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INDIREKTE HIRNSTIMULATION DURCH EEG-NEUROFEEDBACK UND AUDITIVE BEAT STIMULATION

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
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von
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Inhalt

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[*] Anhang, nicht formal Bestandteil der Arbeit

Zusammenfassung

In der vorliegenden Dissertation wurde der Einfluss von EEG-Neurofeedback Training (E-NFT) und Auditiver Beat Stimulation auf Kognition, Emotion und elektrische Gehirnaktivitäten untersucht. Grundlage dieser kumulativen Dissertation sind die folgenden Publikationen:

Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects
H.J. Engelbregt, D. Keeser, L. van Eijk, E.M. Suiker, D. Eichhorn, S. Karch, J.B. Deijen, O. Pogarell
Clinical Neurophysiology 127 (2016) 1931–1937

The effects of binaural and monoaural beat stimulation on cognitive functioning in subjects with different levels of emotionality
Hessel Engelbregt, Nora Meijburg, Marjolein Schulten, Jan Berend Deijen
Advances in Cognitive Psychology (2019)

Effects of binaural and monaural beat stimulation on attention and EEG
Engelbregt, H., Barmentlo, M., Keeser, D., Pogarell, O., & Deijen, J. B.
Experimental Brain Research, 239 ((2021 ,9), 2781-2791.*

Die kumulative Dissertation präsentiert zwei verschiedene Techniken der nicht-invasiven Hirnstimulation. Es wird gezeigt, dass es mehrere Möglichkeiten gibt, die Gehirnaktivität auf vorhersagbare Weise zu beeinflussen, indem man sie über primäre menschliche Sinnesorgane wie Augen oder Gehör stimuliert.

Die erste Studie zeigt die Effekte von EEG-Neurofeedback (E-NFT) auf gesunde Probanden. E-NFT ist eine Therapieform, bei der mit Hilfe eines geschlossenen Kreislaufs Feedback über die elektrische Aktivität eines Probanden gegeben wird, welche von einem Computergerät gemessen und dann auf leicht verständliche Weise an den Probanden zurückgegeben wird. Ein Beispiel ist das Bild eines Delphins, der anfängt zu springen, sobald sich die 8 Hz Gehirnaktivität erhöht. Die Studie zeigt, dass es möglich ist, EEG-Neurofeedback (E-NFT) in einer Gruppe gesunder Studierender nach wissenschaftlichen Maßstäben zu untersuchen. Die Studie wurde randomisiert, doppelblind und Placebo-kontrolliert durchgeführt. Es wurde ein Nachweis für kurz- und langfristige Auswirkungen des E-NFT auf das Elektroenzephalogramm (EEG) im Ruhezustand gefunden. Bei den kognitiven Funktionen wurden keine Änderungen festgestellt.

Diese Ergebnisse werden vorgestellt und erörtert. Die Verteilung, Richtung und das Ausmaß von E-NFT- herbeigeführten Wirkungen auf die Gehirnphysiologie sind noch nicht gut erforscht. Die Entwicklung weiterer Hypothesen in Bezug auf die neurophysiologischen Effekte der präfrontalen E-NFT ist von entscheidender Bedeutung, um Informationen für zukünftige experimentelle und therapeutische E-NFT-Anwendungen zu erhalten.

Die zweite und dritte Studie zeigen die Wirkung von 40 Hz Frequenzen, die auf zwei verschiedene Arten angeboten werden: monaural und binaural. Bei den binauralen Beats (BB) werden dem Zuhörer auf das linke und das rechte Ohr separat ein Ton mit leicht unterschiedlicher Frequenz vorgespielt. Im Gehirn entsteht eine Überlagerung, die vom Teilnehmer bewusst registriert wird in Form eines pulsierenden Tones. In unseren Studien betrug der Unterschied zwischen beiden Schallwellen 40 Hz. Für Mono-Beats (MB) werden beiden Ohren die zwei Frequenzen vorgespielt, jedoch wird von den Probanden nur die 40 Hz Frequenz bewusst registriert. Wir fanden keinen Unterschied zwischen beiden Bedingungen bei der Ausführung einer Aufmerksamkeitsaufgabe, jedoch führten Probanden sowohl in der MB- als BB-Bedingung die Aufmerksamkeitsaufgabe schneller aus als in der Kontrollbedingung bei der weißes und rosa Rauschen vorgespielt wurde. Rosa Rauschen (Pink Noise) ist fast dasselbe wie weißes Rauschen (White Noise). Genau wie beim weißen Rauschen werden auch beim rosa Rauschen alle Frequenzen aus unserem hörbaren Spektrum einbezogen, jedoch mit (deutlich) geringerer Stärke. Beim rosa Rauschen gilt: Je höher die Frequenz, desto geringer die Lautstärke. Die 40Hz Beat Stimulation hatte keine messbaren Auswirkungen auf das Elektroenzephalogramm (EEG) im Ruhezustand.

Die vorliegenden spärlichen und widersprüchlichen Befunde rechtfertigen den Schluss, dass BB keine konsistente Wirkung auf die EEG-Aktivität hat. Daher fanden wir keine überzeugenden neurophysiologischen Beweise dafür, dass neuronale Oszillation, d. h. neuronale Synchronisation, eine Rolle bei der BB-induzierten kognitiven Verbesserung spielt. Da die kognitive Verbesserung nicht der neuronalen Synchronisation im Gehirn zugeschrieben werden konnte, was sich in einer Erhöhung der Leistung von 40–45 Hz widerspiegelte, dürfte die verbesserte kognitive Leistung durch andere Faktoren hervorgerufen werden.

Abstract

The principal purpose of the present thesis was to investigate the possible application of EEG-neurofeedback and Binaural Beat stimulation for brain-state, cognitive and emotional modulation in healthy subjects. The cumulative dissertation is based on the following publications:

Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects
H.J. Engelbregt, D. Keeser, L. van Eijk, E.M. Suiker, D. Eichhorn, S. Karch, J.B. Deijen, O. Pogarell
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Effects of binaural and monaural beat stimulation on attention and EEG
Engelbregt, H., Barmentlo, M., Keeser, D., Pogarell, O., & Deijen, J. B. (2021) *Experimental Brain Research*, 239(9), 2781-2791.

The cumulative dissertation presents two different techniques of non-invasive brain stimulation through eyes and ears. The combined papers show that there are more ways to influencing brain activity in a predictable way input via primary human sensory systems.

The first study shows the effects of EEG-Neurofeedback (E-NFT) on healthy subjects. E-NFT is a closed loop feedback therapy in which a subjects electrical activity is measured by a computer device, which returns the measured activity in an easy to understand way to the subject. An example is a dolphin which jumps when 8 Hz. brain activity enhances. The study shows that EEG-Neurofeedback (E-NFT) can be studied according to scientific standards in a group of healthy students. The study was carried out in a randomized, double blind, placebo controlled manner. Proof was found for both short- and long term effects of E-NFT on resting state electroencephalogram (EEG). No changes were found in cognitive functions.

These results are presented and discussed. The distribution, direction, and extent of E-NFT mediated effects on brain physiology are not well understood. The development of further hypotheses with regard to the neurophysiological effects of prefrontal E-NFT is crucial to obtain information for future experimental and therapeutic E-NFT applications.

The second and third studies show the effect of 40 Hz. beats which are offered to the ears in two different ways, Monaural and Binaural. For Binaural Beats (BB), 2 different frequencies of tics are presented to both ears. The difference between the 2 beats is registered consciously by the participant. In our study, the difference between both frequencies was 40 Hz.. For Monaural beats (MB), both frequencies are presented to both ears. Consciously, the participants also register only a 40 Hz frequency. We found no difference between these condition for performance on an attention task. However, in both MB and BB conditions, subjects outperform white noise control condition and in BB condition, subjects outperform pink noise condition.

The present scarce and conflicting findings only justify the conclusion that 40 Hz. BB has no consistent effect on EEG activity. Thus, we did not find convincing neurophysiological evidence that neural oscillation, i.e. neural synchronization, plays a role in BB-induced cognitive enhancement. As the present cognitive enhancement could not be attributed to neural synchronization in the brain as reflected by an increase of 40–45 Hz power, the improved cognitive performance might be mediated by other factors.

Abkürzungsverzeichnis

ABS	Auditory Beat Stimulation, Auditive Beat Stimulation
ACC	Anterior cingulate cortex, vorderer cinguläre Kortex
ADHD/ADHS	Attention deficit and hyperactivity disorder, Aufmerksamkeitdefizit Hyperaktivitätsstörung
BA	Brodmanarea, Brodmann-Areal
BB	Binaural Beat
BFB	Biofeedback
DAT	Dynamic Attention Theory
EEG	Elektroenzephalographie
EC	Eyes Closed, geschlossene Augen
ECG	Elektrokardiogramm
EO	Eyes Open, geöffnete Augen
EOG	Elektrookulogramm
E-NFT	EEG Neurofeedback
Fig	Figure Abbildung
fMRT	Funktionelle Magnetresonanztomographie
fPZ	prefrontaal zentral
Fz	Fronto-zentral
Hz	Hertz
IQ	Intelligenzquotient
kΩ	Kiloohm
LORETA	Low Resolution Brain Electromagnetic Tomography
MB	Monaural/Monoaural Beat
MEG	Magnetoencephalography
ms	Milisekunde
N	Stichprobe
NFT	Neurofeedback Training
NIBS	Non invasive brain stimulation, Nicht-invasive Gehirnstimulation
RCT	response time, Reaktionszeit
rTMS	repetitive transkranielle Magnetstimulation
s	Sekunde, Sekunde
SD	Standardabweichung
sLORETA	Standardized Low Resolution Brain Electromagnetic Tomography
SS-EP	Steady-State Evoked Potential
t	Zeit (measurement)
tDCS	Transcranial Direct Current Stimulation, Transkranielle Gleichstromstimulation
WN	White Noise, weißes Rauschen
3D	Dreidimensional
%	Prozent

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1 Einleitung

1.1 EEG-Neurofeedback

Ein Elektroenzephalogramm basiertes Neurofeedback (E-NFT) ist eine Spezialform des Biofeedbacks. Biofeedback ist ein Sammelbegriff für externe Messungen und Aufzeichnungen von physiologischen Körperprozessen. So kann Biofeedback z.B. Rückschlüsse über Herzfrequenz-Variabilität, galvanische Hautreaktion, Muskelspannung oder Körpertemperatur geben. Hierfür messen Sensoren die Körpersignale einer Person und vermitteln diese an ein Gerät, welches dann den aktuellen körperlichen Zustand wiedergibt. So können unbewusste Vorgänge des Körpers aufgezeigt und anschließend bewusst kontrolliert werden. Wenn sich zum Beispiel ein Muskel einer Person unbewusst zusammenzieht (z.B. bei einer leichten Verspannung) gibt das Gerät eine Rückmeldung, wodurch die Person auf diesen Vorgang aufmerksam wird. Nach einer gewissen Zeit kann die Person lernen, die Kontraktion des Muskels auch ohne das externe Messgerät wahrzunehmen. Auf diese Weise lassen sich unter anderem Haltungsfehler verbessern oder Muskelverspannungen reduzieren (Gaffney, Maluf, & Davidson, 2016).
E-NFT ist eine neurophysiologische Variante des Biofeedbacks, mit dessen Hilfe Gehirnaktivität gemessen und verändert werden können. So wie andere Methoden des Biofeedbacks beruht auch E-NFT auf dem Prinzip der operanten Konditionierung (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Gruzelier, 2014a; Larsen & Sherlin, 2013). Die operante Konditionierung ist eine Schlüsselfähigkeit des Nervensystems, mit der es eine Verbindung zwischen gegenwärtigen Vorgängen und deren zukünftigen Folgen herstellen kann. Das ermöglicht dem Nervensystem zum Beispiel die Belohnungen und Bestrafungen zu verarbeiten (Skinner, 1963; Thorndike, 1898)

Im E-NFT werden Spannungsschwankungen an der Kopfoberfläche mittels Elektroenzephalografie-Geräten (EEG) gemessen und dem Patienten auf einem Bildschirm präsentiert (siehe Abb. 1). Positive Rückmeldung (Belohnung) ist immer dann gegeben, wenn der Patient eine beabsichtigte Veränderung des EEG-Musters für eine bestimmte Zeit herbeiführen kann. Man geht davon aus, dass das Gehirn auch außerhalb der zeitlichen und räumlichen Begrenzung der E-NFT-Behandlung einen erlernten Zustand halten und auch festigen kann. Die genauen Wirkungsmechanismen, die dem E-NFT zugrunde liegen, sind allerdings noch immer unklar (Gruzelier, 2014a, 2014b). In letzter Zeit sind alternative Theorien über den Wirkungsmechanismus des Neurofeedbacks bekannt geworden. Ros und Kollegen zum Beispiel nehmen an, dass die E-NFT-Behandlung Oszillationen der Hirnströme auf ein homöostatisches Gleichgewicht bringt, sodass eine optimale Balance zwischen der Flexibilität und Stabilität des Netzwerkes gewährleistet wird (Ros, J Baars, Lanius, & Vuilleumier, 2014).

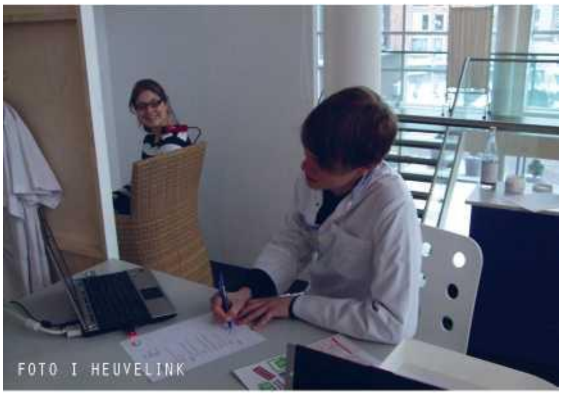

Abbildung 1: eine typische E-NFT-Situation (H.J.; Engelbregt & Koolen, 2013)

1.1.1 EEG und Erregung *(Arousal)*

Unter Erregung (*Arousal*) versteht man eine zunehmende tonische Aktivität des Gehirns die mit einer erhöhten Einsatzbereitschaft einher geht (Kropotov, 2010). Verantwortlich für das Aktivierungsniveau der Hirnrinde (Kortex) sind Nervenzellverbände im Hirnstamm, die anregende und hemmende Verbindungen zum Kortex besitzen. Im Falle des Arousals verursacht eine Synchronisierung einer Vielzahl unabhängiger Nervenzellen ein Signal welches an der Kopfoberfläche abgeleitet werden kann. Aus dem gemessenen Frequenzspektrum lassen sich unter anderem Beta-Wellen (12 – 18 Hz) ermitteln. Im frontalen Kortex entstehen Beta-Wellen zum Beispiel während mentaler Anforderung. In den sensorischen Arealen des Kortex werden Beta-Wellen von einem für das Hirnareal relevanten Reiz stimuliert. Dieser Vorgang geht nicht nur mit einer zunehmenden elektrischen Aktivität einher, sondern steht auch im positiven Zusammenhang mit metabolischer Aktivität (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998). EEG-Komponenten mit einer niedrigen Frequenz werden oft mit Schlaf oder Entspannung in Verbindung gebracht, höhere Frequenzbereiche hingegen verbindet man mit Erregung und mentaler Anforderung. Der angenommene Zusammenhang zwischen höheren EEG-Frequenzen und Erregung ist damit jedoch vereinfacht dargestellt: Die Ursachen der unterschiedlichen EEG-Rhythmen sind noch nicht eindeutig geklärt, darüber hinaus wird der EEG-Rhythmus wahrscheinlich auch von der jeweiligen individuellen Anatomie beeinflusst. Bei bestimmten mentalen Anforderungen können zum Beispiel ereigniskorrelierte Potentiale (EKP) innerhalb des Theta-, Delta-, Alpha- und Gammabereichs beobachtet werden. ERPs sind eine elektrophysiologische Reaktion des Gehirns auf ein Ereignis (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 1999). Die Gehirnwellenaktivität und ihre funktionale Bedeutung ist noch nicht vollständig geklärt, jedoch ist die Forschung auf diesem Gebiet unter Berücksichtigung der verschiedenen Gesichtspunkte hochaktuell und wird in zahlreichen Labors vorangetrieben.

Es wird oft angenommen, dass die gemessene EEG-Aktivität sowohl einen einzelnen kognitiven Prozess als auch den mehrerer gleichzeitig ablaufender kognitiver Prozesse widerspiegeln kann. (Cohen, 2017; Freeman, 2004). Die Frage, ob eine

Zusammenfügung verschiedener elektrischer Eigenschaften von unterschiedlichen Hirnzentren eine zusätzliche qualitative Komponente des Hirns zeigt, bleibt derzeit offen. Unser Augenmerk richtet sich auf die Tatsache, dass im erregten Zustand oder während mentaler Anspannung Betawellenaktivität nicht die einzige positiv korrelierende EEG-Komponente ist. So kann zum Beispiel während der Ausführung einer kognitiven Aufgabe auch eine Zunahme von Gammawellenaktivität des EEG beobachtet werden. (Fitzgibbon, Pope, Mackenzie, Clark, & Willoughby, 2004).

So wie oben beschrieben wird das Arousal des frontalen Kortex vom Hirnstamm aus generiert. Die Erregung muss allerdings ein bestimmtes Niveau erreichen, um eine erhöhte Aufmerksamkeitsfähigkeit erzeugen zu können. Es wird angenommen, dass für die Aufmerksamkeitsfähigkeit drei Elemente nötig sind: Erregung, Orientierung und Konzentration (Ashcraft, 1998). Aufmerksamkeit kann als eine Art „Zündstoff“ verstanden werden, welcher das kognitive System für seine Aktivität „verbrennt“. Anders gesagt: Aufmerksamkeit und Kognition sind eng miteinander verbunden. Dies hat zur Folge, dass eine bessere Aufmerksamkeit bessere kognitive Fähigkeiten erzeugt.

Im Prinzip könnte eine Stimulierung von Betawellenaktivität im Frontallappen zu einem erhöhten Erregungsniveau führen. Eine erhöhte Erregung wiederum könnte die Aufmerksamkeitsfähigkeit steigern, die ihrerseits die mentale Leistungsfähigkeit fördern kann. Das Yerkes-Dodson Gesetz steht mit diesem Gedankengang in Einklang, da es die Leistungsfähigkeit eines funktionalen Systems mit dem Prinzip der Erregung verbindet. Die umgedrehte U-Form (siehe Abb. 2) zeigt, dass Erregung zuerst positiv mit Leistung korreliert, dann aber über den optimalen Erregungswert hinausschießt und sich schließlich negativ auf die Leistungsfähigkeit auswirkt. Sowohl eine zu geringe als auch eine zu hohe Erregung wirkt sich also negativ auf die Leistungsfähigkeit aus. Der Grund hierfür liegt in der Aufmerksamkeitsfähigkeit, die entweder nicht selektiv genug oder zu selektiv arbeitet. Ein optimaler Erregungswert ist allerdings nicht bekannt. Es wird jedoch angenommen, dass ein günstiges Erregungsniveau von den Eigenschaften der jeweiligen Person und den Umständen der zu bewältigenden Aufgabe abhängig ist (Kropotov, 2010).

