Investigating the neural basis of pitch memory depending on musical abilities using non-invasive brain stimulation methods

Inaugural-Dissertation

zur Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultät

der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Nora Kristin Schaal

aus Solingen

Düsseldorf, Februar 2015

aus dem Institut für Experimentelle Psychologie

Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der

Mathematisch-Naturwissenschaftlichen Fakultät der

Heinrich-Heine-Universität Düsseldorf

Referent: Prof. Dr. Martin Heil

Korreferentin: PD Dr. Bettina Pollok

Tag der mündlichen Prüfung: 22.06.2015

What is music for?

It's to make you feel good.

Johann Sebastian Bach

Table of Content

List of Abbreviations

CFMT+	Cambridge Face Memory Test – long form
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
MBEA	Montreal Battery of the Evaluation of Amusia
M1	Primary Motor Cortex
MEG	Magnetoencephalography
PET	Positron Emission Tomography
PPC	Posterior Parietal Cortex
rTMS	Repetitive Transcranial Magnetic Stimulation
SMG	Supramarginal Gyrus
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation

Zusammenfassung

Die Tonhöhe ist ein Hauptbestandteil der Musikwahrnehmung und ein wichtiger Faktor für die Verarbeitung von sprachlichen Aspekten. Das Gedächtnis für Tonhöhen spielt beim Hören und Erinnern von Musik eine bedeutende Rolle und ist auch bei der Verwendung der Sprachmelodie, um eine inhaltliche Aussage zu unterstützen, unerlässlich. Verhaltensexperimente und bildgebende Studien haben ein spezifisches und komplexes neuronales Netzwerk für den Gedächtnisprozess von Tonhöhen gezeigt. Das Ziel der vorliegenden Dissertation war es, die neuronalen Strukturen des Kurzzeitgedächtnisses von Tonhöhen mit Hilfe non-invasiver Gehirnstimulationsmethoden zu untersuchen und dabei auch neuronale Spezialisierungen abhängig von musikalischer Expertise sowie genetischer Dispositionen zu erforschen. Die Arbeit umfasst drei Studien, die zum Verständnis der neuronalen Grundlagen des Tonhöhengedächtnisses bei Nicht-Musikern beitragen sollen. Darüber hinaus untersuchten die Studien, ob Musiker, als Experten im musikalischen Bereich, und Amusiker, die ein Defizit für das Tonhöhengedächtnis aufweisen, Unterschiede der neuronalen Repräsentation des Tonhöhengedächtnisses aufweisen.

In Studie 1 wurde mit Hilfe transkranieller Gleichstromstimulation (engl. *transcranial direct current stimulation*, tDCS) untersucht, ob bei der Beteiligung des Gyrus Supramarginalis (SMG) ein Hemisphären-Unterschied bei Musikern und Nichtmusikern im Tonhöhengedächtnis vorliegt. Die Studie zeigte, dass bei Nichtmusikern die inhibitorische kathodale tDCS über dem linken SMG zu einer signifikanten Verschlechterung der Tonhöhengedächtnisleistung sowohl in einer Rekognitions- als auch in einer Abrufaufgabe geführt hat. Bei den Musikern wurde eine selektive Abnahme der Leistung nur bei der Rekognitionsaufgabe gefunden und, wenn tDCS über dem rechten SMG appliziert wurde. Des Weiteren deuten die Ergebnisse darauf hin, dass die Bedeutung der SMG abhängig von den Aufgabenanforderungen ist. Bei Nichtmusikern wurde eine kausale Beteiligung des linken und bei Musikern des rechten SMG nur bei Aufgaben mit hoher Anforderung beziehungsweise hoher Tonhöheninformationsmenge gefunden. Bei einer visuellen Gedächtnisaufgabe wurden keine Modulationseffekte gefunden. Dieses weist auf eine spezifische Bedeutung der SMG für das Tonhöhengedächtnis beziehungsweise für das auditorische Gedächtnis hin.

Studie 2 prüfte, ob der linke SMG bei Nichtmusikern während des ganzen Tonhöhengedächtnisprozesses involviert ist, oder, ob die Bedeutung auf eine bestimmte Phase des Gedächtnisprozess eingegrenzt werden kann. Zu diesem Zweck wurde eine repetitive

transkranielle Magnetstimulation (engl. *repetitive transcranial magnetic stimulation*, rTMS) verwendet, um eine zeitlich genauere Modulierung zu ermöglichen. Getestet wurde, ob der linke SMG während des Retentionsintervalls (Experiment 1) oder der Enkodierung (Experiment 2) kausal involviert ist. Die Ergebnisse zeigten eine selektive Störung der Tonhöhengedächtnisleitung in Form von verlängerten Reaktionszeiten, wenn die rTMS während der Retention induziert wurde. Keine Modulationseffekte wurden gefunden, wenn die rTMS über dem Vertex (Kontrollareal) oder während der Enkodierung appliziert wurde. Um auszuschließen, dass diese Effekte auf eine motorische Modulation der Reaktionszeiten zurückgeführt werden können, wurde in einem dritten Experiment der Effekt der rTMS auf eine Tonhöhenwahrnehmungsaufgabe untersucht. Hierbei zeigten sich keine Veränderungen der Reaktionszeiten. Zusammengefasst zeigte die Studie eine selektive Beteiligung des linken SMG während der Retentionsphase der Tonhöhenaufgabe bei Nichtmusikern.

Studie 3 untersuchte, ob eine zuvor beschriebene Dysfunktion des dorsolateralen präfrontalen Kortex (DLPFC) bei Amusikern kausal relevant für das Defizit des Tonhöhengedächtnisses ist. Im Bereich des DLPFC wurde bei Amusikern eine Amplitudenabnahme von Oszillationen im niedrigen Gammabereich (30-40 Hz) während einer Tonhöhengedächtnissaufgabe gezeigt. Es stellte sich die Frage, inwieweit diese Veränderungen ein Schlüsselfaktor der Amusie sein können. Diese Störung wird mit musikalischen Wahrnehmungs- und Gedächtnisdefiziten in Verbindung gebracht. In dieser Studie wurde die transkranielle Wechselstromstimulation (engl. *transcranial alternating current stimulation*, tACS) verwendet. Obwohl die genauen Wirkmechanismen der tACS noch nicht vollständig geklärt sind, gibt es experimentelle Hinweise darauf, dass diese Methode ein *Entrainment* enodgener Oszillationen in der Stimulationsfrequenz erlaubt. In der vorliegenden Studie wurde untersucht, inwieweit die tACS mit einer Frequenz von 35 Hz über dem rechten DLPFC das Tonhöhengedächtnis bei Amusikern verbessern kann. Diese führten eine Tonhöhen- sowie eine visuelle Gedächtnisaufgabe vor und während einer 35 Hz oder einer 90 Hz (Kontrollbedingung) tACS durch. Die Studie zeigte eine signifikante Verbesserung der Tonhöhengedächtnisleitung während der 35 Hz Stimulation. Des Weiteren führten gesunde Kontrollprobanden die Aufgaben ohne Stimulation aus. Der Vergleich zwischen Amusikern und Kontrollprobanden zeigte vor der tACS eine selektive Beeinträchtigung des Tonhöhengedächtnisses bei Amusikern. Dieser Unterschied war bei einer 35 Hz tACS nicht mehr erkennbar. Daher unterstützt diese Studie die funktionale Relevanz der modifizierten Oszillationsmuster im rechten DLPFC für die Basis der Amusie.

Die Hauptergebnisse der Dissertation sind (*i*), dass hemisphärische Unterschiede der funktionalen Beteiligung der SMG beim Kurzzeitgedächtnis für Tonhöhen zwischen Musikern und Nichtmusikern gefunden wurden (*ii*), dass die Bedeutung des linken SMG für das Tonhöhengedächtnis bei Nichtmusikern auf das Retentionsinterval des Gedächtnisprozesse eingegrenzt werden konnten und (*iii*), dass verminderte Oszillationen im niedrigen Gammaband im DLPFC bei Amusikern ein kausaler Grund für die Tonhöhengedächtnisdefizite dieser kongenitalen Störung sein könnten.

Abstract

Pitch is a main building block of music perception and also an important factor for processing linguistic aspects. Memory for pitch plays an essential role when it comes to listening and memorising music and when using the prosody in language to convey a meaning. Behavioural research and brain imaging studies have highlighted a distinct and complex neural network underlying the pitch memory process. The aim of the present thesis was to look into the neural basis of short-term memory for pitches using different non-invasive brain stimulation methods and to investigate whether neural specialisations can be found depending on musical expertise and genetic dispositions. The thesis comprises three studies which contribute to the understanding of which brain areas are involved in the pitch memory process. Moreover, the studies investigated whether specificities can be revealed for musicians, as experts in the musical domain, and amusics who dispose a pitch memory deficit.

Study 1 used transcranial direct current stimulation (tDCS) to investigate whether hemispheric differences of the significance of the supramarginal gyrus (SMG) for pitch memory can be revealed in non-musicians and musicians. The study showed that in non-musicians inhibitory cathodal tDCS over the left SMG led to a significant decline in pitch memory performance on a recognition and recall task. In musicians, a selective deterioration was found on the recognition task only and when tDCS was applied over the right SMG. Furthermore, the results of the study suggest that the involvement of the SMG depends on task demands. The causal significance of the left SMG in non-musicians and the right SMG in musicians was found when the task demands were high i.e. the pitch information load which had to be stored was high. No modulation effects were found on a visual memory task, highlighting the specific involvement of the SMG in pitch i.e. auditory memory.

Study 2 explored whether the left SMG in non-musicians is involved in the whole pitch memory process or whether the significance can be linked to a specific stage of the pitch memory process. To allow a temporally more precise modulation, repetitive transcranial magnetic stimulation (rTMS) was used in order to test whether the left SMG is causally involved during the retention period (experiment 1) or the encoding stage (experiment 2). The results revealed a selective disruption of pitch memory performance, reflected by increased reaction times, when rTMS was applied during retention. No modulation effects were found when stimulation was applied over the vertex (control site) or during encoding. Additionally, a third experiment was conducted on a pitch perception task which showed that the effect of increased reaction times was not due to motor interference. Taken together, the study showed a selective involvement of the left SMG in the retention period of a pitch memory task in non-musicians.

Study 3 examined whether the dysfunction of the dorsolateral prefrontal cortex (DLPFC), reflected by decreased low gamma oscillations (in the 30-40 Hz range) during pitch memory, is a key factor for congenital amusia. The disorder is linked to musical perception and memory deficits. Transcranial alternating current stimulation (tACS) was used in this study. Although the exact effectiveness of tACS has yet to be solved, first evidence exists that this method allows the entrainment of ongoing brain oscillations at a certain stimulation frequency. TACS at 35 Hz over the right DLPFC was applied in order to investigate whether pitch memory can be improved in amusics. To this end, amusics performed a pitch and visual memory task before and during either 35 Hz or 90 Hz (control condition) tACS. The study revealed a significant facilitation of pitch memory performance during 35 Hz stimulation. Healthy controls also completed both tasks without stimulation. The comparison of performances between the groups showed a selective impairment for amusics of pitch memory at baseline but interestingly this difference was no longer present during 35 Hz tACS. The study therefore supports the functional relevance of reduced low gamma oscillations in the right DLPFC as a basis of the congenital disorder.

The main findings of the thesis are (*i*) that hemispheric differences of the functional involvement of the SMG for short-term memory for pitches could be revealed for musicians and non-musicians (*ii*) that the significance of the left SMG in non-musicians for pitch memory could be restricted to the retention interval of the memory process and (*iii*) that modified oscillations at the low gamma range during pitch memory in the right DLPFC in amusia are causally related to pitch memory deficits.

1. Introduction

Pitch is next to rhythm and timbre one of the main building blocks of music and a key factor for music and language perception (Bannan, 2008; Krumhansl, 2000). Moreover, pitch memory is an important factor for the communicative role of auditory material. For example, it allows us to recognise whether we are hearing a song for the first time, to remember our favourite song, to associate special feelings and people with a certain song and to use music to convey feelings and thoughts. For language the use of intonation, which is basically using pitch accents and variations, is important for conveying meaning and to structure speech so it can be comprehended well (Cutler, Dahan, & vanDonselaar, 1997; Mitchell & Ross, 2013).

In a musical sense the term *pitch* describes "the position of a sound in a musical scale" (Greenish, 1953, p. 67). As the majority of the population are so called relative pitch possessors (compared to people with absolute pitch who can name or produce a single pitch without a reference tone (Takeuchi & Hulse, 1993)), one usually distinguishes whether one tone is higher or lower in relation to another tone. In order to create a musical melody, tones with certain pitches are combined and result in a unique contour. The term *contour* defines the overall shape the tones move in and more broadly speaking means the way the melody moves up and down in time (Dowling & Fujitani, 1971). Research has shown that for melody recognition and memory contour is one of the main factors (Dowling, 1978; Schubert & Stevens, 2006).

In order to test pitch memory, one can distinguish between two main response methods, namely recall and recognition. Most commonly used in pitch memory experiments are recognition tasks, in which participants are required to learn material and information and then later judge whether an item was presented before or is new. Another form of recognition is to present two stimuli and the task is to judge whether they are the same or different. The latter is used in all three experiments of this thesis. Participants hear two pitch sequences with a short pause between them and are required to judge whether they are the same or different. Hereby, one can distinguish between three different stages of the memory task. In the encoding phase new material e.g. a pitch sequence, is perceived and the tones are encoded in relative relationships to each other. In the retention phase e.g. the pause between the two sequences, the information is stored and maintained and for the retrieval phase this information needs to be retrieved in order to be able to make a decision. Contrary to this form of memory testing, in recall tasks participants are asked to reproduce the learned material in some way. For example participants can be asked to recall a list of words or recall the contour of a melody by ticking boxes according to which tones (high, medium or low in pitch) they heard (see study 1 for more details). It has been shown that recall and recognition tasks rely on different mechanisms and task demands (Berryhill, Wencil, Coslett, & Olson, 2010; Cabeza, Locantore, & Anderson, 2003).

Studies investigating behavioural aspects of pitch memory have mainly used a pitch recognition memory paradigm in which either silence or interfering material was presented between two tones and participants should judge whether the target tones were the same (Deutsch, 1970). The main findings using this task are that the length of the silence has a marginal effect on pitch memory performance whereas inserting and increasing interfering tones between the two target tones leads to an increasing decline in pitch memory performance (Clement, Demany, & Semal, 1999; Deutsch, 1970; Massaro, 1970; Ross, Olson, Marks, & Gore, 2004). Furthermore, studies have shown that pitch memory does not deteriorate when the interfering material was taken from another domain e.g. verbal stimuli (Pechmann & Mohr, 1992; Semal, Demany, Ueda, & Halle, 1996), suggesting that pitch material is stored differently to material from other domains. This assumption also indicates that pitch memory relies on a specialised neural circuit in the brain.

1.1 Pitch Memory – Neural mechanisms

Several brain imaging studies have highlighted a complex neural structure for pitch perception and the pitch memory process emphasising the activation of frontal, temporal and parietal areas (Celsis et al., 1999; Gaab, Gaser, Zaehle, Jancke, & Schlaug, 2003; Janata, Tillmann, & Bharucha, 2002; Jerde, Childs, Handy, Nagode, & Pardo, 2011; Kaiser & Bertrand, 2003; Platel et al., 1997; Schulze, Zysset, Mueller, Friederici, & Koelsch, 2011; Zatorre, Evans, & Meyer, 1994). One of the first studies investigating the neural basis of tonal perception and pitch memory in subjects with no or very little musical training was conducted by Zatorre et al. (1994) using positron emission tomography (PET). The study revealed that the condition with a high memory load of pitch information, compared to the passive listening condition, showed activation in the right frontal and temporal lobes as well as in the parietal and insula cortex bilaterally. Jerde et al. (2011) explored the neural mechanism of memory for rhythm and melody in non-musicians also using PET and revealed that for the melody memory condition activation was found in bilateral inferior parietal lobes and middle and medial frontal gyri as well as in the right superior parietal lobe. In 2003 Gaab and colleagues conducted a functional magnetic resonance imaging (fMRI) study on pitch memory with participants with no or very little musical training and revealed activation in the superior temporal gyrus, supramarginal gyrus as well as in dorsolateral frontal and superior parietal regions, all bilaterally and in the left inferior frontal gyrus. Interestingly, this study also showed that the activation of the left supramarginal gyrus (SMG) and dorsolateral cerebellum correlated positively with task performance, highlighting a specific role of these brain areas for short-term memory for pitches in non-musicians (Gaab, Gaser, Zaehle, et al., 2003).

1.2 Pitch Memory and the influence of expertise

Pitch memory abilities can vary depending on musical expertise and training as well as genetic dispositions. It has been shown that highly trained musicians, as experts in this field, have superior pitch memory abilities than so called non-musicians, who have not experienced any form of musical education (Williamson, Baddeley, & Hitch, 2010). On the other hand individuals with congenital amusia, a lifelong musical disorder, expose impaired pitch perception and memory abilities (Albouy et al., 2013; Gosselin, Jolicoeur, & Peretz, 2009; Hyde & Peretz, 2004; Williamson & Stewart, 2010). As imaging studies have shown anatomical and functional differences between professional musicians and non-musicians as well as for the neural structure of amusic brains, the influence of expertise and genetic disposition on neural mechanisms of pitch memory is one of the main focuses of this thesis.

As a model of neuroplasticity, the musicians' brain has been studied extensively over the last two decades (for recent reviews see Herholz & Zatorre, 2012; Merrete, Peretz, & Wilson, 2013). Hereby, many studies have revealed anatomical differences between musicians and non-musicians in motor areas (Jancke, Schlaug, & Steinmetz, 1997), the corpus collosum (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995) and Heschl's gyrus (Schneider et al., 2002; Schneider et al., 2005). Additionally, functional brain imaging studies have revealed different neural activation patterns in musicians and non-musicians for cognitive tasks, such as verbal and tonal memory (Schulze, Zysset, et al., 2011), pitch perception (Habibi, Wirantana, & Starr, 2013) and rhythm processing (Herdener et al., 2014). One of the sparse longitudinal studies has shown training-induced structural brain plasticity in children after 15 months of musical training (Hyde et al., 2009) supporting the approach that *nurture* i.e. musical training is a key factor for the structural differences found in the vast amount of cross-sectional studies comparing musicians and non-musicians (Jancke et al., 1997; Schlaug et al., 1995; Schneider et al., 2002; Schneider et al., 2005). Additionally, the age of onset effect has shown a close link between musical training and neuroplasticity in the brain of musicians (Barrett, Ashley, Strait, & Kraus, 2013). On the other hand, a recent study has shown genetic basis of musical abilities by reporting preliminary results of specific chromosomes being associated with musical perception and memory abilities (Tan, McPherson, Peretz, Berkovic, & Wilson, 2014).

When looking at the neural basis of pitch memory in musicians, some specialised neural circuits have been revealed. A study by Gaab and Schlaug (2003) compared neural activation patterns of musicians and non-musicians when pitch memory performances were matched between groups. Besides distinctions between groups, the data revealed overlapping activation in the superior parietal lobe as well as the bilateral superior temporal, supramarginal, posterior middle and inferior parietal gyri (all bilateral). The neural distinctions were that musicians showed stronger activation in the right SMG and right temporal gyrus whereas activation was stronger in the right primary and left secondary auditory cortex in non-musicians (Gaab & Schlaug, 2003). However, a study by Gaab, Gaser, & Schlaug (2006) showed increased activation in the left SMG as well as in left Heschl's and left posterior superior temporal gyrus in non-musicians after 5 days of pitch memory training in the group of strong learners compared to the weak leaners. This highlights the crucial role of the left SMG in combination with trained expertise. Along these lines, a fMRI study looking at music processing and memory functions also revealed more activation in the left hemisphere compared to the right hemisphere with peaks in the left SMG and Heschl's gyrus in musicians (Ellis, Bruijn, Norton, Winner, & Schlaug, 2013). This leftward asymmetry also correlated positively to cumulative hours of practice. Additionally, also an included longitudinal approach with children from around 6 to 9 years support a leftward-asymmetry of SMG involvement pointing towards a musical training-related activation pattern with a dominance in the left hemisphere (Ellis et al., 2013). Furthermore, a fMRI study compared the neural architecture of verbal and tonal memory in musicians and non-musicians (Schulze, Zysset, et al., 2011). Looking at neural correlates of the tonal condition where participants heard a sequence of 5 pitches and after a short silence had to indicate whether a presented probe tone was included in the sequence or not, musicians show a much more complex neural system for tonal memory. Additional activations for musicians during tonal memory were the left cerebellum, right globus pallidus and right caudate nucleus. The left inferior parietal lobe (which corresponds to the location of the left SMG) showed activation during tonal memory in musicians and non-musicians (Schulze, Zysset, et al., 2011). As the significance of the SMG for pitch memory in musicians and non-musicians is the main focus of study 1, the debate regarding a hemispheric specialisation of the SMG in musicians warrants a comment here. Several studies highlighted a stronger activation of the left SMG in musicians and in combination with musical training (Ellis et al., 2013; Gaab et al., 2006) whereas the study by Gaab & Schlaug, (2003) showed increased activation in the right SMG associated with pitch memory in musicians. The key difference between the latter study compared to the other studies is that performance levels in the study by Gaab & Schlaug, (2003) were matched between musicians and non-musicians. This indicates that task demands are an important factor for the hemispheric involvement of the SMG in musicians. More precisely, these data imply that in more demanding tasks only the right SMG might be involved in pitch memory in musicians.

In 2002 the neuro-developmental disorder, congenital amusia, was first introduced in the literature (Peretz et al., 2002). Since then the musical disorder has been studied behaviourally and using brain imaging studies to look at the magnitude of the musical impairments as well as the underlying neural structures. In 2003 the Montreal Battery of Evaluation of Amusia (MBEA) was introduced (Peretz, Champod, & Hyde, 2003) and has since then been the most frequently used tool in the diagnosis of congenital amusia (also called tone-deafness). The MBEA involves six subtests from which three tests evaluate melodic i.e. pitch-based features, two are based on rhythmic structures and one is a musical memory test. Even though the basis of the impairment is not fully understood yet, it is likely that genetic factors play a role (Peretz, Cummings, & Dube, 2007) as it is not due to insufficient exposure to music, intellectual impairment or a hearing deficit (Ayotte, Peretz, & Hyde, 2002). The disorder is associated with structural and functional differences in frontal and temporal brain cortices (Stewart, 2008).

The first study comparing the morphology of the amusic brain to the brains of healthy controls using voxel-based morphometry, revealed a reduction of white matter concentration in the right inferior frontal gyrus in amusics that correlated to the pitch-based task performances of the MBEA (Hyde, Zatorre, Griffiths, Lerch, & Peretz, 2006). In a follow up study, the same research group used structural magnetic resonance imaging and could expand their findings by revealing thicker cortices in the right inferior frontal gyrus and right auditory cortex (Hyde et al., 2007) highlighting that a deformed right frontal-temporal pathway might serve as a key factor for this disorder. This assumption found further support in a study by

Loui, Alsop, & Schlaug, (2009) which showed a reduced arcuate fasciculus connectivity in the right hemisphere in tone-deaf participants compared to healthy controls.

Besides structural differences, also functional changes of the amusic's brain have been revealed. A fMRI study exposed that in amusics the right inferior gyrus as well as its functional connectivity to the auditory cortex showed an abnormal deactivation compared to controls while listening to pure-tones. However both groups, amusics and normal healthy controls, showed increased brain activity in the left and right auditory cortex as the tones increased in pitch-distance (Hyde, Zatorre, & Peretz, 2011). In 2013, a study investigated the neural basis of congenital amusic using magnetoencephalography (MEG) and voxel-based morphometry for pitch memory (Albouy et al., 2013). The participants, amusics and controls, had to judge whether two six-tone long sequences were the same or different while being scanned. The study confirmed behavioural deficits in pitch memory and structural abnormalies in the amusic brain in the right inferior frontal and superior temoral gyri. Furthermore, the MEG data revealed that during the encoding of the pitch sequences abnormal N100m responses, reflected by decreased amplitude and increased latency, were evoked for each tone in bilateral frontal and temporal areas. During the retention period of the pitch memory task the induced low gamma oscillations (in the 30-40 Hz range) in the right dorsolateral prefrontal cortex (DLPFC) were decreased in amusics (Albouy et al., 2013). As low gamma oscillations are closely related to memory functions (Jensen, Kaiser, & Lachaux, 2007), the alteration at this frequency may cause an impairment of maintaining pitch information which contributes to the basis of disturbed pitch memory abilities in amusics.

