential $\mathbf{L}$ as well as the channel covariance $\mathbf{R}$ of recorded data:

$$\mathbf{W}(r) = \frac{\mathbf{R}^{-1}\mathbf{L}(r)}{\mathbf{L}^{\mathrm{T}}\mathbf{R}^{-1}\mathbf{L}(r)}, \tag{1}$$

where r represents each solution point. Dipole orientations were fixed such they yielded maximum output signal-to-noise ratio at each solution point (Sekihara et al., 2004; Guggisberg et al., 2011).

FC was quantified as the absolute imaginary part of coherence (IC) (Nolte et al., 2004), representing lagged coherence, between voxel pairs. The advantage of IC over other measures of FC is that it is not subject to biases arising from volume conduction or spatial leakage of the inverse solution (Sekihara et al., 2011). Imaginary coherence was calculated for the frequency band between 8 and 12 Hz by tapering non-overlapping 1 s epochs with a Hanning window and performing a discrete Fourier transform with 1024 frequency bins f. The complex Fourier coefficients $\mathbf{F}$ at all electrodes were projected into the source space:

$$\mathbf{G}(f) = \mathbf{w}^{\mathrm{T}}\mathbf{F}(f), \tag{2}$$

where T indicates the matrix transpose. We could then compute IC from the Fourier transformed source time series $\mathbf{G}$ from each voxel to all other voxels resulting in a full all-to-all voxel connectivity matrix:

$$\mathbf{IC}(f) = \left|\mathrm{Im}\frac{\mathbf{G}(f) * \mathbf{G}(f)}{\mathrm{diag}\left(|\mathbf{G}(f)|^{\mathrm{T}}|\mathbf{G}(f)|\right)\mathrm{diag}\left(|\mathbf{G}(f)|^{\mathrm{T}}|\mathbf{G}(f)|\right)^{\mathrm{T}}}\right|, \tag{3}$$

where * denotes the complex conjugate, Im the imaginary component, and diag(**M**) the vertical vector formed by the diagonal entries of the matrix **M**. IC at the alpha band was obtained by summing the cross- and auto-spectra across the corresponding frequency bins.

Individual voxel connectivity was computed as the average of its coherence with all other voxels. We thereby obtained a measure of global FC in the alpha band of each voxel during each condition (Dubovik et al., 2012). Our calculation of global coherence to the entire brain corresponds to the graph theoretical measure of node degree in weighted networks (Newman, 2004). Hence, it can be seen as an index of the overall importance of an area in the brain network (Stam et al., 2012).

2.1.5. Statistical analysis

The FC map of each task was compared to the pre-session resting-state map in a voxel-wise manner. Differences were averaged across subjects and tested against the null-hypothesis of zero change with statistical non-parametric mapping (SnPM) at each voxel. A correction for testing multiple voxels was obtained by defining a cluster-size threshold based on the cluster size distribution obtained after random reversions of original data (Singh et al., 2003). In addition, differences between conditions were tested in the primary motor cortex region-of-interest with paired *t*-tests as well as voxel-wise across the entire cortex with SnPM.

2.2. Experiment 2

This experiment investigated whether healthy subjects can modulate alpha-band coherence between the motor cortex and the rest of the brain in a single neurofeedback training session.

2.2.1. Participants

Ten healthy subjects participated. They had a mean age of 27.4 years ranging from 25 to 31 years; 6 were females and 2 left-handed.

2.2.2. Neurofeedback

EEG was acquired with a 128-channel Biosemi ActiveTwo EEG-system (Biosemi B.V., Amsterdam, Netherlands). Channels containing artifacts were excluded from further analysis. At the beginning of each session, 5 min of artifact-free data during an eyes open resting-state condition were acquired. An adaptive spatial filter (scalar minimum variance beamformer) was computed based on a SMAC head model created from the individual MRI and the channel covariance of the resting-state data. A region with radius 20 mm centered on the hand notch was defined as target area for visual feedback. Six subjects (1 left-handed) trained the left motor cortex, four (1 left-handed) the right.