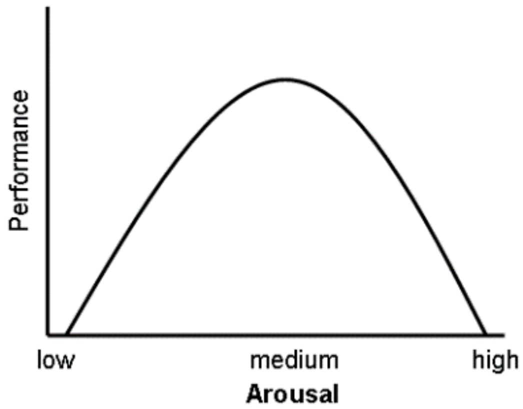

Abbildung 2: Grafik des Yerkes-Dodson Gesetzes

1.1.2 Stand der Neurofeedback Forschung in Bezug auf das Modulieren frontaler EEG Oszillationen

Die Erforschung von E-NFT an gesunden Probanden ist sowohl bei Tieren als auch bei Menschen fortgeschritten. Affen können mit Hilfe von einfachem auditivem oder visuellem Feedback neuronale Aktivität freiwillig steuern. Innerhalb von fünf Sitzungen erreichen sie eine stabile starke oszillierende Aktivität (Philippens & Vanwersch, 2010). Bei Menschen haben einige Untersuchungen eine Zunahme der Betawellenaktivität im Frontalhirn nach Neurofeedback-Behandlungen aufgezeigt (Zoefel, Huster, & Herrmann, 2011; Zotev et al., 2011). Eine Verbesserung der kognitiven Fähigkeiten bei gesunden Probanden durch Neurofeedback-Sitzungen wird angenommen (Gruzelier, 2014a, 2014b). Verschiedene Untersuchungen weisen auf einen Zusammenhang zwischen einer im EEG sichtbaren Veränderung der neuronalen Aktivität und der Neurofeedback-Sitzungen hin. Es zeigten sich auch Veränderungen in der funktionellen Magnetresonanztomographie (fMRT). Ros und Kollegen brachten gesunde Probanden dazu, ihre individuelle Alphawellenfrequenz (8-12 Hz) Aktivität zu unterdrücken. Sie fanden mittels fMRT heraus, dass der Normalzustand der Netzwerkverbindungen bei den Probanden verändert war und sich spiegelbildlich zu den Veränderungen der EEG-Alphawellen verhielten. Diese Veränderung hielt bis zu einer Zeitspanne von 30 Minuten an (Ros et al., 2013).

Einige Untersuchungen mit älteren Probanden zeigten erhöhte Thetawellenaktivitäten ausschließlich in der E-NFT-Gruppe (Wang & Hsieh, 2013). Zusätzlich wurden deutliche Zunahmen in den Gamma- und Beta-Frequenzbändern innerhalb der Sitzungen beobachtet (Staufenbiel, Brouwer, Keizer, & van Wouwe, 2014), so wie eine höhere Aufmerksamkeitsleistung (Wang & Hsieh, 2013) und eine Verbesserung der Sprachfähigkeit (Becerra et al., 2011). Andere Untersuchungen konnten allerdings keine Verbesserung der Aufmerksamkeit oder des Gedächtnisses feststellen (Eijk et al., 2017; Staufenbiel et al., 2014). Derzeit fehlen noch detaillierte Auflistungen und eindeutige Belege für die angenommenen Vorteile der E-NFT-Behandlungen bei älteren Menschen. Vor allem für Menschen in Altersheimen wären eindeutige wissenschaftliche Beweise einer positiven Wirkung der E-NFT-Behandlung von großem Wert, da diese Zielgruppe einem erhöhten Demenzrisiko ausgesetzt ist und deshalb besondere Aufmerksamkeit in diesem Themenfeld bekommen sollte. So bedeutet das Fehlen dieser Daten eine entscheidende Wissenslücke (Stuck et al., 1999).

In der Studie von Arns und Kenemans (Arns & Kenemans, 2014) gibt es Hinweise auf eine positive Langzeitwirkung von E-NFT-Behandlungen, sowohl bei Patienten mit einem Aufmerksamkeits-Defizit-Syndrom mit Hyperaktivität (ADHS) (Leins et al., 2007; Strehl et al., 2006)- als auch bei gesunden Probanden (Gevensleben et al., 2014). Es wurde allerdings bisher nie in randomisierten und kontrollierten Studien belegt, ob E-NFT-Behandlungen bei gesunden Probanden eine stabile Langzeitwirkung über mehrere Jahre aufweisen können.

1.1.3 Zunehmendes Forschungsinteresse an neuromodulatorischen Interventionen

Innerhalb der letzten Jahrzehnte sind etliche neue Studien zum Thema Neurofeedback erschienen. Die Anzahl der Publikationen nahm linear zu. Auf Abbildung 3 ist die Steigerung der Publikationen seit 1990 gemäß Scholar Google dargestellt.

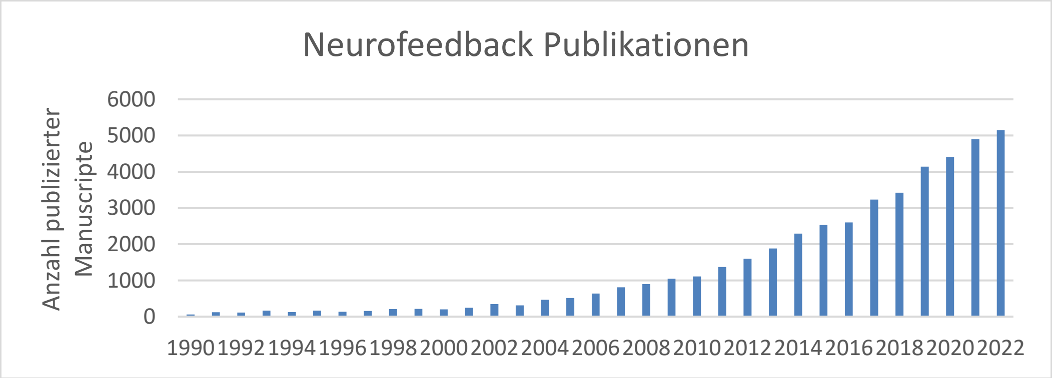

Abbildung 3: Anstieg von Neurofeedback Publikationen auf Scholar Google seit 1990

Die Forschungsergebnisse der Studien zeigen allerdings Widersprüche auf. So belegen einige Publikationen die Wirkung, andere die Wirkungslosigkeit der E-NFT-Behandlungen (Arns et al., 2009; Drechsler et al., 2007; Janssen et al., 2016; Lévesque, Beauregard, & Mensour, 2006; Logemann, Lansbergen, Van Os, Böcker, & Kenemans, 2010; Schabus et al., 2017; Schoneveld et al., 2016; Vollebregt, Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2014). Allen Forschungsarbeiten werden jedoch ernsthafte Fehler und Limitationen vorgeworfen. Studien mit positiven Ergebnissen erhielten Kritik in Bezug auf die Auswahl der Teilnehmer, Vorwürfe das die Gruppen nicht richtig randomisiert waren und Anmerkungen zum fehlerhaften Umgang mit möglichen Placebo-Effekten (H. J. Engelbregt, Kok, Vis, Keeser, & Deijen, 2010; Thibault & Raz, 2016). Studien mit negativen Ergebnissen wiederum wurden technische Fehler sowohl in der Planung als auch in der Ausführung der Forschungsarbeit vorgeworfen (Arns et al., 2017).

Wenn wir jedoch alle Informationen und Kritikpunkte der bisherigen Studien berücksichtigen können wir feststellen, dass eine E-NFT-Behandlung bei ADHS wahrscheinlich wirksamer ist als eine Placebo Behandlung (Leins et al., 2007; Strehl et al., 2006).
Wenn dem so wäre, könnten wir die optimale Behandlungsweise fallspezifisch bestimmen. Diese Erkenntnis würde an die bereits bestehende Annahme anschließen, dass EEG als sogenannter “Neuromarker” für die Vorhersage von möglichen (Neben-) Wirkungen einer medikamentösen Behandlung bei psychiatrischen Krankheiten

eingesetzt werden kann. Die Medikation lässt sich mithilfe dieser Information dann persönlich einstellen. (Arns, 2012; Schork, 2015; Simon & Perlis, 2010).

Momentan liegen nur vorläufige Daten über den Langzeiteffekt von E-NFT vor, auch wenn einige Befürworter in ihren Internetauftritten bereits verheißungsvoll eine positive Langzeitwirkung der Behandlungen bei einer Vielzahl von Krankheiten versprechen.

1.1.4 Fragestellungen der eingereichten Publikationen

Die vorliegende Dissertation sollte Antworten auf folgenden Fragen ermöglichen:

- Ist die Wirksamkeit der E-NFT-Behandlung auf Gehirnaktivität und- Leistung bei kognitiven Aufgaben wissenschaftlich belegbar?
- Lässt sich das Ergebnis von E-NFT-Behandlungen im Ruhezustand und während mentaler Anspannung vorhersagen?
- Lässt sich die Veränderung der Gehirnaktivität durch E-NFT-Behandlungen durch Anwendung von quantitativen EEGs und sLORETA genau lokalisieren?
- Gibt es Erkenntnisse über Langzeitwirkungen der E-NFT-Behandlung?

Ein *4-Kanal Deymed BFB III EEG - System* wurde für die Neurofeedback-Behandlung verwendet. Das System wurde mit Hilfe der BFB III Software mit einem Laptop verbunden. Die Datenausgabe erfolgte über zwei getrennte Kopfhörer und zwei getrennte 15 Zoll RCT Monitore mit *2 ms.* Verzögerung in der Übertragung.
Zur Messung der Veränderungen im Ruhe-EEG wurde ein *Deymed Truscan 32-*Kanalsystem in Kombination mit einer 19-Kanal Elektroden Haube verwendet. Der Elektroden-Hautwiderstand lag immer unter 5 kΩ. Die Elektroden wurden nach dem Internationalen 10/20 System angebracht (Jaspers, 1958). Eine zentral-frontal (Fpz) platzierte Elektrode diente als Masseelektrode. Während der Erstaufnahme wurde das Elektrokardiogram (EKG) and die Elektrookulografie (EOG) weggelassen. Um die kontrollierten Variablen auf einem Minimum zu halten wurde nur das Elektroenzephalogramm (EEG) aufgezeichnet. Das EEG-System war mit einem Laptop verbunden. Die qualitative Analyse und das automatische Screening für epileptische Anzeichen des EEGs wurde mit Hilfe des Programms *Insight II* durchgeführt (Version 2004.11.22, Persyst Development Corporation, Prescott, Arizona). Für die quantitative Analyse wurde *NeuroGuide* (Version 2.6.6) verwendet.

Für eine 3-dimensionale *Stromdichte (current density)* Analyse wurde ein Oberflächen EEG mit geschlossenen Augen durchgeführt und mithilfe von *LORETA package* v20150415 (http://www.uzh.ch/keyinst/loreta.htm) analysiert. sLORETA bestimmt die Verteilung der Stromquellendichte ($\mu V/mm^2$) jedes einzelnen Voxels bei einer räumlichen Auflösung von 5mm (niedrige räumliche Auflösung) im Talairach/MNI

Space. Pascual-Marqui beschreibt die sLORETA Methode ausführlich (Pascual-Marqui, 2002). Das Oberflächen EEG wurde in 2s Abschnitte aufgeteilt und in eine zusammenhängende Datei (sog. „cross spectrum files“) im Frequenzbereich von 12-18 Hz umgewandelt. Die sLORETA Transformation Matrix wurde verwendet, um die elektrische Oberflächenspannung des Schädels in die genormte Stromdichte des Kortex umzurechnen.

1.2 Auditive Beat-Stimulierung

In der zweite und dritte[*] Studie dieser Dissertation wird der Effekt der auditiven Frequenz-Stimulierung (*auditory beat stimulation*, kurz ABS) untersucht. So wie E-NFT ist auch ABS ein vielversprechendes Instrument zur Verbesserung der kognitiven Fähigkeiten. Dennoch können wir, ebenso wie bei E-NFT Studie, keine abschließende Erklärung des Wirkungsmechanismus finden. Es gibt daher noch viele unbeantwortete Fragen. Zwei Fragen können wir allerdings dank der vorliegenden Studie beantworten. Und zwar ob ABS durch eine Binaurale Beat Stimulation (BB) die Aufmerksamkeit verbessert, und ob es wirksamer ist als ABS durch eine Monaurale Stimulation (MB).

Für BB werden über beide Ohren unterschiedliche Tonfrequenzen vorgespielt, die der Hörer bewusst wahrnimmt. Wenn zum Beispiel das linke Ohr einen 160 Hz Ton angeboten bekommt, und das rechte Ohr gleichzeitig einen mit 200 Hz, hört die Person lediglich eine zusammengefügte Frequenz von 40 Hz. Die Zusammenfügung der Frequenzen geschieht im Gehirn im oberen Olivenkomplex (superior nucleus olivary) (Draganova, Ross, Wollbrink, & Pantev, 2008). Möglicherweise spielt dieser Hirnkern eine Rolle bezüglich der Wirkung, die nach Anwendung von BB festgestellt werden kann. Um dieses sicher feststellen zu können, wurde BB nicht nur mit „weißem Rauschen“ und „rosa Rauschen“ (White Noise (WN) und Pink Noise (PN)) verglichen, sondern auch mit MB. Bei MB wird beiden Ohren jeweils dieselbe Frequenz vorgespielt. In der vorliegenden Studie beträgt die Frequenz 40 Hz. Die Versuchspersonen unter Einfluss von sowohl BB als auch MB schneiden während Aufmerksamkeitsübungen besser ab, als wenn sie weißes Rauschen (WN) hören. Die Wirkung der gesteigerten Aufmerksamkeit muss also dieser Studie zufolge im wahrgenommenen Puls von 40 Hz liegen, und kann nicht das Resultat der Aktivität im oberen Olivenkomplex sein. Es scheint jedoch einen Vorteil von BB gegenüber MB in Bezug auf die Aufmerksamkeit zu geben im Vergleich zu PN. Es stellt sich die Frage, welche Kontrollbedingung (WN, PN und/oder MB) in zukünftigen ABS-Studien verwendet werden soll. 40 Hz ABS (BB und MB) hat keine konsistente Wirkung auf die EEG-Aktivität.

40 Hz ABS zeigte keine konsistenten Veränderungen im EEG. Allerdings beeinflusst auch die Persönlichkeit der Versuchspersonen die Wirkung von ABS.

Anhand eines Fragebogens konnten wir zusätzlich die Gefühlsebene der Teilnehmer bestimmen. Bestehender Literatur zufolge wird eine Aktivität von 40 Hz bei

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[*] Anhang, nicht formal Bestandteil der Arbeit

ansteigenden Angstgefühlen entwickelt. Diese Aktivität kann zudem während Panikanfällen beobachtet werden (Hessel J Engelbregt, Keeser, Promes, Verhagen-Schouten, & Deijen, 2012; Guevara et al., 2018; Kara & Polo, 2014; Schicho & Pogarell, 2014). In der vorliegenden Studie wurde festgestellt, dass das Niveau der emotionalen Erregung der Testpersonen tatsächlich Einfluss auf die Prognose der Aufmerksamkeitsübung nach ABS hat.

1.3 Beiträge von Hessel Engelbregt

Beiträge von Hessel Engelbregt zu den Artikeln, die für die kumulative Thesis verwendet wurden

100%
Die Idee für beide Studien wurde von Hessel geformt und geteilt. Darüber hinaus war Hessel für beide Studien die Quelle der Initiierung, der globalen Konzeptualisierung und der groben Skizzierung der Durchführung.

Die folgenden Teile sind zwischen Hessel und den Mitautoren aufgeteilt, und für jeden Artikel wird der Prozentsatz der von Hessel Engelbregt geleisteten Arbeit pro Teil angegeben.

Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects
H.J. Engelbregt, D. Keeser, L. van Eijk, E.M. Suiker, D. Eichhorn, S. Karch, J.B. Deijen, O. Pogarell
Clinical Neurophysiology 127 (2016) 1931–1937

38% Design (u.a. Konzept für die Möglichkeit einer aktiven Kontrollgruppe)
50% Literaturrecherche
25% Datensammlung
33% Statistik
30% Schreiben

The effects of binaural and monoaural beat stimulation on cognitive functioning in subjects with different levels of emotionality
Hessel Engelbregt, Nora Meijburg, Marjolein Schulten, Jan Berend Deijen
Advances in Cognitive Psychology (2019)

30% Design
60% Literaturrecherche
40% Datensammlung
33% Statistik
30% Schreiben

2 Originalarbeiten und Manuskripte

2.1 Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects

(H. J. Engelbregt et al., 2016)

Die Hauptstudie dieser Dissertation wurde von Hessel Engelbregt entworfen und behandelte die Frage ob E-NFT einwandfrei wissenschaftlich methodologisch untersucht werden kann und ob Beweise für Kurz- und Langzeitwirkungen der E-NFT-Behandlungen gefunden werden können. So wurde der Entwurf unter folgenden Voraussetzungen ausgeführt:
- Teilnehmer, Versuchsleiter und Datenanalytiker dürfen die Versuchsbedingungen der Teilnehmer nicht kennen.
- Die Wahl, sowohl der Versuchs- als auch der Placebo-Gruppe, muss randomisiert sein.
- Die Scheinbehandlung weicht von den Versuchsbedingungen nur in der Weise ab, dass sie den hypothetischen Wirkungsmechanismus weglässt.
- Die gut ausgebildeten Versuchsleiter, dürfen nicht so erfahren sein, dass sie den kaum merkbaren Unterschied zwischen dem tatsächlichen und dem Schein-Training wahrnehmen können.

Dieses, wie auch die folgenden Projekte, wurde von der Ethikkommission der Fakultät für Psychologie der VU Amsterdam beurteilt und genehmigt.
Als Versuchsleiter haben sich die zwei Studenten Ruud Vis und Gilles Kok gefunden, die ihre Masterarbeit im Rahmen dieser Studien unter der Leitung von Hessel Engelbregt und Dr. Jan Berend Deijen erfolgreich absolvierten. Hessel Engelbregt war verantwortlich für den Versuchsablauf und achtete auf einen sachgerechten Gebrauch der Materialen. Dr. Jan Berend Deijen sorgte für einen wissenschaftlich korrekten Ablauf der Studie. Zusätzlich beaufsichtigte ein Kliniktherapeut und Forscher die Qualität aller gesammelten Daten. Wir arbeiteten mit einem neuartigen Aufbau der Scheinexposition und ordneten den Ablauf der Versuchs- und Kontrollgruppe zeitgleich an. Beide Gruppen saßen nebeneinander und waren lediglich durch eine einfache Trennwand voneinander getrennt. Der Versuchsleiter bekam alle primären Versuchsdaten auf seinem Laptop zu sehen. Das Feedback wurde über einen Verteiler sowohl den Teilnehmern der Versuchs- und der Kontrollgruppe gesendet.

Auf Abbildung 4 ist eine Skizze der Versuchsanordnung zu sehen. Drei Jahre später lud Evelien Suiker (Masterstudentin, VU Universität Amsterdam) die Teilnehmer zu einem Follow-Up des Versuchs ein. Leider reagierte nur die Hälfte der ursprünglichen Teilnehmer auf die Einladung.

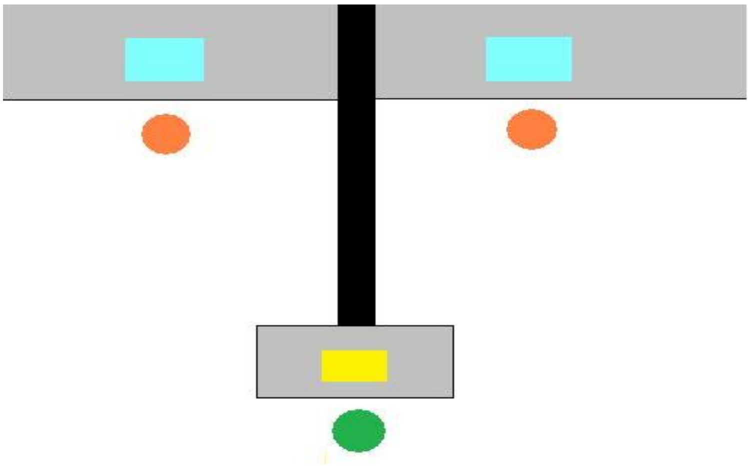

Abbildung 4: Versuchsaufbau mit ♦ = Bildschirm, ♦ = Laptop ♦ = Tisch, ♦ = Trennwand, ♦ = Teilnehmer und ♦ = Versuchsleiter (H. J. Engelbregt et al., 2010)

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Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects

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HIGHLIGHTS

- Controlled EEG neurofeedback study in adult healthy subjects using a novel sham design.
- Altered frontal beta activity in healthy subjects after 15 EEG neurofeedback training sessions.
- Demonstration of long-term effects using resting state EEG after three years.