1.3 Non-invasive brain stimulation methods

In the last 20 years non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and transcranial magnetic stimulation (TMS), have been used in a vast amount of studies investigating the neural basis of cognitive functions and also in order to develop therapeutic interventions. In comparison to brain imaging techniques, such as fMRI and neurophysiological methods like MEG, which highlight functional activation patterns in the brain during task performance, brain stimulation enables one to investigate causal functional involvements of certain brain areas for a specific task (Miniussi, Harris, & Ruzzoli, 2013 for a recent review). Brain stimulation provides a controlled method for transiently modulating brain activity and to see how this modulation affects behaviour. Non-invasive brain stimulation studies are comparable to lesion studies as they allow investigating the necessity of certain brain functions for specific tasks. There are several advantages of brain stimulation studies compared to lesions studies. Firstly, a within-subject design can be applied which strengthens the validity of the conclusions we can draw. Secondly, lesions are rarely spatially discrete and also the studies with brain lesion patients are often performed months after the brain injury and it is hard to disentangle whether the lesioned brain area causes the functions being tested or whether compensation functions of the brain account for the outcome (Robertson & Murre, 1999; Walsh & Rushworth, 1999).

Furthermore, it has been shown that brain stimulation methods are a promising tool for therapeutic interventions where abnormal brain functions, congenital or due to a disease, can be modulated and soothe symptoms. The different techniques are based on different mechanisms which are described briefly in the following sections. Furthermore, all three methods are implemented in the experimental work of this thesis.

1.3.1 Transcranial direct current stimulation

TDCS is a form of transcranial electrical stimulation in which a weak electrical current is passed through the skull applied by two electrodes and leads to a change of neural excitability (Nitsche & Paulus, 2001). The target electrode is placed on the scalp over the brain area of interest and the reference electrode is placed over an area that is known not to be involved in the specific task. Common places for reference electrodes are the vertex, the supraorbital area or the arm. TDCS distinguishes between anodal and cathodal stimulation where the direction of the current flow determines the stimulation mode. For anodal stimulation the anode (positive electrode) is placed over the target area and the cathode (negative electrode) somewhere distant as the reference electrode. The direct current then flows from the anode to the cathode resulting in a depolarisation of the resting membrane potential of the brain area and a facilitation of neural activity under the anode. Contrary to this set-up, for cathodal stimulation the cathode is adjusted above the target area and the anode serves as the reference electrode and the stimulation then leads to a hyperpolarisation of the resting membrane of the neurons and suppresses cortical excitability under the cathode electrode (Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010; Ladeira et al., 2011; Nitsche & Paulus, 2000).

Important parameters which contribute to effective modulation effects are electrode size, current strength and stimulation duration. The focality of tDCS is determined by the size of the electrodes and as the smallest electrodes which are used are 2,5 cm x 2.5 cm large the focality is limited (Gandiga, Hummel, & Cohen, 2006). In this context it is worth noting that because of the size of the electrodes to up to 5 cm x 7 cm adjacent areas of the target area might also be stimulated. Depending on the duration of stimulation the stimulation effects can last up to one hour after the end of stimulation (Nitsche et al., 2008; Nitsche & Paulus, 2000, 2001). Furthermore, the time of administration of tDCS is an important factor for the effects on cognitive outcomes. It has been shown that *online* effects, for which tDCS is applied during task performance can differ from *offline* effects, for which tDCS is administrated before task performance (Martin, Liu, Alonzo, Green, & Loo, 2014; Pirulli, Fertonani, & Miniussi, 2013).

TDCS has been shown to be a safe non-invasive brain stimulation method and the only side effects that have been reported are a slight tingling and skin irritation under the electrodes as well as mild headaches. Stimulation sessions up to 20 minutes with an intensity of 2 mA maximum meet all safety criteria (Iyer et al., 2005; Nitsche, Fricke, et al., 2003; Nitsche, Liebetanz, et al., 2003). A review article by Nitsche et al., (2008) which considered 100 studies shows that no other side effects than the ones mentioned above have occurred.

In order to verify that modulation effects which are found are not due to non-specific stimulation effects, a common control condition is to use sham stimulation where the electrical current is only applied for as little as 30 seconds and does not lead to any neurophysiological changes. It has been shown that participants cannot distinguish between active and sham stimulation as the tingling sensation at the beginning of the stimulation is experienced in the same way (Gandiga et al., 2006). Furthermore, off-target active stimulation conditions are also important to prove that the stimulation effects are site specific (Horvath, Carter, & Forte, 2014).

The research into using tDCS for therapeutic interventions has shown first successful attempts with positive effects of anodal tDCS on patients with depression (Fregni, Boggio, Nitsche, et al., 2006), chronic pain (Fregni, Boggio, Lima, et al., 2006) and on stroke patients (Fregni et al., 2005; Hummel et al., 2005) and of cathodal tDCS in research on epileptic properties (Fregni, Otachi, et al., 2006).

1.3.2 Transcranial alternating current stimulation

Contrary to tDCS which modulates the excitability of neurons under the targeted area, tACS most likely interferes with ongoing brain oscillations. Nevertheless, the exact mechanisms of tACS have not yet been fully understood (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Two electrodes are placed on the scalp and an alternating current with a specific frequency is applied. Hereby the endogenous ongoing brain oscillations may interact with the exogenous oscillations and when the stimulation is applied long enough the endogenous oscillations can synchronise and be entrained by the stimulation frequency (Antal & Paulus, 2013; Zaehle, Rach, & Herrmann, 2010). Using electroencephalography (EEG) Zaehle et al. (2010) could show that tACS applied at the individual's alpha frequency led to an enhancement of alpha amplitudes when stimulation was applied for 10 minutes. This finding supports that tACS can interfere with endogenous brain oscillations. Furthermore, applying 10 Hz tACS to the parieto-occipital cortex resulted in a facilitation of performance in a visual detection task. This improvement was linked to the entrainment of alpha oscillations in the parieto-occipital cortex (Helfrich et al., 2014). A study investigating the effects of applying different gamma frequencies (e.g. 40, 60 and 80 Hz) to the primary visual cortex showed that contrast perception was improved only when 60 Hz tACS was applied. Additionally, the study showed that 60 Hz modulation effects were task specific as no improvement on spatial attention was revealed highlighting the causal significance of 60 Hz oscillation in the primary visual cortex for contrast perception (Laczo, Antal, Niebergall, Treue, & Paulus, 2012). An interesting study in the memory domain showed that theta tACS with a frequency of 4.5 Hz over bilateral DLPFC improved verbal working memory performance when applied online while no offline effects were exposed (Meiron & Lavidor, 2014).

Furthermore, a review of the modulatory effects of tACS on behavioural performances emphasises the crucial role of the applied frequency as well as amplitude and phase of oscillations for successful paradigms to reveal the causal link between frequency specific brain oscillations in a target area and cognitive performances (Herrmann, Rach, Neuling, & Struber, 2013). Moreover, a first clinical implication of tACS has been revealed recently. A case study by Angelakis et al., (2013) reported a reduction of the dystonic symptoms in a patient with idiopathic cervical dystonia when applying 15 Hz tACS bilaterally over the primary motor cortex (M1). The symptom reduction was still measurable after 30 days. This is a first promising result suggesting therapeutic tACS effects outlasting the stimulation period.

1.3.3 Transcranial magnetic stimulation

In 1985 the first study introducing TMS as we know it today was published by Barker and colleagues. The study reported a successful attempt to disrupt the functioning of M1 through TMS by measuring the muscle twitches and recording the motor evoked potentials (Barker, Freeston, Jalinous, Merton, & Morton, 1985).

The basic mechanisms of TMS are that a high voltage discharge is produced in the coil which then leads to a rapidly changing magnetic field around the coil. Through the mechanisms of electromagnetic induction, the electrical currents change the resting potentials of the nerve cells and can lead to either a facilitation or suppression of neural activation (Nagarajan, Durand, & Warman, 1993). The modulation effects can then either be measured evaluating behavioural aspects (e.g. accuracy, reaction times, and thresholds) or using physiological measures (e.g. evoked potentials, functional blood flow). TMS relies on an extremely good temporal and spatial resolution (Pitcher, Charles, Devlin, Walsh, & Duchaine, 2009; Walsh & Cowey, 2000). Along this line, TMS can produce selective activations of specific muscles of the motor homunculus (Singh, Hamdy, Aziz, & Thompson, 1997). Additionally, the good spatial resolution has been shown by functional dissociations of TMS application of discrete brain areas (Pitcher et al., 2009; Stewart, Walsh, Frith, & Rothwell, 2001). For auditory experiments it is important to note that TMS pulses are accompanied by a brief clicking noise which needs to be taken into account as a confounding variable. In order to minimise the interference of the clicking, it is advisable for participants to wear headphones (Rossi, Hallett, Rossini, Pascual-Leone, & Safety, 2009) and to ensure that control conditions are included which can show that the clicking is not the reason for a potential effect.

The extent and duration of the effects are linked to the size of the induced current as well as the orientation of the coil (Richter, Neumann, Oung, Schweikard, & Trillenberg, 2013). Additionally, the choice of magnetic coil is important. Typically, two different types of coils, the circular and the figure of eight coil, are used. The most frequently used coil for research applications is the figure of eight coil which has two windings and the current flows in opposite directions and by doing so the current converges at the centre point where it summates and produces a very focal effect (Ueno, Tashiro, & Harada, 1988). The circular coil induces the maximum electrical current field under the winding of the coil and therefore it is less focal.

TMS can be distinguished in different types of stimulation paradigms. For single pulse paradigms one or two very brief pulses of around 1 ms are applied online during the experimental task and it has been shown that the chosen time window for neural disruption is of great importance as differential effects on behavioural performance have been shown (O'Shea, Muggleton, Cowey, & Walsh, 2004; Rusconi, Dervinis, Verbruggen, & Chambers, 2013). For repetitive TMS (rTMS) repeated single TMS pulses are delivered at the same intensity for a specific duration. For stimulation of 1 Hz or lower the stimulation can last up to 15 minutes whereas higher frequency stimulation is applied for a shorter duration of milliseconds or several seconds (Wassermann, 1998). It has been shown that rTMS has the potential effect to show function-specific involvements of cortical areas on behavioural performance. For example, applying 500 ms of 10 Hz TMS over parietal regions (SMG and angular gyrus) resulted in modulations of modality-specific attention processes (Rushworth, Ellison, & Walsh, 2001). In this study rTMS applied over the right angular gyrus resulted in a disruption of orienting attention while rTMS over the left SMG led to a decline in motor attention. Whereas rTMS with low frequencies (< 1 Hz) commonly results in an inhibitory effect of TMS, rTMS applied with a faster rate (> 1 Hz) is linked to facilitatory effects (Bolognini & Ro, 2010; Fitzgerald, Fountain, & Daskalakis, 2006). However, the directional effects are not that clear, especially for high frequency stimulation protocols, as the state-dependency of the targeted brain region can interact with the induced TMS pulses (Silvanto & Pascual-Leone, 2008).

If all safety guidelines are met (Wassermann, 1998), TMS is a safe method. There are possible side effects such as minor discomfort, non-intended muscle twitches or mild headaches which participants need to be informed about prior to taking part in a TMS session. Furthermore, there is a rare possibility that TMS may induce seizures. Therefore, it is highly important that only participants with no personal or family history of epilepsy or any other kind of neurological condition take part in studies including TMS as well as tDCS and tACS (Pascual-Leone et al., 1993; Stewart, Ellison, Walsh, & Cowey, 2001).

1.4 Modulating pitch perception and memory with non-invasive brain stimulation methods

A study on pitch discrimination revealed that cathodal tDCS over the left and right Heschl's gyrus led to a deterioration of performance in participants with musical background (with a mean of around 13 years of musical experience) whereas anodal stimulation did not show any effects. Furthermore, the study showed that the modulatory effect of cathodal tDCS was larger when stimulation was applied over the right hemisphere. Taken together, the study highlights the involvement of the Heschl's gyrus bilaterally with a predominant significance in the right hemisphere for pitch discrimination (Mathys, Loui, Zheng, & Schlaug, 2010). Andoh & Zatorre, (2011) conducted a TMS study and investigated how 1 Hz and 10 Hz rTMS over the left and right Heschl's gyrus influences the performance of participants with minimal musical training, measured by reaction times, on a melody discrimination task. The study exposed that 10 Hz stimulation had a significant modulation effect when applied over the right Heschl's gyrus. Interestingly, the authors found gender differences by revealing that in women the stimulation resulted in a decrease of reaction times, whereas men showed an increase (Andoh & Zatorre, 2011).

Furthermore, Imm et al., (2008) conducted a TMS study investigating the involvement of the bilateral inferior parietal and DLPFC for tonal and audio-verbal working memory by applying single-pulse TMS to various time-points (250, 450, 650, or 850 ms) after the onset of the sound in a N-back task. The results showed that stimulation over the right inferior parietal cortex and DLPFC resulted in increased reaction times at all time-points for the tonal condition. Contrary to this, only single-pulse TMS over the left inferior parietal cortex at 450 ms led to increased reaction time for the audio-verbal task. The study demonstrates that memory tasks with different auditory material rely on different neural structures and reveals a relevance of the right DLPFC and inferior parietal cortex for tonal memory (Imm et al., 2008).

So far two studies have used tDCS to investigate the neural basis of pitch memory in non-musicians (Schaal, Williamson, & Banissy, 2013; Vines, Schnider, & Schlaug, 2006). Based on the fMRI study by Gaab et al. (2003), which highlighted the activation of the left SMG for pitch memory in non-musicians both studies examined whether the left SMG is causally involved in pitch memory. Vines et al (2006) revealed that cathodal tDCS over the left SMG compared to sham stimulation and stimulation over the vertex, led to deterioration on a pitch recognition task. Building on this finding, we could show that applying anodal tDCS over the left SMG, compared to sham stimulation, resulted in a facilitation of pitch memory recognition and recall whereas no modulation effects were found on a visual control task (Schaal et al., 2013). Taken together, both studies provide strong evidence for a causal significance of the left SMG in pitch memory in non-musicians.

1.5 Aims

The intention of the current thesis was to further investigate the neural basis of the pitch memory process. Using different non-invasive brain stimulation methods, the thesis aims to reveal causal relationships between the function of targeted brain areas and the pitch memory process. Hereby, also the influence of expertise and genetic disposition are taken into account in order to investigate whether superior pitch memory abilities of musicians as well as impaired pitch memory in congenital amusics can be linked to a distinctive neural network.

2. Overview of Studies

Study 1

Research has shown strong evidence for the left SMG involvement for pitch memory in non-musicians whereas functional imaging studies have highlighted contrary activation of the left and right SMG in musicians. Study 1 aimed to identify whether hemispheric differences of the involvement of the SMG for pitch memory can be found between musicians and non-musicians. Additionally, it looked at whether task difficulties could account for potential differences. Here, cathodal tDCS was applied to modulate either the left or right SMG in musicians and non-musicians to investigate whether hemispheric differences between experts (musicians) and novices (non-musicians) can be revealed.

Study 2

As several studies (including study 1 of this thesis) have revealed a causal significance of the left SMG for pitch memory in non-musicians, the aim of study 2 was to investigate whether the left SMG is causally involved throughout the whole pitch memory process or whether its significance is limited to a specific stage of the memory process. In this study TMS was used, to allow a timely more precise modulation of either the retention (experiment 1) or the encoding phase (experiment 2) of a pitch recognition task. Furthermore, a third experiment controlled that potential effects found in experiments 1 and 2 are not due to a disruption of motor performances.

Study 3

A study using MEG has revealed that individuals with congenital amusia show decreased low gamma activity in the right DLPFC cortex during a pitch memory task. Building on this, study 3 examined whether reduced low gamma activity of the DLPFC during pitch memory, is a key factor for pitch memory deficits in amusics. TACS was used to investigate whether applying low gamma oscillations at 35 Hz to the right DLPFC in amusics would improve pitch memory abilities. 90 Hz tACS served as control condition. A successful modulation would seek further insight into the functional relevance of modified oscillatory patterns for the disorder and would add to the growing evidence of non-invasive brain stimulation methods as a potential tool for therapeutic interventions.

3. Study 1: Pitch Memory in non-musicians and musicians: Revealing functional difference using transcranial direct current stimulation (Schaal et al., 2014, Cerebral Cortex)

Previous findings highlighted the functional significance of the left SMG for pitch memory in non-musicians (Gaab, Gaser, Zaehle, et al., 2003; Schaal et al., 2013; Vines et al., 2006) whereas contrary results on the activation of the right and left SMG were found in musicians (Ellis et al., 2013; Gaab & Schlaug, 2003; Schulze, Zysset, et al., 2011). Study 1 (Appendix 1) investigated whether hemispheric differences of the involvement of the SMG can be found between musicians, as experts in the musical domain, and non-musicians. The aim of the study was to replicate the causal involvement of the left SMG for pitch memory in non-musicians (Schaal et al., 2013; Vines et al., 2006) and to investigate whether musicians rely on the left or right SMG for the pitch memory process. Furthermore, the study examined whether task demands could be the reason for possible differences between musicians and non-musicians. Here, tDCS was used to modulate the excitability of the left and right SMG and to measure the possible behavioural effects on two pitch memory tasks, recognition and recall, as well as on a visual control task. According to previous data we hypothesised that in non-musicians cathodal tDCS over the left SMG would lead to a deterioration of pitch memory performance. As functional imaging data of the activation of the SMG in pitch memory in musicians are not consistent, three different outcomes were possible: (*i*) as Ellis, Bruijn, Norton, Winner, & Schlaug, (2013) show a stronger activation of the left SMG in musicians, cathodal tDCS over the left SMG could also lead to a deterioration in musicians (*ii*) cathodal tDCS over the right SMG leads to a decline in pitch memory abilities as musicians activate a more rightward hemispheric activation for musical memory (Gaab & Schlaug, 2003) (*iii*) as musicians rely on a more complex neural system for pitch memory (Schulze, Zysset, et al., 2011) no modulation effects are found as musicians can compensate for any stimulation interference.

Methods

36 musicians and 36 non-musicians took part in this study and were assigned to one of three stimulation groups (cathodal tDCS over the left SMG vs. cathodal tDCS over the right SMG vs. sham stimulation over the left SMG). Musicians were music students from a music college who have played their instrument for more than 10 years and non-musicians were

defined as people who have had less than two years of musical training in the past and not playing an instrument at present. The three stimulation groups (cathodal tDCS over the left SMG, cathodal tDCS over the right SMG and sham stimulation over the left SMG) within musicians and non-musicians were matched by age, gender and baseline pitch memory performance (evaluated in a pretesting session).

In the brain stimulation session, participants received 20 minutes (2 mA, 15 seconds fade in and out) of cathodal tDCS or sham stimulation (30 seconds of stimulation). After 10 minutes of stimulation, they completed two pitch memory tasks (recognition and recall) as well as a visual control task (Cambridge Face Memory Test long form, CFMT+; (Russell, Duchaine, & Nakayama, 2009)). The active electrode was either placed over the left or right SMG (the target sites were identified using CP3 or CP4 of the 10-20 system for EEG electrode placement) and the reference electrode was adjusted above the contralateral supraorbital area. For the evaluation of pitch recognition the pitch span task (Williamson & Stewart, 2010) was chosen where participants heard two tone sequences with a 3 second pause between them and should decide whether they were the same or different. The task started with two tones per sequence and then followed an adaptive staircase procedure and the participants' pitch memory span was calculated. In the pitch recall task, participants heard four to eight long sequences consisting of three different tones (low, medium, high) and were asked to recall the contour of the sequences by ticking boxes according to the movement of the sequence on a grid immediately after the sequence finished playing. In the CFMT+ participants were familiarised with faces in the learning phase which then had to be recognised in the following test trials. The CFMT+ comprises two parts. In the first part faces are presented one after each other which then have to be recognised in the immediately following test trials. Contrary to this, in the second part six faces have to be memorised at once and are tested in the following test trials. Participants also filled in the German version of the Gold-MSI questionnaire (Schaal, Bauer, & Müllensiefen, 2014) which evaluates musical sophistication (e.g. musical training and engagement).

Additionally, a Neuronavigation session was conducted with a small exemplary sample (2 musicians and 2 non-musicians from the original sample) in order to validate the location of the SMG using P3 and P4 of the international 10-20 system. The procedure of the tDCS sessions was reconstructed by marking the stimulation area with a highlighter. Then the Neuronavigation procedure began by measuring the participants head by predefined points and mapping these measures onto a standardised brain. Two markers were then inserted into the system at the two highlighted points on the scalp and the identified coordinates confirmed that the targeted brain areas correspond to Brodmann Area 40 and thus the location of the SMG.

Results and Discussion

As expected, non-musicians showed declined pitch memory performance on both pitch memory tasks when cathodal tDCS was applied over the left SMG. An additional analysis for the recall task revealed that this effect was only significant for longer sequences (seven and eight long tone sequences) when memory load was particularly high. Musicians showed a selective deterioration on the pitch span task (recognition memory) only and interestingly when tDCS was applied over the right SMG. No modulation effects were found on the recall task in musicians nor on the face memory task (control task) for any stimulation site in non-musicians or musicians.

The results are in line with previous findings by showing a significance of the left SMG for pitch memory in non-musicians (Gaab, Gaser, Zaehle, et al., 2003; Jerde et al., 2011; Schaal et al., 2013; Vines et al., 2006). The study showed that cathodal tDCS over the left SMG led to a deterioration of pitch memory performance on both tasks, recall and recognition and therefore extended a previous study by our group which showed that anodal tDCS over the left SMG led to a facilitation of pitch memory abilities in non-musicians (Schaal et al., 2013). Additionally, a more detailed analysis of sequence length in the pitch recall task in non-musicians showed that the disruptive effect of cathodal tDCS over the left SMG is only significant for longer sequences of seven and eight tones in the pitch memory recall task. This new finding suggests that the significance of the left SMG in non-musicians is more predominant when the pitch memory load is high.

Furthermore, the study revealed that in the musicians group left SMG stimulation had no significant effect but musicians showed a selective decline in pitch memory performance on the recognition task when cathodal tDCS was applied over the right SMG. This novel finding provides evidence of functional hemispheric differences in pitch memory in musicians and non-musicians using tDCS and is in accordance with frequently reported anatomical differences of the musician’s brain (Hyde et al., 2009; Jancke et al., 1997; Schlaug et al., 1995; Schneider et al., 2002; Schneider et al., 2005). Additionally, the results provided further evidence that task demands and difficulty are key factors for the involvement of the SMG in pitch memory. In the pitch span task (recognition memory) every participant is pushed to his or her limit of pitch memory. On the other hand the recall task is fixed in difficulty and musicians showed very good performance throughout the trials. Mean performance of musicians in the block with eight-tone long sequences was still above 80 percent correct. In this respect, it can be hypothesised that a modulation effect on the recall task may be found when sequence lengths would be increased which would also challenge the musicians' pitch memory. The selective modulation of pitch memory performance on the recognition task in musicians supports the assumption that the SMG is causally involved when task demands are high.

As several brain imaging studies have reported increased activation of the left SMG for pitch memory in combination with musical training in non-musicians (Ellis et al., 2013; Gaab et al., 2006), the result that we did not find a modulation effect in musicians after cathodal tDCS over the left SMG was surprising. As musicians rely on a more complex neural system for the pitch memory process than non-musicians (Schulze, Zysset, et al., 2011), it is reasonable that musicians are able to compensate for modulation effects of one brain area by activating another area of the multifaceted network of pitch memory. On the other hand, a stronger activation of the right SMG in musicians has been reported by Gaab & Schlaug, (2003) when the performance of musicians and non-musicians were matched. This corresponds well to the results of the present study. We found a selective deterioration on the recognition and not the recall pitch memory task where task parameters adapt to the individual performance level and measure the maximum capacity of pitch memory information. In this sense, the groups were matched in task demands and it is likely that the right SMG is particularly involved when task demands are high and when also musicians are challenged to memorise the pitch information. In line with this hypothesis, it has been shown that musicians rely on a more right hemisphere specialization for processing pitch and melody information (Bermudez, Lerch, Evans, & Zatorre, 2009; Patston, Kirk, Rolfe, Corballis, & Tippett, 2007). It is also plausible that musicians used their visuo-motor representation when memorising the pitches in the more demanding trials of the pitch recognition task. Therefore, by suppressing the right SMG which has been shown to be activated in musicians during sight reading (Sergent, Zuck, Terriah, & Macdonald, 1992) this additional resource is not available anymore following cathodal tDCS and led to a decline in pitch memory. It is likely that musicians did not need to recruit this additional mechanism for the recall task as it has been shown that the task demands were relatively low for the musicians in the recall task and therefore no modulation effect was revealed.

Another point to consider is that different task paradigms may rely on different neural systems. For example, a study in the visual domain showed a significant deterioration on a recognition task after cathodal tDCS over the right inferior parietal cortex whereas the recall task was not affected (Berryhill et al., 2010). In this respect one can also consider that different memory types (i.e. recall and recognition) with specific task demands rely on overlapping but also specialised neural circuits. As the present study also showed this pattern in the musicians group when cathodal tDCS was applied over the right SMG, it might also be the case that not task difficulty but task requirements depending on recall or recognition procedures might account for the difference. Therefore, it might be the case that the left SMG is involved overall in memory tasks in non-musicians and the right SMG in musicians may only be involved in pitch recognition.