Data was then made available for real-time analysis through the FieldTrip buffer at a sampling rate of 512 Hz (Oostenveld et al., 2011) and was simultaneously recorded for offline analysis. Real-time analysis was updated every 300 ms. At each update, a data segment of 500 ms was average referenced and bandpass filtered between 1 and 20 Hz with a 4th-order butterworth filter. The signal was then projected to the gray-matter voxels with the adaptive spatial filter computed at the beginning of the session. Global functional connectivity in the alpha band (8–12 Hz) between the voxels in the target region and the rest of the brain was calculated. In order to obtain a more stable feedback of current alpha-band coherence, the global FC was averaged over the last 15 overlapping segments (last 4.7 s). Coherence magnitudes can be influenced by changes in signal-to-noise ratios. To minimize this potential confound, we normalized local IC magnitude by calculating *z*-scores (Dubovik et al., 2012). This was achieved by subtracting the mean IC value of all voxels of the subject from the IC values at target voxels and by dividing by the standard deviation over all voxels. The mean normalized IC of voxels in the target region was then used for visual feedback.

2.2.3. Task

Subjects received visual feedback on their current alpha-band coherence on a scale made of 12 white horizontal stacked bars. Subjects were instructed to raise the bar as high as possible. Given the result of experiment 1, no particular strategy was proposed. The scale of the feedback was adapted for each participant such that the value of the top bar was reached during about 10% of the feedback trial time.

One session of neurofeedback training consisted of 40 neurofeedback trials lasting 45 s each for a total duration of 40 min. A longer pause between trials was offered every five minutes.

2.2.4. Offline analysis

We assessed the effect of feedback training on the brain by investigating the change in alpha-band FC over time. Artifacts like eye movements, muscular contractions and electrode artifacts were excluded by visual inspection of the data. Trials were then grouped into four blocks of 10 trials each. Each block represented ten minutes of neurofeedback training. Alpha-band FC of the target voxels was calculated as described above for each of the four blocks.

The evolution of FC during the neurofeedback session was estimated at each voxel by computing the linear regression (least-square minimization) slope over the 4 blocks. This produced new maps with the slope in alpha-band FC at each voxel. Images were flipped along the midsagittal plane in subjects who trained the right motor cortex such that all trained voxels were on the left side of the brain. The average FC evolution slope was then computed at each voxel.

2.3. Experiment 3

This experiment tested the feasibility and usefulness of our network variant of neurofeedback in a patient with chronic stroke.

2.3.1. Participant

One 57 years old, right-handed male patient participated 40 months after a first ischemic stroke in the left internal capsule. The stroke produced severe right sided hemiparesis, right sided hypoesthesia and Broca type aphasia for which the patient had benefited from intensive rehabilitation. At the time of the experiment, he had reached a stable clinical state of moderate impairment without significant changes for more than a year. He had recovered the ability to walk without aid, but the right upper extremity was not functional and not used for activities of daily living. He had maintenance physical therapy once every 2 weeks.

2.3.2. Neurofeedback

The real-time analysis was similar as for experiment 2 with the following exceptions. A realistic boundary element model (BEM) with 10 mm grid spacing was used based on the individual MRI and electrode positions digitized with a Polhemus Fastrak system. Target area for alpha-band FC training was the left (ipsilesional) hand motor cortex. The average of the last 12 overlapping segments (3.8 s) was used for feedback. Sessions were composed of 50 neurofeedback trials of 45 s each for a total duration of 50 min. The patient trained twice a week over one month for seven neurofeedback sessions. He did not receive particular instructions other than to raise the feedback bar as high as possible.

2.3.3. Offline analysis

The neural effects of neurofeedback training were investigated similarly as in experiment 2. Trials were grouped into five blocks.

Each block represented ten minutes of neurofeedback training. A normalized global alpha-band FC map was calculated for each of the five blocks.