ABSTRACT

Objective: In this study we evaluated long-term effects of frontal beta EEG-neurofeedback training (E-NFT) on healthy subjects. We hypothesized that E-NFT can change frontal beta activity in the long-term and that changes in frontal beta EEG activity are accompanied by altered cognitive performance.
Methods: 25 healthy subjects were included and randomly assigned to active or sham E-NFT. On average the subjects underwent 15 E-NFT training sessions with a training duration of 45 min. Resting-state EEG was recorded prior to E-NFT training (*t*1) and in a 3-year follow-up (*t*3).
Results: Compared to sham E-NFT, which was used for the control group, real E-NFT increased beta activity in a predictable way. This increase was maintained over a period of three years post training. However, E-NFT did not result in significantly improved cognitive performance.
Conclusion: Based on our results, we conclude that EEG-NFT can selectively modify EEG beta activity both in short and long-term.
Significance: This is a sham controlled EEG neurofeedback study demonstrating long-term effects in resting state EEG.

1. Introduction

Neurofeedback training (NFT) is a neurophysiological training method for altering brain activity. It is thought to be based on the principle of operant conditioning. Operant conditioning is a key ability of neural systems to link the contingency of the reward signal to the probability of a future reward (Arns et al., 2009; Larsen and Sherlin, 2013; Gruzelier, 2014a). EEG is recorded and is fed back in real-time by means of auditory and/or visual feedback. Reinforcement is provided when a desired pattern of brain activity/EEG is held for a certain amount of time. However, the specific underlying mechanisms of NFT efficacy are still unclear and are under systematic investigation (Gruzelier, 2014a,b). Research on EEG-NFT (E-NFT) in healthy subjects has been completed in both animal and human studies. Monkeys are able to voluntarily control neuronal activity by means of simple auditory or visual feedback resulting in strong oscillatory activity changes within five training sessions (Philippens and Vanwersch, 2010). In humans, previous studies found an enhancement of beta activity in the frontal brain after neurofeedback training (Zoefel et al., 2011; Zotev et al., 2014). Cognitive enhancement regarding neurofeedback training in healthy subjects has been efficaciously established in the past (Gruzelier, 2014a,b). There is data demonstrating the change of neuronal activity measured with EEG after EEG

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neurofeedback training, but there is also a direct link to fMRI changes. Ros and colleagues trained healthy subjects to suppress the alpha frequency band (8–12 Hz) and found by means of fMRI that the default mode network connectivity was altered and inversely correlated with EEG alpha changes for a prolonged time period of 30 min (Ros et al., 2013).

As also mentioned in the recent study of Arns and Kenemans (2014), there are indications that E-NFT can induce long-term effects in patients with attention deficit/hyperactivity disorder (ADHD) (Strehl et al., 2006; Leins et al., 2007) and in healthy subjects (Gevensleben et al., 2014). However, so far it has not been investigated in a randomized sham controlled study, whether E-NFT will remain stable over multiple years in healthy subjects.

Our hypotheses were as follows: (1) there will be cognitive changes after frontal beta E-NFT; (2) an increase of resting state EEG beta power (12–18 Hz) at Fz is expected directly after a series of E-NFT; (3) an increase of resting state EEG beta power (12–18 Hz) at Fz is expected after a period of three years post training.

2. Subjects and methods

The study was approved by the Scientific and Ethical Review Committee at the Faculty of Psychology and Education (VCWE) at the VU University of Amsterdam. Subjects were recruited via email or by phone and agreed to participate by written informed consent. They were informed that they could either be part of the experimental or the control group.

2.1. Subjects

25 healthy subjects (19 women, 6 men) participated in this study. All of them were first-year psychology students of the Free University (VU) in Amsterdam and were compensated with elective credit points for participation. The students were randomly assigned to either sham or control group by use of the random sample function of SPSS with a sample size of approximately 50% of all cases for both groups. This procedure was separately applied to both male and female students. A Mann–Whitney test indicated equality of the age within the groups. (Average of 241.1 months for group 1 and 253.2 months for group 2; $U = 43.5$, $N1 = 11$, $N2 = 14$, $p < 0.63$, two-tailed.) There were no sociodemographic differences between the groups at the three time points of measurement. Three participants, one male subject of the experimental group and two women of the control group, dropped out before the start of the study due to personal reasons. Thus, the real E-NFT group consisted of ten subjects (three men, average age 19.7 years, SD 2.6, range 18–25 years), the sham group consisted of 12 subjects (two men, average age 21.08 years, SD 3.85, range 18–32 years), who underwent the study procedures as described below. Three participants (2 control) did not show up during the post EEG measurement procedure. After a period of three years, all subjects were contacted via email or by phone and asked to voluntarily participate in the follow-up study. After three years, ten participants (45, 5%) completed the follow-up measurements. At long-term follow-up, the real E-NFT group consisted of two men and three women ($n = 5$, mean age 23.33 years, SD 3.26, range 20.99–28.14 years) and the control sham group of five women ($n = 5$, mean age 23.59 years, SD 2.15, range 20.99–26.25 years). See Fig. 1 for schematic representation of the study design.

2.2. Methods

EEGs were recorded using a Deymed Truscan 32-channel EEG amplifier in combination with a 19-channel electrode cap. Electrode skin impedance was kept below 5 kΩ. The sampling rate was 128 Hz. Electrodes were placed according to the International 10/20 System (Jaspers, 1958). An electrode at Fpz served as ground electrode. The EEG system was connected to a portable computer. EEG was analyzed by means of the program Insight II (Version 2004.11.22, Persyst Development Corporation, Prescott, Arizona) for qualitative analysis. For quantitative analysis NeuroGuide (Version 2.7.5) was used. A 4-channel Deymed BFB III system was used for the neurofeedback trainings. The system was connected to a laptop computer via BFB III software, output was given to two separate headphones and two separate 15″ RCT monitors with 2 ms delay in transfer time.

2.3. Study procedures

Cognitive performance was measured by use of an abbreviated version of the Groninger Intelligentie Test (GIT) (Luteijn and Barelds, 2004) at measurement 1 and 2, combined with a digital version of 9 mazes, which are part of the digital test program Digoloog (Engelbregt et al., 2004). Since we found no time *x* group effect between measurements 1 and 2 (Engelbregt et al., 2010), we decided to skip the digital tests of the protocol to reduce the effort of the participants. Therefore, only the abbreviated GIT pen and paper tests were taken at measurement 1 (*t*1), 2 (*t*2) and 3 (*t*3).

Baseline EEG was captured one week previous to the E-NFT training sessions. The post measurement was performed within one week after the final training session and the follow-up after approximately three years post training, during both eyes open and eyes closed condition. On average, the total duration of EEG measurements was 30 min. The resting state EEG was recorded for 5 min during eyes closed (EC) and for 5 min during eyes open (EO). Subjects were sitting in a comfortable seat and were

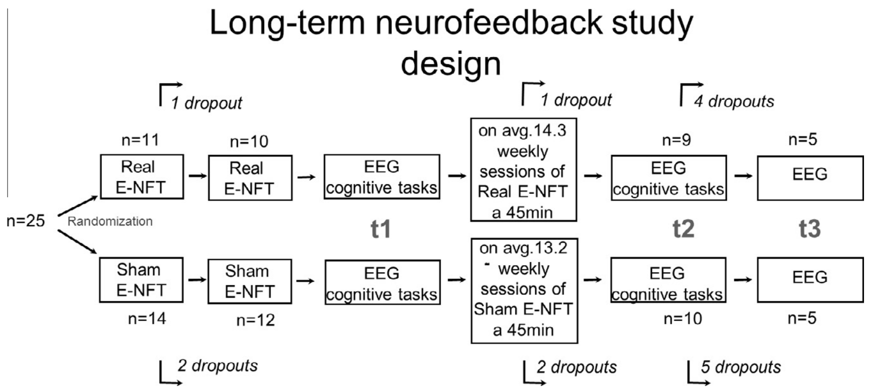

Fig. 1. Illustration of the study design.

instructed to relax and to avoid eye blinks. The lab was located in a sound attenuated room. All EEG recordings were done in a timeframe of between 9 am and 1 pm, before lunch break. Although we aimed to do an average of 15 training sessions, an average of respectively 14.3 (within a range of 13–15 trainings) and 13.2 (within a range of 13–15 trainings) trainings were completed for the experimental and the sham group. Trainings were aimed to enhance 12–18 Hz beta activity within the range of one central frontally located electrode (Fz according to the International 10–20 System for electrode placement (Jaspers, 1958). In order to control possible benefits of facial muscle contractions, an increase of 35–45 Hz activity overruled the possible reward due to increasing 12–18 Hz activity. There was no averaging of EEG data, which practically meant that subjects received real-time EEG feedback as long as the state continued for a minimum of 1 s. Each training session took approximately 45 min, of which two minutes were used for measuring baseline signals of EC and EO conditions respectively. Trainings consisted of 10 different three minute games. The study instructor rewarded parameters on an ad-hoc basis leading to an average score of about 15 points per game session. Both discrete and continuous auditory and visual feedback of EEG parameters were offered to the subjects. One example of continuous visual feedback is a videogame where a swimming dolphin appears as soon as the activity of both 12–18 Hz is increased and 35–45 Hz is inhibited. If this situation endures for longer than one second, a score of one is being earned, which is accompanied by an auditory, rewarding sound. The latter is known as discrete feedback. Subjects in the control sham group were given exactly the same feedback as the neighbor subject of the real E-NFT group. Since there was no connection between their brain activity and feedback, we expect no unconscious learning effect considering the increase of 12–18 Hz frontal lobe activity. A folding screen was placed between subjects of both groups, so no one could see what was displayed on the other screen. See Figs. 1 and 2 for details of the study procedures and the setting.

The study instructor was unaware of the condition since a second instructor put electrodes in the EEG amplifier that was placed on top of the separating wall between the subjects (black line). The electrodes of the sham subject were placed in an inactive channel slot of the recorder. A blanket was placed on top of the EEG recorder to prevent the trainer from gaining any information of the subject's condition. Curious subjects who asked for more information about the sham condition were held back regarding any technical details and referred to the end of the study. After the final training session, all participants were asked about their experience of the training. None of them mentioned any doubt about the experimental condition of the training. Only after the follow-up measurement, three years later, interested subjects were informed whether they were in the sham or in the experimental condition.

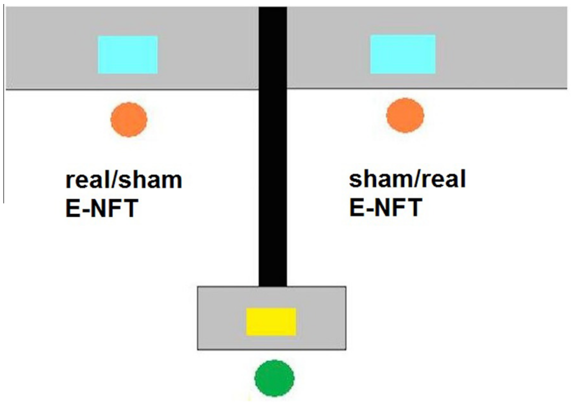

Fig. 2. Presentation of the study settings: the green dot represents the instructor of the study, the orange dots represent both subjects that were randomly assigned to the real E-NFT or to the sham E-NFT condition. The subjects were separated by a folding screen. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.3.1. EEG recordings and selections

22 participants took part in the pre-training measurement procedure, 19 of which were present at the post-measurement after the training procedure and 10 attended the follow-up after three years. One entire individual EEG recording lasted about 10 min. For quantitative analyses Laplacian montage was used for the comparison between conditions.

Data selection for the EEG analysis was done by a neuropsychologist (H.E.). These data were verified by an independent EEG expert (D.K.).

2.3.2. EEG transformations and analyses

Prior to both analyses, EEG recordings were screened by a neurologist for seizure activity and/or abnormal EEG patterns (J.F.). There were no signs of any abnormality. Data of individual EEG recordings were included only when there was a minimum of 30 s artifact free data. For two subjects, the total amount of artifact free data was too low during the post-training recording ($t2$). This was due to a defect electrode in the EEG cap. For the analysis, the absolute power data of 12–18 Hz of the target electrode Fz and the other frontal areas (FP1, FP2, F3, F4, F7 and F8) were included. Data sets were analyzed with SPSS Version 22. Data of both open- and closed eyes conditions of 12–18 Hz were included for the selection of outliers. Outliers (5% trimmed mean) were found by creating z-scores using the descriptives function in SPSS, and by ignoring those scores $(-2.3 \leqslant z \geqslant 2.3)$ by labeling them as missing values. Thus outliers were ignored for the described analyses. For eyes open, there were 7 subjects left in both experimental and sham group for the comparison of measurement 1 ($t1$) and measurement 2 ($t2$). For closed eyes the number of subjects was 10 and 7, respectively. For the comparison of $t1$ and the follow up ($t3$) there were 5 couples for the eyes open- and 4 for the eyes closed comparison. For eyes open, there were a maximum of 10 subjects left in the experimental and 7 in the sham group for the comparison of measurement 1 ($t1$) and measurement 2 ($t2$). For closed eyes the number of subjects was 10 and 7, respectively. For the comparison of $t1$ and the follow up ($t3$) there were a maximum of 5 in the experimental and 5 in the sham group for both the eyes open comparison as for eyes closed.

Due to the relatively high variability between the number of subjects of $t1$–$t2$ and $t3$, with only a maximum of 19 retested participants, we transformed the data into z-scores using Shapiro Wilk test in order to demonstrate relevant figures (see Fig. 3). Repeated measures ANOVA were conducted to evaluate whether there was an interaction between group and time with regard to EEG power (μV^2) between the experimental (E-NFT) and the sham group. The between-subject factor was *group* with two levels (experimental and control, respectively) and the within-subject factor was *time* with two levels (baseline and post-training baseline and follow-up, respectively). The effects were analyzed post hoc using paired-samples t tests, in order to gain insight into existing significant interactions. For the other frontal channels we also conducted Bonferroni corrected repeated measures ANOVA, only to gain insight into the specificity of the found effects.

2.3.3. LORETA analysis

A surface recorded scalp EEG with eyes closed was used for a 3D current density analysis using the LORETA package v20150415 (http://www.uzh.ch/keyinst/loreta.htm). LORETA estimates the current source density ($\mu V/mm^2$) distribution of each voxel at

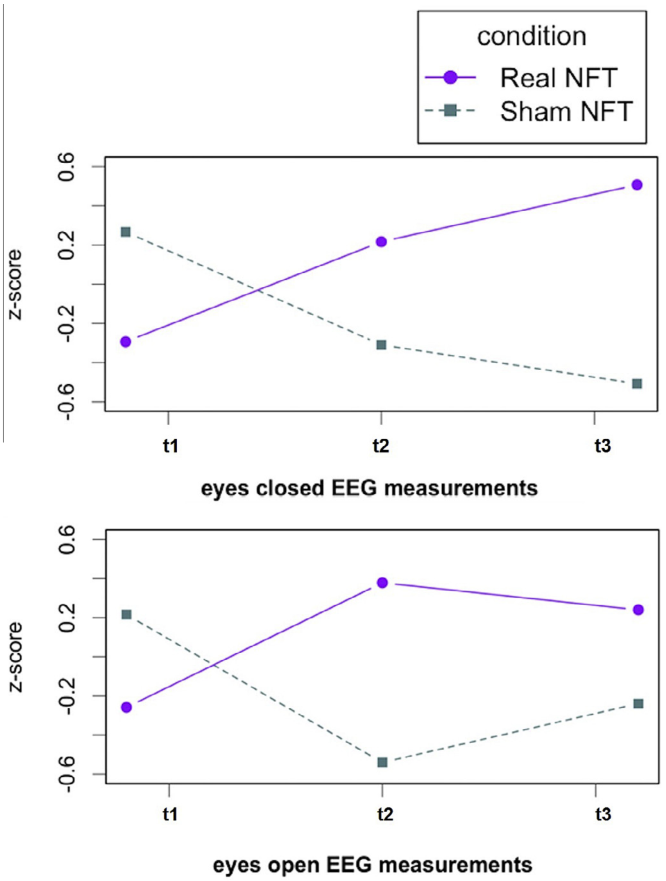

Fig. 3. Interaction effects of group (real E-NFT and sham E-NFT) *x* time for 12–18 Hz frequency band of EEG electrode Fz. Displayed are mean *z*-scored power differences of both eyes closed and eyes open for measurement 1–2 (*t*1–*t*2) and measurement 1–3 (*t*1–*t*3), respectively.

5 mm spatial resolution (low resolution) in the Talairach/MNI space. A detailed description of the sLORETA method is explained by Pascual-Marqui (2002). The scalp EEG was segmented into 2s segments and converted into cross spectrum files for the discrete frequency range of 12–18 Hz using the sLORETA transformation matrix in order to convert the electrical scalp activity into standardized current density in the cortex. Due to the variability of structural brain tissue and conductivity levels in small sample sizes we used a subject-wise data normalization to eliminate a global source of variability. Nine subjects were included for the comparison *t*2 vs. *t*1 resting state EEG data, for the conditions eyes closed and eyes open (18 EEG data sets). For the five remaining subjects, the comparison *t*3 vs. *t*1 resting state EEG data was used again for the condition eyes closed and eyes open (10 EEG data sets). The statistical comparisons between *t*3 vs. *t*1 and between *t*2 vs. *t*1 were done for real E-NFT and sham E-NFT using the implemented statistical nonparametric mapping tool. The statistical level was set at $p < 0.05$ (two-tailed) and $p < 0.01$ (two-tailed).

3. Results

3.1. EEG

The results indicate significant time *x* group interaction effects for channel Fz for closed eyes (EC) conditions between measurement 1 (*t*1) and 2 (*t*2) and measurement 1 and 3 (*t*3). For open eyes (EO), a significant time *x* group interaction effect within subjects was found between *t*1 and *t*3, and a trend towards a significant effect between *t*1 and *t*2 (see Table 1, Fig. 3). No significant effects or trends on other channels were found.

The results of the post hoc paired-samples *t* tests indicate a significant increase of 12–18 Hz activities at *t*2 in comparison to the *t*1 measurement for the experimental group (real E-NFT) in both EC and EO condition on Fz. For eyes open, there was a significant increase of 12–18 Hz activity on location Fz between *t*1 and *t*3 for the experimental group (see Table 2).

3.1.1. sLORETA results

The sLORETA analysis revealed a significant effect in the beta frequency band (12–18 Hz) for the comparison *t*2 vs. *t*1 in frontal brain regions, such as the right and left medial frontal gyrus and the left and right superior frontal gyrus ($t_{max} = 6.18$, 86 voxels, BA 8, BA 9, BA 6, $p < 0.05$), predominantly in the right hemisphere (Table 3, Fig. 4A). A second larger cluster was found in the right inferior frontal gyrus and the right middle frontal gyrus ($t_{max} = 6.05$, 36 voxels, BA 45, BA 46, BA 47, $p < 0.05$). Increasing the statistical threshold to $p < 0.01$, a cluster of 9 voxels was found encompassing the right superior frontal gyrus and the right medial frontal gyrus ($t_{max} = 6.18$, 9 voxels, BA 9, BA 46). For the comparison between *t*3 vs. *t*1, increased beta activity (12–18 Hz) was found in cortical regions, such as the right inferior frontal gyrus and the right superior temporal gyrus ($t_{max} = 7.08$, 19 voxels, BA 45, BA 47, BA 22, $p < 0.05$), see Table 3, Fig. 4B. We did not find any significant effects for the sham E-NFT group.

3.2. Cognitive tests

There was no indication of altered performances on cognitive tasks due to E-NFT. Only a main effect for time was found, both past the initial series of E-NFT and three years later, $F(2,5) = 7.2$, $p < .05$, $\eta^2 = .74$. There was no significant interaction between group and measurement *t*, $F(2,5) = 0.57$, $p = .6$, $\eta^2 = .19$ (see Fig. 5).