Additionally, the study also supports two other, more general aspects of memory research which should be mentioned briefly here. Musicians, as experts in the field of musical memory, outperformed the non-musicians on both pitch memory tasks indicating that they have developed a more pronounced memory system for pitches which is in accordance with previous research (Schulze, Mueller, & Koelsch, 2011; Williamson et al., 2010). Secondly, in the pitch recall task both groups, musicians and non-musicians, showed a significant linear decline in performance when sequences increased in length and therefore memory load which shows that memory capacity is limited (Baddeley, 1987). In non-musicians the performance scores descended from 92% correct in the block with four-tone long sequences to 65% for the eight-tone long sequences. In musicians the decline was also significant even though it was much smaller ranging from 98% correct for the four-tone long sequence to still very good 81% correct for the eight-tone long sequences.

For the visual control tasks no modulation effects were found in the tDCS sessions neither in musicians nor in non-musicians. This is in accordance with the results of a previous study by our group (Schaal et al., 2013) and supports the idea of the SMG being selectively involved in pitch or more broadly speaking auditory memory. In this context, we would like to acknowledge that the task demands of the visual control task were not perfectly matched to the memory demands of the pitch tasks. The CFMT+ includes trials for short-term and long-term memory. But the fact that no modulatory effects were found on either block supports the specific involvement of the left and right SMG respectively for pitch memory processes.

Conclusion

In conclusion this study revealed a hemispheric specialisation of the SMG for pitch memory between non-musicians and musicians. Furthermore, it showed that the significance of the SMG is linked to more demanding tasks when the pitch memory load is high.

4. Study 2: A causal involvement of the left supramarginal gyrus during the retention of musical pitches in non-musicians (Schaal et al., 2015, Cortex)

In accordance with previous tDCS studies (Schaal et al., 2013; Vines et al., 2006), study 1 showed that the left SMG is causally involved in the pitch memory process of non-musicians. Study 2 (Appendix 2) built on this finding and aimed to investigate whether the left SMG is causally involved throughout the whole pitch memory process or whether a stage-specific significance for either the retention or the encoding phase can be revealed. In order to do so, the retention phase of a recognition pitch task (modelled after the pitch span task of study 1) was modulated using rTMS in experiment 1 whereas in experiment 2 rTMS was applied during the encoding phase. Stimulation was applied over the left SMG and the vertex as a control site. Furthermore, in experiment 3 rTMS was applied over the left SMG on a pitch perception task *late* vs. *early* corresponding to the retention and encoding phases investigated in experiments 1 and 2. The third experiment was included to control for potential non-specific interference of the stimulation on motor responses and to show that potential modulation effects on reaction times in experiment 1 and 2 are not due to motor interference. TMS was used in order to ensure a stimulation with a higher temporal and spatial resolution. As several studies have postulated that the left SMG is involved in the storage of pitch information (Gaab, Gaser, Zaehle, et al., 2003; Sakurai et al., 1998; Vines et al., 2006), the hypothesis was that only rTMS over the left SMG (and not the vertex) during the retention period will show a significant modulation effect on the performance of the pitch recognition task. No effects were expected when stimulation was applied during encoding.

Methods

Study 2 comprises 3 experiments. Overall 39 participants took part of which 13 participated in experiment 1, 14 in experiment 2 and 12 in experiment 3. All were non-musicians with less than two years of musical training in the past and not playing an instrument at present, which was confirmed by a very low mean score on the musical training dimension of the Gold-MSI questionnaire (Schaal, Bauer et al., 2014) of 10,9 (possible range 7-49). In experiment 1 and 2 participants completed three blocks of a pitch recognition task (modelled after the pitch span task used in study 1, (Williamson & Stewart, 2010)) with rTMS either over the left SMG or the Vertex (control site) or no stimulation. In every trial, participants heard two six-tone long sequences with an inter-stimulus interval of 3 seconds and were asked to judge whether they were the same or different. Participants were asked to respond as accurately and quickly as possible using their right index and middle fingers and the keys “1” for same and “2” for different on the keyboard. Reaction times as well as accuracy were recorded. For the analysis of accuracy, percent correct and d’ scores were calculated. Since both measures revealed the same pattern of results and d’ scores are the more sensitive measure, taking possible bias into account, the d’ score analysis is reported in the results section. In experiment 1, a 3 second long rTMS train with a frequency of 5 Hz (15 pulses per train) was applied on a trial-by-trial bases during the retention interval, whereas in experiment 2, rTMS with the same parameters was applied during the encoding of the first pitch sequence. A third experiment was included, in which participants completed a pitch perception task where they only heard the second sequence of the trials and had to judge whether the last tone was higher or lower than the second to last one. Reaction times after the sequence had finished were recorded using the keys “1” for lower and “2“ for higher. Experiment 3 also comprised three blocks: one without stimulation, one block where rTMS was applied over the left SMG *early*, namely six to three seconds before the pitch sequence reflecting the timing of the second experiment (rTMS during encoding) and a third block where rTMS was triggered over the left SMG *late*, starting three seconds before the sequence until the onset of the pitch sequence imitating the timing of experiment 1 (rTMS during retention).

Results and Discussion

Experiment 1 revealed that reaction times on the pitch memory span task were significantly slower when rTMS was applied during retention stage over the left SMG compared to the vertex or no stimulation. No modulation effects were found in experiment 2 in which rTMS was applied during encoding of the first pitch sequence. Furthermore, the third experiment revealed no modulatory effects on reaction times when rTMS was applied over the left SMG at an early (reflecting the timing of experiment 2) and late (reflecting the timing of experiment 1) time point during a pitch perception task. The analysis of accuracy, measured by d’ scores, showed no significant modulatory effects of TMS in all three experiments. But it is worth noting that in experiment 1, also performance scores are lowest when rTMS was applied over the left SMG. Taken together, the results of the study showed a selective impairment of pitch memory, reflected by slower reaction times, when rTMS was applied over the left SMG during the retention period of a recognition task, revealing a specific significance of the left SMG for the retention but not encoding of pitch information.

This TMS study supports previous tDCS studies which have shown a causal involvement of the left SMG for pitch memory in general (Schaal et al., 2013; Vines et al., 2006). The present study extends these findings by revealing a stage-specific effect of rTMS during the retention interval and not during the encoding phase of a pitch memory recognition task. By doing so, this study provides first evidence for a selective causal role of the left SMG for maintaining pitch information during the retention interval which has been hypothesised in previous studies (Gaab, Gaser, Zaehle, et al., 2003; Sakurai et al., 1998; Vines et al., 2006).

Additionally, the findings of this study are in accordance with a TMS study in the verbal memory domain which has shown that left Brodmann's area 40 (the location of the left SMG) is causally involved during the retention period of phonological judgements and not during a visual pattern span control task (Romero, Walsh, & Papagno, 2006). As neural activation of the SMG has also been highlighted during tonal and verbal rehearsal (Schulze, Zysset, et al., 2011) but not during visual memory (study 1), one may propose that the involvement of the left SMG is modality specific for auditory memory.

The present study is one of the rare contributions to the investigation of neural distinctions of the memory system in the auditory domain using TMS. To the best of my knowledge, the only other study using TMS to investigate auditory memory functions is a study by Imm et al., (2008) which explored the involvement of the right and left DLPFC as well as inferior parietal cortices for pitch and audio-verbal memory. They applied single pulse TMS at time points between 250 and 800 ms after stimulus onset. Interestingly, the study revealed increased reaction times for pitch memory at all time points when TMS was applied over the right inferior parietal cortex whereas for the auditory-verbal memory condition only a significant effect at 450 ms and over the left inferior parietal cortex was found (Imm et al., 2008). When comparing these results to ours, a different hemispheric involvement of the parietal region is noticeable. One should note that the inferior parietal site targeted by Imm et al., (2008) was more posterior than the SMG we identified and also that a working memory task was used and we explored short-term recognition memory. This could explain the different hemispheric relevance. Nevertheless, the study by Imm et al., (2008) highlights the importance of the kind of auditory material which defines which underlying neural mechanisms are involved.

A couple of limitations of the study should also be discussed. The use of the 10-20 system for electrode placement to localise the position of the SMG is not the most precise method but it is common to do so when targeting brain areas for non-invasive stimulation studies (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003). In order to improve the precision of TMS effects, it would be beneficial to use brain imaging guided targeting in the future. As the study was partially conducted during a laboratory visit in London, it was not possible to use the Neuronavigation system in this study. Additionally, the relatively modest sample sizes of the experiments which are common in the TMS community or more broadly speaking non-invasive brain stimulation studies warrants a comment as it is likely that potential small effects are not detected which could be of theoretical interest. In this context the current data hints at another potential effect which may turn out to be significant with an enlarged sample and therefore increased power. In experiment 1, the d' scores were lowest when rTMS was applied over the left SMG during retention supporting the disruption of pitch memory performance as reflected by the increased reaction times.

Conclusion

Taken together the study revealed a selective involvement of the left SMG for the ongoing maintenance and storage of the pitch information during the retention stage of the pitch memory process.

5. Study 3: From amusic to musical? - Improving pitch memory in congenital amusia with transcranial alternating current stimulation (Schaal et al., under review)

Congenital amusia is a life-long disorder which is characterised by pitch perception and pitch memory deficits (Albouy et al., 2013; Foxton, Dean, Gee, Peretz, & Griffiths, 2004; Gosselin et al., 2009; Hyde & Peretz, 2004; Tillmann, Schulze, & Foxton, 2009; Williamson & Stewart, 2010). Brain imaging studies have highlighted structural and functional brain anomalies which are associated with amusia (Albouy et al., 2013; Hyde et al., 2007; Hyde et al., 2006; Hyde et al., 2011; Loui et al., 2009). One brain area which has attracted much attention is the right inferior frontal cortex as brain imaging studies have shown cortical malformations (e.g. thicker cortex) in amusics (Hyde et al., 2007) and reduced white matter concentration in this area (Hyde et al., 2006). Furthermore, a study using MEG has revealed that the amplitude of low gamma oscillations in the right DLPFC which is increased during the retention period of a pitch memory recognition task in healthy controls is decreased in amusia (Albouy et al., 2013). As research has shown that endogenous brain oscillations can be entrained by applying tACS with a specific frequency (Herrmann et al., 2013), tACS was used in this study in order to enhance low gamma oscillations. Relating to the interesting findings of Albouy et al., (2013), study 3 (Appendix 3) investigated whether applying a low gamma frequency of 35 Hz to the right DLPFC of congenital amusics would improve their pitch memory abilities. We also included a control stimulation session where a high gamma frequency (i.e. 90 Hz) was applied as well as including a visual span task to show that potential modulatory effects on pitch memory performance are task and frequency specific. The hypothesis was that amusics will show a selective impairment in pitch memory compared to healthy controls before stimulation and an improvement of pitch memory performance during 35 Hz tACS.

Methods

Nine participants with congenital amusia as well as nine on age, gender and years of musical training matched controls took part in this study. Individuals were diagnosed as amusic using the Montreal Battery of Evaluation of Amusia (MBEA, Peretz et al., 2003) where they had to score below the cut-off score of 75% to be eligible to take part. The MBEA is a most widely used tool to diagnose amusia (e.g. (Albouy et al., 2013; Gosselin et al., 2009;

Hyde et al., 2006) and contains six subtests. Three subtests evaluate melodic aspects and pitch perception (scale, contour and interval), two subtests test temporal features (rhythm and metre) and one subtest is a musical memory test. Furthermore, the pitch detection and direction abilities were evaluated with two standardised tasks (Williamson & Stewart, 2010) in order to ensure that the pitch intervals used in the pitch memory task were above discrimination thresholds of all participants. By ensuring this, impaired pitch memory cannot be explained by poor pitch discrimination.

Amusics then participated in two stimulation sessions on two different days (one week apart). They completed a pitch recognition task and a visual control task before stimulation (evaluating baseline performance) as well as while receiving tACS over the right DLPFC with a frequency of 35 Hz (target frequency) or 90 Hz (control frequency) in counterbalanced order. To measure pitch recognition, the pitch span task (Williamson & Stewart, 2010) of study 1 was used. Additionally, a visual span task was composed which followed the same experimental parameters as the pitch span task, only that the stimuli were visual symbols (letters from Hindi alphabet Devanagari). We chose these fairly unknown symbols in order to ensure that participants could not use any form of auditory or phonological representations for this memory task. The right DLPFC was identified using Neuronavigation and the target was set to the MNI coordinates x=45, y=31, z=25 taken from Albouy et al., (2013). Two 5 x 5 cm electrodes were used for the application of tACS. One electrode was placed over the right DLPFC and the reference electrode was adjusted over the left supraorbital area. Amusics received a maximum of 20 minutes (with 15 seconds fade in and fade out) of 1 mA tACS with a frequency of either 35 Hz or 90 Hz and completed the two memory tasks in counterbalanced order. The stimulation was aborted as soon as the participant finished the two memory span tasks.

In order to compare the memory performances of the amusics with pitch and visual memory abilities of healthy controls, the matched controls completed the pitch and visual span tasks as well as the MBEA and pitch detection and direction tasks without taking part in a stimulation session. All participants also filled in a short questionnaire about the tasks asking whether specific memory strategies were used and about their musical and linguistic background.

Results and discussion

When looking at baseline performances on the pitch and visual span tasks, a selective impairment of pitch memory abilities in amusics was revealed which is in accordance with previous research (Williamson & Stewart, 2010). The amusics' pitch span was significantly below their visual span at baseline. Additionally, when comparing abilities on the pitch and visual span tasks between amusics and healthy controls, only a significant difference was shown for the pitch span task. Amusics revealed a significantly shorter span capacity for pitch information than controls but on the visual span task both groups performed comparably. Furthermore, the analysis in the amusics group examining the effects of 35 Hz and 90 Hz tACS stimulation over the right DLPFC revealed that amusics showed a significant improvement of pitch memory performance when 35 Hz was applied. No stimulation effects were found on the visual control task or when 90 Hz tACS was induced. Most interestingly, performance of the amusics on pitch memory during 35 Hz tACS was no longer significantly lower than the pitch span of healthy controls.

The finding that pitch memory abilities in amusics improved significantly when 35 Hz stimulation was applied over the right DLPFC shows that the decreased low gamma oscillations reported by Albouy et al., (2013) could be a key factor for the congenital disorder. It is in accordance with several brain imaging studies highlighting a specialised role of the right DLPFC in amusia (Hyde et al., 2007; Hyde et al., 2006) as well as the activation and involvement of the right DLPFC in normal pitch memory (Jerde et al., 2011; Zatorre et al., 1994). In this context, it is important to note that the study concentrated on the right DLPFC but surely the structural and functional basis of other brain areas such as the inferior frontal gyrus and the auditory cortex which have been linked to congenital amusia are also relevant (Hyde et al., 2007; Hyde et al., 2006; Hyde et al., 2011; Loui & Schlaug, 2009).

Additionally, the results contribute to the growing evidence that gamma oscillations are closely connected to memory functions in the auditory domain (Howard et al., 2003; Kaiser, Ripper, Birbaumer, & Lutzenberger, 2003; Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser, 2002) as well as serving as additional evidence that the DLPFC is closely connected to memory processes in several domains (McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Narayanan et al., 2005). Furthermore, this study adds to the literature investigating the causal involvement of gamma oscillations in the DLPFC for memory processes using non-invasive brain stimulation methods (Brunoni & Vanderhasselt, 2014).

This study supports the hypothesis that amusics show a selective impairment in pitch memory and not in other memory functions as amusics showed a comparable visual memory but impaired pitch memory to healthy controls at baseline (Akiva-Kabiri, Vecchi, Granot, Basso, & Schon, 2009; Williamson, Cocchini, & Stewart, 2011; Williamson & Stewart, 2010). Additionally, the study revealed that the selective impairment is no longer present when comparing pitch memory span of amusics while receiving 35 Hz tACS over the right DLPFC and task performance of healthy controls. This finding highlights the prospective use of tACS and transcranial electrical stimulation in general, as a potential tool for the treatment of congenital and developmental disorders. Recent work has highlighted the efficiency of tDCS in dyslexic children (Vicario & Nitsche, 2013) as well as for aphasia (Monti et al., 2008). One of the sparse clinical studies using tACS has revealed that applying 15 Hz tACS bilaterally over M1 in repeated sessions led to reduced dystonic symptoms in a patient with idiopathic cervical dystonia. The reduction of symptoms was still measurable after 30 days of the treatments (Angelakis et al., 2013). In this respect, it would be desirable to investigate whether multiple sessions of tACS with a frequency of 35 Hz over the right DLPFC in participants with congenital amusia would lead to after effects as reported by Angelakis et al., (2013).

A couple of limitations of this study warrant a comment. As no neurophysiological measures like EEG or MEG were included parallel to the tACS stimulation, the interpretation of the exact effect and influence of the applied stimulation is limited. Previous research has shown that ongoing brain oscillations can be entrained by the externally applied frequency using tACS (Heimrath, Kuehne, Heinze, & Zaehle, 2014; Zaehle et al., 2010). Bearing this in mind, it is plausible that our results of the improvement of pitch memory in amusia during 35 Hz stimulation also rely on this neural mechanism. We therefore would argue that the facilitation of pitch memory is due to an entrainment of the brain oscillations at 35 Hz yielding in an increase of pathologically low gamma oscillations in the DLPFC in amusics (Albouy et al., 2013).

Additionally, it is important to note that baseline performances in the two stimulation sessions were not perfectly matched even though we counterbalanced stimulation conditions. I would like to point out that these differences are descriptively noticeable but not significantly different and the significant improvement of 35 Hz stimulation is worth highlighting at this point. Furthermore, also the visual control task should be discussed here briefly. Previous research has shown that perception of phosphenes is likely when applying frequencies below 40 Hz (Turi et al., 2013). As also reported by two thirds of our sample, the sensation of phosphenes is more likely to occur at the low gamma frequency of 35 Hz (Turi et al., 2013). With this in mind, one might speculate that phosphenes may have interfered with visual memory performance. But the comparison of performances in the 35 Hz condition between the participants who reported phosphenes and the ones who did not did not show any disadvantages. This weakens the assumption of an interference of phosphenes on visual memory performance.

Conclusion

The study demonstrated that impaired pitch memory abilities in congenital amusia can be improved by applying 35 Hz tACS to the right DLPFC. This finding reveals a functional relevance of the altered oscillation patterns of the DLPFC for the impairment in amusics and highlights the potential use of tACS to interact with cognitive processes.

6. General Discussion and Conclusion

The aim of the thesis was to contribute to the understanding of the neural basis of pitch memory. Therefore, different brain stimulation methods were used in order to externally modulate the function of targeted brain areas and to explore whether causal relationships to pitch memory can be revealed. Additionally, the thesis looked at the influence of musical expertise and genetic dispositions by including three different groups of participants (musicians, non-musicians and amusics) who rely on different pitch memory abilities. The ambition was to investigate whether performance differences in pitch memory can be linked to specialised neural circuits in the brain.

The significance of the left SMG for the pitch memory process in non-musicians was revealed in study 1 and 2. Using tDCS, study 1 has shown that the left SMG is causally involved in pitch recognition as well as recall in non-musicians and furthermore links the contribution of the left SMG to higher memory demands of the pitch memory task. Additionally, study 2 expanded the knowledge of the role of the left SMG in the pitch memory process in non-musicians by highlighting the significance of the left SMG for the retention stage of the pitch memory process. TMS applied over the left SMG during the retention interval of the pitch memory task resulted in increased reaction times. These findings are in accordance with previous research (Gaab, Gaser, Zaehle, et al., 2003; Schaal et al., 2013; Vines et al., 2006) and provide important additional knowledge about the specific role of the left SMG in pitch memory in non-musicians. A further question at this point is whether the left SMG is also involved in other auditory memory processes. In order to investigate this, we recently conducted a study including the pitch memory span task as well as a newly developed rhythm span task (Schaal et al., 2015) and applied anodal tDCS over the left and right SMG in non-musicians. The study confirmed the significance of the left SMG for pitch memory by showing a significant improvement of performance when tDCS was applied over the left SMG compared to sham stimulation. Interestingly, no modulatory effects on the rhythm span task were found indicating that the left SMG is specifically involved in pitch memory. Additionally, when tDCS was applied over the right SMG an improvement in rhythm memory and not pitch memory could be revealed (Schaal et al., in preparation). These interesting findings suggest a hemispheric functional difference of the SMG for the memory processes of the different two main building blocks of music, pitch and rhythm may exist in non-musicians.

Musicians show superior pitch memory abilities which they developed with many years of intense musical training. Furthermore, many studies have explored the musicians' brain as a model of neuroplasticity and have revealed structural specialisations in several brain areas (Merrete et al., 2013; Munte, Altenmuller, & Jancke, 2002). In order to investigate whether functional differences of a targeted brain area can be found between musicians and non-musicians, the causal involvement of the left and right SMG for pitch memory was explored in study 1. Here, cathodal tDCS over the right SMG resulted in declined pitch memory performance on the recognition pitch memory task in musicians. The results revealed a hemispheric specialisation of the SMG for pitch memory depending on expertise and therefore provide causal evidence for functional neural differences between musicians and non-musicians. Along these lines, a recently published study comparing the effects of bilateral tDCS over the motor cortices on the control of sequential finger movements between musicians and non-musicians has also shown that musicians rely on a different functional architecture of the motor cortex (Furuya, Klaus, Nitsche, Paulus, & Altenmueller, 2014). Whereas applied tDCS led to a facilitation of finger movement control in non-musicians, skilled pianists did not show any improvement but instead the contralateral hand to the anodal stimulation showed a decline in fine finger movement control. The different outcomes in non-musicians and musicians indicate an expertise-dependent functional role of the motor cortices (Furuya et al., 2014).

In the third study of this thesis, the opposite side of the musical spectrum was investigated by exploring the functional role of gamma oscillations in the right DLPFC in participants with congenital amusia, a disorder that is linked to pitch perception and memory deficits. The results showed a significant improvement in pitch memory in amusic when 35 Hz tACS was applied to the right DLPFC pointing towards an important role of gamma oscillations in the right DLPFC for pitch memory. The study highlights the potential use of tACS to modulate oscillatory patterns in the brain and to influence cognitive performances. Along these lines, a study by Santarnecchi et al., (2013) showed that fluid intelligence could be improved by applying a gamma frequency of 40 Hz to the middle frontal gyrus and the authors propose an involvement of gamma oscillations for higher cognitive functions in humans.

A point which warrants a comment in this overall discussion is that several studies and reviews have highlighted remote effects in tDCS and TMS applications (Chib, Yun, Takahashi, & Shimojo, 2013; Notturno, Marzetti, Pizzella, Uncini, & Zappasodi, 2014;

Reithler, Peters, & Sack, 2011). When considering the results of study 1 and 2, indicating the significance of the left SMG in non-musicians and the right SMG for musicians for the pitch memory process, one might debate whether a spread of activation to closely connected brain areas of the SMG could also influence the outcome. As a potential role of the SMG in pitch memory was proposed to be a top-down modulator which is connected to the activation of temporal regions by Gaab et al. (2003), it is possible that the stimulation of the SMG also led to secondary functional changes in the auditory cortex which is known to be important for pitch memory (Celsis et al., 1999; Gaab, Gaser, Zähle, et al., 2003; Zatorre et al., 1994). Furthermore, it has been shown that stimulation effects of tACS are not restricted to the stimulation frequency applied (Wach et al., 2013) and also inter-areal oscillatory effects have been reported (Antal & Paulus, 2013; Herrmann et al., 2013). In this respect, one could argue that the improved pitch memory abilities during 35Hz tACS can also be linked to a positive effect on the in amusics reduced right frontal-temporal connection shown in previous imaging studies (Hyde et al., 2007; Loui et al., 2009). It may be the case that tACS applied over the right DLPFC has secondary effects to the closely connected auditory cortex which has been shown to also be critical in pitch perception and memory in amusics (Albouy et al., 2013; Hyde et al., 2007; Hyde et al., 2011; Loui et al., 2009).

In sum, this thesis contributes to the understanding of which brain areas are involved in the pitch memory process in combination with musical training and genetic dispositions. Study 1 revealed that musicians show a hemispheric different involvement of the SMG for pitch memory compared to non-musicians which is also dependent on task demands. The study showed that tDCS over the left SMG resulted in a decline in pitch memory in non-musicians whereas musicians showed a selective impairment of pitch memory on the recognition task when tDCS was applied over the right SMG. Building on this, study 2 showed that the involvement of the left SMG for pitch memory in non-musicians is stage specific as only rTMS over the left SMG during the retention period resulted in significant slower reaction times. This indicates the significance of the left SMG during retention when the maintenance of pitch information takes place. Study 3 exposed that applying a low gamma frequency of 35 Hz to the right DLPFC while congenital amusics perform a pitch memory task improves their pitch memory performance. This points towards a functional importance of gamma oscillations in the right DLPFC for pitch memory. Pitch memory was comparable to normal healthy controls performance and therefore highlights the potential use of non-invasive stimulation for therapeutic interventions.

7. Outlook

Building on the presented findings several avenues for further research are considerable.