At each voxel, the evolution of normalized FC during one neurofeedback session was estimated by computing the linear regression slope (least-square minimization) over the five blocks. In order to look for changes in alpha-band FC within each of the 7 sessions, we tested against the null hypothesis of 0 slope across blocks with a one sample t-test performed at each voxel. The evolution of FC across sessions during the month of training was investigated voxelwise through a linear regression slope computed with the seven FC values of the pre-training resting states.

In addition, a spectrogram of the FC evolution slope during the session, as calculated above, was computed between 1 and 20 Hz.

Power evolution during one neurofeedback session was estimated analogously by computing the linear regression slope over the five blocks.

2.2.4. Clinical assessment

To assess the clinical effect of our resting-state neurofeedback training, a trained physical therapist performed standardized tests of motor function 3 days before the first training session, as well as one day and 6 weeks after the last training session.

Upper limb motricity was measured using the Fugl-Meyer motor assessment for the upper extremity with a maximal score of 66 points (Fugl-Meyer et al., 1975). The grip strength was evaluated with a Jamar dynamometer (Schmidt et al., 1970) and a Nine Hole Peg test was performed for dexterity assessment (Kellor et al., 1971; Gladstone et al., 2002).

We also investigated changes in somatosensory function. Light touch perception was quantified with monofilaments on the thumb and index finger pulp as well as on the hypothenar and forearm.

3. Results

3.1. Experiment 1

All task instructions produced an increase in alpha-band coherence between the medial parietal cortex and the rest of the brain as compared to resting-state (Fig. 1). No significant change was observed in the motor cortex ($p > 0.15$). The global pattern of FC difference was similar between the different tasks and no significant difference in lateralization was found between the left and right homologous tasks nor between different tasks ($p > 0.05$, corrected).

3.2. Experiment 2

Seven out of the ten subjects (5/6 training the left, 2/4 training the right motor cortex) were able to enhance alpha-band coherence between the target motor cortex (Fig. 2A) and the rest of the brain during a single neurofeedback session. On average across all patients, FC increased primarily in the motor and posterior regions of the brain (Fig. 2B).

In contrast to traditional neurofeedback training of *mu* desynchronization, our approach did not require movement imagery and none of the subjects reported to use such a strategy. There was therefore no reason to suspect confounding EMG activation. In order to further exclude the possibility of muscle activations, we analyzed EMG root mean square values of thumb abductor and digit extensor muscles during the neurofeedback in 2 subjects. No increase of muscle activity could be observed compared to rest periods ($p > 0.22$), confirming that participants used pure mental activity for this neurofeedback task.

3.3. Experiment 3

The patient learned to significantly increase alpha-band FC between the target area (Fig. 3A) and the rest of the brain within each training session ($t_6 = 3.8$, $p = 0.009$) (Fig. 3B). This also led to a progressive increase of resting-state global alpha-band FC before each session, as confirmed by a linear regression analysis across sessions ($\beta = 0.17$, $R^2 = 0.6$, $t_5 = 2.8$, $p = 0.040$). This increase was specific to the trained region with a significant positive slope only around trained voxels (Fig. 3C). Moreover, the FC increase in these

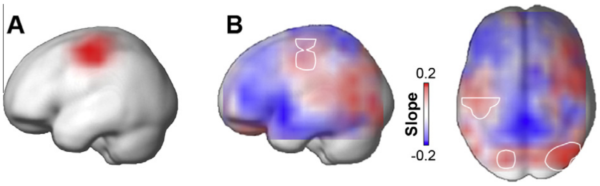

Fig. 2. Mean slope of alpha-band coherence evolution during neurofeedback training of 10 healthy subjects. Subjects tried to voluntarily enhance alpha-band coherence between the left or right hand motor cortex and the rest of the brain in a single session. Subjects with right target are flipped to left for visualization. (**A**) The target area is marked in red. (**B**) Red color indicates regions which global alpha-band coherence increase during the feedback session, blue regions which coherence decrease. Increases occurred relatively specifically in the target area. Maps are unthresholded, significant areas ($p < 0.05$, uncorrected) are marked with white contour lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