4. Discussion

The key finding of the current study was an increase of 12–18 Hz frontal lobe activity, specifically at Fz location in the experimental group compared to the sham condition within one week after the final E-NFT trainings. Post-hoc *t*-tests showed a significant increase of 12–18 Hz activity in both EC and EO condition between measurement *t*1 and *t*2, and between measurement *t*1 and *t*3 for the EO condition. LORETA source analysis for the resting state, including both conditions EC and EO, showed a significant 12–18 Hz increase in frontal brain regions such as the medial

Table 1
Interaction effects for target channel Fz (mean square, *df*, *F*, and *p*-value) of, group and time of measurement. The table displays the interactions of the differences in EEG power (μV^2, 12–18 Hz frequency band) between measurements *t*1–*t*2 and *t*1–*t*3, respectively, electrode position and group with both eyes closed, eyes open condition. The number of subjects differs due to selection criteria as mentioned in the section 'EEG transformations and analyses'. R = real E-NFT, S = sham E-NFT. *p* values below .05 are marked in bold.

Eyes open /eyes closed	Real E-NFT (*n*)	Sham E-NFT (*n*)	Type of effect	Mean square	*df*	*F*	*p*
EC	10	7	Fz time *x* group *t*1 vs. *t*2	4899	1	5.518	.080
EO	10	7	Fz time *x* group *t*1 vs. *t*2	6085	1	5.722	**.030**
EC	5	4	Fz time *x* group *t*1 vs. *t*3	18973	1	5.757	**.048**
EO	5	5	Fz time *x* group *t*1 vs. *t*3	2375	1	5.485	**.047**

Table 2
Paired sample *t*-tests for EEG power (μV^2) differences on electrode location Fz (12–18 Hz frequency band), measurements *t*1 (baseline) vs. *t*2 (post training), and *t*1 vs. *t*3 (follow-up) for both groups (R, S) and either condition (EC, EO). R: real E-NFT; S: sham E-NFT, EC: eyes closed, EO: eyes open. EEG power differences are presented as mean ± standard deviation (SD) with 95% confidence intervals (CI). *p* values below .05 are marked in bold.

Condition		Mean	SD	95% CI		*t*-value	*df*	*p*
				Lower	Upper			
Fz EC, *t*1–*t*2	R	−53.67	47.85	−87.90	−19.45	−3.55	9	**.006**
Fz EC, *t*1–*t*2	S	−4.89	59.41	−59.84	50.06	−.218	6	.835
Fz EC *t*1–*t*3	R	−90.46	106.01	−222.09	41.17	−1.91	4	.129
Fz EC *t*1–*t*3	S	69.27	67.20	−14.17	152.71	2.305	4	.083
Fz EO *t*1–*t*2	R	−46.02	45.32	−78.44	−13.60	3.21	9	**.011**
Fz EO *t*1–*t*2	S	8.35	47.30	−35.40	52.09	.467	6	.657
Fz EO *t*1–*t*3	R	−170.42	120.97	−320.62	−20.22	−3.15	4	**.035**
Fz EO *t*1–*t*3	S	24.27	19.63	−.11	48.64	2.76	4	.051

Table 3
Statistically significant differences of cortical current density values (LORETA, 12–18 Hz frequency band); clusters of neighboring voxels are depicted in MNI (Montreal Neurological Institute) brain coordinates, Brodman areas, and anatomical regions. First line: comparison *t*3 vs. *t*1, real E-NFT vs. baseline, 3-year-follow-up. Second and third line: *t*2 vs *t*1, real E-NFT vs. baseline after the end of E-NFT-training.

Measurement	Cluster	Voxels (5 * 5 * 5 mm)	*X*, *Y*, *Z* (MNI space), max value	Brodman area	Anatomical region
*t*3–*t*1	1	7	−10, 55, 5	10	Medial frontal gyrus, superior frontal gyrus
*t*2–*t*1	1	9	5, 40, −20	10, 11	Medial frontal gyrus, orbital gyrus, rectal gyrus
*t*2–*t*1	2	8	5, 40, −10	32	Anterior cingulate

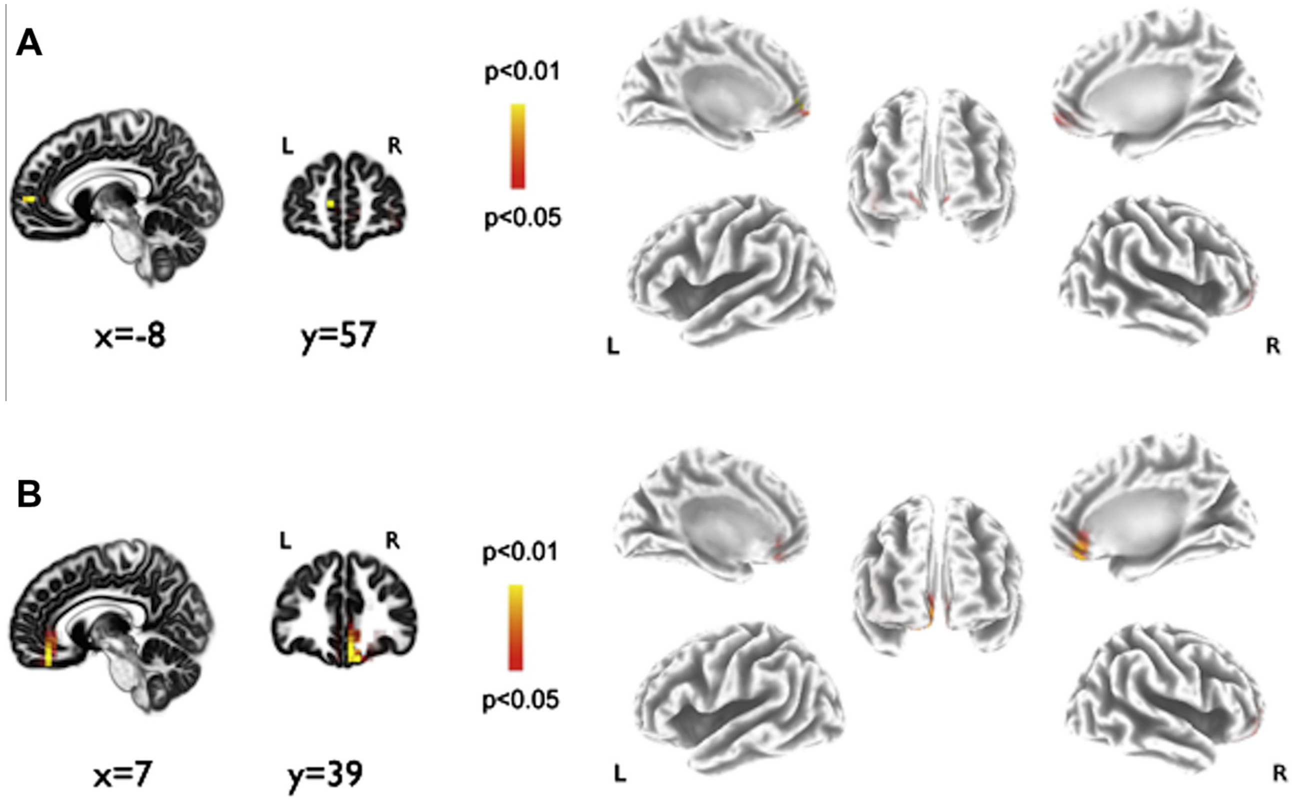

Fig. 4. Long-term effects of E-NFT on a standard volumetric MRI template (left) and on cortical surfaces (right). A. Left: source localization post E-NFT (*t*2 vs. *t*1), increase of 12–18 Hz current density after NFB training at the right and left medial frontal cortex (BA 9) and the left and right superior frontal cortex (BA 8), predominantly in the right hemisphere. Right: cortical surfaces post E-NFT (*t*2 vs. *t*1). B. Left: source localization post E-NFT (*t*3 vs. *t*1), increase of 12–18 Hz current density after NFB training at the right inferior frontal gyrus (BA 45, 47) and the right superior temporal gyrus (BA 22). Right: cortical surfaces post E-NFT (*t*3 vs. *t*1).

frontal cortex and the superior frontal cortex, predominantly in the right hemisphere. The medial distribution of current density is related to the increase in the Fz sensor electrode. It is possible that the low resolution distorted the results slightly. The long-term effects were located even more right sided and also in the superior temporal gyrus. The temporal cortex/hippocampus region is known for long-term potentiation and even though it is speculative, plasticity effects may still occur in the real E-NFT group after three years. The sample size decreased at long-term follow-up, nevertheless, we found that the reported effects in the remaining study participants were stable even three years later at follow-up and remained statistically significant in the open eyes condition.

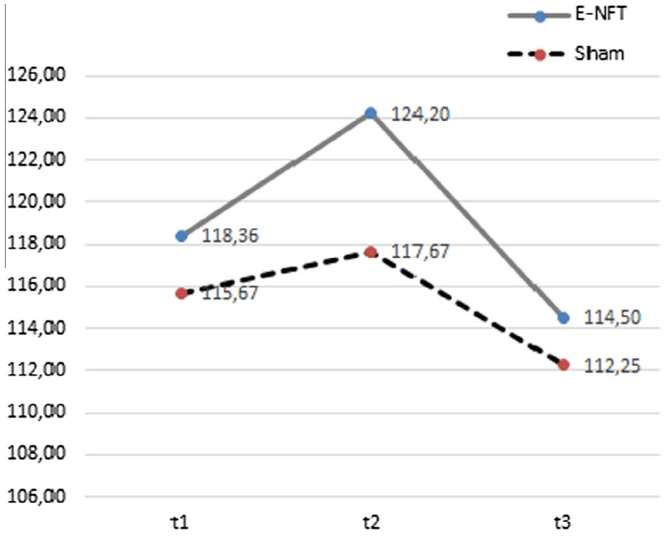

Fig. 5. Averaged IQ scores of both sham E-NFT and real E-NFT group (*t*1 = baseline, *t*2 = week after final training, *t*3 = three years post-training).

As we've only trained with eyes open, the sample size might have been too small to maintain a statistically significant effect for the eyes closed condition. However, the provided data indicate that it might be possible to induce a stable long-term effect after 14 sessions of E-NFT training. The short term-effects are in accordance with early and recent neurofeedback studies using upper EEG alpha or EEG beta frequency training of the frontal brain (Egner and Gruzelier, 2004; Cho et al., 2008; Keizer et al., 2010; Zoefel et al., 2011; Zotev et al., 2014). Based on our results, we conclude that non-invasive EEG-NFT using frontal scalp electrodes can selectively change frontal EEG beta activity, in both short-term and long-term. E-NFT is considered to be based on operant conditioning and in the past it has been shown that healthy subjects can learn to control neuro-electric brain activity by displaying subjects' ongoing changes in the EEG (Elbert et al., 1980; Birbaumer et al., 2000). The process of long-term potentiation (LTP) is suggested to take place by sensitization of neurons after repeated excitation, followed by persistent changing and creation of new synapses and synaptic connections (Kandel, 2006). Using a different non-invasive stimulation approach (continuous theta burst stimulation, cTBS) and a different frontal brain region, McAllister and colleagues found that oscillatory beta activity mediates neuroplastic effects of motor cortex stimulation in humans (McAllister et al., 2013). Regarding our data, we can only speculate whether synaptic strengthening of neurons within frontal brain regions has been induced after continuous reward of beta activity at electrode Fz. Activity in the medial frontal brain region might be more easily induced and is more likely to generate beta 12–18 Hz activity and neuronal-within communication after continuous neurofeedback training sessions. Recently, it was found that 30 min of real-time ACC neurofeedback in healthy subjects induced long-term Hebbian-like restructuring in the following way: Voxels co-activated during the initial training session were found to have increased one day later (Harmelech et al., 2013).

Compared to more passive non-invasive brain stimulation methods (NIBS) such as tDCS or rTMS where effects are lasting for weeks up to months post-treatment, the active involvement of neurofeedback may stabilize training effects. Another main difference between neurofeedback and NIBS is that the latter delivers a fixed stimulation protocol to activate or inactivate certain brain regions, whereas in neurofeedback neuronal activities and responses are individually adjusted and an individualized feedback is applied.

Nevertheless, there are several shortcomings in our study that need to be mentioned. The sample size was low and unfortunately, only 10 of the initial 22 subjects could be included in the longitudinal assessments. Since there were no differences in cognitive performance, the neuropsychological tests used in this study may not have been specific enough to detect subtle changes, because they only globally screened executive capabilities. One alternative explanation would be that the specific neurofeedback protocol in this study was not appropriate to induce cognitive effects in healthy subjects. More specific tasks, such as the n-back or the Go-NoGo-task, should be considered in further study trials. Another explanation for the lack of changes in cognitive function could be a ceiling effect in our sample of healthy, relatively high performing students.

Altogether, our subjects underwent about 302 forty-five minute neurofeedback sessions. The long-term data of study participants remained stable and statistically significant for the EO condition. We only used single channel EEG neurofeedback training in this pilot study. Future studies should integrate EEG connectivity analyses or EEG connectivity neurofeedback since phase synchronization will probably induce even stronger synaptic plasticity of selected brain regions of interest.

With respect to the above limitations, our longitudinal data require future replication in order to validate the relevance of our findings. Nevertheless, we could demonstrate stable long-term effects in a cohort of subjects under E-NFT and the data should be considered as an exploratory approach for a further hypothesis generation.

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2.2 The effects of binaural and monoaural beat stimulation on cognitive functioning in subjects with different levels of emotionality

(H. Engelbregt, Meijburg, Schulten, Pogarell, & Deijen, 2019)

Auch die zweite Studie dieser Dissertation wurde von Hessel Engelbregt entworfen und behandelte die Frage ob ABS wissenschaftlich methodologisch untersucht werden kann und ob ABS-Behandlungen die Aufmerksamkeit verbessern. So wurde die Untersuchung unter folgenden Voraussetzungen ausgeführt:

- Teilnehmer und Versuchsleiter kennen nicht die Versuchsbedingungen der Teilnehmer.
- Die Einteilung der Probanden in Versuchs- oder Placebo-Gruppe ist randomisiert.
- Die Scheinbehandlung weicht nur von der Versuchsbedingung ab indem der hypothetische Wirkungsmechanismus weggelassen wird.

- Alle Faktoren müssen messbar und analysierbar sein. Daher dürfen nur die Beats ohne Hintergrundmusik angeboten werden.

Die Versuchsleiter dieser Studien waren Dr. Jan Berend Deijen und Hessel Engelbregt. Hessel war verantwortlich für den Versuchsablauf und Jan Berend achtete auf einen sachgerechten Gebrauch der Materialen. Binaurale Beats werden auf vielen Internetseiten angeboten, jedoch werden diese fast immer durch Hintergrundmusik begleitet. Um die Beats auch ohne Hintergrundmusik anbieten zu können, und genaue Frequenzen zu ermitteln, hat die Technische Abteilung der Freien Universität (VU) in Amsterdam Audio Dateien mit binauralen Beats, monauralen Beats und weißem Rauschen zusammengestellt. Wir haben uns für ein Crossover-Design entschieden, bei dem die Probanden binaurale Beats, monaurale Beats und weißes Rauschen hörten. Es gibt viele offene Fragen zu ABS. Unser Ziel war es, zumindest die Fragen beantworten zu können ob ABS durch eine Binaurale Beat Stimulation (BB) die Aufmerksamkeit verbessert, und ob es wirksamer ist als ABS durch eine Monaurale Stimulation (MB).

Advances in Cognitive Psychology

The Effects of Binaural and Monoaural Beat Stimulation on Cognitive Functioning in Subjects with Different Levels of Emotionality

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ABSTRACT

Today, binaural and monaural beats are offered over the Internet or by mental health institutes to improve wellbeing or cognitive functioning. This improvement is explained by the assumption that the brain adapts its brainwave frequency to the frequency of the auditory beat. The present study examined the effects of binaural and monaural beat stimulation on attention and working memory in high and low emotional participants. A group of 24 participants (16 females, 8 males) between 19 and 31 years old ($M = 22.33$, $SD = 3.42$) performed a Flanker task to measure attention and a Klingberg task to measure working memory while listening to white noise (WN), 40 Hz gamma binaural beat (BB) and 40 Hz gamma monaural beat (MB). Speed of performance on all three levels of difficulty of the Flanker attention task was faster under the BB and MB condition than under WN. No differences were found between BB and MB conditions. With respect to the quality of performance on the Flanker attention task and the Klingberg working memory task no significant differences under the WN, MB, and BB condition were found. Finally, as participants with low or high emotionality did not respond differently to BB and MB under any of the conditions, effects of BB and MB seem similar in high and low emotional participants. The present study supports the notion that faster attention processing may equally be attributed to the influence of BB and MB. Further research is recommended to gain more insight in the role of factors such as duration of stimulation of BB and MB, frequency range, most appropriate carrier tones, and the role of personality traits.

KEYWORDS

binaural beats
monaural beats
attention
auditory beat stimulation
emotionality
memory
Flanker task
Klingberg task

INTRODUCTION

Nowadays, society is characterized by a lot of distraction due to the use of electronic devices like smartphones. As a consequence, people are searching for methods to help them focus. One frequently used method for increasing focus is the creation of a nondistractive environment, for example listening to specific audio files which can create a focused or relaxed state of mind. These audio files usually contain music or nature sounds, accompanied by tones that aim to influence brainwave activity in such a way that listeners are better able to focus. This method, called auditory beat stimulation (ABS), uses pulsating auditory stimuli to induce a frequency-following brainwave response. Many years ago, it was already suggested that ABS can elicit entrainment of brainwave activity (Lane, Kasian, Owens, & Marsh, 1998). The assumption is that the brain can adapt its brainwave frequency to the frequency of the auditory beat by a synchronization process between neural activity and the auditory stimuli (Wahbeh, Calabrese, & Zwickey, 2007). For exam-

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ple, when listening to a 20 Hz binaural beat, the frequency of brainwave activity should change to 20 Hz.

Long before the application of ABS, dynamic attending theory (DAT) proposed synchronization of endogenous perceptual rhythms with temporally structured sequences of external stimuli, generating expectancies for future events (Jones, 1976). This theory further addressed the issue of how neural rhythms may be exploited by an organism to enable attentional coordination with the dynamic external world (Large & Jones, 1999).

Later, electroencephalography (EEG) and magnetoencephalography (MEG) studies have directly examined the role of endogenous oscillation. For instance, MEG and EEG studies revealed that fluctuation in induced beta- and gamma-band power synchronized with periodic and metrical rhythms, revealing sensory and anticipatory responses to tones (Fujioka, Trainor, Large, & Ross, 2009; Snyder & Large, 2005). Additional EEG studies, using the steady-state evoked potential (SS-EP) found that a periodic rhythm produced a sustained response in the delta band and meter imagery stimulated an additional subharmonic resonance corresponding to the metric interpretation (Nozaradan, Peretz, & Mouraux, 2012a). In addition, complex rhythms were found to elicit multiple SS-EPs in the EEG spectrum at frequencies corresponding to the rhythmic pattern envelope. Moreover, the amplitude of the SS-EPs at pulse and meter frequencies was selectively enhanced, suggesting a role for neural oscillations in pulse and meter induction (Nozaradan, Peretz, & Mouraux, 2012b). These studies of MEG- and EEG- recorded delta, beta and gamma band responses to auditory rhythms confirm predictions of the DAT. Thus, it can be concluded that the hypothesis of neural resonance to musical rhythms originally proposed by Jones (1976) has been supported by the results of subsequent behavioral and electrophysiological studies (Jones, 2009; Large, Herrera, & Velasco, 2015).

It has been suggested that entrainment of ongoing neural oscillations may be a potent mechanism for the brain to generate temporal predictions and to aid active perception (Obleser, Henry, & Lakatos, 2017). Entrainment to music is shared by humans of all cultures and involves a large network of brain structures. It is a highly complex activity, which involves auditory, visual, proprioceptive and vestibular perception, also requiring attention, motor synchronization, performance, and coordination. (Nozaradan, 2014). However, the concept of rhythm is not well defined yet. Although rhythm is frequently assumed to refer to isochrony, that is, strict regularity, many studies on neural entrainment did not use isochronous sequences but allowed for substantial jitter between distinct stimuli (Obleser et al., 2017).