It would be desirable to conduct research combining non-invasive brain stimulation and imaging techniques in order to further examine the exact mechanisms behind the stimulation effects found in the studies. Especially for the third study where tACS was used, the exact mechanisms of how the stimulation affects the neural populations are not fully explored yet. We can only derive our assumption of a resulting entrainment of low gamma oscillations from other studies showing an entrainment of ongoing brain oscillations according to external applied oscillations (Antal & Paulus, 2013; Helfrich et al., 2014; Reato, Rahman, Bikson, & Parra, 2013). In order to confirm that our result of improved pitch memory in amusics during 35 Hz tACS is indeed due to an entrainment of brain oscillations in the right DLPFC, a continuous EEG or MEG recording would be desirable.

Furthermore, the technical development of being able to combine TMS with consecutively fMRI and tDCS with concurrent or consecutively fMRI is a valuable research combination in order to be able to investigate the spread and interhemispheric connections of the stimulation input (Bestmann & Feredoes, 2013; Luft, Pereda, Banissy, & Bhattacharya, 2014; Saiote, Turi, Paulus, & Antal, 2013). There is to my knowledge only one study up to know which has combined TMS with fMRI investigating auditory processing in participants with minimal musical training (Andoh & Zatorre, 2013). Continuous theta-burst TMS was applied over the right or left Heschl’s gyrus or the vertex and immediately afterwards fMRI scanning began while participants performed a melody discrimination task. One interesting finding is that when TMS was applied over the right Heschl’s gyrus, an increase of activation was found in the left Heschl’s gyrus and furthermore, that this increase in activation was positively correlated to a decrease in reaction times on the cognitive task (Andoh & Zatorre, 2013). Including fMRI or MEG recordings in order to examine whether remote effects or interhemispheric connections are present in the stimulation protocols and behavioural effects of study 1 and 2, is desirable. This would seek further insight into the neural structures and connections of brain areas underlying the pitch memory process and the effectiveness of tDCS and rTMS. In this respect, the role of the auditory cortex is of special interest as described in the overall Discussion.

To explore the functional spread of activation of tDCS using fMRI is especially interesting when contrary results are revealed. In this context, we have recently conducted a study using tDCS examining the function of the right posterior parietal cortex (PPC) for memory for melodies where pitch memory is next to rhythm memory an important factor. Interestingly, we found a decrease in performance after anodal tDCS compared to sham stimulation and not an expected improvement in experiment 1. This unexpected finding could be replicated in a second experiment in which we compared anodal tDCS over the right and left PPC and only right PPC stimulation led to a decline in memory for melody performance (Schaal et al., in press). Concurrent fMRI would be desirable to see whether remote effects to adjusted brain areas could account for this outcome.

Future research should also investigate whether multiple sessions of tDCS or tACS combined with pitch memory training could lead to long lasting improvements in pitch memory performance. Along these lines, Meinzer et al., (2014) showed that anodal tDCS over the left posterior temporo-parietal junction for five consecutive days led to a significantly faster improvement in language learning than sham stimulation. Furthermore, the beneficial learning success of anodal stimulation was maintained during a follow-up session one week after the last stimulation session (Meinzer et al., 2014). In this respect, investigating whether the improvement of pitch memory in amusia through tACS could be maintained when multiple sessions are applied is an interesting research question for future studies which would further highlight the potential use of tACS for clinical treatments. It has been shown that multiple sessions of tDCS combined with training with aphasic patients led to promising improved verb naming up to 16 weeks after stimulation (Manenti et al., 2015; Vestito, Rosellini, Mantero, & Bandini, 2014). Whether long-term effects of cognitive performances with tACS combined with training can be achieved is still an open question which further research will hopefully answer in the future.

8. References

Akiva-Kabiri, L., Vecchi, T., Granot, R., Basso, D., & Schon, D. (2009). Memory for Tonal Pitches A Music-Length Effect Hypothesis. *Neurosciences and Music Iii: Disorders and Plasticity, 1169*, 266-269. doi: 10.1111/j.1749-6632.2009.04787.x

Albouy, P., Mattout, J., Bouet, R., Maby, E., Sanchez, G., Aguera, P. E., . . . Tillmann, B. (2013). Impaired pitch perception and memory in congenital amusia: the deficit starts in the auditory cortex. *Brain, 136*, 1639-1661. doi: 10.1093/brain/awt082

Andoh, J., & Zatorre, R. J. (2011). Interhemispheric connectivity influences the degree of modulation of TMS-induced effects during auditory processing. *Frontiers in Psychology, 2*, 13. doi: 10.3389/fpsyg.2011.00161

Andoh, J., & Zatorre, R. J. (2013). Mapping interhemispheric connectivity using functional MRI after transcranial magnetic stimulation on the human auditory cortex. *Neuroimage, 79*, 162-171. doi: 10.1016/j.neuroimage.2013.04.078

Angelakis, E., Liouta, E., Andreadis, N., Leonardos, A., Ktonas, P., Stavrinou, L. C., . . . Sakas, D. E. (2013). Transcranial alternating current stimulation reduces symptoms in intractable idiopathic cervical dystonia: A case study. *Neuroscience Letters, 533*, 39-43. doi: 10.1016/j.neulet.2012.11.007

Antal, A., & Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in Human Neuroscience, 7*, 4. doi: 10.3389/fnhum.2013.00317

Ayotte, J., Peretz, I., & Hyde, K. L. (2002). Congenital amusia - A group study of adults afflicted with a music-specific disorder. *Brain, 125*, 238-251. doi: 10.1093/brain/awf028

Baddeley, A. D. (1987). *Working Memory*: Clarendon Press.

Bannan, N. (2008). Language out of Music: The Four Dimensions of Vocal Learning. *Australian Journal of Anthropology, 19*(3), 272-293.

Barker, A. T., Freeston, I. L., Jalinous, R., Merton, P. A., & Morton, H. B. (1985). Magnetic stimulation of the human-brain. *Journal of Physiology-London, 369*(DEC), P3-P3.

Barrett, K. C., Ashley, R., Strait, D. L., & Kraus, N. (2013). Art and science: how musical training shapes the brain. *Frontiers in Psychology, 4*, 13. doi: 10.3389/fpsyg.2013.00713

Bermudez, P., Lerch, J. P., Evans, A. C., & Zatorre, R. J. (2009). Neuroanatomical Correlates of Musicianship as Revealed by Cortical Thickness and Voxel-Based Morphometry. *Cerebral Cortex, 19*(7), 1583-1596. doi: 10.1093/cercor/bhn196

Berryhill, M. E., Wencil, E. B., Coslett, H. B., & Olson, I. R. (2010). A selective working memory impairment after transcranial direct current stimulation to the right parietal lobe. *Neuroscience Letters, 479*(3), 312-316. doi: 10.1016/j.neulet.2010.05.087

Bestmann, S., & Feredoes, E. (2013). Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. *Year in Cognitive Neuroscience, 1296*, 11-30. doi: 10.1111/nyas.12110

Bolognini, N., & Ro, T. (2010). Transcranial Magnetic Stimulation: Disrupting Neural Activity to Alter and Assess Brain Function. *Journal of Neuroscience, 30*(29), 9647-9650. doi: 10.1523/jneurosci.1990-10.2010

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition, 86*, 1-9. doi: 10.1016/j.bandc.2014.01.008

Cabeza, R., Locantore, J. K., & Anderson, N. D. (2003). Lateralization of prefrontal activity during episodic memory retrieval: Evidence for the production-monitoring hypothesis. *Journal of Cognitive Neuroscience, 15*(2), 249-259. doi: 10.1162/089892903321208187

Celsis, P., Boulanouar, K., Doyon, B., Ranjeva, J. P., Berry, I., Nespoulous, J. L., & Chollet, F. (1999). Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. *Neuroimage, 9*(1), 135-144. doi: 10.1006/nimg.1998.0389

Chib, V. S., Yun, K., Takahashi, H., & Shimojo, S. (2013). Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. *Translational Psychiatry, 3*, 9. doi: 10.1038/tp.2013.44

Clement, S., Demany, L., & Semal, C. (1999). Memory for pitch versus memory for loudness. *Journal of the Acoustical Society of America, 106*(5), 2805-2811.

Cutler, A., Dahan, D., & vanDonselaar, W. (1997). Prosody in the comprehension of spoken language: A literature review. *Language and Speech, 40*, 141-201.

Deutsch, D. (1970). Tones and numbers - specificity of interference in immediate memory. *Science, 168*(3939), 1604-&. doi: 10.1126/science.168.3939.1604

Dowling, W. J. (1978). Scale and contour - 2 components of a theory of memory for melodies. *Psychological Review, 85*(4), 341-354. doi: 10.1037//0033-295x.85.4.341

Dowling, W. J., & Fujitani, D. S. (1971). Contour, interval, and pitch recognition in memory for melodies. *The Journal of the Acoustical Society of America, 49*(2), Suppl 2:524+.

Ellis, R. J., Bruijn, B., Norton, A. C., Winner, E., & Schlaug, G. (2013). Training-mediated leftward asymmetries during music processing: A cross-sectional and longitudinal fMRI analysis. *Neuroimage, 75*, 97-107. doi: 10.1016/j.neuroimage.2013.02.045

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology, 117*(12), 2584-2596. doi: 10.1016/j.clinph.2006.06.712

Foxton, J. M., Dean, J. L., Gee, R., Peretz, I., & Griffiths, T. D. (2004). Characterization of deficits in pitch perception underlying 'tone deafness'. *Brain, 127*, 801-810. doi: 10.1093/brain/awh105

Furuya, S., Klaus, M., Nitsche, M. A., Paulus, W., & Altenmueller, E. (2014). Ceiling Effects Prevent Further Improvement of Transcranial Stimulation in Skilled Musicians. *Journal of Neuroscience, 34*(41), 13834-13839. doi: 10.1523/jneurosci.1170-14.2014

Furuya, S., Klaus, M., Nitsche, M. A., Paulus, W., & Altenmüller, E. (2014). Ceiling Effects Prevent Further Improvement of Transcranial Stimulation in Skilled Musicians. *Journal of Neuroscience, 34*(41), 13834-13839. doi: 10.1523/jneurosci.1170-14.2014

Gaab, N., Gaser, C., & Schlaug, G. (2006). Improvement-related functional plasticity following pitch memory training. *Neuroimage, 31*(1), 255-263. doi: 10.1016/j.neuroimage.2005.11.046

Gaab, N., Gaser, C., Zaehle, T., Jancke, L., & Schlaug, G. (2003). Functional anatomy of pitch memory - an fMRI study with sparse temporal sampling. *Neuroimage, 19*(4), 1417-1426. doi: 10.1016/s1053-8119(03)00224-6

Gaab, N., Gaser, C., Zähle, T., Jäncke, L., & Schlaug, G. (2003). Functional anatomy of pitch memory - an fMRI study with sparse temporal sampling. *Neuroimage, 19*(4), 1417-1426. doi: 10.1016/s1053-8119(03)00224-6

Gaab, N., & Schlaug, G. (2003). The effect of musicianship on pitch memory in performance matched groups. *Neuroreport, 14*(18), 2291-2295. doi: 10.1097/01.wnr.0000093587.33576.f7

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (OCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117*(4), 845-850. doi: 10.1016/j.clinph.2005.12.003

Gosselin, N., Jolicoeur, P., & Peretz, I. (2009). Impaired Memory for Pitch in Congenital Amusia. *Neurosciences and Music Iii: Disorders and Plasticity, 1169*, 270-272. doi: 10.1111/j.1749-6632.2009.04762.x

Greenish, A. J. (1953). *The Student's Dictionary of Musical Terms*: J. Williams.

Habibi, A., Wirantana, V., & Starr, A. (2013). Cortical activity during perceptiom of musical pitch: Comparing musicians and nonmusicians. *Music Perception, 30*(5), 463-479. doi: 10.1525/mp.2013.30.5.463

Heimrath, K., Kuehne, M., Heinze, H. J., & Zaehle, T. (2014). Transcranial direct current stimulation (tDCS) traces the predominance of the left auditory cortex for processing of rapidly changing acoustic information. *Neuroscience, 261*, 68-73. doi: 10.1016/j.neuroscience.2013.12.031

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation. *Current Biology, 24*(3), 333-339. doi: 10.1016/j.cub.2013.12.041

Herdener, M., Humbel, T., Esposito, F., Habermeyer, B., Cattapan-Ludewig, K., & Seifritz, E. (2014). Jazz Drummers Recruit Language-Specific Areas for the Processing of Rhythmic Structure. *Cerebral Cortex, 24*(3), 836-843. doi: 10.1093/cercor/bhs367

Herholz, S. C., & Zatorre, R. J. (2012). Musical Training as a Framework for Brain Plasticity: Behavior, Function, and Structure. *Neuron, 76*(3), 486-502. doi: 10.1016/j.neuron.2012.10.011

Herrmann, C. S., Rach, S., Neuling, T., & Struber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience, 7*, 13. doi: 10.3389/fnhum.2013.00279

Herwig, U., Satrapi, P., & Schonfeldt-Lecuona, C. (2003). Using the International 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topography, 16*(2), 95-99. doi: 10.1023/B:BRAT.0000006333.93597.9d

Horvath, J. C., Carter, O., & Forte, J. D. (2014). Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). *Frontiers in systems neuroscience, 8*, 2-2. doi: 10.3389/fnsys.2014.00002

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., . . . Kahana, M. J. (2003). Gamma oscillations correlate with working memory load in humans. *Cerebral Cortex, 13*(12), 1369-1374. doi: 10.1093/cercor/bhg084

Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., & Schlaug, G. (2009). Musical Training Shapes Structural Brain Development. *Journal of Neuroscience, 29*(10), 3019-3025. doi: 10.1523/jneurosci.5118-08.2009

Hyde, K. L., Lerch, J. P., Zatorre, R. J., Griffiths, T. D., Evans, A. C., & Peretz, I. (2007). Cortical thickness in congenital amusia: When less is better than more. *Journal of Neuroscience, 27*(47), 13028-13032. doi: 10.1523/jneurosci.3039-07.2007

Hyde, K. L., & Peretz, I. (2004). Brains that are out of tune but in time. *Psychological Science, 15*(5), 356-360. doi: 10.1111/j.0956-7976.2004.00683.x

Hyde, K. L., Zatorre, R. J., Griffiths, T. D., Lerch, J. P., & Peretz, I. (2006). Morphometry of the amusic brain: a two-site study. *Brain, 129*, 2562-2570. doi: 10.1093/brain/aw1204

Hyde, K. L., Zatorre, R. J., & Peretz, I. (2011). Functional MRI Evidence of an Abnormal Neural Network for Pitch Processing in Congenital Amusia. *Cerebral Cortex, 21*(2), 292-299. doi: 10.1093/cercor/bhq094

Imm, J. H., Kang, E., Youn, T., Park, H., Kim, J., Kang, J. I., . . . Park, H. J. (2008). Different hemispheric specializations for pitch and audioverbal working memory. *Neuroreport, 19*(1), 99-103.

Janata, P., Tillmann, B., & Bharucha, J. J. (2002). Listening to polyphonic music recruits domain-general attention and working memory circuits. *Cognitive Affective & Behavioral Neuroscience, 2*(2), 121-140. doi: 10.3758/cabn.2.2.121

Jancke, L., Schlaug, G., & Steinmetz, H. (1997). Hand skill asymmetry in professional musicians. *Brain and Cognition, 34*(3), 424-432. doi: 10.1006/brcg.1997.0922

Jensen, O., Kaiser, J., & Lachaux, J. P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences, 30*(7), 317-324. doi: 10.1016/j.tins.2007.05.001

Jerde, T. A., Childs, S. K., Handy, S. T., Nagode, J. C., & Pardo, J. V. (2011). Dissociable systems of working memory for rhythm and melody. *Neuroimage, 57*(4), 1572-1579. doi: 10.1016/j.neuroimage.2011.05.061

Kadosh, R. C., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating Neuronal Activity Produces Specific and Long-Lasting Changes in Numerical Competence. *Current Biology, 20*(22), 2016-2020. doi: 10.1016/j.cub.2010.10.007

Kaiser, J., & Bertrand, O. (2003). Dynamics of working memory for moving sounds: An event-related potential and scalp current density study. *Neuroimage, 19*(4), 1427-1438. doi: 10.1016/s1053-8119(03)00233-7

Kaiser, J., Ripper, B., Birbaumer, N., & Lutzenberger, W. (2003). Dynamics of gamma-band activity in human magnetoencephalogram during auditory pattern working memory. *Neuroimage, 20*(2), 816-827. doi: 10.1016/s1053-8119(03)00350-1

Krumhansl, C. L. (2000). Rhythm and pitch in music cognition. *Psychological Bulletin, 126*(1), 159-179. doi: 10.1037//0033-2909.126.1.159

Laczo, B., Antal, A., Niebergall, R., Treue, S., & Paulus, W. (2012). Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. *Brain Stimulation, 5*(4), 484-491. doi: 10.1016/j.brs.2011.08.008

Ladeira, A., Fregni, F., Campanha, C., Valasek, C. A., De Ridder, D., Brunoni, A. R., & Boggio, P. S. (2011). Polarity-Dependent Transcranial Direct Current Stimulation Effects on Central Auditory Processing. *Plos One, 6*(9), 6. doi: 10.1371/journal.pone.0025399

Loui, P., Alsop, D., & Schlaug, G. (2009). Tone Deafness: A New Disconnection Syndrome? *Journal of Neuroscience, 29*(33), 10215-10220. doi: 10.1523/jneurosci.1701-09.2009

Loui, P., & Schlaug, G. (2009). Investigating Musical Disorders with Diffusion Tensor Imaging A Comparison of Imaging Parameters. In S. DallaBella, N. Kraus, K. Overy, C. Pantev, J. S. Snyder, M. Tervaniemi, B. Tillmann, & G. Schlaug (Eds.), *Neurosciences and Music Iii: Disorders and Plasticity* (Vol. 1169, pp. 121-125).

Luft, C. D. B., Pereda, E., Banissy, M. J., & Bhattacharya, J. (2014). Best of both worlds: promise of combining brain stimulation and brain connectome. *Frontiers in systems neuroscience, 8*, 132. doi: 10.3389/fnsys.2014.00132

Lutzenberger, W., Ripper, B., Busse, L., Birbaumer, N., & Kaiser, J. (2002). Dynamics of gamma-band activity during an audiospatial working memory task in humans. *Journal of Neuroscience, 22*(13), 5630-5638.

Manenti, R., Petesi, M., Brambilla, M., Rosini, S., Miozzo, A., Padovani, A., . . . Cotelli, M. (2015). Efficacy of semantic-phonological treatment combined with tDCS for verb retrieval in a patient with aphasia. *Neurocase, 21*(1), 109-119. doi: 10.1080/13554794.2013.873062

Martin, D. M., Liu, R., Alonzo, A., Green, M., & Loo, C. K. (2014). Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Experimental Brain Research, 232*(10), 3345-3351. doi: 10.1007/s00221-014-4022-x

Massaro, D. W. (1970). Retroactive interference in short-term recognition memory for pitch. *Journal of Experimental Psychology, 83*(1), 32-&. doi: 10.1037/h0028566

Mathys, C., Loui, P., Zheng, X., & Schlaug, G. (2010). Non-invasive brain stimulation applied to Heschl's gyrus modulates pitch discrimination. *Frontiers in Psychology, 1*, 7. doi: 10.3389/fpsyg.2010.00193

McDermott, K. B., Jones, T. C., Petersen, S. E., Lageman, S. K., & Roediger, H. L. (2000). Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: An event-related fMRI study. *Journal of Cognitive Neuroscience, 12*(6), 965-976. doi: 10.1162/08989290051137503

Meinzer, M., Jaehnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., . . . Floel, A. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex, 50*, 137-147. doi: 10.1016/j.cortex.2013.07.013

Meiron, O., & Lavidor, M. (2014). Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. *Clinical Neurophysiology, 125*(1), 77-82. doi: 10.1016/j.clinph.2013.06.013

Merrete, D. L., Peretz, I., & Wilson, S. J. (2013). Moderating variables of music training-induced neuroplasticity: a review and discussion. *Frontiers in Psychology, 4*, 8. doi: 10.3389/fpsyg.2013.00606

Miniussi, C., Harris, J. A., & Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. *Neuroscience and Biobehavioral Reviews, 37*(8), 1702-1712. doi: 10.1016/j.neubiorev.2013.06.014

Mitchell, R. L. C., & Ross, E. D. (2013). Attitudinal prosody: What we know and directions for future study. *Neuroscience and Biobehavioral Reviews, 37*(3), 471-479. doi: 10.1016/j.neubiorev.2013.01.027

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., . . . Priori, A. (2008). Improved naming after transcranial direct current stimulation in aphasia. *Journal of Neurology Neurosurgery and Psychiatry, 79*(4), 451-453. doi: 10.1136/jnnp.2007.135277

Munte, T. F., Altenmuller, E., & Jancke, L. (2002). The musician's brain as a model of neuroplasticity. *Nature Reviews Neuroscience, 3*(6), 473-478. doi: 10.1038/nrn843

Nagarajan, S. S., Durand, D. M., & Warman, E. N. (1993). Effects of induced electric-fields on finite neural structures - A stimulation study. *Ieee Transactions on Biomedical Engineering, 40*(11), 1175-1188. doi: 10.1109/10.245636

Narayanan, N. S., Prabhakaran, V., Bunge, S. A., Christoff, K., Fine, E. M., & Gabrieli, J. D. E. (2005). The role of the prefrontal cortex in the maintenance of verbal working memory: An event-related fMRI analysis. *Neuropsychology, 19*(2), 223-232. doi: 10.1037/0894-4105.19.2.223

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., . . . Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation, 1*(3), 206-223. doi: 10.1016/j.brs.2008.06.004

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology-London, 527*(3), 633-639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.

Notturno, F., Marzetti, L., Pizzella, V., Uncini, A., & Zappasodi, F. (2014). Local and remote effects of transcranial direct current stimulation on the electrical activity of the motor cortical network. *Human Brain Mapping, 35*(5), 2220-2232. doi: 10.1002/hbm.22322

O'Shea, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2004). Timing of target discrimination in human frontal eye fields. *Journal of Cognitive Neuroscience, 16*(6), 1060-1067. doi: 10.1162/0898929041502634

Pascual-Leone, A., Houser, C. M., Reese, K., Shotland, L. I., Grafman, J., Sato, S., . . . Hallett, M. (1993). Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalography and Clinical Neurophysiology, 89*(2), 120-130. doi: 10.1016/0168-5597(93)90094-6

Patston, L. L. M., Kirk, I. J., Rolfe, M. H. S., Corballis, M. C., & Tippett, L. J. (2007). The unusual symmetry of musicians: Musicians have equilateral interhemispheric transfer for visual information. *Neuropsychologia, 45*(9), 2059-2065. doi: 10.1016/j.neuropsychologia.2007.02.001

Pechmann, T., & Mohr, G. (1992). Interference in memory for tonal pitch - Implications for a working-memory model. *Memory & Cognition, 20*(3), 314-320. doi: 10.3758/bf03199668

Peretz, I., Ayotte, J., Zatorre, R. J., Mehler, J., Ahad, P., Penhune, V. B., & Jutras, B. (2002). Congenital amusia: A disorder of fine-grained pitch discrimination. *Neuron, 33*(2), 185-191. doi: 10.1016/s0896-6273(01)00580-3

Peretz, I., Champod, A. S., & Hyde, K. L. (2003). Varieties of musical disorders - The Montreal battery of evaluation of amusia. *Neurosciences and Music, 999*, 58-75. doi: 10.1196/annals.1284.006

Peretz, I., Cummings, S., & Dube, M. P. (2007). The genetics of congenital amusia (tone deafness): A family-aggregation study. *American Journal of Human Genetics, 81*(3), 582-588. doi: 10.1086/521337

Pirulli, C., Fertonani, A., & Miniussi, C. (2013). The Role of Timing in the Induction of Neuromodulation in Perceptual Learning by Transcranial Electric Stimulation. *Brain Stimulation, 6*(4), 683-689. doi: 10.1016/j.brs.2012.12.005

Pitcher, D., Charles, L., Devlin, J. T., Walsh, V., & Duchaine, B. (2009). Triple Dissociation of Faces, Bodies, and Objects in Extrastriate Cortex. *Current Biology, 19*(4), 319-324. doi: 10.1016/j.cub.2009.01.007

Platel, H., Price, C., Baron, J. C., Wise, R., Lambert, J., Frackowiak, R. S. J., . . . Eustache, F. (1997). The structural components of music perception - A functional anatomical study. *Brain, 120*, 229-243. doi: 10.1093/brain/120.2.229

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2013). Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. *Frontiers in Human Neuroscience, 7*, 8. doi: 10.3389/fnhum.2013.00687

Reithler, J., Peters, J. C., & Sack, A. T. (2011). Multimodal transcranial magnetic stimulation: Using concurrent neuroimaging to reveal the neural network dynamics of noninvasive brain stimulation. *Progress in Neurobiology, 94*(2), 149-165. doi: 10.1016/j.pneurobio.2011.04.004

Richter, L., Neumann, G., Oung, S., Schweikard, A., & Trillenberg, P. (2013). Optimal Coil Orientation for Transcranial Magnetic Stimulation. *Plos One, 8*(4), 10. doi: 10.1371/journal.pone.0060358

Robertson, I. H., & Murre, J. M. J. (1999). Rehabilitation of brain damage: Brain plasticity and principles of guided recovery. *Psychological Bulletin, 125*(5), 544-575. doi: 10.1037/0033-2909.125.5.544

Romero, L., Walsh, V., & Papagno, C. (2006). The neural correlates of phonological short-term memory: A repetitive transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 18*(7), 1147-1155. doi: 10.1162/jocn.2006.18.7.1147

Ross, D. A., Olson, I. R., Marks, L. E., & Gore, J. C. (2004). A nonmusical paradigm for identifying absolute pitch possessors. *Journal of the Acoustical Society of America, 116*(3), 1793-1799. doi: 10.1121/1.1758973

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety, T. M. S. C. G. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039. doi: 10.1016/j.clinph.2009.08.016

Rusconi, E., Dervinis, M., Verbruggen, F., & Chambers, C. D. (2013). Critical Time Course of Right Frontoparietal Involvement in Mental Number Space. *Journal of Cognitive Neuroscience, 25*(3), 465-483.