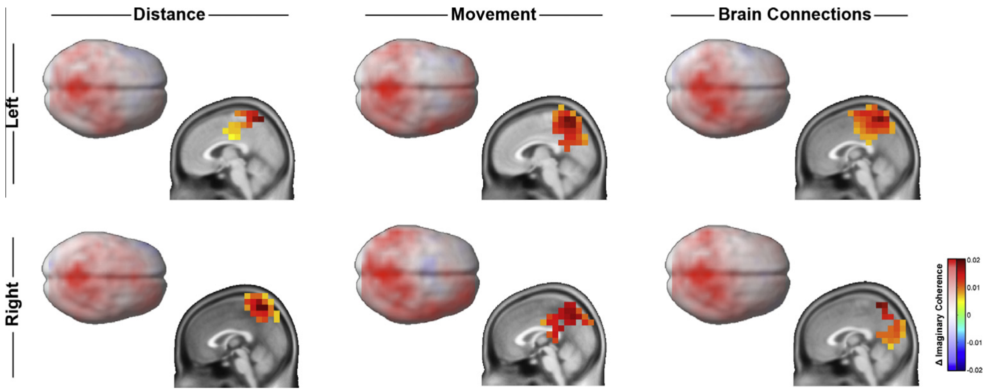

Fig. 1. Different tasks of mental imagery without feedback induce similar changes in alpha-band coherence. Alpha-band coherence between red/yellow areas and the rest of the brain increased during mental imagery tasks as compared to rest (unthresholded in 3D renderings, thresholded at $p < 0.05$ cluster corrected in sagittal cuts). In the *Distance* task, subjects imagined the space between their fingers. In the *Movement* task, they imagined movements of the corresponding hand. In the *Brain Connections* task, they visualized synchronous activity in the corresponding hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