Because of the hypothesized capacity of the brain to synchronize its brainwave frequencies with the rhythm of periodic external stimuli, ABS has been suggested to elicit particular states of awareness, resulting in an increase of people's cognitive functioning or a change in state of mind (Marsh, Worden, & Smith, 1970; Mathewson et al., 2011; Will & Berg, 2007). Three types of ABS can be distinguished: isochronic tones, *monaural* beats (MBs) and *binaural* beats (BBs). Isochronic tones are tones that turn on and off with evenly-spaced intervals, creating a beat with a frequency depending on the length of the intervals. Isochronic tones are similar to monaural tones in that they are combined into a cohesive listening experience before they reach the ear. Because of their predictable patterns, isochronic tones are supposed to be a hallmark of rhythm making them an effective type of beat in brainwave entrainment (Obleser et al., 2017).

In contrast, MBs are generated by simultaneously presenting sine waves of two different, neighbouring frequencies to both ears and BBs are generated by presenting the sine waves of neighbouring frequencies to each ear separately. Unlike with BBs, MBs also use two different frequencies (e.g., 400 Hz and 440 Hz, but they are merged together within one headphone speaker and presented to one or both ears at the same time (Becher et al., 2015; Chaieb, Wilpert, Reber, & Fell, 2015; Oster, 1973). The presentation of two frequencies results in a perceived single beat in a frequency that equals the difference between the two beats. For example, when a 380 Hz beat and a 420 Hz beat are presented at the same time, a beat of 40 Hz is perceived (Colzato, Barone, Sellaro, & Hommel, 2017; Schwarz & Taylor, 2005).

There is a slight difference in neurophysiological processing of BBs and MBs: BBs are referred to as central beats because the interaction of the auditory stimuli most likely occurs in the superior olivary nuclei in the brainstem (Draganova, Ross, Wollbrink, & Pantev, 2008). Neurons in the brainstem are sensitive to phase shifts between both ears. When these phase shifts occur, brainstem neurons fire action potentials which correspond in rate to the phase difference between both ears (Chaieb et al., 2015). In MBs, the auditory stimuli interact in the cochlear and are therefore called peripheral beats (Draganova et al., 2008). From the cochlear, the auditory stimuli are relayed to the cochlear nucleus on the brainstem and to the auditory cortex.

Currently, it is still unclear whether presenting BBs leads to a frequency following response of the presented frequencies or whether it evokes different responses in the brain. Gao et al. (2014) presented BBs in delta (1 Hz), theta (5 Hz), alpha (10 Hz), and beta (20 Hz) band frequencies to 13 healthy participants. Each type of BB was presented for 5 min at a time, with 2-min breaks in between. Participants were asked to keep their eyes closed while listening to the BB, without performing any task; EEG was recorded during the whole experiment. Gao et al. found an increase in relative power (RP) of theta and alpha band EEG and a decrease in RP of beta band EEG after presenting delta and alpha band BB. Furthermore, they found a decrease in RP of beta band EEG after presenting theta band BB and they found a decrease in RP of theta band EEG after presenting beta band BB. These results indicate that there was no frequency following response of the presented BB. In addition, connectivity changes in the brain were examined.I Increased anterior-posterior intra-cerebral connectivity in the theta band was observed under delta, alpha, and beta BBs. These effects suggest that BBs could affect functional brain connectivity, but not necessarily by inducing a frequency-following response.

A small number of studies examined the relationship ABS and attention in healthy people. Results of these studies are conflicting. For instance, Lane et al. (1998) studied whether BBs affected performance on a vigilance task. On three different days, 29 volunteers listened to pink noise, beta (16 and 24 Hz) and theta/delta (1.5 and 4 Hz) for

30 min while performing a vigilance task. Results showed that in the delta BB condition, more targets were detected and fewer errors were made, compared to the theta/delta BB condition. This indicates that high frequency BBs seem to affect vigilance more than low frequency BBs. Additionally, the monotonous task was found to lead to negative changes in mood in all conditions, but these were less pronounced when beta range BBs were presented, as compared to theta or delta range BBs. The authors suggest that beta range BBs may in particular reduce the negative mood effects when performing an unexciting task (Lane et al., 1998). In a more recent study, high frequency (40 Hz) BBs were presented to 36 students (22 female, 14 male; aged 18–28 years old) and it was shown that the presentation of these BBs increased attentional focusing (Colzato et al., 2017). In contrast, in a placebo controlled study in healthy adults, no significant differences were found between the BB group and control group on any of the presented attention tasks (Crespo, Recuero, Galvez, & Begona, 2013).

In addition, the relationship between ABS and memory has been studied, with contrasting results. In one study, 4 healthy participants listened to a 7 Hz (theta) BB for 30 min with an overlay of rain sound, or to rain sounds only (Wahbeh, Calabrese, Zwickey, & Zajdel, 2007). Results showed that immediate recall memory was significantly decreased in the experimental condition compared to the control condition, which suggests a negative effect of BB on memory. In contrast, participants undergoing a 12-minute BB stimulation of 9.55 Hz achieved a significant increase in the capacity of their working memory (Kraus & Porubanová, 2015) and a series of 5 Hz BBs twice a day for 15 days resulted in improvement of immediate word recall (Ortiz et al., 2008). Another controlled study showed that listening to 15 Hz BBs increased response accuracy on a visual-spatial working memory task, while the three control conditions and 5 Hz and 10 Hz BBs all decreased accuracy (Beauchene, Abaid, Moran, Diana, & Leonessa, 2016).

With respect to the effects of BB on cognition, most evidence available concerns the effects of BB on attention and memory. Present meta-analytic evidence indicates that alpha, beta, gamma, and theta BB exposure improves the performance on attention and memory tasks (Garcia-Argibay, Santed, & Reales, 2018).

In addition, a number of studies exploring the effectiveness of BBs on anxiety levels were included in the meta-analysis of Garcia et al. (2018). The included studies of Padmanabhan, Hildreth, and Laws (2005), Wahbeh, Calabrese, Zwickey et al. (2007) revealed that theta-frequency BB reduced anxiety scores compared to the control group, and lead to an increase in quality of life scores. McConnell, Froeliger, Garland, Ives, & Sforzo, (2014), who recorded heart rate variability when participants were exposed to theta-frequency BBs, found differences in the sympathetic and parasympathetic activities compared to the control group, which, in turn, indicated a greater self-reported relaxation. Isik, Esen, Buyukerkmen, Kilinc, & Menziletoglu, (2017) demonstrated that a 10 min exposure to theta-frequency BBs reduced anxiety levels prior to a dental operation compared to the control group that listened to a blank tape. The results of the meta-analysis on these studies confirmed the efficacy of BBs in the reduction of anxiety scores after delta/theta exposure. Other studies, which focused primarily on brain activity during high levels of anxiety, mention relatively reduced theta activity and relatively increased beta activity (Engelbregt, Keeser, Promes, Verhagen-Schouten, & Deijen, 2012; Guevara et al., 2018; Kara & Polo, 2014; Schicho & Pogarell, 2014). It is therefore important that while studying BB, researchers pay attention to possible side effects. For example, researchers studying the effects of 40 Hz frequency BB should be attentive of possible increases in anxiety levels of participants.

The aim of the current study was to establish the effects of a 40 Hz gamma frequency MB and BB on attention and memory. We focused on attention and memory in healthy participants because the effects of BBs on these cognitive skills have been previously studied mainly in healthy participants, which allows for obtaining more conclusive evidence. Moreover, as BBs have been found to decrease anxiety levels, it may well be true that the effects of BBs on cognition may be different for participants with different levels of anxiety. Therefore, we included measurements of the Emotionality scale of the HEXACO-SPI, high scores indicating fear of physical dangers, anxiety in response to life's stresses, need for emotional support from others, empathy, and sentimental attachments with others (De Vries, Ashton, & Lee, 2009)

In our study, we used white noise as the control condition because, by definition, its power spectral density is constant and does not depend on frequency (Garcia-Argibay et al., 2018). However, white noise has been found to differentially affect cognitive performance. For instance, white noise improved the performance of executive function tasks in subattentive children and worsened the memory and executive performance in superattentive children, while the performance of normal-attentive children was unaffected (Helps, Bamford, Sonuga-Barke, & Soderlund, 2014). With respect to the pleasantness of the auditory environment, it was found that task performance was closely related to the participants' feelings of pleasantness of the noise. In healthy participants, short-term memory task performance increased when they felt the white noise was pleasant while performance decreased in the group that felt the noise was unpleasant (Hiwa, Katayama, & Hiroyasu, 2018).

To control for these unpredictable effects of white noise in the control condition, we masked the MB and BB conditions with white noise. In this way, the possible positive or negative cognitive effect of white noise could be assumed to be present in all three conditions. However, as a BB masked in pink noise or white noise was found to have similar effects on cognition as an unmasked BB (Garcia-Argibay et al., 2018), the present masking of ABS could be considered not to alter the potential cognitive effects.

All in all, by comparing MBs and BBs against white noise, we aimed to compare two conditions with active auditory stimulation in which auditory beats supposedly enhance the performance and white noise acts as a neutral stimulus (Goodin et al., 2012). Notably, a number of studies in this field have also used white noise as a control condition (Dabu-Bondoc, Vadivelu, Benson, Perret, & Kain, 2010).

We chose to examine the effects of this frequency band because (a) 40 Hz is related to the highest level of consciousness (Kaiser & Lutzenberger, 2005), (b) it seems to have maximal steady state responses (Schwarz & Taylor, 2005), (c) it may enhance information transmission from one brain region to another (Fell & Axmacher, 2011), and (d) it has been shown to increase attentional focusing and visual working memory (Colzato et al., 2017).

Additionally, we hypothesized that participants with high emotionality scores would benefit more from ABS based on the findings cited above that the level of anxiety declined during or after ABS.

METHODS

Participants

Twenty-four healthy participants (8 males, 16 females) with higher education, aged between 18 and 35 years (*M* = 22.3; *SD* = 3.42), participated in the study. Participants were recruited by using the social networks of the experimenters. All had normal or corrected-to-normal sight and none of the participants reported a history of hearing problems or psychiatric disorders. They were not allowed to use medication or drugs before or during the experiment.

Instruments

The Emotionality subscale of the HEXACO-SPI personality questionnaire (De Vries et al., 2009) was used. This self-reported personality questionnaire is a Dutch adaptation of the HEXACO model (Lee & Ashton, 2004).

Two cognitive tests were presented on an tablet, a Flanker task and a Klingberg test. The Flanker task is an attention and inhibition test based on the Eriksen Flanker task (Eriksen & Eriksen, 1974). Instead of using letters, as in the original Flanker Task, arrows were used as target stimuli. The test consisted of three stages. Before each stage started, written instructions appeared on the screen, followed by practice trials. In the first stage, five green arrows appeared on the screen. Participants were instructed to press one of the two arrow-shaped buttons on the bottom of the screen that pointed in the same direction as the middle arrow. In the second stage, five red arrows appeared. This time, the participants were instructed to press the button that pointed in the opposite direction as the middle arrow. In the third stage, five arrows appeared again, this time either green or red. Participants were instructed to press the button that pointed in the same direction as the middle arrow if the arrows were green, or the button that pointed in the opposite direction as the middle arrow if the arrows were red. In all three stages, the participants were instructed to press the correct button as fast as possible. The reaction times (RTs) and number of errors were taken as output variables.

The Klingberg task is a visuospatial working memory test, based on the Corsi block-tapping test (Bouma, Mulder, Lindeboom, & Schmand, 2012) and consisted of two series. In the first series, participants were presented with a 4 × 4 square grid. A yellow dot appeared for 2250 ms in random order in two different squares, with an interstimuli interval of 750 ms. Participants were then asked to follow the pattern by tapping the same squares in the same order. If the pattern was replicated correctly, the yellow dot appeared two times again. The pattern increased in length and difficulty in subsequent stages after correctly replicating the sequences of at least three out of four trials within one stage. The task ended when two mistakes were made within the same stage. The maximum reached stage was taken as the output variable. In the second series of the test, squares needed to be tapped in a reversed order to the one they were presented in. Again, by tapping the squares in the correct order, higher, more difficult stages could be achieved, but the test ended when two mistakes were made in the same stages. The maximum reached stage was taken as the output variable again.

Auditory Beats

The white noise, MBs and BBs used in the experiment were created by the IT department of the Vrije Universiteit. The sounds were presented on a tablet, through wired headphones with separate channels for right and left ear. Auditory volume was adjusted to a comfortable listening level (speech volume). The selected frequencies for the MB and BB were 440 Hz and 480 Hz. As a consequence, the perceived frequency was 40 Hz. To create the MB, both frequencies were broadcast through both channels. To create the BB, 440 Hz was broadcast through one channel and 480 Hz was broadcast through the other channel. The BB and MB were masked with white noise.

Procedure

Participants were instructed not to drink any coffee or tea or other drinks that contain caffeine at least 2 hr prior to testing. Testing took place in a quiet environment in a home setting. Participants were informed about a sham condition, but not about the presence of BBs and MBs. First, they were asked to fill out a paper version of the HEXACO-SPI. Subsequently, participants put on the headphones and their age and gender were recorded on the tablet. Auditory volume was adjusted to a comfortable listening level (speech volume). We used a within-subject cross over design, that is, all participants performed under all three conditions: white noise (WN), BB (40 Hz; 440 and 480 Hz), and MB (40 Hz; 440 and 480 Hz).

Participants started with listening to white noise. Then, the BB and MB condition were presented. The order of BB and MB was randomly counterbalanced across participants; one half started with the BB, the other half with the MB. All conditions started with the Flanker task, followed by the Klingberg task. Conditions were separated by a 2 min break. To minimize learning effects, there were three parallel versions of the Klingberg task. The Flanker task was randomly predefined. When participants had finished the tasks, they were asked to report ow they had experienced the tasks and the sounds. Testing took about one hour.

Written informed consent was obtained from all participants. This study was positively assessed by the Scientific and Ethical Review Committee of the Faculty of Behavioral and Movement Sciences of the Vrije Universiteit.

Statistical Analysis

Before testing the hypotheses, we assessed the normality of the dependent variables with the Kolmogorov-Smirnov test. Its results were significant for almost all variables, indicating that normality was not achieved. Therefore, we decided to apply the nonparametric Friedman test of differences among repeated measures to compare the total group scores under each condition (WN, MB, and BB). In the cases the Friedman test was significant, pairwise comparisons between conditions were made by means of the Wilcoxon signed ranks test and effect sizes were calculated ($r = z$ / sqrt(N).

Thereafter, we used the median split to make a distinction between low- and high-emotional people. To avoid large differences in gender in these two groups, we made this distinction between low and high emotionality separately for men and women. We merged high-emotional men and women and low-emotional men and women, establishing groups of high- and low-emotional participants. Friedman tests (and, if appropriate, Wilcoxon signed ranks tests) were ran separately for the low- and high-emotional groups. The dependent variables were: (a) the number of errors and mean RTs for each condition (WN, MB, BB) and for each level of the Flanker Task, and (b) the maximum reached stage of the Klingberg task for each of the three conditions and the two series. Data were analysed using SPSS version 22.0.

RESULTS

First, to determine the presence of order effects (the BB or MB condition), Wilcoxon signed ranks tests were applied on all dependent variables separately for the BB-MB and the MB-BB order. There were no significant effects between MB and BB in orders of presentation ($p > .05$), excluding the presence of learning effects between these conditions. Non-parametric Friedman tests of differences among repeated measures regarding the RTs of the Flanker task yielded significant effects for the lowest stage, $X^2(2) = 16.08$, $p < .001$, the medium stage, $X^2(2) = 18.08$, $p < .001$, and the highest stage of difficulty, $X^2(2) = 21.70$, $p < .001$). Regarding all stages of difficulty, the Wilcoxon signed ranks tests indicated significant differences between MB and WN as well as BB and WN conditions (MB vs. WN: $Z = -3.86$, $p < .001$, $r = -0.79$; BB vs. WN: $Z = -3.74$, $p < .001$, $r = -0.76$ for the lowest stage, MB vs. WN: $Z = -3.09$, $p = .002$, $r = -0.62$; BB vs WN: $Z = -3.49$, $p < .001$, $r = -0.71$ for the medium stage, and MB vs. WN: $Z = -3.73$, $p < .001$, $r = -0.76$; BB vs. WN: $Z = -3.85$, $p < .001$, $r = -0.78$ for the highest stage). All significant differences indicated a slower RT under the WN condition as compared to the MB and BB conditions. No significant differences between the MB and the BB were found. Results are shown in Figure 1. We performed the same analyses regarding the RTs of the Flanker task separately for the low- ($n = 12$) and high- ($n = 12$) emotional groups. In

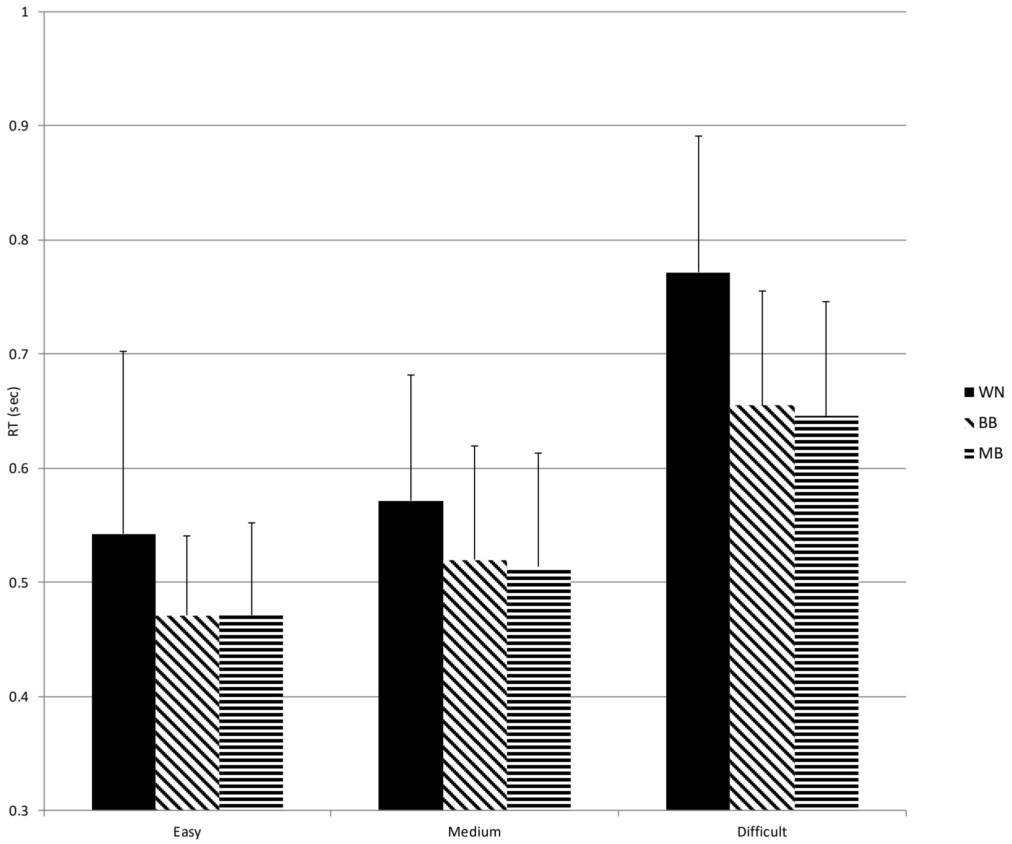

FIGURE 1.

Median RTs and *SD*s under the white noise (WN), binaural beat (BB), and monaural beat (MB) condition on the three difficulty stages of the Flanker task.

the low-emotional group, Friedman tests yielded significant effects for the lowest stage, $X^2(2) = 6.17$, $p = .046$, the medium stage, $X^2(2) = 8.67$, $p = .013$, and the highest stage of difficulty, $X^2(2) = 12.20$, $p = .002$). The Wilcoxon signed ranks tests indicated significant differences on all levels of difficulty between MB and WN as well as BB and WN conditions (MB vs. WN: $Z = -2.35$, $p = .019$, $r = -0.68$; BB vs. WN: $Z = -2.43$, $p = .070$, $r = -0.76$ for the lowest stage, MB vs. WN: $Z = -1.25$, $p = .21$, $r = -0.36$; BB vs. WN: $Z = -2.20$, $p = .028$, $r = -0.63$ for the medium stage, and MB vs. WN: $Z = -2.60$, $p = .009$ $r = -0.75$; BB vs. WN: $Z = -2.93$, p = .003, $r = -0.85$). Notably, for the medium stage, no significant difference was found between the MB and WN. All significant differences indicated a slower RT under the WN condition as compared to the MB and the BB conditions. No significant differences between the MB and the BB were found.