Rushworth, M. F. S., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience, 4*(6), 656-661. doi: 10.1038/88492

Russell, R., Duchaine, B., & Nakayama, K. (2009). Super-recognizers: People with extraordinary face recognition ability. *Psychonomic Bulletin & Review, 16*(2), 252-257. doi: 10.3758/pbr.16.2.252

Saiote, C., Turi, Z., Paulus, W., & Antal, A. (2013). Combining functional magnetic resonance imaging with transcranial electrical stimulation. *Frontiers in Human Neuroscience, 7*, 7. doi: 10.3389/fnhum.2013.00435

Sakurai, Y., Takeuchi, S., Kojima, E., Yazawa, I., Murayama, S., Kaga, K., . . . Kanazawa, I. (1998). Mechanism of short-term memory and repetition in conduction aphasia and related cognitive disorders: a neuropsychological, audiological and neuroimaging study. *Journal of the Neurological Sciences, 154*(2), 182-193. doi: 10.1016/s0022-510x(97)00227-x

Santarnecchi, E., Polizzotto, N. R., Godone, M., Giovannelli, F., Feurra, M., Matzen, L., . . . Rossi, S. (2013). Frequency-Dependent Enhancement of Fluid Intelligence Induced by Transcranial Oscillatory Potentials. *Current Biology, 23*(15), 1449-1453. doi: 10.1016/j.cub.2013.06.022

Schaal, N. K., Banissy, M. J., & Lange, K. (2015). The rhythm span task: Comparing memory capacity for musical rhythms in musicians and non-musicians. *Journal of New Music Research*, 44(1), 3-10.

Schaal, N. K., Bauer, A-K. R., & Müllensiefen, D. (2014). Der Gold-MSI: Replikation und Validierung eines Fragbogeninstrumentes zur Messung Musikalischer Erfahrenheit anhand einer deutschen Stichprobe. *Musicae Scientiae*, 18(4), 423-447.

Schaal, N. K., Javadi, A. H., Halpern, A.R., Pollok, B. & Banissy, M. J. (in press). Right parietal cortex mediates memory for melodies. *European Journal of Neuroscience.*

Schaal, N. K., Pollok, B., & Banissy, M. J. (in preparation). Pitch and rhythm memory: Hemispheric differences for the significance of the supramarginal gyri.

Schaal, N. K., Williamson, V. J., & Banissy, M. J. (2013). Anodal transcranial direct current stimulation over the supramarginal gyrus facilitates pitch memory. *European Journal of Neuroscience, 38*(10), 3513-3518. doi: 10.1111/ejn.12344

Schlaug, G., Jancke, L., Huang, Y. X., Staiger, J. F., & Steinmetz, H. (1995). Increased corpus-callosum site in musicians. *Neuropsychologia, 33*(8), 1047-&. doi: 10.1016/0028-3932(95)00045-5

Schneider, P., Scherg, M., Dosch, H. G., Specht, H. J., Gutschalk, A., & Rupp, A. (2002). Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nature Neuroscience, 5*(7), 688-694. doi: 10.1038/nn871

Schneider, P., Sluming, V., Roberts, N., Scherg, M., Goebel, R., Specht, H. J., . . . Rupp, A. (2005). Structural and functional asymmetry of lateral Heschl's gyrus reflects pitch perception preference. *Nature Neuroscience, 8*(9), 1241-1247. doi: 10.1038/nn1530

Schubert, E., & Stevens, C. (2006). The effect of implied harmony, contour and musical expertise on judgments of similarity of familiar melodies. *Journal of New Music Research, 35*(2), 161-174. doi: 10.1080/09298210600835000

Schulze, K., Mueller, K., & Koelsch, S. (2011). Neural correlates of strategy use during auditory working memory in musicians and non-musicians. *European Journal of Neuroscience, 33*(1), 189-196. doi: 10.1111/j.1460-9568.2010.07470.x

Schulze, K., Zysset, S., Mueller, K., Friederici, A. D., & Koelsch, S. (2011). Neuroarchitecture of Verbal and Tonal Working Memory in Nonmusicians and Musicians. *Human Brain Mapping, 32*(5), 771-783. doi: 10.1002/hbm.21060

Semal, C., Demany, L., Ueda, K., & Halle, P. A. (1996). Speech versus nonspeech in pitch memory. *Journal of the Acoustical Society of America, 100*(2), 1132-1140. doi: 10.1121/1.416298

Sergent, J., Zuck, E., Terriah, S., & Macdonald, B. (1992). Distributed neural network underlying musical sight-reading and keyboard performance. *Science, 257*(5066), 106-109. doi: 10.1126/science.1621084

Silvanto, J., & Pascual-Leone, A. (2008). State-dependency of transcranial magnetic stimulation. *Brain Topography, 21*(1), 1-10. doi: 10.1007/s10548-008-0067-0

Singh, K. D., Hamdy, S., Aziz, Q., & Thompson, D. G. (1997). Topographic mapping of trans-cranial magnetic stimulation data on surface rendered MR images of the brain. *Electromyography and Motor Control-Electroencephalography and Clinical Neurophysiology, 105*(5), 345-351. doi: 10.1016/s0924-980x(97)96699-6

Stewart, L. (2008). Fractionating the musical mind: insights from congenital amusia. *Current Opinion in Neurobiology, 18*(2), 127-130. doi: 10.1016/j.conb.2008.07.008

Stewart, L., Ellison, A., Walsh, V., & Cowey, A. (2001). The role of transcranial magnetic stimulation (TMS) in studies of vision, attention and cognition. *Acta Psychologica, 107*(1-3), 275-291. doi: 10.1016/s0001-6918(01)00035-x

Stewart, L., Walsh, V., Frith, U., & Rothwell, J. (2001). TMS produces two dissociable types of speech disruption. *Neuroimage, 13*(6), S45-S45.

Takeuchi, A. H., & Hulse, S. H. (1993). Absolute Pitch. *Psychological Bulletin, 113*(2), 345-361. doi: 10.1037//0033-2909.113.2.345

Tan, Y. T., McPherson, G. E., Peretz, I., Berkovic, S. F., & Wilson, S. J. (2014). The genetic basis of music ability. *Frontiers in Psychology, 5*, 19. doi: 10.3389/fpsyg.2014.00658

Tillmann, B., Schulze, K., & Foxton, J. M. (2009). Congenital amusia: A short-term memory deficit for non-verbal, but not verbal sounds. *Brain and Cognition, 71*(3), 259-264. doi: 10.1016/j.bandc.2009.08.003

Turi, Z., Ambrus, G. G., Janacsek, K., Emmert, K., Hahn, L., Paulus, W., & Antal, A. (2013). Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during transcranial alternating current stimulation. *Restorative Neurology and Neuroscience, 31*(3), 275-285. doi: 10.3233/rnn-120297

Ueno, S., Tashiro, T., & Harada, K. (1988). Localized stimulation of neural tissues in the brain my means of a paired configuration of time-varying magnetic-fields. *Journal of Applied Physics, 64*(10), 5862-5864. doi: 10.1063/1.342181

Vestito, L., Rosellini, S., Mantero, M., & Bandini, F. (2014). Long-term effects of transcranial direct-current stimulation in chronic post-stroke aphasia: a pilot study. *Frontiers in Human Neuroscience, 8*, 7. doi: 10.3389/fnhum.2014.00785

Vicario, C. M., & Nitsche, M. A. (2013). Transcranial Direct Current Stimulation: a remediation tool for the treatment of childhood congenital dyslexia? *Frontiers in Human Neuroscience, 7*.

Vines, B. W., Schnider, N. M., & Schlaug, G. (2006). Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. *Neuroreport, 17*(10), 1047-1050. doi: 10.1097/01.wnr.0000223396.05070.a2

Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A., & Pollok, B. (2013). The effect of 10 Hz transcranial alternating current stimulation (tACS) on corticomuscular coherence. *Frontiers in Human Neuroscience, 7*, 10. doi: 10.3389/fnhum.2013.00511

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1*(1), 73-79. doi: 10.1038/35036239

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia, 37*(2), 125-135.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, June 5-7, 1996. *Evoked Potentials-Electroencephalography and Clinical Neurophysiology, 108*(1), 1-16. doi: 10.1016/s0168-5597(97)00096-8

Williamson, V. J., Baddeley, A. D., & Hitch, G. J. (2010). Musicians' and nonmusicians' short-term memory for verbal and musical sequences: Comparing phonological similarity and pitch proximity. *Memory & Cognition, 38*(2), 163-175. doi: 10.3758/mc.38.2.163

Williamson, V. J., Cocchini, G., & Stewart, L. (2011). The relationship between pitch and space in congenital amusia. *Brain and Cognition, 76*(1), 70-76. doi: 10.1016/j.bandc.2011.02.016

Williamson, V. J., & Stewart, L. (2010). Memory for pitch in congenital amusia: Beyond a fine-grained pitch discrimination problem. *Memory, 18*(6), 657-669. doi: 10.1080/09658211.2010.501339

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial Alternating Current Stimulation Enhances Individual Alpha Activity in Human EEG. *Plos One, 5*(11), 7. doi: 10.1371/journal.pone.0013766

Zaghi, S., Acar, M., Hultgren, B., Boggio, P. S., & Fregni, F. (2010). Noninvasive Brain Stimulation with Low-Intensity Electrical Currents: Putative Mechanisms of Action for Direct and Alternating Current Stimulation. *Neuroscientist, 16*(3), 285-307. doi: 10.1177/1073858409336227

Zatorre, R. J., Evans, A. C., & Meyer, E. (1994). Neural mechanisms underlying melodic perception and memory for pitch. *Journal of Neuroscience, 14*(4), 1908-1919.

9. Original Research Articles

This work is based on:

Appendix 1

Schaal, N. K., Krause, V., Lange, K., Banissy, M. J., Williamson, V. J., & Pollok, B. (2014). Pitch Memory in non-musicians and musicians: Revealing functional differences using transcranial direct current stimulation. *Cerebral Cortex*, advance online publication, doi: 10.1093/cercor/bhu075.

Personal contribution: 90%
Impact Factor (2015): 8.305

Appendix 2

Schaal, N. K., Williamson, V. J., Kelly, M., Muggleton, N. G., Pollok, B., Krause, V., & Banissy, M. J. (2015). A causal involvement of the left supramarginal gyrus during the retention of musical pitches, *Cortex*, 64, 310-317, doi:10.1016/j.cortex.2014.11.011.

Personal contribution: 90%
Impact Factor (2015): 6.042

Appendix 3

Schaal, N. K., Pfeifer, J., Krause, V., & Pollok, B. (under review). From amusic to musical? – Improving pitch memory in congenital amusia with transcranial alternating current stimulation. *Behavioural Brain Research*.

Personal contribution: 80%
Impact Factor (2015): 3.393

Other aspects are taken from:

Schaal, N.K., Williamson, V. J., & Banissy, M. J. (2013). Anodal transcranial direct current stimulation over the supramarginal gyrus fascilitates pitch memory. *European Journal of Neuroscience*, 38(19), 3513-3518.

Schaal, N. K., Bauer, A-K. R., & Müllensiefen, D. (2014). Der Gold-MSI: Replikation und Validierung eines Fragbogeninstrumentes zur Messung Musikalischer Erfahrenheit anhand einer deutschen Stichprobe. *Musicae Scientiae*, 18(4), 423-447.

Schaal, N. K., Banissy, M. J., & Lange, K. (2015). The rhythm span task: Comparing memory capacity for musical rhythms in musicians and non-musicians. *Journal of New Music Research*, 44(1), 3-10.

Schaal, N. K., Javadi, A. H., Halpern, A.R., Pollok, B. & Banissy, M. J. (2015). Right parietal cortex mediates memory for melodies. European Journal of Neuroscience, advance online publication.

Schaal, N. K., Pollok, B., & Banissy, M. J. (in preparation). Pitch and rhythm memory: Hemispheric differences for the significance of the supramarginal gyri.

10. Erklärung

Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die Dissertation wurde in der vorliegenden oder ähnlichen Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den

11. Acknowledgements

Looking back at the last couple of years, I very much realise that I have been extremely lucky to be surrounded by very special people who have all contributed to the success of my thesis and who I would like to thank at this point for their valuable support.

First of all, I would like to thank Prof. Dr. Martin Heil for giving me the opportunity to work and complete my doctoral thesis in his department and for providing me with great working conditions as well as much appreciated advice and for supporting me in my career plans.

Secondly, I would like to say a huge thank you to PD Dr. Bettina Pollok who has ‘adopted’ me without hesitation and has been a continuous and indispensable support. Thank you for your help and guidance, for making me feel so welcome and for being a place to go when I had questions and needed advice. At this point, I would also like to thank Dr. Vanessa Krause for her support, help and valuable advice. The cooperation with you both has been so ‘stimulating’ ☺.

Furthermore, I am very thankful that Dr. Victoria Williamson and Dr. Michael Banissy have continued to work with me and support me through my doctoral thesis. Thank you Vicky for your contagious enthusiasm in music psychology, your expertise knowledge and your cheers along the way. And a very special thank you to Michael for introducing me to the brain stimulation world, arousing my interest in the scientific world, being the one who said I can do this (at one time I had doubts), for valuable input, ideas and support and telling me to relax from time to time.

Thank you also to my wonderful colleagues and friends who were there to share the joy and hard times of my doctoral thesis. DANKE also for making sure I had enough chocolate and post-its so I could work productively. I won’t mention names but I hope the people who I am addressing here know how happy and thankful I am for you being there in person, on the phone/skype or via email.

Last but not least I thank my parents for supporting me in whatever I am doing, my sisters Anna and Lena for being there and Leonard, Matilda and Jonathan for their smiles and hugs and for making me a very proud aunty. Thank you Mum and Lena for proofreading my thesis.

And I say thank you for the music, for giving it to me!

12. Appendix

Cerebral Cortex Advance Access published April 25, 2014

Cerebral Cortex
doi:10.1093/cercor/bhu075

Pitch Memory in Nonmusicians and Musicians: Revealing Functional Differences Using Transcranial Direct Current Stimulation

N.K. Schaal[1], V. Krause[2], K. Lange[1], M.J. Banissy[3], V.J. Williamson[4,5] and B. Pollok[2]

[1]Department of Experimental Psychology, Heinrich-Heine-University, Düsseldorf, Germany, [2]Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany, [3]Department of Psychology, Goldsmiths University of London, London, UK, [4]Lucerne University of Applied Sciences and Arts, Lucerne, Switzerland and [5]Department of Music, University of Sheffield, Sheffield, UK

Address correspondence to Nora K. Schaal, Department of Experimental Psychology, Heinrich-Heine-University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany. Email: nora.schaal@uni-duesseldorf.de

For music and language processing, memory for relative pitches is highly important. Functional imaging studies have shown activation of a complex neural system for pitch memory. One region that has been shown to be causally involved in the process for nonmusicians is the supramarginal gyrus (SMG). The present study aims at replicating this finding and at further examining the role of the SMG for pitch memory in musicians. Nonmusicians and musicians received cathodal transcranial direct current stimulation (tDCS) over the left SMG, right SMG, or sham stimulation, while completing a pitch recognition, pitch recall, and visual memory task. Cathodal tDCS over the left SMG led to a significant decrease in performance on both pitch memory tasks in nonmusicians. In musicians, cathodal stimulation over the left SMG had no effect, but stimulation over the right SMG impaired performance on the recognition task only. Furthermore, the results show a more pronounced deterioration effect for longer pitch sequences indicating that the SMG is involved in maintaining higher memory load. No stimulation effect was found in both groups on the visual control task. These findings provide evidence for a causal distinction of the left and right SMG function in musicians and nonmusicians.

Keywords: cathodal stimulation, expertise, functional involvement, plasticity, supramarginal gyrus

Introduction

The musicians' brain has been studied extensively as a model for neuroplasticity over the last 2 decades (Herholz and Zatorre 2012; Merette et al. 2013 for recent overviews). Findings from cross-sectional brain imaging studies comparing brain structures of musicians and nonmusicians suggest that multiple anatomical differences exist including motor areas (Jäncke et al. 1997), gray matter volume in Heschl's gyrus (Schneider et al. 2002) and the corpus callosum (Schlaug et al. 1995). Furthermore, studies have shown different activation patterns for musicians and nonmusicians for several cognitive tasks (e.g., verbal and tonal memory: Schulze, Zysset et al. 2011; processing rhythms: Herdener et al. 2012; pitch perception: Habibi et al. 2013). A longitudinal intervention study by Hyde et al. (2009) found that after 15 months of musical training children show anatomical differences in the motor hand area, corpus callosum, and right auditory cortex compared with a control group.

Even though such longitudinal studies are relatively sparse, the reasons behind the specialization of neural structures in individuals with musical training can be traced back to the fact that learning an instrument requires extensively regular and deliberate practice (Ericsson et al. 1993), often starting at a very young age. Furthermore, playing an instrument is a highly complex skill whereby one has to integrate higher-order cognitive functions and control very fine motor movements (Wan and Schlaug 2010). Evidence cited in support of a link between musical training and neuroplasticity includes consistent age of onset effects (Barrett et al. 2013 for a review). Thus, it is likely that the brain adapts to these exceptional demands (Münte et al. 2002; Gaser and Schlaug 2003).

Functional imaging studies investigating neural networks of pitch memory in nonmusicians have shown involvements of frontal, temporal, and parietal areas (Zatorre et al. 1994; Koelsch et al. 2009; Jerde et al. 2011). More specifically, in subjects with no or very little musical training, Gaab et al. (2003) showed that pitch memory recruits a network of neural regions, including the superior temporal gyri, bilateral posterior dorsolateral frontal regions, bilateral superior parietal regions, bilateral lobes V and VI of the cerebellum, the supramarginal gyri, and the left inferior frontal gyrus. The activation of the left supramarginal gyrus (SMG) was of particular interest as higher activation in this region was linked to superior pitch memory performance (Gaab et al. 2003).

To investigate the causal involvement of specific brain areas in pitch memory, noninvasive brain stimulation methods, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are useful, as they enable the manipulation of cortical excitability in a targeted area (Nitsche and Paulus 2001; Antal et al. 2004). Whereas anodal tDCS leads to a facilitation of neural activity, cathodal tDCS suppresses the cortical excitability under the site of stimulation (Nitsche and Paulus 2000; Cohen Kadosh et al. 2010; Ladeira et al. 2011). Previous tDCS studies have supported the causal involvement of the left SMG in pitch memory recognition by showing a deterioration of performance after cathodal stimulation (Vines et al. 2006) and an improvement of pitch memory on a recognition and recall task (but not visual memory) after anodal stimulation in nonmusicians (Schaal et al. 2013). To date however, there are no tDCS studies of the SMG in trained musicians, so the causal role of the left SMG in superior pitch memory performance remains to be tested.

One other relevant feature of SMG activation during music processing in musicians and nonmusicians has been contrary hemispheric patterns. Gaab and Schlaug (2003) revealed stronger activation in the right SMG in musicians compared with nonmusicians during a pitch memory task when performances of both groups were matched, indicating different underlying cognitive processing. However, several other studies have reported stronger activation in the left SMG in musicians during music listening (Seung et al. 2005) and pitch memory (Ellis et al. 2013). Schulze, Zysset et al. (2011) compared verbal (memorizing syllables) and tonal (memorizing pitches) working memory in musicians and nonmusicians and revealed overlapping activation patterns including the left inferior parietal lobe (corresponding to the location of the SMG), in both groups for the memory processes. Furthermore, in the musician group, additional activation was found in the right globus pallidus, right caudate nucleus, and left cerebellum during tonal working memory suggesting that musicians use a specialized and more complex neural system for memorizing pitches.

An important note in this context is that the functional magnetic resonance imaging (fMRI) studies mentioned above all used recognition tasks to investigate neural correlates of pitch memory (Zatorre et al. 1994; Gaab et al. 2003; Gaab and Schlaug 2003; Koelsch et al. 2009; Jerde et al. 2011; Schulze, Zysset et al. 2011; Ellis et al. 2013). In general, short-term memory can be tested by 2 response methods, recognition and recall. Whereas recognition relies on a monitoring process for re-presented stimuli, recall tasks include more demanding production processes. A study comparing memory for auditorily and visually presented words has shown that underlying activity of neural structures varies depending whether recall or recognition processes were required (Cabeza et al. 2003). This is often traced back to different strategies used in different task procedures. Furthermore, activation differences found in studies using different recognition tasks may also be due to subtle but important task demand differences which require varying memory processes such as maintenance and rehearsal. For example, the study by Gaab et al. (2003) used a recognition task which only emphasized maintenance of pitch information, whereas the task demands in the study by Schulze, Zysset et al. (2011) required maintenance and explicitly instructed participants to use rehearsal processes. These task demand differences could explain why the activation found in the SMG in the study by Gaab et al. (2003) is more inferior than the inferior parietal activation found by Schulze, Zysset et al. (2011).

The aim of the present study is to investigate whether functional differences of the SMG can be found between musicians and nonmusicians in pitch memory and to clarify whether any such differences can be attributed to memory task demands. Therefore, performances on 2 pitch memory tasks (recognition and recall) and a visual control task were investigated following cathodal tDCS over the left SMG, right SMG, or sham stimulation. In line with previous studies, we hypothesized that in nonmusicians, cathodal stimulation over the left SMG would lead to a deterioration of performance on both pitch memory tasks (Vines et al. 2006; Schaal et al. 2013). Regarding the musicians group, 3 outcomes are possible: (1) cathodal stimulation over the left SMG results in deterioration of pitch memory performance, as stronger activation in the left SMG of musicians was found by Ellis et al. 2013, (2) cathodal tDCS over the right SMG would lead to a drop in pitch memory performance, as musicians show more right hemispheric activation for musical memory (Gaab and Schlaug 2003), or (3) no stimulation effect would be found as musicians activate a more complex neural system for the pitch memory process and can compensate for any stimulation modulations (Schulze, Zysset et al. 2011).

Materials and Methods

Participants

Forty-one nonmusicians and 38 musicians took part in the pretesting phase of the experiment and 36 participants from each group returned for the tDCS session (4 participants had to be excluded for health reasons and 3 subjects did not return for the second session). Nonmusicians were defined as individuals with <2 years of musical training in the past and who were not playing an instrument at present. They were all students, mostly psychology students, at the Heinrich-Heine-University in Düsseldorf, and received either course credits or 6 Euro per hour for their participation. The musicians were all students of a professional music college aiming to make music as their profession and all had at least 10 years of formal musical training. Six string players, 12 wind players, 8 singers, 7 pianists, and 3 musicians playing a plucked instrument comprised the musicians group. None of the musicians were absolute pitch possessors. Musicians received 6 Euro per hour for their participation as well as travel expenses.

All participants were self-report right-handed and reported normal hearing abilities. For the tDCS session, nonmusicians and musicians were split into 3 groups, depending on type and location of stimulation (i.e., left SMG vs. right SMG vs. sham). Groups were matched by age, sex, musical training, as evaluated by the dimension *Musical Training* from the Goldsmiths Musical Sophistication Index questionnaire (Gold-MSI, Müllensiefen et al. 2014), and general pitch memory abilities, which were evaluated in a pretest session. See Table 1 for full demographical details.

Additionally, 4 participants (2 nonmusicians and 2 musicians) came back a third time to take part in a neuronavigation session to control the location of stimulation targeting at either the left or right SMG. The ethics committee of the Medical Department of the Heinrich-Heine-University in Düsseldorf approved this study and all subjects gave their informed written consent to participate.

Materials and Procedure

All participants completed 2 parts, preliminary testing and the tDCS session, which were at least 48 h apart.