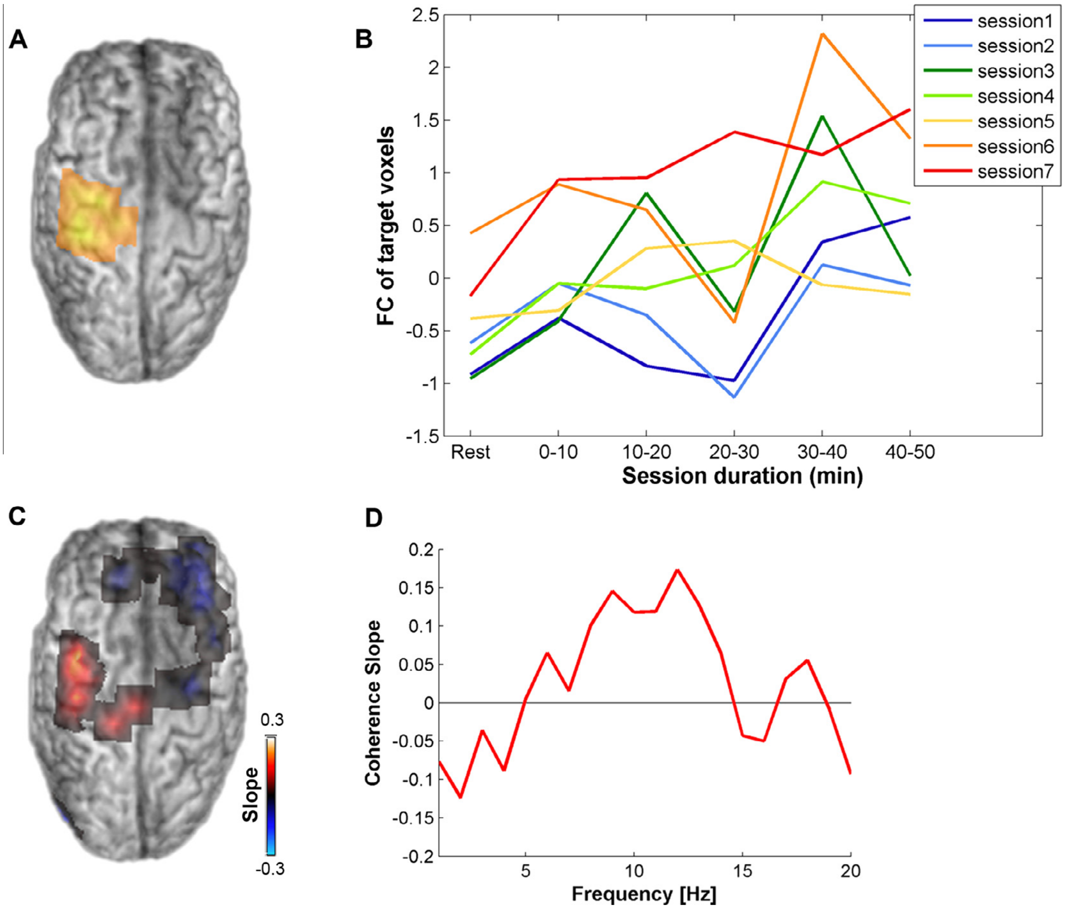

Fig. 3. Alpha-band coherence training in a patient with chronic left hemispheric stroke and right hemiparesis. (**A**) Target area used for feedback. (**B**) Evolution of alpha-band coherence between the target area and the rest of the brain. The patient was able to enhance alpha-band coherence within and across training sessions. (**C**) This enhancement concerned specifically the targeted primary motor cortex ($p < 0.05$, uncorrected). (**D**) The enhancement was specific to the trained alpha frequency band.

Table 1
Clinical assessment of sensorimotor function of the right upper limb in the patient.

	3 Days before training	1 Day after training	6 Weeks after training
Motor assessment			
Upper limb Fugl-Meyer Assessment	37/66	44/66	45/66
Jamar	11.5 kg	11 kg	10 kg
Nine Hole Peg Test	0 pegs placed in 2 min	6 pegs placed in 2 min	7 pegs placed in 2 min
Somatosensory assessment			
Pressure perception (nylon filament)			
D1 pulp	0.6 g	0.4 g	0.4 g
D2 pulp	0.4 g	0.4 g	0.4 g
Hypothenar	0.6 g	0.4 g	0.4 g
Forearm	0.6 g	0.6 g	0.6 g

voxels was specific to the alpha band (Fig. 3D). Conversely, FC training did not induce significant change in alpha power at the target area ($t_6 = -0.4$, $p = 0.71$).

Clinically, the patient improved his right upper limb motor function with an increase of seven points in the Fugl-Meyer score from the pre-training to the post-training session. This improvement was maintained until the third follow-up evaluation 6 weeks later. Dexterity as measured with the nine hole peg test and somatosensory function measured with monofilaments improved as well (Table 1). The patient also reported a subjective improvement and started to use his affected upper limb for activities of daily living. In fact, he became able to participate in a modified constraint-induced movement therapy protocol (Shi et al., 2011) which started about 2 months after the neurofeedback training sessions. Constraint-induced movement therapy had not been possible before our neurofeedback therapy because of insufficient ability to use the affected arm for activities in daily living.

4. Discussion

Our study proposes a new strategy for neurofeedback training. Rather than enhancing local neural activations relevant for task execution, our BCI system trains resting-state network correlates of behavioral performance. This proof-of-principle study confirms that this approach can induce region and band-specific enhancement of network synchrony, in agreement with other recent reports (Sacchet et al., 2012; Koush et al., 2013). Furthermore, our study provides first evidence that network training can translate into lasting clinical improvement of stroke-induced handicap.