Similarly, in the high-emotional group, Friedman tests yielded significant effects for the lowest stage, $X^2(2) = 10.17$, $p = .046$, the medium stage, $X^2(2) = 10.50$, $p = .005$, and the highest stage of difficulty, $X^2(2) = 9.60$, $p = .008$). The Wilcoxon signed ranks tests indicated significant differences on all stages of difficulty between MB and WN as well as BB and WN conditions (MB vs. WN: $Z = -2.30$, $p = .003$, $r = -0.86$; BB vs. WN: $Z = -2.28$, $p = .005$, $r = -0.81$ for the lowest stage, MB vs. WN: $Z = -2.98$, $p = .003$, $r = -0.86$; BB vs. WN: $Z = -2.67$, $p = .008$, $r = -0.77$ for the medium stage, and MB vs. WN: $Z = -2.70$, $p = .007$, $r = -0.78$; BB vs. WN: $Z = -2.67$, $p = .008$, $r = -0.77$ for the highest level). All significant differences indicated a slower RT under the WN condition as compared to the MB and BB conditions. No significant differences between the MB and the BB were found. Notably, all effect sizes for significant effects were large according to Cohen's classification of effect sizes, which is 0.1 for a small effect, 0.3 for a moderate effect, and 0.5 and above for a large effect (Cohen, 1992).

These analyses performed separately for low- ($n = 12$) and high- ($n = 12$) emotional participants resulted in similar effects of MB and BB on the RTs in the Flanker task as in the total group of participants ($N = 24$), except for one nonsignificant effect of MB versus WN for the medium stage of difficulty in the low-emotional group. Mann-Whitney U tests indicated that the RTs in the Flanker task for the low- and high-emotional groups were not significantly different under the WN, MB, and BB conditions for any difficulty stage (*ps* > .05). The median RTs of the low- and high-emotional groups are shown in Table 1.

With respect to the quality of performance on the Flanker attention task and the Klingberg working memory task, no significant differences under the WN, MB, and BB conditions were found.

DISCUSSION

The aim of the present study was to examine the effects of MB and BB stimulation on cognitive functioning, in particular attention and working memory. The expectation was that participants would perform better under MB and/or BB as compared to WN. In addition, the potential differential effects of MB versus BB were examined. With respect to personality characteristics, we expected that participants with higher levels of emotionality would benefit the most from MB and/or BB stimulation.

The present results indicate that with respect to attention, as measured by the Flanker task, speed of performance was higher in the MB and BB conditions, relative to WN. The calculated effect sizes indicate that all significant effects can be considered large.

In contrast to reduced RTs, the number of errors on the Flanker task was similar in all conditions. As a consequence, the increased speed of attention processes can be assumed not to be at the expense of an increase of the number of errors. This finding makes it plausible that the enhanced speed of performance under MB and BB reflects a higher cognitive efficacy.

Although the presence of learning effects cannot be excluded, it is unlikely. The Flanker task was presented in three blocks of progressively increasing difficulty stages. Each difficulty stage was preceded by practice trials. After completing the highest stage of difficulty, the participants had to start with the easiest stage in the next condition. The alternation of stages can be assumed to interfere with the occurrence of transfer of learning. Moreover, no significant order effects were present between MB and BB conditions.

The absence of effects of MB and BB on the quality of attention in the present study is also in line with previous studies which examined the relationship between ABS and attention (Crespo et al., 2013; Kennel, Taylor, Lyon, & Bourguignon, 2010). In these studies, no significant improvement was found in attention performance with BB stimulation. Kennel et al. (2010) suggested that the small sample size (10 participants in the experimental group) might be an explanation for not finding significant results. Crespo et al. (2013) attributed the results to the small sample size as well (20 participants in the experimental group) and to the short duration of stimulation (20 min). In the present study, a small sample size (24 participants) may have played a part as well, but the extent to which duration of stimulation plays a role is still unclear. Other authors, who did find a significant improvement in performance while listening to BBs, presented ABS for

TABLE 1.
Median RT and *SDs* for Low- and High-Emotional Groups Under White Noise, Binaural Beat, and Monaural Beat Condition on Three Difficulty Stages of the Flanker Task

	Easy			Medium			Difficult		
	WN	BB	MB	WN	BB	MB	WN	BB	MB
Low Emotional	.50 (.07)	.46 (.07)	.48 (.08)	.55 (.09)	.51 (.10)	.50 (.13)	.66 (.12)	.63 (.07)	.62 (.08)
High Emotiona;	.66 (.20)	.48 (.07)	.47 (.09)	.60 (.13)	.53 (.09)	.53 (.08)	.80 (.11)	.66 (.12)	.66 (.13)

Note. WN = white noise, BB = binaural beat, MB = monoaural beat.

a relatively long duration (30 min on three different days, Lane et al., 1998). However, a long stimulation period (20 min, three times a week for three weeks) has been found not to yield significant results (Kennel et al., 2010), while listening to BBs for only 12 min improved cognitive performance (Kraus & Porubanová, 2015). Thus, it seems that the duration of ABS might not be the key factor to improve performance, and other, still unknown factors should be examined.

However, the finding that only speed and not the quality of performance on the Flanker attention task improved under the MB and BB condition may be explained by a ceiling effect, that is, the low degree of difficulty of the Flanker task. The very few errors that were made in the entire task might indicate that the task was quite easy, making a reduction of errors unlikely.

The present results can be explained as additional evidence that MBs and BBs improve the performance on an attention task. However, we must consider the possibility that the performance decreased in the WN condition compared to the BB and MB conditions. It may be that participants were more annoyed under the WN condition than under the BB and MB conditions, impairing their performance . Indeed, the choice of the control condition is debatable and WN may be less preferable than a control condition with isochronous stimulation or without any stimulation. However, about 30% of our participants reported that they experienced both WN, BB, and MB as annoying. In spite of this experience, performance under the BB and the MB was better relative to the equally annoying WN condition.

Notably, isochronous stimulation or no stimulation at all may be mind-numbing and thus also impair performance as compared to the performance in natural settings. Therefore, by masking BB and MB in WN, the specific difference between control and experimental condition was the additional BB and MB. As a consequence, we are quite convinced that the present results indicate an improvement of performance under the BB and MB conditions relative to the WN control condition.

The MEG and EEG studies regarding the entrainment of neuronal oscillations to rhythmic stimulation provide evidence of synchronization of beta- and gamma-band power with periodic and metrical rhythms (Fujioka et al., 2009; Snyder & Large, 2005). Also neural oscillations in pulse and meter induction have been suggested as the amplitude of the SS-EPs at pulse and meter frequencies was selectively enhanced (Nozaradan et al., 2012b). Thus, in the present study, neural resonance to 40 Hz MBs and BBs may have occurred. As this particular frequency is associated with a high level of awareness (Kaiser & Lutzenberger, 2005) and enhanced transmission from one brain region to another (Fell & Axmacher, 2011), it is conceivable that neural oscillations have contributed to the observed faster performance on the Flanker attention task.

In many commercial products, BBs are accompanied by music. It is possible that the music mediates the effects described by the users and producers. Especially when BBs are intended for relaxation, it seems plausible that the music partly induces mood changes in the listener. To avoid these kinds of confounding effects and to be able to draw conclusions about the pure nature of the effects of MBs and BBs, the beats in the current study were not accompanied by music. Positive significant results were found in studies using carrier tones with a frequency of respectively 230 and 220.45 Hz, and 240 and 255 Hz (Beauchene et al., 2016; Kraus & Porubanová, 2015). The carrier tones used in the present study were as high as 440 and 480 Hz, and although the BB with a carrier tone around 440 Hz has been shown to be perceived the best (Oster, 1973), these tones might be too high for comfortable listening. Unfortunately, not all studies reported the carrier tones of the BB. It is important that future studies are aware of the importance of carrier tones and further investigation into which tones are best received is needed.

With respect to personality characteristics, we expected that high-emotional people would benefit more from ABS than low-emotional people. However, our results show that the whole group of participants was, relative to WN, faster under the BB and MB conditions on all stages of the Flanker task. In addition, exactly the same results were observed in high-emotional and low-emotional participants. Therefore, we have to conclude that the effects of MB and BB are similar in high- and low-emotional participants.

Contrary to expectation, we found no evidence of any influence of ABS on working memory performance. This is not in line with results of studies in which improvements in working memory capacity were found after listening to alpha and beta BB stimulation, respectively (Beauchene et al., 2016; Kraus & Porubanová, 2015).

The present findings are in line with those of a recent study which also found faster reaction times in participants who had listened to BBs of 40 Hz (Colzato et al., 2017). In a global-local task, participants who had listened to a BB previous to the task were better able to focus their attention to target stimuli than participants who had not listened to a BB. Similar to the global-local task, in the current study, the participants had to switch between reacting to congruent and incongruent stimuli in the Flanker Task. Thus, the study of Colzato et al. and the present study support the notion that faster attention processing may be attributed to the influence of BBs.

Although MBs and BBs are processed in different ways (Draganova et al., 2008), no differences were found between the effects of MBs and BBs, which was in line with the participants' evaluation. The participants did not notice any difference between the two sounds. Thus, subjective experience may suggest that the MB and BB of 40 Hz have similar effects.

Many aspects of ABS are still unclear. The importance of duration of stimulation and the time the effect of auditory beats may persist is still unknown. Moreover, it is unclear whether ABS elicits brain entrainment or alters brain connectivity. In addition, it is not clear yet which particular MB or BB frequency works best to enhance cognitive performance and which two carrier tones are most appropriate. With respect to personality traits, not everyone is assumed to be affected in the same way by auditory beats (Reedijk, Bolders, & Hommel, 2013). Moreover, cognitive performance seems to depend on the supply of striatal dopamine (Ashby, Isen, & Turken, 1999). Spontaneous eye-blink rates (EBR), which are a clinical marker of dopamine functioning (Karson, 1983), were measured in participants in the study of Reedijk et al. Results showed that people with low EBRs (low dopamine levels) did benefit from BBs, while participants with high EBRs (high dopamine levels) did not. This was explained by the assumption that low EBRs are associated with less effective cognitive performance and therefore, these individuals might have more opportunity to improve their cognitive performance. Moreover, musicians may be better at processing auditory beats than nonmusicians. Musicians seem not only to have a larger gray matter volume of the auditory cortex, but also the activity in their cortex after hearing sinusoidal tones seems to be larger than normal (Schneider et al., 2002). Indeed, there is increasing evidence that the synchronization process between the auditory beat and neural activity works better in musicians compared to nonmusicians (Ioannou, Pereda, Lindsen, & Bhattacharya, 2015).

Because ABS is a safe and noninvasive method to potentially enhance cognitive functions, it is worth further study. It is important that future studies take individual differences into account.

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3 Fazit und Ausblick

Die Hauptstudie ist die erste veröffentlichte Placebo-kontrollierte Studie, die aufzeigt, dass es möglich ist ein EEG-Bild gesunder Probanden mit Hilfe von Neuromodulationstechniken (wie z.B. E-NFT) zu beeinflussen. Außerdem ist diese Studie die erste Placebo-kontrollierte Studie, die beweist, dass Langzeiteffekte der E-NFT Behandlung bis zu einer Dauer von drei Jahren möglich sind. Diese Langzeiteffekte wirken sich laut unseren Forschungsergebnissen jedoch nicht auf die kognitiven Fähigkeiten aus. Dies haben wir auch in der E-NFT Studie bei Probanden der älteren Altersklasse erforscht und belegt. Eine Veränderung der EEG Aktivität führte nicht zu einer messbaren Veränderung der kognitiven Fähigkeiten. Allerdings können wir Veränderungen in der Wahrnehmung auch nicht ganz ausschließen. Möglicherweise beeinflussten zum Beispiel bestimmte Teilnehmergruppen unserer Studie das Resultat. So gab es bei den Studenten eventuell ein „Höchstwerteffekt“, der verhinderte, dass mögliche Veränderungen auftraten oder Veränderungen so abgeschwächt wurden, dass sie nicht mehr messbar waren. Möglich ist auch, dass die von uns verwendeten Messinstrumente eventuelle Veränderung der Wahrnehmung nicht messen konnten.

Im Verlauf der Studien gab es einige logistische Herausforderungen. So sollten zum Beispiel die Versuchsbedingungen sowohl dem Versuchsleiter als auch den Teilnehmern unbekannt bleiben. Dadurch musste ein zweiter Versuchsleiter jeweils die nötigen Kabel mit den entsprechenden Geräten verbinden. Bei jeder Sitzung waren folglich immer zwei Versuchsleiter anwesend, was einen enormen Arbeitsaufwand bedeutete - bei 300 Sitzungen von jeweils 45 Minuten.

Zurückblickend hätten wir alternative Versuchsprotokolle und vielleicht andere Geräte zur Messung der Gehirnaktivität verwenden sollen. Zu Beginn unserer Studienreihe im Jahr 2007 setzten wir andere Prioritäten und stellten uns vor allem die Frage, wie eine Studie über die Wirkung von E-NFT wissenschaftlich adäquat ausgeführt werden kann. Logistische Probleme während der Erhebung der Daten stellten sich dabei als eine der größten Herausforderungen heraus. Im Laufe der Zeit haben wir alle diese Herausforderungen erfolgreich gemeistert.

Die wichtigsten Übereinstimmungen zwischen den Ergebnissen der EEG-Neurofeedback (E-NFT) Studien und der Auditive Beat Stimulation (ABS) Studien sind einerseits der nicht eingreifende (non-invasive) Charakter und andererseits die vielversprechenden Möglichkeiten der kurzzeitigen Verbesserungen für die kognitiven Fähigkeiten (das Konzentrationsvermögen). ABS ist im Gegensatz zu E-NFT einfach auszuführen, denn fast jede Person besitzt ein Medienabspielgerät und Kopfhörer – dies sind für die Behandlung die einzigen benötigten Geräte. Es gibt kaum Aussicht auf Langzeiteffekte der ABS Behandlung, selbstnach fortdauernder oder wiederholter Durchführung der

Methode, jedoch können nach einer Behandlung von ein paar Minuten bis zu einer Stunde durchaus kurzfristige Verbesserungen festgestellt werden.

Doch bevor wir die genaue Wirkung der wiederholten Behandlungen durch Messungen feststellen, richten wir unser Augenmerk auf die Wirkungsmechanismen der ABS Behandlung an sich. In dieser Studie untersuchten wir dafür die Wirkung auf die Aufmerksamkeitsfähigkeit nach einer Behandlung von Binaural Beats (BB), Monaural Beats (MB) und einer neutralen Behandlung mit weißem Rauschen, (White Noise (WN)) oder rosa Rauschen (Pink Noise (PN)). Um die Neutralität zu verstärken, wurde WN oder PN den beiden anderen Behandlungen hinzugefügt. Sowohl die Behandlung mit BB als auch die Behandlung mit MB erhöhte die Konzentrationsfähigkeit im Vergleich zur WN Behandlung. Nur die Behandlung mit BB erhöhte die Konzentrationsfähigkeit im Vergleich zur PN Behandlung. Obwohl wir während des ABS einige signifikante Veränderungen im EEG festgestellt haben, die die vorliegenden widersprüchlichen Befunde rechtfertigen, ist festzuhalten, dass 40 Hz BB keine konsistente Wirkung auf die EEG-Aktivität hat.

Die ABS Behandlung benötigt, ebenso wie die E-NFT Behandlung, noch weiterführende Forschungen zu den Wirkungsmechanismen. Für ABS ist es von Interesse, ob mit anderen Frequenzen als der in dieser Studie verwendeten BB und MB, noch immer gleichwertige Ergebnisse erzielen werden können. Zusätzlich sollten zukünftige Forschungen Gehirnscantechniken verwenden, um den Wirkungsmechanismus von BB und MB genauer verstehen zu können. Zu guter Letzt sollten die Ergebnisse der E-NFT Forschungen und anderen Neuromodulationstechniken auch für die ABS Behandlung verwendet werden. So kann beispielsweise der Abstand der Wiederholungen oder die Dauer der Behandlung an bereits bestehenden Erkenntnissen angepasst werden. Neue Studien könnten so herausfinden, ob ABS in wiederholten Behandlungen vergleichbare Resultate aufzeigt, wie andere Gehirnstimulationstechniken. Möglicherweise könnten zusätzlich doch Langzeiteffekte aufgedeckt werden.

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Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

INDIREKTE HIRNSTIMULATION DURCH EEG-NEUROFEEDBACK UND AUDITIVE BEAT STIMULATION

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Bergen NH, die Niederlande, 27.03.2023

Ort, Datum

H.J. Engelbregt

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*Anhang 1

Effects of binaural and monaural beat stimulation on attention and EEG Wirkung von binauraler und monauraler Beat Behandlung auf Konzentration und EEG

Der ergänzende Artikel wurde als Anhang hinzugefügt, um die zuvor beschriebenen Informationen zu erweitern und zu verdeutlichen. Die Studie wurde ebenfalls von Hessel Engelbregt und Jan Berend Deijen entworfen und behandelte die Frage, ob ABS-Behandlungen das EEG in vorhersagbarer Weise verändern. Weiterhin haben wir die zweite Kontrollbedingung (Rauschen) von weißem in rosa Rauschen geändert, um eine häufig gestellte Frage nach einem möglichen negativen Effekt von weißem Rauschen auf die Aufmerksamkeit zu beantworten. Rosa Rauschen (Pink Noise) ist fast dasselbe wie weißes Rauschen (white noise). Genau wie beim weißen Rauschen werden auch beim rosa Rauschen alle Frequenzen aus unserem hörbaren Spektrum einbezogen, jedoch mit (deutlich) geringerer Stärke. Beim rosa Rauschen gilt: Je höher die Frequenz, desto geringer die Lautstärke.
Die Untersuchung wurde unter folgenden Bedingungen durchgeführt:

- Teilnehmer und Experimentator kennen die Versuchsbedingungen der Teilnehmer nicht.

- Die Probanden wurden der Experimental- oder Placebogruppe nach dem Zufallsprinzip zugeordnet.

- Die Scheinbehandlung weicht nur durch Weglassen des hypothetischen Wirkmechanismus von der experimentellen Bedingung ab.

- Alle Faktoren müssen messbar und analysierbar sein. Daher dürfen nur die Beats ohne Hintergrundmusik angeboten werden.

Die Versuchsleiter dieser Studien waren Dr. Jan Berend Deijen und Hessel Engelbregt. Hessel war für das Testverfahren verantwortlich und Jan Berend kümmerte sich um die ordnungsgemäße Verwendung der Materialien. Die in Abschnitt 2.2 beschriebenen individuell zusammengestellten Audiodateien wurden erneut verwendet, diesmal jedoch mit rosa Rauschen anstelle von weißem Rauschen als Kontrollbedingung. Auch für diese Studie wählten wir ein Crossover-Design, bei dem die Probanden binaurale Beats, monaurale Beats und rosa Rauschen hörten. Unser Ziel war es, die Frage beantworten zu können, ob 40 Hz BB und oder 40 Hz MB die EEG-Leistung in einem Spektrum von 40-45 Hz ändert, und um unsere Ergebnisse, die eine Verbesserung der Aufmerksamkeit nach BB- und MB-Stimulation zeigten, zu replizieren.