Table 1
Characteristics of participants

Group	Stimulation group	N	Sex	Mean age (in years)	Musical training score—Gold-MSI (range: 7–49)	Pretest pitch memory recognition task (in tones)
Nonmusicians	Cathodal lSMG	12	4 Males 8 Females	23.3 ± 4.5	12.83 ± 5.2	5.86 ± 1.1
	Cathodal rSMG	12	3 Males 9 Females	21.7 ± 2.3	14.58 ± 4.8	5.84 ± 1.5
	Sham lSMG	12	5 Males 7 Females	26.2 ± 8.3	15.50 ± 5.5	5.99 ± 1.2
Musicians	Cathodal lSMG	12	5 Males 7 Females	22.5 ± 2.7	42.08 ± 3.9	7.24 ± 0.9
	Cathodal rSMG	12	5 Males 7 Females	23.9 ± 4.2	42.42 ± 3.9	7.24 ± 1.0
	Sham lSMG	12	3 Males 9 Females	23.8 ± 3.0	41.50 ± 1.7	7.35 ± 1.2

Preliminary Testing

Preliminary testing was conducted in order to match the stimulation groups on musical training and general pitch memory abilities. The pitch memory span task (Williamson and Stewart 2010) was used to test general pitch memory capacity. The participants listened to the stimuli via headphones (AKG Pro Audio, K77). Tone sequences were formed of 10 triangle-waveform tones (equally tempered, whole tone steps) with fundamental pitches ranging from 262 Hz (C4) to 741 Hz (F#5). Tones were 500-ms long with a 383-ms pause between tones when they were in sequence. For each trial, 2 tone sequences of equal length were presented, with an intersequence interval pause of 2 s. On 50% of trials, the 2 sequences were identical and in 50% they varied; in the latter case 2 tones of the second sequence were presented in the reversed position (i.e., list probe method). The task was to decide whether the 2 sequences were the same or different. After the participant's decision was recorded, a 2-s long pink noise burst was presented to minimize carry-over effects before the next trial. Sequences were 2 tones long to start with and then increased and decreased according to the participant's performance. A 2-up, one-down adaptive tracking procedure (2 right answers = increase in sequence length by one tone, one wrong answer = decrease in sequence length by one tone) was used. The task was complete when the procedure had run for 8 reversals. The longest sequence played to this sample was 11 tones long.

To ensure that participants were able to discriminate the 3 different tones that were used in the main pitch recall task (Williamson et al. 2010), which was part of the tDCS session, the participants also completed a short single pitch recognition test. In the exposure phase of this preliminary test, participants heard a C-major (C4, E4, G4) chord followed by a sequence of the 3 tones (low-C4, medium-G4, and high-B4) played in succession, 10 times. In the test phase, a C-major chord was played as a get-ready signal, followed after a 2-s pause by one of the 3 tones. The participant was required to mark on a grid, if the tone was the low, medium, or high one. There were 12 trials, where each tone was randomly presented 4 times. Participants had to score at least 10 out of 12 to qualify for the main tDCS phase of the study.

After the 2 pitch memory tasks, the participants filled in a German version of the self-report questionnaire of the Gold-MSI version 1.0 (Müllensiefen et al. 2014) to evaluate their level of musical training. The participants scored statements on a 7-point scale from "completely disagree" to "completely agree". The questionnaire consists of 38 statements and comprises 5 dimensions: *Active Engagement*, *Perceptual Abilities*, *Musical Training*, *Emotions* and *Singing Abilities*. The dimension of interest *Musical Training* contains 7 statements, so the score range is 7–49 points.

tDCS Session

At least 2 days after the preliminary test, participants returned to complete the tDCS session. The participants from both groups (nonmusicians and musicians) were matched as described above and randomly split into 3 stimulation groups: one group receiving cathodal tDCS over the left SMG, another group receiving cathodal stimulation over the right SMG and the third group receiving sham stimulation over the left SMG.

The active electrode (5×5 cm = 25 cm^2) was placed over either the left or right SMG. The areas were located using area CP3 for the left and CP4 for the right hemisphere according to the international 10–20 system for electroencephalogram electrode placement, successfully used in previous studies to place the electrodes over the targeted site (Antal et al. 2004, Rogalewski et al. 2004, Vines et al. 2006). CP3 and CP4 are common locations for targeting the SMG on either hemisphere (Mottaghy et al. 2002; Schaal et al. 2013). The reference electrode (5×7 cm = 35 cm^2) was placed over the contralateral supraorbital area. A slightly smaller active electrode compared with the size of the reference electrode was used to receive a more selective and focally precise stimulation (Nitsche et al. 2007). The electrodes were covered in saline-soaked sponges. The 2 active stimulation groups received 20 min of 2-mA stimulation including 15 s fade-in and fade-out time. An identical setup was used for the sham group, but the stimulator was only turned on for the first 30 s. This evokes the sensation of being stimulated but does not lead to a neurophysiological change that can influence performance. It has been shown that naive subjects cannot distinguish between sham and active tDCS stimulation (Gandiga et al. 2006).

The first 10 min of the stimulation period were used to familiarize the participants with the memory tasks. Altogether the 3 memory tasks of the tDCS session took ~35–40 min. The order of the 3 memory tasks was counterbalanced using a latin-square design.

The pitch memory recognition task (pitch span task) was conducted exactly in the same manner as in the preliminary test. For the pitch memory recall task (Williamson et al. 2010), 3 tones (C4 = 262 Hz, G4 = 392 Hz, and B4 = 494 Hz) were recorded, played by a piano (Disklavier Pro, Yamaha Corporation), and edited to .wav files using Adobe Audition. Each tone was 800-ms long, edited in Adobe Audition, and a 200-ms pause was added to the end so that every file was 1-s long. Pitch sequences were 4–8 tones long and made up of the 3 different tones (low: C4, medium: G4, high: B4) without direct repetition (there was always a movement in the contour). There were 5 blocks (one for each sequence length: 4, 5, 6, 7, and 8 tones) with 6 trials each. To ensure that task demands were clear, a short practice phase with 5 trials (one for each sequence length) was conducted before the first test block. The stimuli were presented via speakers and the participants received an answer booklet, containing blank grids of 3 rows in height (representing high, medium, and low tones) and a number of columns according to the sequence length, and a pen for their responses. To signal the onset of a test sequence, a C-major chord (C4, E4, and G4) was played at the beginning of a trial. Participants then listened to the first sequence (4 tones long), while the answer booklet was turned upside-down and were instructed to listen to the contour (movement of the tones) and try to memorize it. They were instructed to turn over the booklet as soon as the sequence finished and to tick the boxes to record their memory of the pitch sequence. For example, if for a 4-tone-long sequence, the tones "C4–G4–B4–C4" were played, the correct answer would be to tick the boxes "low–medium–high–low" on the grid. When happy with their response, the subjects turned over the booklet again and triggered the next sequence by pressing the spacebar.

A visual task was included as control condition. The Cambridge Face Memory Test—long form (CFMT+, Russell et al. 2009) was chosen as it does not require any auditory or phonological encoding, but has previously been shown to be sensitive to detecting differences in face memory performance (e.g., Russell et al. 2009). In this task participants were instructed to memorize 6 unfamiliar male faces from 3 different views and were then tested on their ability to recognize them in a 3-alternative forced-choice task. The test comprises 102 trials (proceeded by 3 practice trials), subdivided into 4 sections varying in difficulty. The first section of the task tested recognition with the same images that were used during training. This was followed by a section involving presentation of novel images that show the target faces from untrained views and lighting conditions in the test phase. A third section consisting of novel images with visual noise added. The final section contained trials in which distractor images repeated more frequently, targets and distractors contained more visual noise than the images in the third section, cropped (only showing internal features) and uncropped images (showing hair, ears, and necks, which had not been shown in the previous sections) were used, and images showing the targets and distractors making emotional expressions were included. The first and second sections used a trial-by-trial recognition paradigm, whereas sections 3 and 4 employed a more long-term memory approach. The percentage of correct responses was measured.

Neuronavigation

To validate the location of stimulation and to show that the electrode was placed over the targeted area of the SMG (Brodmann area 40) a Neuronavigation session was conducted with a small exemplary sample of 4 participants (2 musicians and 2 nonmusicians). To reconstruct the procedure of the tDCS session the international 10–20 system was used to locate the area of the left (CP3) and right (CP4) SMG on the participant's scalp. After marking this localization with a highlighter, the Neuronavigation (Localite GmbH, Sankt Augustin, Germany) procedure began with measuring the head using predefined points (i.e., left and right preauricular points and nasion). After mapping the anatomical landmarks onto a standardized brain, 2 markers were inserted according to the highlighted points on the scalp located at CP3 and CP4. The program then identified the Talairach coordinates for the markers.

Results

Pitch Memory Recognition Task

As participants completed the pitch span task twice (in the preliminary session and after tDCS) a mixed factorial analysis of variance (ANOVA) with *time* (pre vs. poststimulation) as a within subject factor and *group* (nonmusicians vs. musicians) and *stimulation group* (cathodal left SMG vs. cathodal right SMG vs. sham) as between subject factors was conducted. The analysis revealed a trend for the factor *time*, $F_{1,66} = 3.67$, $P = 0.06$, and a nonsignificant result for factor *stimulation group*, $F_{2,66} = 1.18$, $P = 0.32$, whereas the main effect of factor *group* was significant, $F_{1,66} = 31.21$, $P < 0.001$. The interactions *time* × *group*, *time* × *stimulation group* and *group* × *stimulation group* are all nonsignificant ($P > 0.14$) but the *time* × *group* × *stimulation group* interaction yielded a significant result, $F_{2,66} = 4.73$, $P = 0.012$. Data are summarized in Table 2.

In order to explore the significant *time* × *group* × *stimulation group* interaction, 2 univariate ANOVAs were applied, one for the prestimulation and one for the poststimulation phase. Where appropriate, all post hoc tests were subject to sequential Bonferroni correction (Holm 1979) in order to compensate for multiple tests and to protect type I errors. Therefore, for every post hoc set *P*-values were ranked and the smallest *P*-value was tested with a Bonferroni correction including all tests, the second smallest was tested involving one less test and so forth for the remaining tests.

Before stimulation a significant main effect of *group*, $F_{1,66} = 24.16$, $P < 0.001$ was revealed. The main effect of *stimulation group* as well as the *group* × *stimulation group* interaction were nonsignificant (*P*-values > 0.92). Poststimulation, the ANOVA revealed a significant main effect of *group*, $F_{1,66} = 25.72$, $P < 0.001$ and a significant *group* × *stimulation group* interaction, $F_{2,66} = 5.16$, $P = 0.016$. The main effect of *stimulation group* was nonsignificant ($P = 0.082$).

Furthermore, independent sample *t*-tests were applied in order to dissolve the significant *group* × *stimulation group* interaction of the poststimulation session. In the stimulation group receiving cathodal tDCS over the left SMG, a highly significant difference of the factor *group* was revealed, $t_{(22)} = 5.96$, $P < 0.001$. In the stimulation group receiving cathodal tDCS over the right SMG, the result was nonsignificant, $t_{(22)} = 0.88$, $P = 0.39$, and in the sham group, a trend towards superior performance of the musicians compared with the performance of nonmusicians was present, $t_{(22)} = 2.32$, $P = 0.06$. This series of results suggests that the musicians' superior performance in all stimulation groups before stimulation was not present anymore after stimulation only in the group who received cathodal tDCS over the right SMG.

To explore this interesting finding, a pre- and poststimulation comparison in the musicians group receiving cathodal stimulation of the right SMG was applied and showed a significant result, $t_{(11)} = 2.76$, $P = 0.02$ indicating that cathodal stimulation over the right SMG in musicians led to a deterioration of pitch memory performance. Additionally, in nonmusicians a pre- and poststimulation comparison in the group receiving cathodal tDCS over the left SMG revealed a significant deterioration of pitch memory, $t_{(11)} = 3.67$, $P = 0.008$ (see Fig. 1).

Table 2
Overview of performances for all 3 stimulation groups in nonmusicians and musicians

Group	Stimulation group	Pitch memory recognition task (in tones)	Pitch memory recall task (percent correct)	CFMT+ percent correct)
Nonmusicians	Cathodal lSMG	**5.04** ± 0.8	**72.56** ± 8.2	62.26 ± 11.4
	Cathodal rSMG	6.08 ± 1.0	80.95 ± 4.9	66.58 ± 8.0
	Sham lSMG	6.26 ± 1.1	80.75 ± 6.2	63.24 ± 12.8
Musicians	Cathodal lSMG	7.11 ± 0.9	90.37 ± 5.8	60.93 ± 15.3
	Cathodal rSMG	**6.42** ± 0.9	91.67 ± 4.5	62.83 ± 6.8
	Sham lSMG	7.25 ± 1.0	91.09 ± 4.3	66.99 ± 8.9

Note: The bold values highlight the group performances which show a significant deterioration after cathodal stimulation.

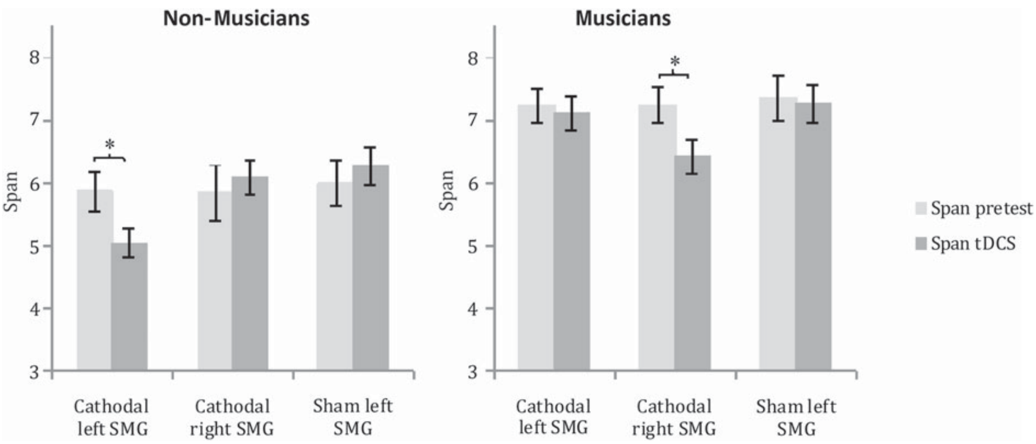


Figure 1. Bargraphs representing the results of the pitch memory recognition task. A mixed factorial ANOVA with the factors *time* (pre vs. poststimulation), *group* (nonmusicians vs. musicians) and *stimulation group* (cathodal left SMG vs. cathodal right SMG vs. sham) reveals a significant *time* × *group* × *stimulation group* interaction, $F_{2,66} = 4.73$, $P = 0.012$. In nonmusicians, cathodal tDCS over the left SMG leads to a significant deterioration of pitch recognition ($t_{(11)} = 3.67$, $P = 0.008$), while in musicians cathodal tDCS over the right SMG results in declined performance ($t_{(11)} = 2.76$, $P = 0.02$).

Pitch Memory Recall Task

An ANOVA with factors *group* (nonmusicians vs. musicians) and *stimulation group* (cathodal left SMG vs. cathodal right SMG vs. sham) on overall recall performance scores yielded main effects of *group*, $F_{1,66} = 89.5$, $P < 0.001$, and *stimulation group*, $F_{2,66} = 5.14$, $P = 0.008$, and a significant *group* × *stimulation group* interaction, $F_{2,66} = 3.15$, $P = 0.049$. Data are summarized in Table 2.

Post hoc independent sample *t*-tests with sequential Bonferroni correction (Holm 1979) in nonmusicians showed significant differences between the group receiving cathodal stimulation over the left SMG and the groups receiving stimulation over the right SMG, $t_{(22)} = 3.04$, $P = 0.018$, and sham stimulation, $t_{(22)} = 2.76$, $P = 0.024$. The group with cathodal tDCS over the left SMG performed significantly below the sham group, and the group stimulated with cathodal tDCS over the right SMG (Fig. 2*A*). The difference between the groups receiving cathodal tDCS over the right SMG and sham stimulation was nonsignificant, $t_{(22)} = 0.08$, $P = 0.93$.

For the musicians group, no significant differences in overall performance could be found in the 3 stimulation groups ($P >$ 0.55), indicating that cathodal stimulation over the left or right SMG did not affect task performance.

A 5 × 2 × 3 mixed factorial ANOVA with *sequence length (5)* as the repeated measure variable and *group (2)* and *stimulation group (3)* as between subject variables revealed a significant main effect of *sequence length*, $F_{4,264} = 144.35$, $P < 0.001$, and a follow-up trend analysis revealed a significant linear trend ($P <$ 0.001) indicating that performances decreased as sequence length increased. Furthermore, the ANOVA confirmed significant main effects of *group* ($P < 0.001$) and *stimulation group* ($P = 0.017$) and also showed significant interaction effects of *sequence length* × *group* ($P < 0.001$) and *group* × *stimulation group* ($P = 0.023$). The *sequence length* × *stimulation group* as well as the 3-way interaction *sequence length* × *group* × *stimulation group* were nonsignificant (*P*-values > 0.155).

In order to further investigate the significant *sequence length* × *group* and *group* × *stimulation group* interaction, performance on the pitch memory recall task for every sequence length (percent correct for 4-tone-long sequences, 5-tone-long sequences etc.) was analyzed. In nonmusicians, the ANOVA revealed nonsignificant main effects of factor *stimulation group* for 4-, 5- and 6-tone-long sequences (*P*-values > 0.10). For the 7-tone sequences a significant main effect of factor *stimulation group* was found, $F_{2,35} = 5.86$, $P < 0.01$, $\eta^2_p = 0.26$. Post hoc comparisons (Tukey-HSD) revealed significant differences between the group receiving tDCS over the left SMG and the sham group ($P < 0.01$) and a marginally significant difference between the groups receiving cathodal tDCS over the left or right SMG ($P = 0.054$). For 8-tone-long sequences, also a significant main effect of factor *stimulation group* was found, $F_{2,35} = 8.25$, $P < 0.001$, $\eta^2_p = 0.33$, with significant differences between the group receiving tDCS over the left SMG and the other 2 groups (cathodal tDCS over right SMG vs. sham stimulation, *P*-values < 0.01). These results indicate that the group who received cathodal tDCS over the left SMG showed a deterioration in their performance on longer sequences with higher memory load only (Fig. 2*B*). When conducting the same analysis for every sequence length in the musicians group, all 5 ANOVAs reported *P*-values > 0.381 for the main effect of *stimulation group*, confirming that on the recall task no stimulation effects could be found on the performance of any sequence length in the musicians group.

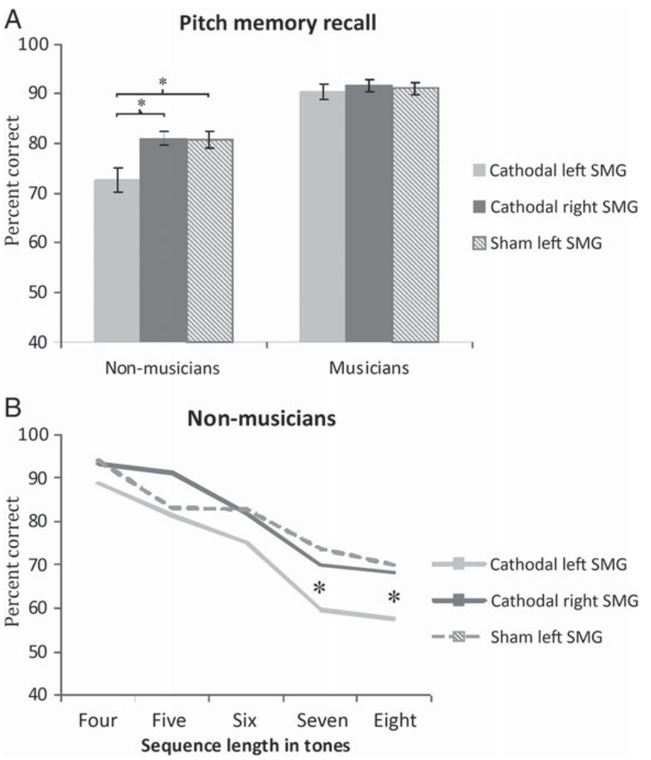


Figure 2. (*A*) For the pitch recall task, there is a significant main effect of stimulation group in nonmusicians showing that performance of the group receiving cathodal tDCS over the left SMG is below the group receiving cathodal stimulation over the right SMG and sham stimulation (*P*-values < 0.05). (*B*) When looking at the performance in nonmusicians for every sequence length, the analysis reveals significant differences of the factor stimulation group for longer sequences (7 and 8 tones) indicating that the deterioration of pitch memory after cathodal stimulation over the left SMG is more pronounced in trials with higher memory load.

Cambridge Face Memory Test—Long Form

For the CFMT+, an ANOVA was conducted with factors *group* (nonmusicians vs. musicians) and *stimulation group* (cathodal left SMG vs. cathodal right SMG vs. sham). The results revealed neither significant main effects nor interaction (*P*-values > 0.48). Data are summarized in Table 2. As the CFMT+ uses 2 different recognition memory paradigms, a trial-by-trial paradigm in Part 1 (blocks 1 and 2) and a more long-term memory approach in Part 2 (blocks 3 and 4), separate ANOVAs were conducted on the percent correct scores for each part with the factors *group* and *stimulation group*: no significant main effects or interactions were found (*P*-values > 0.19). Overall, the evidence strongly suggests that there is no effect of stimulation on the visual control task in either musicians or nonmusicians, thereby indicating that the SMG are not causally involved in the process of remembering faces.

Neuronavigation

The evaluation of the targeted site of all 4 sample participants confirmed that the site which was stimulated corresponds to Brodmann area 40, the location of the SMG. The averaged Talairach coordinates were −44; −43; 49 for the left SMG and 45; −48; 55 for the right SMG corresponding to Brodmann area 40 (Fig. 3).

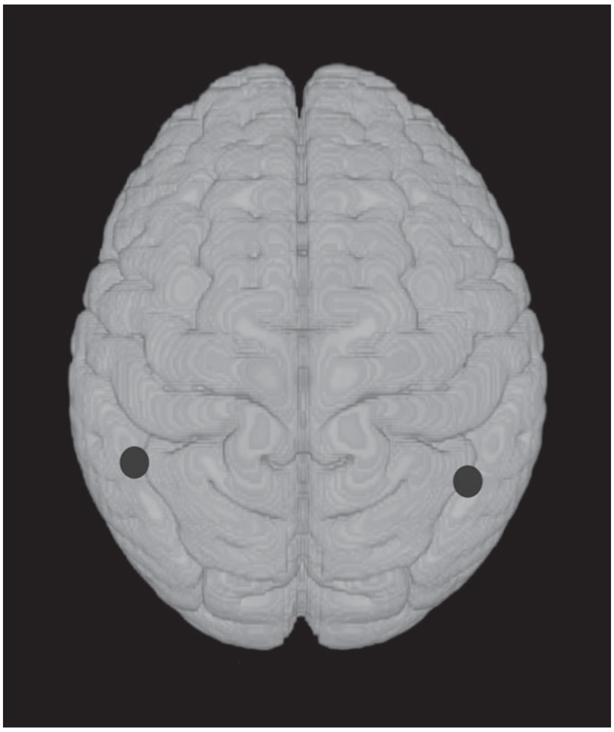


Figure 3. Localization of the left (−44; −43; 49) and right SMG (45; −48; 55) averaged across an exemplary sample of 4 participants (2 nonmusicians and 2 musicians) using neuronavigation.

Discussion

The present study investigated the causal involvement of the left and right SMG in pitch memory ability, as determined by pitch memory recall and recognition paradigms, and how this involvement varies in musicians and nonmusicians indicating functional differences. Whereas cathodal stimulation over the left SMG led to a deterioration of performance in both pitch memory tasks in nonmusicians, the musicians showed a decline only in recognition pitch memory performance and interestingly, only after cathodal tDCS over the right SMG.

In the nonmusicians group, cathodal tDCS over the left SMG led to a significant deterioration of task performance on the pitch recognition task as well as on the pitch recall task compared with the groups receiving cathodal tDCS over the right SMG or sham stimulation. These findings are in line with previous studies showing the activation and causal involvement of specifically the left SMG in the pitch memory process in nonmusicians (Gaab et al. 2003; Vines et al. 2006). These results also extend previous findings showing that anodal tDCS over the left SMG leads to superior pitch memory in nonmusicians (Schaal et al. 2013). In addition, the more detailed analysis of the sequence lengths used in the pitch recall task of the present study showed that the effect of cathodal tDCS over the left SMG is significant for longer pitch sequences only. This new evidence adds to the literature by suggesting that nonmusicians rely more heavily on the left SMG when they are required to either store or rehearse a large amount of material in pitch memory (Sakurai et al. 1998; Gaab et al. 2003; Vines et al. 2006).

The present study also revealed key differences between the effects of SMG tDCS on musicians and nonmusicians. A variety of studies have looked at musicians' brains as a model of neuroplasticity and revealed structural differences compared with nonmusicians (e.g., Schlaug et al. 1995; Jäncke et al. 1997; Schneider et al. 2002; Gaser and Schlaug 2003; Hyde et al. 2009), but to our best knowledge this is the first study to show functional differences in pitch memory tasks using noninvasive brain stimulation. As opposed to the nonmusicians, the pitch memory performance of the musicians group did not show a detrimental effect of cathodal tDCS over the left SMG, neither in the recognition nor recall task. But, cathodal stimulation to the right SMG led to a decrease in their pitch recognition span.