The first experiment revealed that several mental imagery tasks enhance alpha-band coherence even without any feedback or training. Hence, typical strategies used for voluntary modulation of brain rhythms are associated with immediate increases in alpha-band coherence. However, this increase was observed mainly in medial parietal regions, but not in the motor cortex. Interestingly, the medial parietal region is part of the so-called default-mode network, which is known to be activated during tasks requiring inward attention to the own body or self, but deactivated during tasks requiring outward attention to external events or objects (Raichle et al., 2001; Cavanna et al., 2006). Since all tested instructions required attention to the own body, it would be possible that they all implicated the default-mode network. This might be associated with a corresponding increase in alpha-band coherence between its nodes and the rest of the brain. Our results do not exclude that some more specific instructions might have more immediate impact on motor cortex alpha-band coherence. For instance our movement imagery condition did not include specific instructions with regards to the aspects of the movement that subjects had to imagine. Previous studies have suggested that imagery of kinesthetic aspects have greater effect on cortico-spinal excitability than visual movement imagery (Stinear et al., 2006) and that it might lead to modulation of alpha-band coherence between the motor cortex and fronto-parietal areas in a neurofeedback environment (Vukelic et al., 2014).

In experiments 2 and 3, we observed that voluntary enhancement of coherent alpha oscillations is also possible in other brain regions such as the motor cortex, but these modulations seem to require at least one session of neurofeedback learning.

Most importantly, the voluntary enhancement of oscillation synchrony between a target area and the rest of the brain was behaviorally useful in our stroke patient. This may be surprising given the large literature on the importance of intensive, task-specific exercises for recovery (Kwakkel et al., 1999; Langhorne et al., 2011). Our patient trained resting-state interactions of the brain without specific motor exercises which are useful for daily living. Yet, he still experienced clinically significant improvements. This adds to growing body of evidence that human behavior in general (Fox et al., 2007), and clinical recovery after stroke in particular (Westlake et al., 2011; Westlake et al., 2012), do not depend only on task-induced brain activation, but also on synchronous intrinsic brain activity at rest. Moreover, while previous studies showed mostly correlational evidence for the importance of resting-state oscillation coherence in behavior, this study shows that manipulation of resting-state alpha-band coherence with neurofeedback leads to behavioral changes. Similarly, transcranial theta-burst stimulation can modulate resting-state alpha-band coherence and this leads to corresponding changes in behavioral performance (Rizk et al., 2013).

Our neurofeedback system trained alpha-band coherence between the target area and the whole brain. This choice was based on our previous observation that these interactions correlated best with performance (Dubovik et al., 2012). Training other frequencies or more specific connectivity patterns would in principle be possible, but the definition of these parameters should be based on evidence for their behavioral usefulness.

Our network variant of neurofeedback has the advantage that it takes into account the massive interconnections in the human brain (Sporns et al., 2004; Stam et al., 2012). Cortical regions are interconnected in a specific topography that ensures efficiency. Brain disease typically affects not only local neural function, but also remote areas and interactions between them (Alstott et al., 2009). The reorganization of connections is thus an important process in post-stroke recovery (Rehme et al., 2011) and training task-induced activations of circumscribed brain areas may not be the most efficient way for repairing the intrinsic brain architecture.

Another advantage of our approach is that it uses a general marker of performance that is not limited to motor function. Alpha-band coherence is also associated with performance in other domains such as language, spatial attention, and memory, both in patients with brain disease and in healthy participants (Dubovik et al., 2012; Dubovik et al., 2013; Rizk et al., 2013). Hence, our approach may also be useful for improving aphasia, executive dysfunction, neglect, and memory disturbances, or even for enhancing performance in healthy subjects. The improvement of somatosensory function seen in our patient might be a good indicator of such potential.

In order to obtain reliable coherence values, the network approach requires acquisition of at least 3–4 s of data. This could lead to feedback delay which could hinder learning (Weinberg et al., 2012). However fMRI based neurofeedback has been proven possible for controlling activations (Weiskopf, 2012) and FC (Koush et al., 2013) while also presenting a delay of several seconds due to haemodynamic response properties and processing time.

Our findings will need to be confirmed in more patients and with a valid control group. Yet, our chronic patient had received intensive standard therapy for three years and reached a stable clinical state before entering the study. Furthermore, he did not receive additional physical training during the study other than his usual maintenance therapy every two weeks. This reduces the risk for non-specific effects. In clinical practice, a combination with intensive physical therapy can be offered which might further enhance the clinical benefits.

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