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[*] Anhang, nicht formal Bestandteil der Arbeit

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RESEARCH ARTICLE

Effects of binaural and monaural beat stimulation on attention and EEG

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Abstract

Nowadays a popular technique to improve mood and cognition is auditory beat stimulation (ABS), which is thought to induce a frequency-following response of brainwaves. The main types of ABS are monaural beats (MB) and binaural beats (BB). BB involves the presentation of a specific frequency to one ear and another frequency to the other ear which may induce neural entrainment. A difference between the frequencies of 40 Hz is assumed to improve cognition. The present study examined the effect of 40 Hz binaural beats (BB) and monaural beats (MB) on attention and electroencephalography (EEG). A total of 25 first-year psychology students (11 males, 14 females) performed a Flanker task while EEG was recorded during the 5 min-presentation of pink noise (PN), MB and BB. With respect to attention, as measured by the Flanker task, the number of false responses in the BB condition was smaller than that in the PN condition while the number of false responses in the MB condition was larger as compared to the PN condition. As there was no association of BB with a consistent increase in absolute 40 or 45 Hz power compared to PN or MB, EEG recordings could not confirm the hypothesized neural entrainment in the brain. Overall, the current findings show that listening to 40 Hz BB improves attention but do not show the occurrence of neural entrainment. Future research is recommended to include a larger sample, to use a broader cognitive test battery and to present auditory beats with a longer duration.

Keywords Attention · Flanker task · Binaural beats · Monaural beats · Auditory beat stimulation · EEG

Introduction

Nowadays, our competitive society is characterized by a lot stress due to the digital overload of information from desktops, laptops, tablets, and smartphones. All day and even night, people are bombarded with so many messages and alerts that focussing becomes increasingly harder and nearly impossible. As a consequence, people are searching for methods to unwind and get relaxed. In addition to the increasingly used method for relaxation of mindfulness meditation, a popular technique to improve mood and cognition is auditory beat stimulation (ABS), which is thought to induce a frequency-following response of brainwaves associated with an improvement of mood and cognition. The main forms of ABS are binaural beats (BB) and monaural beats (MB), which are both characterized as two simultaneously presented sine waves with a stable amplitude and slightly different frequencies (Chaieb et al. 2015). Although two tones are presented, subjects hear them as one tone, at the frequency of the difference between these two inputs. For example, when two tones of 200 and 240 Hz are presented, the subject perceives a 40 Hz beat. These auditory stimuli are called monaural beats when they are both presented to each ear and binaural beats when the one tone is presented to one ear and the other tone separately to the other ear. In response to BB, hearing nerves in the brain send the sound to the superior olivary nucleus before it reaches the cortex, where a tone is consciously perceived (Kasprzak 2011). In the superior olivary complex neurons are especially sensitive

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to phase shifts between both ears and will thus fire in a rate corresponding to the phase difference of the BB (Chaieb et al. 2015). The phase difference of the BB will eventually lead to neural entrainment in the brain. This means that a neural resonance, i.e., neural synchronization, may occur as the eventual consequence of the auditory stimuli (Large et al. 2015). The manifestation of neural entrainment has been supported by the results of electrophysiological studies. For instance, steady-state evoked potential (SS-EP) studies found that a periodic rhythm produced a sustained response in the delta (2.4 Hz) band (Nozaradan et al. 2012a) and complex rhythms were found to elicit multiple SS-EPs at frequencies in the electroencephalography (EEG) corresponding to the rhythmic pattern envelope, while the selectively enhanced SS-EPs amplitude at pulse suggests the occurrence of neural oscillations (Nozaradan et al. 2012b).

A number of studies using magnetoencephalography (MEG) and EEG confirmed that fluctuations in delta (2.4 Hz), beta (20–37 Hz) and gamma (40 Hz) band power synchronize with intermittent and metrical auditory rhythms (Fujioka et al. 2009; Nozaradan 2014; Schneider et al. 2002). With respect to specifically the gamma band, rhythmic tone sequences have been found to evoke short-latency gamma-band (20–60 Hz) activity which diminished during tone omissions (Snyder and Large 2005).

In spite of the above evidence of neural entrainment, it is not fully confirmed yet that BB leads to a frequency following response in the brain. To examine the specific effect of BB on EEG recordings Gao (2014) presented BB in delta (1 Hz), theta (5 Hz), alpha (10 Hz), and beta (20 Hz) band frequencies. Healthy participants listened to each type of BB for 5 min at a time, with 2-min breaks in between, while EEG was recorded. Not any type of the BB elicited clear brain entrainment in the relative power of EEG. During delta and alpha BB, the relative power of theta and alpha increased and that of beta decreased, while during theta BB the relative power of beta decreased and during beta BB the relative power of theta decreased. The authors conclude that there was no frequency following the response of the presented BB. In a similar study BB were created by adding a sinewave, differing in 4.53 Hz, (theta-beat), 8.97 Hz (alpha-beat), 17.93 Hz (beta-beat), 34.49 Hz (gamma-beat) or 57.3 Hz (upper gamma-beat), to a pure tone of 373 Hz in all conditions. Results indicated no significant effects of BB for any of the beat frequencies within the corresponding EEG bands (López-Caballero and Escera 2017). Based on the number of oscillations per second these BB-induced phase differences can be categorized into different clusters which are associated with specific brain functions. As a consequence, the effects of BB on brain activity are thought to be dependent on increasing the power of particular frequency bands. For instance, delta frequency (0.5–4 Hz) BB may increase delta band power and induce its associated deep sleep. Similarly, theta (4–8 Hz) BB may increase theta power and its associated state of deep relaxation, alpha BB (8–13 Hz) the power of alpha band which is associated with a quiet and relaxed attention, beta BB (13–40 Hz) beta band power and its associated thinking, concentrating and processing information and, finally, gamma BB (40 Hz and higher) gamma-band power and its associated attentional selection, memory, associative learning and positive emotional feelings (Teplan 2002). A number of studies of BB inducing these different frequencies have yielded a diversity of results.

For instance, it has been found that alpha (9.55 Hz) improves working memory (Kraus and Porubanová 2015) and beta frequency (16 and 24 Hz) BB improves the performance on a number vigilance task (Lane et al. 1998). In addition, anxiety was found to decrease in people after listening to delta (0–4 Hz) frequency BB for 60 days (Wahbeh et al. 2007). With respect to gamma BB, in a study by Reedijk et al. (2015) participants listened to gamma (40 Hz) BB, alpha (10 Hz) BB or a constant tone of 340 Hz as control condition before they performed an attentional blink task. Results indicated that gamma BB, but not alpha BB, reduced the attentional blink in individuals with low striatal dopamine, using spontaneous eye blink rates as a marker of the individual striatal dopamine level. The authors conclude that gamma BB led to increase of divergent thinking, reflecting more cognitive flexibility. A subsequent study investigated whether gamma BB increases the flexibility of cognitive-control style. Participants were presented with gamma (40 Hz) BB or a constant tone of 340 Hz (control condition) during 3 min before performing a dual task. After exposure to gamma BB a more pronounced response-compatibility effect, reflecting distributed parallel processing, was found supporting the assumption that gamma BB promotes cognitive flexibility (Hommel et al. 2016). In a slightly more recent study examining attentional focusing healthy adults listened for 3 min before and during a global–local task to gamma-frequency (40 Hz) binaural beats based on a 340 Hz carrier tone, which was used as constant tone in the control condition. Results indicated that visual attention became more focused after gamma frequency BB compared to the control condition, suggesting that gamma BB may enhance the focus of attention (Colzato et al. 2017). Recently, the effects of 40 Hz gamma BB and 40 Hz gamma MB on attention and working memory in healthy adults were compared with those of white noise. As speed of performance of the Flanker attention task was faster under the BB and MB condition than under WN, it appeared that high-frequency BB as well as MB may increase the efficiency of attention processing (Engelbregt et al. 2019).

The present study was aimed to examine whether high-frequency auditory beats would improve attention and induce neural synchronization.

We presented frequencies of 440 Hz and 480 Hz to induce gamma BB of 40 Hz. These frequencies are not fully in line with the notion that BB are perceived when the tone frequencies are approximately between 100 and 400 Hz with an upper-frequency limit for the perception of BB of about 1000 Hz and with differences of no more than 35 Hz (Licklider et al. 1950). However, significant beat frequency responses have been found after the presentation of 40 Hz BB induced by a pair of 380 and 420 Hz (Schwarz and Taylor 2005). Comparably, a more recent study in young adults (21–29 years) used primary tones of 390 and 430 Hz, and 810 and 850 Hz, both pairs inducing a BB rate of 40 Hz. Results indicated that frequency-following responses were elicited by tones in both the lower-frequency range of 390 and 430-Hz and, to a lesser extent, by tones in the higher frequency range of 810 to 850 Hz (Grose and Mamo 2012).

With respect to the measurement of attention, an adapted version of the Eriksen Flanker task was used. This task measures the ability to suppress responses that are inappropriate in a particular context and is categorized as a selective attention task (Eriksen and Eriksen 1974). When subjects perform the Eriksen Flanker Task, a frontal brain structure, the anterior cingulate cortex (ACC), is activated, being more active in response to processing incongruent stimuli than congruent stimuli (Davelaar 2013). In addition, a meta-analysis of neuroimaging studies indicated increased activation in the right dorsolateral prefrontal cortex and the right insula (which separates the frontal and temporal lobe) during the performance of the Flanker task (Nee et al. 2007). In addition to these studies on the Flanker task, it has been found that the capacity to shift attention to new stimuli is mediated by the right temporoparietal junction (rTPJ). In particular, the anterior part of rTPJ is activated during attentional shifting (Krall 2015). Further, functional magnetic resonance imaging (fMRI) revealed that the posterior inferotemporal cortex is involved in attentional control, in addition to parietal and frontal areas (Stemmann and Freiwald 2019).

In accordance with the results of studies measuring gamma-band power we selected relevant electrode locations. For instance, healthy participants receiving 40 Hz-transcranial alternating current stimulation (tACS) over the right temporal lobe showed increased spectral power derived from electrodes T7 and T8 (i.e., T3 and T4 of the International 10/20 system) in the low-mid gamma band (i.e., 30–45 Hz) (Santarnecchi, 2019). Auditory stimulation of 40 Hz) in the right auditory canal of healthy participants induced the largest 40 Hz power spectrum increase at the F3 electrode, contralateral to the stimulated side (Pastor et al. 2002). Van Deursen et al. (2008) evaluated gamma-band oscillations as a diagnostic biomarker in Alzheimer's disease (AD) and mild cognitive impairment (MCI). The effects of resting state, music listening, story listening and visual stimulation in AD patients, MCI patients and healthy controls were compared. In the subject group as a whole and compared to resting state, music listening increased gamma-band power at electrode locations Fz, F3, F4, F7, F8, Cz, T4, T5 and T6, story listening at F3, F4, F5, F7, F8, Fp1, T5 andT6, and the visual task at F3, F4, F5, F7, F8, Fp1, T5 and T6. From these particular electrode locations, we selected F3, F4, F7, F8, Fz, Pp1, T3, T4, T5 and T6, while Fp2 was added to check for ocular artifacts.

Based on above-cited findings, we expected that in particular BB would improve the performance on the attention task. With respect to EEG recordings, we expected that BB and to a lesser degree MB stimulation would increase the power of EEG lower gamma frequencies. As there is no clear evidence of the precise location in the frontal, temporal and parietal areas where gamma BB-induced EEG spectral power increase can be expected, we could not hypothesize effects on more specific electrode locations than the selected ones.

Materials and methods

Participants

The study sample consisted of 25 first-year psychology students between 18 and 28 years of the Vrije Universiteit Amsterdam, the Netherlands (11 males, 14 females; mean age 21.8 years ($SD = 2.5$). Participants were recruited by means of an online student pool (i.e., vu.sona-systems.com) and were rewarded with credit points. As this student pool consisted of psychology students, the recruitment of particularly psychology students was for practical reasons. Being at the start of their study, they could be assumed to represent the population of young adults A priori exclusion criteria were attention deficit (hyperactivity) disorder (AD(H)D), hearing problems and physical disorders that could interfere with EEG measurements (e.g., epilepsy) or for which EEG could pose a health risk.

Materials

Attention task

Attention was measured by means of an adapted version of the Eriksen Flanker Task (Eriksen and Eriksen 1974). The task was programmed (programming languages Objective-C and Swift) by the IT department of the Vrije Universiteit. Arrows, instead of letters as in the original task, were used as target stimuli. The test was presented on an iPad and included three series with increasing difficulty levels. Prior to the start of each series, written instructions were presented on the screen, followed by a practice trial. There are two trial types, with either congruent or incongruent stimuli. The congruent trial is a horizontally arranged array of arrows presented in the same direction (e.g., < < < < < or > > > > >). The incongruent trial has a similar array of arrows, but the middle arrow, the target, is displayed in the opposite direction (e.g., < < > < < or > > < > >). The first series consisted of trials presenting five green arrows. Participants had to touch, as fast as possible, one of the two arrow-shaped buttons on the bottom of the screen, that pointed in the same direction as the middle arrow. In the next series trials of five red arrows were presented. This time participants were instructed to touch the button that pointed in the opposite direction of the middle arrow. The third series consisted of trials of green or red arrows. If the arrows were green, participants had to touch the button that pointed in the same direction as the middle arrow, and if the arrows were red, they had to touch the button that pointed in the opposite direction of the middle arrow.

All trials started with a fixation cross on the center of the screen for 1000, 1500 or 2000 ms (random), followed by the presentation of five arrows during 2500 ms. The interstimulus interval (ISI) was 100 ms, and maximum response time 2500. In each series 60 trials were presented, with a randomized order of congruent and incongruent trials. The total task duration was approximately 3.5 min. The reaction time (RT) and the number of false responses on incongruent trials of the third series were taken as output variables.

EEG recording

EEG was recorded using 19-channel electrode caps with international 10–20 electrodes placement (Jaspers 1958) on a 32-channel Deymed system (sampling rate 1024 Hz downsampled to 128 Hz, Notch filter 50/60 Hz, anti-aliasing filter 50 Hz, Butterworth filter 0.1–100 Hz). Electrode skin impedance was kept below 8 kΩ. An electrode at Fpz served as ground electrode. In addition, electrodes were placed on the left and on the right earlobes which were used for offline linked-ear (LE) reference. The EEG system was connected to a portable computer. For each electrode, the absolute power was recorded in μV2.

Auditory stimuli

Pink noise (PN), monaural beats and binaural beats were presented with a comfortable speech volume through headphones (Sennheiser) connected to an iPod. The headphones were wired through the tubes of a stethoscope to prevent any influence on the EEG recording.

MB as well as BB were presented with frequencies of 440 Hz and 480 Hz, resulting in a perceived frequency of 40 Hz. With respect to MB, both frequencies were transmitted through both channels, whereas the BB 440 Hz was transmitted through one channel and 480 Hz through the other channel. The auditory stimuli were programmed by means of the audio editor Audacity (V2.3) by the IT department of the Vrije Universiteit.

Procedure

The study took place in a sound-attenuated room at the Vrije Universiteit. Before the start of the experiment the participants received information and signed an informed consent. They were seated in a comfortable chair and were instructed to sit quiet and relaxed and to look forward at the clean wall. Besides eye blinking, no movements were allowed. After the electrode cap was placed, participant number, age and gender were entered in the tablet and the participant started with the practice trials of the Flanker task. Thereafter, participants put on the headphones and auditory volume was set to a level that the participant indicated as comfortable. Subsequently, one of the three conditions started. The order of presentation of PN, BB and MB was randomized, using a within-subject crossover design, meaning that all participants performed the Flanker task during PN, BB and MB. The exposure to PN, MB and BB was 5 min. Conditions were separated by a 1 min break. The parameters of the Flanker task were randomly predefined, which can be assumed to minimize learning effects. During the whole test procedure, the EEG was recorded. The start and end of each auditory condition were indicated by marks on the sampled EEG signals. The total test procedure took about 1.5 h. After the last condition was finished, the EEG cap was taken off and the participants received a debriefing.

This study was positively assessed by the Scientific and Ethical Review Committee of the Faculty of Behavioural and Movement Sciences of the Vrije Universiteit.

EEG processing

Selection of artifact-free EEG data for further analysis was done by an EEG expert after screening for seizure activity and/or abnormal EEG patterns. Data files were screened for eye blinks, eye-movement in vertical and lateral ways, technical flaws and distortion by frontal and temporally located muscle contractions. For this aspect, the EEG expert visually inspected the EEG data and additionally used the program Persyst 14 (Persyst Development Corporation, San Diego) with the automated—built in tool—for spike analysis. The Persyst spike algorithm allows the detector to be extremely sensitive while maintaining a low false-positive rate and was found to perform similar to human EEG readers. The algorithm uses a set of advanced neural networks, applied across several different montages, to monitor EEG background, the presence or absence of artifacts, the waveform morphology and voltage field spread of possible abnormalities. A more detailed description of the algorithm and comparison with the performance of human EEG readers can be found in Scheuer et al. (2017). For artifact rejection, the automated selection tool of another program (i.e., NeuroGuide (V3.0.0.1)) was used. For ocular artifact rejection electrodes Fp1 and Fp2 were used. Default for eye movement and drowsiness selection is 'high' which is the most sensitive setting and 1.5 standard deviations threshold for the Amplitude Multiplier. The Z Score of 1.5 standard-deviations means that if at least one second of successive instantaneous Z Scores are equal to or less than 1.5 standard deviations then a selection is made (Applied Neuroscience 2018). Data of individual EEG recordings were included only when there was a minimum of 20 s artifact-free data.

Statistical analysis

The mean reaction time (RT) and number of false responses on incongruent trials of the third series of the Flanker task were used to measure the effect of the different conditions on speed and quality of attention performance. The data were explored to check for normality. All variables deviated from a normal distribution. After square root transformation the data of the false responses appeared to be normally distributed. Therefore, the number of false responses were analyzed by means of mixed Anova, with gender as between subjects factor and condition (e.g., PN, MB and BB) as repeated measures factor. As different gender appeared to influence RT of the Flanker task, we included gender as between subjects factor. To correct for possible baseline differences between males and females, data of false responses in the PN condition served as covariate. As planned comparisons, we used simple contrasts to compare the false responses of the MB condition and the BB condition with those of the PN condition. In spite of square root, log or log 10 transformation Kolmogorov–Smirnov test indicated that RT data in the MB and BB condition remained deviant from normal (SQRT transformation: $p = 0.039$ and $p = 0.008$; log/log 10 transformation, $p = 0.052$ and $p = 0.026$). Therefore, the non-parametric Friedman test for repeated measures was used to test for a difference in RT over the three conditions. As post hoc test the Wilcoxon Signed-Rank test was used. Effect sizes were calculated as $r = Z/\sqrt{N}$ (Rosenthal 1994), with values 0.10—< 0.030 defined as being small, 0.30–0.50 as being medium and ≥ 0.50 as being large (Cohen 1977).

NeuroGuide (Version 3.0.0.1) with LE reference was used for generating tables of absolute power spectra of each individual for further analyses in SPSS (IBM SPSS Statistics for Macintosh, version 24.0). The power spectral value for any frequency intensity is: $F(x) = (a^2\ (x) + b^2\ (x))$. That is, the power spectrum is the sum of the squares of the sine and cosine coefficients at a specific frequency. A full description of the computation of the power spectrum can be found in Thatcher et al. (2007).

All variables were continuous and paired over the subjects, as all the subjects were exposed to all three conditions. To measure the effect of the auditory stimulation on the EEG, the absolute power in μV^2 for each electrode for the frequencies 1–50 Hz was recorded and Linked Ears (LE) was chosen as reference for EEG analysis. Out of all recordings, the frequencies of 40 and 45 Hz of frontal electrodes F3, F4, F7, F8, Fp1, Fp2 and Fz as well as temporal electrodes T3, T4, T5 and T6 were chosen to focus on in this study. We choose to include the frequency of 45 Hz because auditory stimulation of 30–60 Hz induced maximal potentials around 45 Hz (Artieda et al. 2004) and visually evoked oscillations in the gamma band (40–48 Hz) have been found to reach values up to 46 Hz (Başar et al. 2015).

As electrodes T5 and T6 are also called parietal-temporal electrodes and have been renamed in the higher-resolution nomenclature (Modified Combinatorial Nomenclature; MCN) P7 and P8 (Oostenveld and Praamstra 2001), we selected these electrode locations to cover parietal measurements.

In addition, all data of the frontal electrodes were averaged and the same applies to the temporal electrodes.