A recent electroencephalography study by Habibi et al. (2013) suggested that the left hemisphere involved in tasks differentiated nonmusicians and musicians, as they found behavioral and electrophysiological differences when stimuli were presented to the right ear. The present data are in line with this idea, showing that musicians and nonmusicians have a differentiated causal involvement of the left SMG during pitch memory tasks. However, when looking at the involvement of the right SMG in the present study, a causal distinction was found as well, indicating that the neural distinction for the pitch memory process between musicians and nonmusicians is not limited to the left hemisphere.

The fact that musicians do not demonstrate a causal involvement of the left SMG in pitch memory is surprising as several fMRI studies have shown increased activation of the left SMG in musicians and in participants after receiving musical training (Gaab et al. 2006; Ellis et al. 2013). One possible explanation for this apparent contradiction is that trained musicians are able to compensate the suppression of a particular brain area during tDCS by activating other areas of their complex neural network for pitch memory. Schulze, Zysset et al. (2011) showed that musicians activate unique and additional neural areas for tonal memory including the right globus pallidus, right caudate nucleus, and left cerebellum. Furthermore, Andoh and Zatorre (2013) have shown an interhemispheric compensation effect by combining TMS and fMRI during a melody discrimination task. When they applied repetitive TMS over the right Heschl's gyrus, an increase of activation was identified in the left hemisphere, thereby revealing potential compensation mechanisms across brain areas, in addition, the same study found positive correlation between the extent of compensated increase of activation in the left Heschl's gyrus and faster reaction times (Andoh and Zatorre 2013).

Another possible explanation for the lack of a left SMG tDCS effect in musicians relates to the way in which this population reacts to brain stimulation. A recent study revealed that bilateral tDCS over the primary motor cortex showed no effect on fine finger movements of pianists (Furuya et al. 2013), while bihemispheric tDCS over the motor cortex in nonmusicians led to a facilitation of such movements (Vines et al. 2008). The results of the musicians were explained to be traced back either simply to a ceiling effect as pianists have developed extremely exact finger movements during their many years of training and deliberate practice or to the neuroplasticity of a musician's brain, which has already optimized its function to highly complex musical demands and is therefore less sensitive to stimulation effects (Furuya et al. 2013).

In the musician group of the present study, suppression of the right SMG with cathodal tDCS resulted in a deterioration of pitch memory recognition performance and leads to the assumption that musicians evoke a more right lateralized network for pitch memory. It has been shown that musicians dispose a more equalized neuroanatomy and function in both hemispheres (Patston et al. 2007; Bermudez et al. 2009). Furthermore, Gaab and Schlaug (2003) reported higher activation of the right SMG in musicians compared with nonmusicians when behavioral performance was matched. The pitch memory span task of the present study measures the capacity of pitch memory information that can be held in the memory system and adapts to individual performance level. Therefore, it ensures that every nonmusician and musician is pushed to their limit of memory ability. The results of the pitch span task indicate that the right SMG is involved particularly in higher task demands in musicians, while in nonmusicians the left SMG may be more strongly involved in such tasks. In this context, Foster and Zatorre (2010) conducted an fMRI study on melody transposition with musicians and nonmusicians and revealed a key role of the intraparietal sulcus (IPS) for melody transposition (also see Foster et al. 2013) and showed that the activation of the right IPS could predict task performance in both groups. As the IPS is located adjacent to the SMG, this correlational finding is very interesting, especially, as melody transposition also requires pitch memory and relies on maintaining relative pitch information.

Another possible explanation for the involvement of the right SMG in the pitch memory recognition task of this group could be that the musicians usually use their visual-motor representation to memorize pitch sequences: the right SMG has been shown to be activated during sight reading in musicians (Sergent et al. 1992). When interrupting this additional memory resource by suppressing the activity of the right SMG by cathodal tDCS, the musicians' performance deteriorates to the level of the nonmusicians ability as shown in the present results.

As well as specific differences, general task demands differences between recall and recognition tasks must also be considered. Schulze, Mueller et al. (2011) showed that different neural activation patterns emerged in musicians during a pitch memory recognition task depending on whether unstructured (atonal) or structured (tonal) material was used. Similar differentiations have also been shown for a spatial task (Bor et al. 2003) and when using audio-visual material (Bor et al. 2004). Both these studies indicate that strategy is an important factor in memory tasks which could also be responsible for the lack of effect on the present recall task (which uses a tonal and structured approach) after cathodal stimulation of the right SMG in musicians. It is likely that musicians were able to chunk the pitch information in the recall task (Schulze, Mueller et al. 2011) and that this strategy relies on other neural systems, which are less sensitive to stimulation effects.

No effect of stimulation was found on the pitch recall task in musicians. One factor that may contribute to this finding is that musicians performed at ceiling (91% accuracy). However, another consideration is that different memory tasks, and task demands may recruit different neural networks. For example, a tDCS study by Berryhill et al. (2010) showed impaired working memory performance on a recognition but not a recall task, after cathodal stimulation over the right inferior parietal cortex, therefore indicating that different processes and underlying neural circuits were involved. Moreover, in the present nonmusicians group, the diminished performance in the pitch recall task after cathodal tDCS over the left SMG was only significant for longer sequences with higher memory demands.

All the above evidence leads to the conclusion that the SMG in general is involved in more demanding pitch memory processes and—particularly—in the storage of pitch information (Sakurai et al. 1998; Rinne et al. 2009). This is also in accordance with a study by Wehrum et al. (2011) who reported the activation of the SMG in a pitch discrimination task in children only in harder trials with subtle pitch changes and not during easier trials with robust changes. Furthermore, a review of behavioral performances in fMRI studies, reveals that those which reported activation in the SMG also found lower performances on the pitch memory task (Gaab et al. 2003; Rinne et al. 2009; Schulze, Zysset et al. 2011) compared with studies which do not show an activation of the SMG and high task performances of 90% (Zatorre et al. 1994; Jerde et al. 2011).

Regarding the CFMT+ (Russell et al. 2009), the results show, as expected, no effect of cathodal stimulation (Schaal et al. 2013), neither over the left nor right SMG, indicating that the causal involvement of the left and right SMG, respectively, is specific to pitch memory in the present study. Even though the visual control task is not perfectly matched in terms of task procedure and demands, the lack of modulation effect across conditions, the trial-by-trial working memory paradigm in Part 1 and the more long-term memory approach in Part 2, strongly supports the specific involvement of the SMG in pitch memory. Furthermore, the performance on the visual control task did not differ between musicians and nonmusicians, confirming that musicians do not show overall superior memory abilities (Tierney et al. 2008).

Finally, the present data show that the musicians outperformed the nonmusicians on both pitch memory tasks indicating that, as experts in the auditory domain, they have developed and dispose a pronounced memory system that allows them to memorize more musical material (Williamson et al. 2010; Schulze et al. 2011). However, the analysis of the recall task also shows that musicians as well as nonmusicians show a linear decline of pitch memory performance, as sequence length increases, showing that memory capacity is limited (Baddeley 1986). It can be proposed that the decline in performance in nonmusicians after cathodal tDCS over the left SMG that was only significant in longer sequences with higher memory load might also be found in the musicians group (probably with right hemispheric specialization) if sequences were longer (up to 10 tones per sequence). This hypothesis needs to be investigated in future research. In this context, it is also important to note that the study uses a cross-section approach by comparing musicians and nonmusicians, and therefore we cannot rule out preexisting structural and functional differences. In order to shed further light on this issue a study including participants with a broader range of musical experience and a correlation analysis with years of training would be desirable.

In summary, the present study provides evidence for the different and distinctive causal involvement of the SMG in nonmusicians and musicians in the pitch memory process. A significant downward modulation of pitch memory performance (recognition and recall) after cathodal tDCS over the left SMG was only found in nonmusicians. In the musicians group, a selective effect was found on the pitch recognition task but only after stimulation of the right SMG. These combined results suggest a hemispheric specialization of the SMG for pitch memory depending on musical expertise and training.

Notes

Kathrin Lange is now at the Federal Institute for Drugs and Medical Devices, Bonn, Germany. *Conflict of Interest*: None declared.

Funding

This work was supported by grants from the Heinrich-Heine-University (9772440, 9772467 to V.K. and B.P., 9772558 to B.P.), the Deutsche Forschungsgemeinschaft (PO806-3 to B.P.), the Economic and Social Research Council (ES/K00882X/1 to M.J.B.) and the British Academy (PF100123 to M.J.B.)

References

Andoh J, Zatorre RJ. 2013. Mapping interhemispheric connectivity using functional MRI after transcranial magnetic stimulation on the human auditory cortex. Neuroimage. 79:162–171.

Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann K-P, Paulus W. 2004. Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci. 16:521–527.

Baddeley AD. 1986. Working memory. Oxford, UK: Oxford University Press.

Barrett KC, Ashley R, Strait DL, Kraus N. 2013. Art and science: how musical training shapes the brain. Front Psych. 4:713.

Bermudez P, Lerch JP, Evans AC, Zatorre RJ. 2009. Neuroanatomical correlates of musicianship as revealed by cortical thickness and voxel-based morphometry. Cereb Cortex. 19:1583–1596.

Berryhill ME, Wencil EB, Coslett HB, Olson IR. 2010. A selective working memory impairment after transcranial direct current stimulation to the right parietal lobe. Neurosci Lett. 479:312–316.

Bor D, Cumming N, Scott CE, Owen AM. 2004. Prefrontal cortical involvement in verbal encoding strategies. Eur J Neurosci. 19:3365–3370.

Bor D, Duncan J, Wiseman RJ, Owen AM. 2003. Encoding strategies dissociate prefrontal activity from working memory demand. Neuron. 37:361–367.

Cabeza R, Locantore JK, Anderson ND. 2003. Lateralization of prefrontal activity during episodic memory retrieval: evidence for the production-monitoring hypothesis. J Cogn Neurosci. 15:249–259.

Cohen Kadosh R, Soskic S, Iuculano T, Kanai R, Walsh V. 2010. Modulating neuronal activity produces specific and long-lasting changes in numerical competence. Curr Biol. 20:2016–2020.

Ellis RJ, Bruijn B, Norton AC, Winner E, Schlaug G. 2013. Training-mediated leftward asymmetries during music processing: a cross-sectional and longitudinal fMRI analysis. Neuroimage. 75:97–107.

Ericsson KA, Krampe RT, Clemens T. 1993. The role of deliberate practise in the acquisition of expert performance. Psychol Rev. 100:363–406.

Foster NEV, Halpern AR, Zatorre RJ. 2013. Common parietal activation in musical mental transformations across pitch and time. Neuroimage. 75:27–35.

Foster NEV, Zatorre RJ. 2010. A role for the intraparietal sulcus in transforming musical pitch information. Cereb Cortex. 20:1350–1359.

Furuya S, Nitsche MA, Paulus W, Altenmüller E. 2013. Early optimization in finger dexterity of skilled pianists: implication of transcranial stimulation. BMC Neurosci. 14:35.

Gaab N, Gaser C, Schlaug G. 2006. Improvement-related functional plasticity following pitch training. Neuroimage. 31:255–263.

Gaab N, Gaser C, Zaehle T, Jäncke L, Schlaug G. 2003. Functional anatomy of pitch memory—an fMRI study with sparse temporal sampling. Neuroimage. 19:1417–1426.

Gaab N, Schlaug G. 2003. The effect of musicianship on pitch memory in performance matched groups. Neuroreport. 14:2291–2295.

Gandiga PC, Hummel FC, Cohen LG. 2006. Transcranial DC stimulation (OCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 117:845–850.

Gaser C, Schlaug G. 2003. Brain structures differ between musicians and non-musicians. J Neurosci. 23:9240–9245.

Habibi A, Wirantana V, Starr A. 2013. Cortical activity during perception of musical pitch: comparing musicians and non-musicians. Music Percept. 30:463–479.

Herdener M, Humbel T, Esposito F, Habermeyer B, Cattapan-Ludewig K, Seifritz E. 2012. Jazz drummers recruit language-specific areas for the processing of rhythmic structure. Cereb Cortex. doi: 10.1093/cercor/bhs367.

Herholz SC, Zatorre RJ. 2012. Musical training as a framework for brain plasticity: behavior, function, and structure. Neuron. 76:486–502.

Holm S. 1979. A simple sequentially rejective multiple test procedure. Scand J Stat. 6:65–70.

Hyde KL, Lerch J, Norton A, Forgeard M, Winner E, Evans AC, Schlaug G. 2009. Musical training shapes structural brain development. J Neurosci. 29:3019–3025.

Jäncke L, Schlaug G, Steinmetz H. 1997. Hand skill asymmetry in professional musicians. Brain Cogn. 34:424–432.

Jerde TA, Childs SK, Handy ST, Nagode JC, Pardo JV. 2011. Dissociable systems of working memory for rhythm and melody. Neuroimage. 57:1572–1579.

Koelsch S, Schulze K, Sammler D, Fritz T, Müller K, Gruber O. 2009. Functional architecture of verbal and tonal working memory: an fMRI study. Hum Brain Map. 30:859–873.

Ladeira A, Fregni F, Campanha C, Valasek CA, De Ridder D, Bruoni AR, Boggio PS. 2011. Polarity-dependent transcranial direct current stimulation effects on central auditory processing. PLoS ONE. 6: e25399.

Merette DL, Peretz I, Wilson SJ. 2013. Moderating variables of music training-induced neuroplasticity: a review and discussion. Front Psychol. 4:606.

Mottaghy FM, Döring T, Müller-Gärtner HW, Töpper R, Krause BJ. 2002. Bilateral parieto-frontal network for verbal working memory: an interference approach using repetitive transcranial magnetic stimulation. Eur J Neurosci. 16:1627–1632.

Müllensiefen D, Gingras B, Musil J, Stewart L. 2014. The musicality of non-musicians: an index for assessing musical sophistication in the general population. PLoS ONE. 9:e89642.

Münte TF, Altenmüller E, Jäncke L. 2002. The musician's brain as a model of neuroplasticity. Nat Rev Neurosci. 3:473–478.

Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W. 2007. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol. 97:3109–3117.

Nitsche MA, Paulus W. 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 527:633–639.

Nitsche MA, Paulus W. 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 57:1899–1901.

Patston L, Kirk IJ, Rolfe MHS, Corballis MC, Tippett LJ. 2007. The unusual symmetry of musicians: Musicians have equilateral interhemispheric transfer for visual information. Neuropsychologia. 45:2059–2065.

Rinne T, Koistinen S, Salonen O, Alho K. 2009. Task-dependent activations of human auditory cortex during pitch discrimination and pitch memory tasks. J Neurosci. 29:13338–13343.

Rogalewski A, Breitenstein C, Nitsche MA, Paulus W, Knecht S. 2004. Transcranial direct current stimulation disrupts tactile perception. Eur J Neurosci. 20:313–316.

Russell R, Duchaine B, Nakayama K. 2009. Super-recognizers: people with extraordinary face recognition ability. Psychon B Rev. 16:252–257.

Sakurai Y, Takeushi S, Kojima E, Yazawa I, Murayama S, Kaga K, Momose T, Nakase H, Sakuta M, Kanazawa I. 1998. Mechanism of short-term memory and repetition in conduction aphasia and related cognitive disorders: a neuropsychological, audiological and neuroimaging study. J Neurol Neurosci. 154:182–193.

Schaal NK, Williamson VJ, Banissy MJ. 2013. Anodal transcranial direct current stimulation over the supramarginal gyrus facilitates pitch memory. Eur J Neurosci. 38:3513–3518.

Schlaug G, Jäncke L, Huang Y, Staiger JF, Steinmetz H. 1995. Increased corpus collosum size in musicians. Neuropsychologia. 33: 1047–1055.

Schneider P, Scherg M, Dosch HG, Specht HJ, Gutschalk A, Rupp A. 2002. Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. Nat Neurosci. 5:688–694.

Schulze K, Mueller K, Koelsch S. 2011. The use of a strategy in musicians leads to the activation of a more right-lateralised network. Eur J Neurosci. 33:189–196.

Schulze K, Zysset S, Mueller K, Friederici AD, Koelsch S. 2011. Neuroarchitecture of verbal and tonal working memory in nonmusicians and musicians. Hum Brain Map. 32:771–783.

Sergent J, Zuck E, Terriah S, MacDonald B. 1992. Distributed neural network underlying musical sight-reading and keyboard performance. Science. 3:106–109.

Seung Y, Kyong J-S, Woo S-H, Lee B-T, Lee K-M. 2005. Brain activation during music listening in individuals with or without prior music training. Neurosci Res. 52:323–329.

Tierney AT, Bergeson TR, Pisoni DB. 2008. Effects of early musical experience on auditory sequence memory. Empir Musicol Rev. 3:178–186.

Vines BW, Cerruti C, Schlaug G. 2008. Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC Neurosci. 9:103.

Vines BW, Schnider NM, Schlaug G. 2006. Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. Neuroreport. 17:1047–1050.

Wan CY, Schlaug G. 2010. Music making as a tool for promoting brain plasticity across the life span. Neuroscientist. 16:566–577.

Wehrum S, Degé F, Ott U, Walter B, Stippekohl B, Kagerer S, Schwarzer G, Vaitl D, Stark R. 2011. Can you hear a difference? Neuronal correlates of melodic deviance processing in children. Brain Res. 1402:80–92.

Williamson VJ, Baddeley AD, Hitch GJ. 2010. Musicians' and nonmusicians' short term memory for verbal and musical sequences: comparing phonological similarity and pitch proximity. Mem Cogn. 38:163–175.

Williamson VJ, Stewart L. 2010. Memory for pitch in congenital amusia: beyond a fine-grained pitch discrimination problem. Memory. 18:657–669.

Zatorre RJ, Evans AC, Meyer E. 1994. Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci. 14:1908–1919.

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

A causal involvement of the left supramarginal gyrus during the retention of musical pitches

Nora K. Schaal [a,b,*], Victoria J. Williamson [c,d], Maria Kelly [b], Neil G. Muggleton [b,e,f], Bettina Pollok [g], Vanessa Krause [g] and Michael J. Banissy [b,f]

[a] Department of Experimental Psychology, Heinrich-Heine-University, 40225 Düsseldorf, Germany
[b] Department of Psychology, Goldsmiths, University of London, SE14 6NW, London, UK
[c] Lucerne University of Applied Sciences and Arts, 6003 Lucerne, Switzerland
[d] Department of Music, University of Sheffield, S3 7RA, Sheffield, UK
[e] Brain and Behavior Laboratory, Institute of Cognitive Neuroscience, National Central University, Jhongli 320, Taiwan
[f] Institute of Cognitive Neuroscience, University College London, London, UK
[g] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

ARTICLE INFO

Article history:
Received 17 October 2014
Reviewed 17 November 2014
Revised 20 November 2014
Accepted 20 November 2014
Action editor Chris Chambers
Published online 15 December 2014

Keywords:
Pitch memory
Transcranial magnetic stimulation
Retention
Left supramarginal gyrus

ABSTRACT

Brain stimulation studies have previously demonstrated a causal link between general pitch memory processes and activity within the left supramarginal gyrus (SMG). Building on this evidence, the present study tested the impact of left SMG stimulation on two distinct pitch memory phases, retention and encoding. Repetitive transcranial magnetic stimulation (rTMS) was employed during the retention stage (Experiment 1) and the encoding phase (Experiment 2) of a pitch recognition task. Stimulation was applied on a trial-by-trial basis over the left SMG (target site) or the vertex (control site). A block without TMS was also completed. In Experiment 1, rTMS over the left SMG during pitch retention led to significantly increased reaction times compared to control conditions. In Experiment 2 no rTMS modulation effects were found during encoding. Experiment 3 was conducted as a control for non-specific stimulation effects; no effects were found when rTMS was applied over the left SMG at the two different time points during a perceptual task. Taken together, these findings highlight a phase-specific involvement of the left SMG in the retention phase of pitch memory, thereby indicating that the left SMG is involved in the maintenance of pitch information.

* *Corresponding author*. Heinrich-Heine-University Düsseldorf, Department of Experimental Psychology, Universitätsstraße 1, 40225 Düsseldorf, Germany.
E-mail address: nora.schaal@uni-duesseldorf.de (N.K. Schaal).
http://dx.doi.org/10.1016/j.cortex.2014.11.011

1. Introduction

Functional brain imaging studies of pitch memory have revealed the involvement of a complex neural system in parietal, temporal and frontal areas (e.g., Koelsch et al., 2009). One area that is consistently highlighted across studies is the left supramarginal gyrus (SMG) (Ellis, Bruijn, Norton, Winner, & Schlaug, 2013; Gaab, Gaser, Zaehle, Jäncke, & Schlaug, 2003). Recently, studies using transcranial direct current stimulation (tDCS) have implied that the left SMG is causally involved in pitch memory processes (Schaal, Williamson, & Banissy, 2013; Vines, Schnider, & Schlaug, 2006). Suppressing left SMG function using cathodal tDCS leads to a deterioration in pitch recognition ability (Vines et al., 2006), while increasing left SMG excitability with anodal tDCS results in a facilitation of pitch memory (Schaal et al., 2013). In combination, these studies provide evidence that left SMG activity is important for the output of pitch memory, but the exact role of the left SMG in the pitch memory process remains unknown.

Another issue with previous work is that tDCS provides a relatively large window in which cortical excitability within a brain region can be modulated. In this regard, it is not clear whether the left SMG plays a causal role throughout the pitch memory process or in specific phases. Two major time-specific phases of pitch memory are of interest to the present study: encoding and retention. In the encoding phase, new pitch information is perceived and the tones are encoded in relative relationships with each other, whereas in the retention interval this same information is maintained and rehearsed. Schulze, Müller, and Koelsch (2011) showed that encoding and retention in auditory memory rely on dissociable brain activations.

Transcranial magnetic stimulation (TMS) is a method better suited for investigating a phase-specific involvement of the left SMG in pitch memory. This method enables a spatially and temporally precise modulation of neural mechanisms on a trial-by-trial basis (Walsh & Cowey, 2000). For example, 5 Hz repetitive TMS (rTMS) over the precuneus has been shown to interfere with a visual working memory task differently when applied in the retention interval or during the re-presentation of the recognition probe (Luber et al., 2007). This finding demonstrates the effective use of TMS for interfering with the time-specific stages of a memory process.

Here, we used rTMS to examine the causal role of the left SMG at different time-specific phases of the pitch memory process (retention and encoding), by adopting a similar phase-specific stimulation design to Luber et al. (2007). In Experiment 1, we examined the role of the left SMG in the retention phase of pitch memory. In Experiment 2, we focused on the encoding phase. In both experiments, participants completed a pitch memory recognition task, where they heard two six-tone long pitch sequences and judged whether they were the same or different (a protocol adapted from Williamson & Stewart, 2010). Participants completed this task under three stimulation condition: rTMS over the left SMG; rTMS over the vertex (active control site); No TMS. The onset of stimulation was varied between each experiment with rTMS being applied either during the retention phase (after hearing the first sequence) or during the encoding phase (while hearing the first sequence). Finally, a control experiment was conducted to test for non-specific disruption effects of rTMS. In Experiment 3, participants completed a perceptual task while rTMS was applied over the left SMG at the two time points used in Experiments 1 and 2.

2. Experiment 1 and 2

2.1. *Experiment 1 and 2 methods*

2.1.1. *Participants*

27 participants took part with a mean age of 27.22 years (SD ± 6.51, range 18–38 years). 13 (seven female) subjects participated in Experiment 1, and 14 (eight female) in Experiment 2. Participants were all non-musicians (less than two years of musical training in the past, not playing an instrument at present) and right-handed (see Table 1 for demographical details). The study was approved by the ethics committee of Goldsmiths, University of London and participants gave informed written consent.

To evaluate musical training, the Musical Training Dimension from the Goldsmiths Musical Sophistication Index (Gold-MSI, Müllensiefen, Gingras, Musil, & Stewart, 2014) was used. This Gold-MSI dimension is comprised of 7 items that assess an individual's musical training and practice habits. The participant is asked to rank the items on a seven-point agreement scale, giving a possible score range of between 7 and 49 points. The mean score from our sample was 10.9 points, confirming that they had little or no musical training in the past.

2.1.2. *Materials*

A pitch memory recognition task was created, modeled on the pitch memory span task (Williamson & Stewart, 2010) that was used in one of our previous brain stimulation studies (Schaal et al., 2013). The task parameters were adjusted to match the TMS parameters.

80 pairs of six tone long pitch sequences were created. In 40 trials the two sequences were the same (same tones in identical order) and 40 were different (same tones in both sequences but in the latter sequence two tones were in reversed order). All sequences were created from a pool of 10 triangle-waveform tones (equally tempered, whole tone steps) with fundamental pitches ranging from 262 Hz (C4) to 741 Hz (F#5). Tones were 350 msec long, with a 150 msec pause at the end of each tone, so in total each sequence was 3 sec long.

In order to create the pitch sequences, the tones were randomly sampled with the restriction that beginning and end tones were counterbalanced. There were no direct repetitions of a tone and adjacent tones were at least two whole tones

Table 1 – Demographical details of participants for Experiments 1, 2 and 3.