As EEG data appeared to deviate from a normal distribution, the non-parametric Friedman test for repeated measures was used to test for a difference in μV^2 over the three conditions. This test is the non-parametric alternative to the one-way ANOVA with repeated measures and provides the test statistic χ^2, degrees of freedom and the significance level. Samples do not need to be normally distributed and dependent variables should be measured at the ordinal or continuous level. As this test does not allow for multivariate testing we repeated the Friedman test for each electrode, i.e., 11 tests were performed for 40 Hz and 11 tests for 45 Hz. In case of a significant effect, the Wilcoxon Signed-Rank test was used for post hoc testing. This test is the non-parametric equivalent to the dependent *t* test and provides a *Z* statistic and significance level.

We controlled for multiple comparisons of the frontal and temporal electrodes by applying Benjamini–Hochberg with a false discovery rate (FDR) of 0.20. This particular FDR was applied because hypothesis testing on power spectra changes in particular electrodes is quite exploratory and a higher FDR may avoid missing important results (McDonald 2014). The FDR can be applied in smaller studies and has the advantage to increase power when analysing multiple tests. The practical implications and benefits of applying an FDR level of 0.2 has been illustrated in real examples (Glickman et al. 2014).

To test whether results would be different by reducing multiple testing, we additionally performed Friedman tests for the averaged frontal and averaged temporal electrodes for 40 Hz and applied the same procedure for 45 Hz.

Bivariate Spearman correlations were calculated of RT and false responses on the Flanker task with the magnitude of the absolute power of the specific frequencies. Statistical significance was defined as $p < 0.05$. Tests concerning the results of the Flanker task were one-tailed.

Results

The data of the performance on the Flanker task was checked for outliers. One extreme outlier of > 4 SD was found concerning the number of false responses. This outlier was based on a number of 32 false responses in the MB and BB condition and 31 false responses in the PN condition. As the maximum number of false responses was 32 this participant likely had misunderstood the instruction. As a consequence, the data from this participant was excluded from data analysis. Results of the Friedman test indicated no significant differences in RT over the three conditions ($p > 0.05$). However, Anova indicated a significant difference between the PN, MB and BB condition for the number of false responses, $F(2,42) = 5.972$, $p = 0.005$, *partial* $\eta^2 = 0.221$. Simple contrasts indicated a significant smaller number of false responses in the BB condition as compared to the PN condition, $F(1,21) = 3, 486$, $p = 0.038$, *partial* $\eta^2 = 0.142$. In contrast, the number of false responses in the MB condition appeared to be larger than in the PN condition, $F(1,21) = 18.711$, $p < 0.001$, *partial* $\eta^2 = 0.471$. A post hoc paired samples t-test indicated a significant smaller number of false responses in the BB condition than in the MB condition ($t(23) = 1.78$, $p = 0.044$, *partial* $\eta^2 = 0.122$). No significant interaction between Gender and Condition was found ($p > 0.05$). Descriptive statistics are shown in Table 1 (RT) and Fig. 1 [number (SQRT) of false responses].

For the EEG recordings data from 5 participants were excluded from data analysis due to noise in the recordings. The remaining data were analyzed for each frontal and temporal electrode. To establish the power to detect the hypothesized effects of the remaining 19 EEG datasets, we conducted a post-hoc power analysis using the program G*power 3.1.9.4 (Faul et al. 2007). After applying an effect size (eta)$\eta^2 = 0.03$ (similar to $f = 0.17$, correlation = 0.85 and 3 conditions (PN, BB and MB), the obtained power was 0.82.

For the frequency of 40 Hz in the Fz electrode the Friedman test showed a significant difference, $X^2(2) = 8.444$, $p < 0.05$. After controlling for the FDR by the Benjamini–Hochberg procedure with a false discovery rate of 0.2 for 7 frontal electrodes this difference remained significant. A post hoc test Wilcoxon Signed-Rank test indicated that the absolute power of 40 Hz in electrode Fz for the MB condition was significantly higher than for the PN condition, $Z = -2.635$, $p < 0.01$, $r = 0.59$. The test also showed that the absolute power for the condition MB was higher than the absolute power for the BB condition, $Z = -2.678$, $p < 0.01$, $r = 0.60$.

Table 1 Mean (M), standard deviation (SD) and median (Mdn) of reaction time (ms) on the Flanker task in the pink noise (PN), monaural beat (MB) and binaural beat (BB) condition ($n = 24$)

	PN			MB			BB		
	M	SD	Mdn	M	SD	Mdn	M	SD	Mdn
Reaction time (ms)	0.712	0.024	0.673	0.7108	0.019	0.702	0.733	0.035	0.686

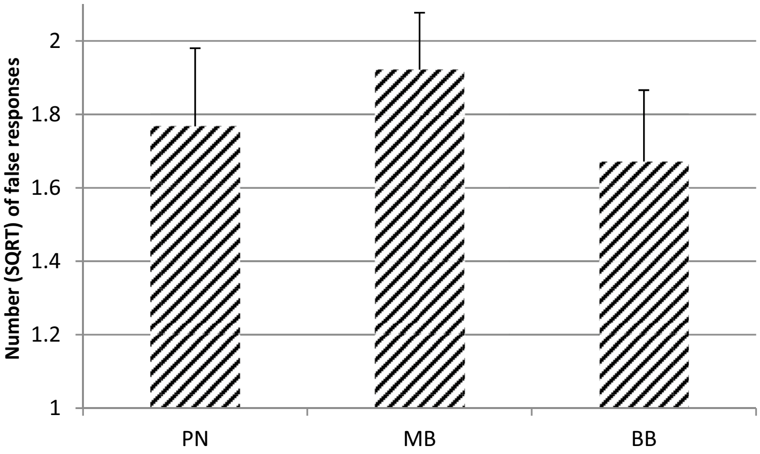

Fig. 1 Mean (square root of) number (+SE) of false responses on the Flanker task in PN, MB and BB condition ($n = 24$)

For 45 Hz in electrode T5 the Friedman test showed a significant difference, $X^2(2)=7.111$, $p<0.05$. After controlling for the FDR by the Benjamini–Hochberg procedure with a false discovery rate of 0.2 for 4 temporal electrodes this difference remained significant. A post hoc test Wilcoxon Signed-Ranks test indicated that the absolute power of 45 Hz in electrode T5 for the BB condition was significantly higher than for the MB condition, $Z=-2.243$, $p<0.05$, $r=0.50$. A summary of the Friedman test results for electrodes 40 Hz and 45 Hz is shown in Tables 2, 3. In addition, topoplots of differences in absolute power between the BB and MB condition and between BB and PN condition are shown in Fig. 2. The first topoplot shows the significantly higher absolute power in the MB condition as compared to the BB condition.

Additionally, the averaged power of frontal and temporal electrodes was compared between the PN, MB and BB conditions. Neither significant difference was found for the frontal nor for the temporal electrodes. The results of the analyses are shown in Table 4. Finally, Spearman's correlations were calculated within each condition to assess the relationship between the RT as well as number of false responses of the Flanker task and the total absolute power of 40 Hz and 45 Hz EEG frequencies. In the MB condition positive correlations were found between the RT and 40 as well as 45 Hz absolute power, indicating that higher power was associated with a longer RT. In addition, in the MB as well as BB condition higher power in the 40 as well as 45 Hz frequencies was associated with less false responses. No significant correlations were found in the PN condition. The results of the Spearman correlations are shown in Table 5.

Table 2 Friedman test results of absolute power (μV2) of separate electrodes for 40 Hz ($n=19$)

	PN			MB			BB			*p*
	M	SD	Mdn	*M*	SD	Mdn	*M*	SD	Mdn	
F3	0.224	0.179	0.186	0.247	0.159	0.217	0.176	0.084	0.158	0.249
F4	0.247	0.324	0.179	0.245	0.150	0.209	0.200	0.135	0.174	0.211
F7	0.715	1.321	0.341	0.709	1.419	0.337	0.674	1.585	0.213	0.348
F8	0.755	1.587	0.272	0.741	1.374	0.333	0.724	1.572	0.271	1.000
Fp1	0.257	0.159	0.210	0.268	0.193	0.237	0.237	0.170	0.172	0.411
Fp2	0.372	0.417	0.241	0.487	0.759	0.282	0.294	0.524	0.167	0.066
Fz	0.183	0.101	0.160	0.232	0.146	0.176	0.166	0.070	0.160	**0.015**
T3	0.513	0.952	1.040	0.620	2.502	7.603	0.628	1.222	1.917	0.604
T4	0.946	0.961	0.720	0.802	2.018	4.034	0.633	0.978	0.904	0.728
T5	0.801	0.643	0.515	0.545	0.657	0.630	0.369	0.575	0.377	0.452
T6	0.846	0.756	0.547	0.610	0.815	0.835	0.520	0.674	0.525	0.571

PN pink noise, *MB* monaural beats, *BB* binaural beats, *M* mean, *SD* standard deviation, *Mdn* median

Benjamini–Hochberg significant *p* value is shown in bold

Table 3 Friedman test results of absolute power (μV2) of separate electrodes for 45 Hz ($n=19$)

	PN			MB			BB			*p*
	M	SD	Mdn	*M*	SD	Mdn	*M*	SD	Mdn	
F3	0.234	0.195	0.173	0.207	0.137	0.172	0.195	0.146	0.158	0.678
F4	0.279	0.440	0.136	0.184	0.117	0.152	0.206	0.162	0.154	0.411
F7	0.687	1.340	0.347	0.724	1.360	0.295	0.556	1.128	0.202	0.348
F8	0.639	1.238	0.267	0.671	1.395	0.245	0.686	1.579	0.228	0.846
FP1	0.415	0.501	0.204	0.278	0.248	0.199	0.358	0.520	0.188	0.066
FP2	0.344	0.366	0.228	0.331	0.448	0.168	0.285	0.440	0.169	0.092
Fz	0.201	0.150	0.112	0.172	0.109	0.122	0.181	0.112	0.161	0.801
T3	1.075	1.200	0.731	2.865	9.207	0.576	1.146	1.835	0.535	0.801
T4	0.927	0.666	0.867	1.716	3.960	0.478	0.911	0.842	0.633	0.348
T5	0.585	0.436	0.450	0.573	0.713	0.350	0.645	0.506	0.498	**0.029**
T6	0.674	0.509	0.429	0.661	0.635	0.401	0.565	0.387	0.539	0.678

PN pink noise, *MB* monaural beats, *BB* binaural beats, *M* mean, *SD* standard deviation, *Mdn* median

Benjamini–Hochberg significant *p* value is shown in bold

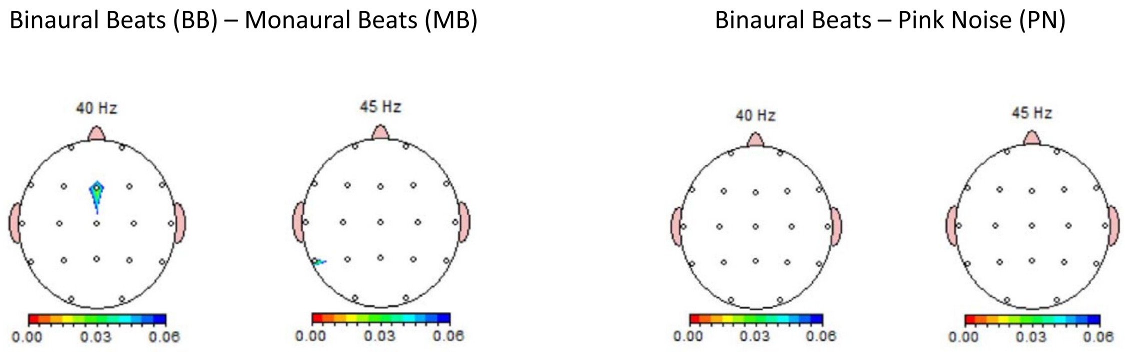

Fig. 2 Topoplots of differences in absolute power between the BB and MB condition and between BB and PN condition

Table 4 Non-parametric Friedman test results of the absolute power (μV2) of averaged frontal and averaged temporal electrodes under the pink noise (*PN*), monaural beat (*MB*) and binaural beat (*BB*) condition (*n* = 19)

	Hz	*p*	PN			MB			BB		
			M	SD	Mdn	*M*	SD	Mdn	*M*	SD	Mdn
Frontal	40	0.494	0.404	0.563	0.261	0.428	0.495	0.317	0.360	0.574	0.187
	45	0.291	0.412	0.541	0.293	0.372	0.487	0.239	0.360	0.500	0.204
Temporal	40	0.801	0.828	0.530	0.658	1.498	3.099	0.672	0.862	0.777	0.724
	45	0.801	0.815	0.555	0.711	1.454	3.579	0.577	0.817	0.725	0.651

Hz hertz, *M* mean, *SD* standard deviation, *Mdn* median

Table 5 Spearman correlations of the total absolute power (μV2) and performance (RT and number of false responses) on the Flanker task under the pink noise (*PN*), monaural beat (*MB*) and binaural beat (*BB*) condition (*n* = 19)

	Reaction time				False responses			
	40 Hz		45 HZ		40 Hz		45 Hz	
	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*
PN	−0.009	0.355	0.096	0.191	0.036	0.626	0.049	0.509
MB	0.184	**0.012**	0.177	**0.015**	−0.250	**0.001**	−0.242	**0.001**
BB	0.100	0.174	0.094	0.201	−0.151	**0.039**	−0.156	**0.033**

Hz hertz

Significant *p* values are in bold

Discussion

In this study, the effects of BB and MB on RT and number of false responses on a Flanker task were measured while recording EEG. We expected that in particular BB would improve the performance on the attention task and would induce more absolute power of 40 or 45 Hz frequencies in the frontal and temporal electrodes. Thus, if BB indeed improves the performance on the Flanker task, a simultaneous increase of gamma power would indicate that the attention improvement might be the result of the BB-induced increase of gamma power. In the present study, the separate effects of the Flanker task performance and the BB on power spectra cannot be differentiated. However, the effects of the Flanker task itself on the power spectra can be assumed to be equal during the PN, MB and BB condition. As a consequence, we believe that the expected larger power during the BB condition can be attributed to the application of BB. However, although less likely, an improved task performance may in turn yield an additional increase in gamma power. In that case, increased gamma power may be the sum of task- and BB-induced gamma power.

With respect to attention, there was no difference in RT between any of the three conditions. However, the number of false responses in the BB condition was smaller than that in the PN condition while the number of false responses in the MB condition was larger than that in de PN condition. It appeared that the mean square root of false responses was largest in the MB condition, intermediate in the PN condition and smallest in the BB condition. The effect sizes of these differences were large, which can be considered to be quite substantial. Thus, in particular BB seems to increase attentional performance as compared to MB or PN. This finding is in line with the results of previous studies which found that beta and gamma BB improved the performance of vigilance and attention tasks (Colzato et al. 2017; Engelbregt et al. 2019; Lane et al. 1998). Notably, the designs of these studies were different. In the study of Lane et al. Colzato et al. and the present study the tasks were performed during the presentation of auditory stimuli whereas the tasks in the study of Engelbregt et al. were performed immediately after the presentation of the auditory stimuli. It may well be true that attention is more substantially improved during listening than after listening to BB. That would mean that the present effects of BB on attention are more pronounced because the Flanker task was performed during the presentation of BB. It may be recommended that future studies include a comparison of the direct and indirect effects of BB on attentional parameters.

According to our hypothesis, the BB-induced improvement on the Flanker task was expected to be accompanied by an increase in the absolute power of 40 or 45 Hz in frontal and/or temporal electrodes. However, against expectation, the 40 Hz absolute power of electrode Fz increased in the MB condition as opposed to PN and BB conditions. In addition, partly in line with our expectation the 45 Hz absolute power of electrode T5 increased in the BB condition relative to MB but did not differ from the PN condition. The present scarce and conflicting findings only justify the conclusion that BB has no consistent effect on EEG activity. Thus, we did not find convincing neurophysiological evidence that neural oscillation, i.e. neural synchronization, plays a role in BB-induced cognitive enhancement. This is in line with studies indicating that gamma BB do not enhance EEG spectral power in any frequency band or only induces a weak cortical entrainment (López-Caballero and Escera 2017; Perez et al. 2020). However, as is mentioned in the Introduction, the synchronization of fluctuations in gamma band power with intermittent and metrical auditory rhythms has been observed in MEG and EEG recordings (Fujioka et al. 2009; On et al. 2013). As the present cognitive enhancement could not be attributed to neural synchronization in the brain as reflected by an increase of 40–45 Hz power, the improved cognitive performance might be mediated by other factors. It has been proposed that BB enhances cognitive processing by the involvement of norepinephrine/glutamate dynamics, particularly the increase of phasic norepinephrine (Hommel et al. 2016; Mather et al. 2016). Although increased noradrenergic activity can be reflected by changes in the EEG, these changes may be observed in frequency bands other than we investigated. In a rat study, increased neuronal discharge activity of noradrenergic neurons of the locus coeruleus (LC) was found to alter forebrain and hippocampal electroencephalographic (EEG) activity. LC activation was consistently followed by high-frequency EEG activity (frequency bands 20.0–34.7 Hz and 34.7–43.8 Hz) in the frontal cortex and by the appearance of intense theta rhythm (2.7–6.8 Hz) in the hippocampus (Berridge and Foote 1991). Pharmacological studies and human brain imaging (MEG) or intracranial EEG studies in rats on theta and beta frequency band may be useful to further elucidate the effects of gamma BB.

To further explore any evidence of an association between performance on the Flanker task and EEG power measures we calculated the correlation between response parameters of the Flanker task and the total absolute power of 40 and 45 Hz EEG frequencies.

As gamma waves are associated with attentional selection, memory and associative learning (Teplan 2002), we expected that higher absolute power would be associated with a faster RT and a smaller number of false responses on the Flanker task. In line with our expectation, higher absolute power of 40 and 45 Hz EEG frequencies in the MB as well as BB condition appeared to be associated with a smaller number of false responses, meaning a better performance. However, we also found that a higher absolute power of 40 and 45 Hz in the MB condition was associated with a longer reaction time, reflecting worse performance. This finding is opposite to expectation. As a consequence, we may conclude that a better cognitive performance in the BB condition is associated with a higher 40 and 45 Hz power, whereas in the MB condition the better cognitive performance is accompanied by a slower reaction time. It must be noted that these higher absolute power in the MB or BB condition cannot be attributed to synchronization with ABS.

Summarizing, the present results indicate that BB can improve the quality of cognitive performance, in particular attention. As there was no association of BB with an increase in absolute 40 or 45 Hz power compared to PN or MB, the hypothesized neural entrainment in the brain, i.e., neural synchronization with gamma BB could not be confirmed by our EEG recordings. However, the present findings suggest that the quality of the performance of the Flanker task, at least in the BB condition, is positively related to the absolute gamma power. Thus, in spite of some evidence that cognitive performance seems to be associated with brain activity, as measured by EEG power, the cognitive enhancing effect of BB could not be explained by the notion of BB increasing the gamma power.

An explanation for the present controversial findings concerning the EEG recordings could be that the number of useable EEG recordings was quite low. A further limitation of the present study is the quite small and specific sample of students. It may well be true that the Flanker task is not sensitive enough for this highly educated sample, which may have caused Flanker RT parameters to deviate from a normal distribution. Furthermore, the minor heterogeneity of the sample might have caused that EEG power measures were also not normally distributed. As we, therefore, had to apply non-parametric tests more subtle differences between conditions could have been unnoticed. Finally, the present exposure of the participants to the auditory stimuli for 5 min could have been of a too short duration to induce major effects.

Based on the above-mentioned limitations we recommend that future research on BB should make use of a larger sample of participants to be sure that participants are a better representation of the overall population. Moreover, it could be preferred to study participants with a specific disorder, for example AD(H)D. Additional recommendations could be to focus on a broader range of cognitive functions to determine the effects of BB on the performance of other tasks. Finally, a better design could be to expose participants to the auditory stimuli for a longer time than 5 min as used in the present study.

Overall, the current findings show that listening to 40 Hz BB improves attention, as measured by the Flanker task. Although we found some evidence that the performance of the Flanker task was associated with a higher absolute power of 40 and 45 Hz frequencies, we could not confirm that BB improves attention by inducing a higher gamma power, reflecting the occurrence of neural entrainment.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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