	N	Age	Gold-MSI-Score	Musical training
Experiment 1	13 (7f/6m)	26.2 years	12.2	0.77 years
Experiment 2	14 (8f/6m)	28.2 years	9.5	0.32 years
Experiment 3	12 (7f/5m)	23.9 years	10.5	0.58 years

apart. In the different trials, we counterbalanced for the position of the two reversed tones as well as the size of their tone interval.

Each trial consisted of two sequences (either same or different) with an inter-sequence interval of 3 sec. The sequence length of six tones was chosen as previous studies have shown that non-musicians have a mean capacity score of six tones on the related pitch memory span task (Schaal et al., 2013; Williamson & Stewart, 2010). A pilot study with 12 participants confirmed that sequences were at the desired level of difficulty (Mean: 74.5% correct).

As three blocks were required for the TMS procedure, three blocks of 24 trials (12 same, 12 different) were created, leaving 8 trials for a practice block. The three blocks were matched for difficulty based on the results of the first pilot test. A second pilot test was then conducted, with 10 novel participants who completed the blocks in counterbalanced order and confirmed that all three blocks were of equal difficulty (mean scores: 71.3%, 74.5%, 70.0%).

2.1.3. *TMS protocol*

TMS was applied by a figure of eight shaped coil (70 mm diameter) using a Magstim Super Rapid Stimulator (Magstim Co., UK). The Stimulator was set to 60% intensity of the maximum stimulator output as per previous studies (e.g., Pitcher, Garrido, Walsh, & Duchaine, 2008; Tseng et al., 2010). rTMS was applied for every trial and a rTMS train lasted 3 sec at 5 Hz (15 pulses). The coil was placed either over the targeted area, the left SMG or the vertex. The vertex was included as a control site in order to control non-specific effects such as tactile and auditory sensations. The left SMG was located using CP3 of the 10–20 system for electrode placement, which has been shown to be a reliable method to identify this brain region (Mottaghy, Döring, Müller-Gärtner, Töpper, & Krause, 2002; Schaal et al., in press). The vertex was identified as the middle of the head, by measuring the point equidistant between the inion and nasion as well as the left and right intertragal notches.

The coil was placed above the stimulation site (left SMG or vertex) throughout the trials and the correct localization was checked constantly between trials. On every trial (24 trials per block; two blocks with active stimulation) 3 sec long rTMS was applied in the retention interval (starting as soon as the first sequence finished playing and ending with the onset of the second sequence; Experiment 1) or encoding interval (rTMS is triggered with the onset and duration of the first sequence; Experiment 2) of the trial.

2.1.4. *Procedure*

Experiments 1 and 2 used a within-subject design. The order of blocks (block 1, 2 and 3) as well as the order of stimulation (No TMS, rTMS over the left SMG and rTMS over the vertex) were counterbalanced.

To begin with the participants completed the practice phase of the pitch recognition task. In every trial two six-tone long sequences were played through speakers at a comfortable listening level and the participant indicated by button press whether the sequences were the same or different. They were instructed to use their index and middle finger of their right hand to press "1" for same and "2" for different. Participants heard a burst of pink noise after each trial to minimize carry over effects (Fig. 1 details the exact procedure). Instructions were given on screen and participants were asked to respond as accurately and quickly as possible. After completing the practice phase, the two stimulation sites, the left SMG and the vertex, were marked on the participant's scalp. Finally, before beginning the experiment, one test trial of 3 sec of 5 Hz rTMS was applied to each site of stimulation, in order to check that the participant was fine with the experience of rTMS. The participants all reported that the perceptual sensations for both stimulation sites were the same.

Participants were instructed to concentrate on the sequences they heard and to ignore the TMS pulses as far as possible. Instructions were given on screen, the coil was placed according to the stimulation condition and the first block began, containing 24 trials. After completing one block (with a short pause in the middle to exchange coils), a five minute break was taken before starting the next block. After participants completed all three blocks, they filled in the Gold-MSI questionnaire. In Experiment 1 rTMS was applied during

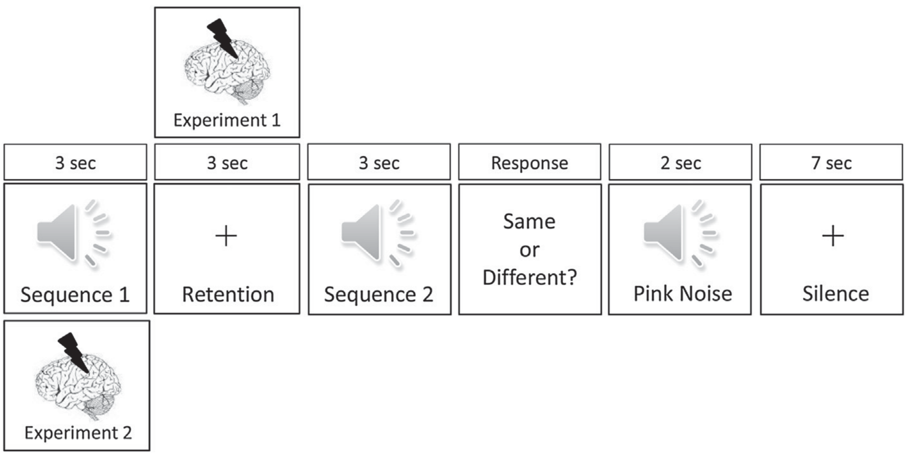


Fig. 1 – Timing of a single trial for Experiments 1 and 2. In Experiment 1, 5 Hz rTMS was applied during the retention period and in Experiment 2, rTMS was applied during encoding of the first sequence.

the retention phase of each trial and in Experiment 2 rTMS was applied during the encoding phase of the first pitch sequence.

2.2. Experiment 1 and 2 results

Median reaction times for correct trials were calculated, as well as percent correct and *d'* scores for the analysis of accuracy. The data from percent correct and the *d'* score analysis revealed the same pattern, so only the analysis from the more sensitive measure of *d'* scores are reported in the following results section.

For the statistical analysis, three outliers were excluded from the sample. One participant had reaction times more than four standard deviations above the group mean and two participants had accuracy scores below chance in at least one block, indicating that they did not meet the task demands.

2.2.1. Reaction time analyses

For Experiment 1, a repeated measure ANOVA was conducted with *stimulation condition* (rTMS over left SMG vs rTMS over vertex vs No TMS) as the within-subject factor and reaction times as the dependent variable. This analysis revealed a main effect of *stimulation condition* [$F_{(2,22)} = 6.50$, $p = .006$, $\eta_p^2 = .371$]. Contrasts revealed that the reaction times obtained during rTMS over the left SMG were significantly slower than reaction times when rTMS was over the vertex [$F_{(1,11)} = 21.66$, $p = .001$, $\eta_p^2 = .663$] and also significantly slower than No TMS performance [$F_{(1,11)} = 5.10$, $p = .045$, $\eta_p^2 = .317$]. In sum, the results indicated that stimulation over the left SMG during the retention phase significantly disrupted the reaction times for pitch memory (Fig. 2).

For Experiment 2, the same repeated measure ANOVA was conducted. Unlike Experiment 1, there was no main effect of *stimulation condition* for reaction times [$F_{(2,22)} = 1.33$, $p = .285$, $\eta_p^2 = .108$]. When applying rTMS during encoding of the pitch sequence in the memory process, no differences were found (Fig. 2).

Finally, a post-hoc analysis across the two experiments was conducted. A mixed ANOVA on reaction times with *stimulation condition* as the within-subject factor and *experiment* (Experiment 1 vs Experiment 2) as the between-subject factor, revealed a significant *stimulation condition*experiment* interaction [$F_{(2,44)} = 6.83$, $p = .003$, $\eta_p^2 = .237$], confirming the differential involvement of the left SMG during the retention and encoding phases of pitch memory.

2.2.2. Accuracy analyses

For Experiments 1 and 2, two seperate repeated measure ANOVAs were conducted with *stimulation condition* (3) as the within-subject factor and accuracy measured by *d'*. No significant differences were found in Experiment 1 [$F_{(2,22)} = .68$, $p = .519$, $\eta_p^2 = .058$] or Experiment 2 [$F_{(2,22)} = .19$, $p = .832$, $\eta_p^2 = .017$] (Fig. 2).

3. Experiment 3

The findings from Experiment 1 and 2 suggest a phase-specific disruption by modulation of the left SMG during the retention but not encoding phase of pitch memory. However, it remained possible that this effect may be due to a non-specific modulation of motor performance. The left SMG has been reported to be involved in the process of motor attention (Rushworth, Ellison, & Walsh, 2001) and, given the spatial distance between the left SMG and the motor cortex, one might posit that the results of Experiment 1 could result from an interference with motor responses. To address this possibility, we conducted a control experiment in which rTMS was applied either late (reflecting the timing of the stimulation during retention) or early (timing of the encoding interference) while participants completed a perceptual task ("is the last tone higher or lower than the second to last tone?") in which memory demands were minimal.

3.1. Experiment 3 methods

3.1.1. Participants

Twelve participants (seven female) with a mean age of 23.92 years (SD ± 2.19, range 20–27 years) took part in Experiment 3. They were all non-musicians (less than two years of musical training in the past, not playing an instrument at present) with a mean of 0.58 years of musical training and a mean Gold-MSI score of 10.5 (Table 1, see Section 2.1.1 for information about the Gold-MSI questionnaire). The ethics committee of the Medical Department of the Heinrich-Heine-University in Düsseldorf approved this study and participants gave informed written consent.

3.1.2. Materials

The same six-tone long sequences were used. Experiment 3 also consisted of three experimental blocks and a practice block. Only the second sequence of every sequence pair was used for the perceptual task in Experiment 3. The three blocks (24 trials each) all consisted of 12 trials where the last tone compared to the second to last tone was higher and 12 trials where it was lower.

3.1.3. TMS protocol

The TMS parameters were the same as those reported in Experiment 1 and 2. The timeline for the TMS application was identical even though in Experiment 3 no first sequence was played. The 3 sec long rTMS trains were either applied 3 sec before the tone sequence (*late* condition) or 6 sec before the tone sequence (*early* condition). A block without rTMS was also included. Stimulation was applied over the left SMG.

3.1.4. Procedure

Participants completed three blocks of the perceptual task as part of the within subject design. The order of blocks (block 1, 2 and 3) as well as the order of stimulation (no TMS, *late* rTMS over the left SMG and *early* rTMS over the left SMG) were counterbalanced.

Before the experiment, participants completed a practice block of the perception task. After a 6 sec long pause (in which rTMS was applied at two different time points in the experimental blocks) a six-tone-long sequence was played and participants were asked to judge whether the last tone was higher or lower than the second to last tone. As in the first two experiments, participants were asked to give their response as

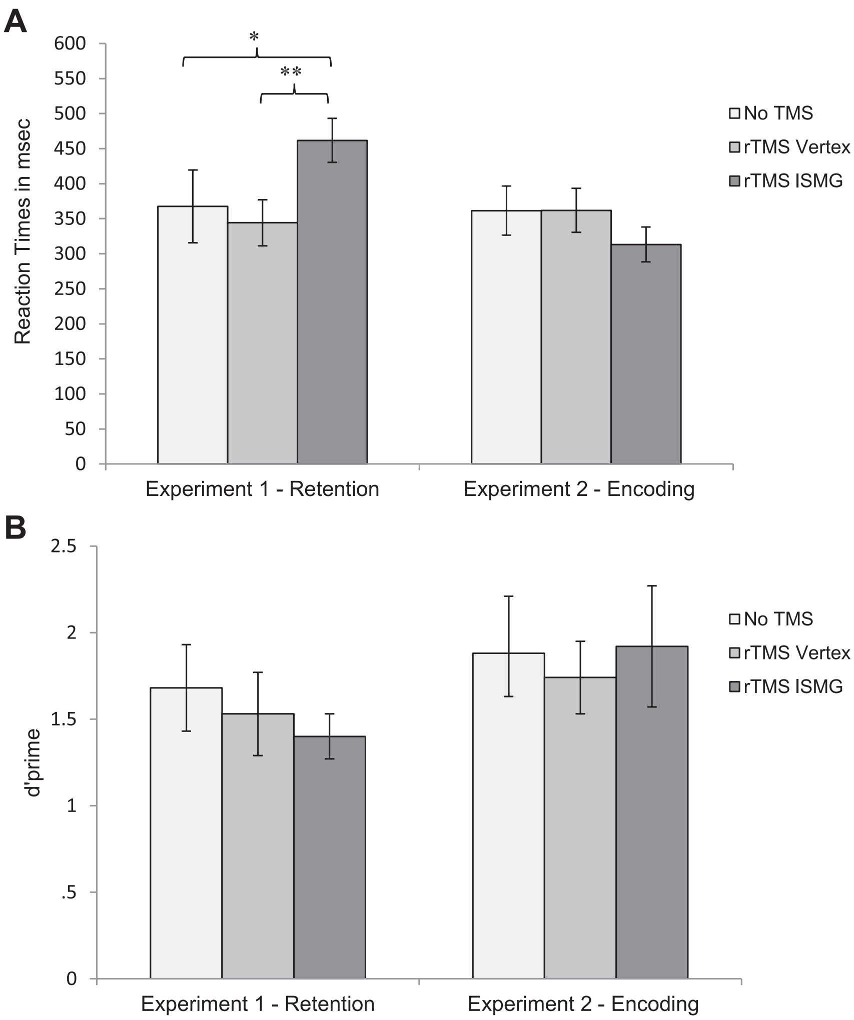


Fig. 2 – A Bargraphs representing the median reaction time scores for all three blocks for Experiment 1 (left) and Experiment 2 (right). rTMS over the left SMG during the retention period (Experiment 1) led to a significant increase in reaction times. No modulating effects could be found when applying rTMS during encoding (Experiment 2). The error bars represent SEM **$p = .002$, *$p = .046$ B Bargraphs representing the accuracy scores (d′) for all three blocks for Experiment 1 (left) and Experiment 2 (right). No significant effects of stimulation condition were found. The error bars represent SEM.

accurately and quickly as possible using their index and middle finger of their right hand and the keys "1" for "lower" and "2" for "higher. Participants heard a burst of pink noise between every trial to minimize carry-over effects.

After the practice block, the location corresponding to the left SMG was marked on the participants scalp and a test train of TMS was applied over the left SMG in order to make participants familiar with the sensation of the stimulation before starting the actual task and to ensure that they were fine with the perceptual sensation of TMS (as per Experiment 1 and 2).

Participants then completed the three experimental blocks. The procedure was the same as that reported in Experiment 1 and 2, except that the task was perceptual in nature and not a memory task. Stimulation was applied according to the stimulation condition either *late* (3 sec before the tone sequence) or *early* (6 sec before the tone sequence) over the left SMG. After completing all three blocks, participants filled in the German version of the Gold-MSI questionnaire (Schaal, Bauer, & Müllensiefen, 2014).

3.2. *Experiment 3 results*

3.2.1. *Reaction time analysis*

The group mean reaction times for the block without stimulation were 440.54 msec (SD ± 186.09), for the early rTMS condition 448.67 msec (SD ± 191.91) and for the late rTMS condition 423.08 msec (SD ± 207.65).

A repeated measure ANOVA with *stimulation condition* (late rTMS vs early rTMS vs No TMS) as the within subject factor and median reaction times as the dependent factor revealed no main effect of *stimulation condition* [$F_{(2,22)} = .363$, $p = .699$, $\eta_p^2 = .032$]. rTMS over the left SMG at the late (reflecting the time point of the retention interval) or early (reflecting the encoding phase) time point did not affect reaction times during the perception task compared to No TMS.

3.2.2. *Accuracy analysis*

The mean d' scores, reflecting the accuracy performance, for the block without TMS were 1.60 (SD ± 0.71), for the early rTMS condition 1.55 (SD ± 0.75) and the late rTMS condition 1.30 (SD ± 0.52).

A repeated measures ANOVA with *stimulation condition* (3) as the within factor and d' scores was conducted and also showed no main effect of *stimulation condition* [$F_{(2,22)} = 1.67$, $p = .21$, $\eta_p^2 = .132$]. The analysis showed no effects of stimulation condition on accuracy performance.

4. Discussion

This study sought to investigate the causal role of the left SMG across different time-specific stages of pitch memory processing. Using a non-invasive brain stimulation method (rTMS), we disrupted the pitch memory process during the retention (Experiment 1) and encoding (Experiment 2) phases of a recognition pitch memory paradigm. In both cases, stimulation over the left SMG was compared to performance without stimulation as well as stimulation over the vertex (control site). The results showed that only rTMS over the left SMG during retention resulted in a significant increase in reaction times, therefore supporting the theory that the left SMG is causally involved in the ongoing maintenance of pitch information in memory. A third experiment confirmed that rTMS over the left SMG at the two stimulation time points of Experiment 1 and 2 (late and early) did not have an effect on motor responses to a perceptual task; thus our findings from Experiment 1 cannot be explained by a non-specific modulation of the motor cortex or motor attention. Taken together, our three experiments support the critical involvement of the left SMG during retention of pitch information in memory.

The increase in reaction times when rTMS was applied over the left SMG in the retention phase supports previous tDCS evidence showing that pitch memory can be modulated following anodal or cathodal stimulation over the left SMG (Schaal et al., 2013; Vines et al., 2006). Our findings extend this prior work by showing that modulating neural activity in the left SMG leads to a phase-specific shift in the retention, but not the encoding phase of the pitch memory processes. Several previous studies have postulated that the left SMG is involved in pitch memory retention (Gaab et al., 2003; Sakurai et al., 1998; Vines et al., 2006), but we provide the first casual evidence for the specific role of the left SMG in the ongoing maintenance of pitch traces as opposed to earlier encoding processes.

The present study is a step forward in investigating neural distinctions of the auditory memory system for the different stages of memory processing (encoding, retention), a largely unexplored field. Previous non-invasive brain stimulation studies using tDCS have revealed causal relationships between targeted areas and pitch memory (Schaal et al., 2013; Vines et al., 2006) and pitch discrimination (Mathys, Loui, Zheng, & Schalug, 2010), but few have used non-invasive brain stimulation to probe how different stages of processing may be influenced by cortical modulation. One rare TMS study on melodic pitch perception investigated the effect of off-line TMS (stimulation before the task) on melody discrimination and found significant modulation effects of 10 Hz rTMS targeted over the right Heschl's Gyrus (Andoh & Zatorre, 2011), a region associated with melody perception (Zatorre & Belin, 2001). This finding, alongside the present study, corroborates the idea that TMS is an effective tool for investigating the causal involvement of brain areas in pitch processing.

The involvement of the left SMG for the retention phase in memory has also been shown by Romero, Walsh, and Papagno (2006), who investigated the causal involvement of left parietal areas (Brodmann's areas 44 and 40, the latter is comparable with the location of the left SMG) for verbal short-term memory. They showed that rTMS, applied during the retention phase over the targeted areas (compared to the vertex), affected phonological judgments. This finding is also in accordance with other studies that have reported SMG activation during tonal and verbal rehearsal (Schulze, Zysset, Mueller, Friederici, & Koelsch, 2012) using fMRI, and which have demonstrated involvement of the SMG in phonological processing and reading tasks using TMS (Celsis et al., 1999; Hartwigsen et al., 2010; Stoeckel, Gough, Watkins, & Devlin, 2009). In this context, one may suggest the left SMG plays a modality general role in auditory memory retention. It will be important for future studies to examine this directly.

There is some debate with regards to the lateralization of neural activity relating to pitch memory. Imm et al. (2008) applied single-pulse TMS at different time points (ranging between 250 msec and 800 msec after stimulus onset) over the dorsolateral prefrontal and inferior parietal regions. They found that during the pitch task reaction times increased when stimulation was applied over the *right* inferior parietal site for all time points and for the audio-verbal condition only single-pulse TMS at 450 msec over the left inferior parietal cortex increased reaction times (Imm et al., 2008). These results contribute to the understanding of how specialized neural mechanisms may be involved in different auditory domains. With reference to our study, it should be noted that the parietal site targeted by Imm et al. (2008) was more posterior to the SMG and also that the working memory task used by Imm et al. (2008) has different, more complex demands compared to the pitch memory tasks used in our study. The selective hemispheric involvement of the SMG in our results is more comparable to the pitch memory recognition tasks that have been shown to be left lateralized (Gaab et al., 2003; Vines et al., 2006). Furthermore, a tDCS study from our laboratory (Schaal et al., in press) revealed that only cathodal stimulation over the left SMG but not the right SMG led to a deterioration of pitch memory performance in non-musicians.

A broader caveat related to TMS studies relates to the choice of active control site, which in our study was the vertex (based on the common use of this region in visual and auditory domains; e.g., Romero et al., 2006; Pitcher et al., 2008; Andoh & Zatorre, 2013; Banissy et al., 2010). The choice of an active control site is frequently contentious and there is the possibility that the vertex may produce less superficial scalp effects relative to left SMG stimulation. However, if superficial effects of TMS caused the slower reaction times reported in Experiment 1 then we would expect a similar effect in Experiment 2. As this was not the case, it is unlikely that the results reported in Experiment 1 are due to non-specific general effects of TMS. Additionally, we acknowledge that using the 10–20 system for electrode placement is not the most precise method to localize the left SMG. This method is commonly used for targeting brain areas in brain stimulation studies (e.g., Gallace, Soravia, Cattaneo, Moseley, & Vallar, 2014; Imm et al., 2008; Schaal et al., in press) even though brain imaging guided targeting would be desirable in future studies to optimize the precession of TMS.

A further broader issue raised by our study relates to the constraints of the relatively modest sample sizes used in TMS experiments. We tested 12–14 participants in each experiment, which is commensurate with the majority of TMS experiments. Although consistent with other work, a sample of this size does limit the ability to detect small effects that may be of theoretical interest. In this regard, it is worth mentioning that our data hints at two interesting potential effects: firstly, in Experiment 1 the d' scores were the lowest when stimulation was applied over the left SMG and secondly, the reaction times in Experiment 2 were decreased when rTMS was applied over the left SMG during encoding. These potential effects, which were in line with our hypothesis, may have reached significance if sample size and subsequently power had been enlarged. The issue of modest sample sizes in TMS studies is an important area for wider consideration in the TMS community.

In conclusion the present study demonstrates a causal role for the left SMG in the retention phase of pitch memory. In doing so, the finding broadens our knowledge regarding the involvement of the left SMG in the pitch memory process: only rTMS during the retention phase of the pitch sequence recognition task, and not encoding, modulated performance. This result confirms that the left SMG is selectively involved in the ongoing maintenance of pitch information in memory and offers avenues for future investigations on this topic.

Acknowledgments

We would like to thank Sven Thönes for preparing the auditory material for the pitch task.

The work was supported by grants from the DAAD and G.A. Lienert Stiftung awarded to NKS. VJW was supported by a Vice Chancellor's Fellowship from the University of Sheffield. MJB was supported by grants from the British Academy [pf100123] and ESRC [ES/K00882X/1]. NGM was supported by the National Science Council, Taiwan.

[NSC-100-2410-H-008-074-MY3 and NSC-102-2410-H-008-021-MY3].

REFERENCES

Andoh, J., & Zatorre, R. J. (2011). Interhemispheric connectivity influences the degree of modulation of TMS-induced effects during auditory processing. *Frontiers in Psychology, 2*, 161.

Andoh, J., & Zatorre, R. J. (2013). Mapping interhemispheric connectivity using functional MRI after transcranial magnetic stimulation on the human auditory cortex. *NeuroImage, 79*, 162–171.

Banissy, M. J., Sauter, D. A., Ward, J., Warren, J. E., Walsh, V., & Scott, S. K. (2010). Suppressing sensorimotor activity modulates the discrimination of auditory emotions but not speaker identity. *The Journal of Neuroscience, 30*(41), 13552–13557.

Celsis, P., Boulanouar, K., Doyon, B., Ranjeva, J. P., Berry, I., Nespoulus, J. L., et al. (1999). Differential fMRI responses in left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change dectection in syllables and tones. *NeuroImage, 9*, 135–144.

Ellis, R. J., Bruijn, B., Norton, A. C., Winner, E., & Schlaug, G. (2013). Training-mediated leftward asymmetries during music processing: a cross-sectional and longitudinal fMRI analysis. *NeuroImage, 75*, 97–107.

Gaab, N., Gaser, C., Zaehle, T., Jäncke, L., & Schlaug, G. (2003). Functional anatomy of pitch memory- an fMRI study with sparse temporal sampling. *NeuroImage, 19*, 1417–1426.

Gallace, A., Soravia, G., Cattaneo, Z., Moseley, G. L., & Vallar, G. (2014). Temporary interference over the posterior parietal cortices disrupts thermoregulatory control in humans. *PLoS One, 9*, e88209.

Hartwigsen, G., Baumgaertner, A., Price, C. J., Koehnke, M., Ulmer, S., & Siebner, H. R. (2010). Phonological decisions require both the left and right supramarginal gyri. *Proceedings of the National Academy of Sciences, USA, 107*, 16494–16499.

Imm, J.-H., Kang, E., Youn, T., Park, H., Kim, J. I., Kang, J. I., et al. (2008). Different hemispheric specializations for pitch and audioverbal working memory. *NeuroReport, 19*, 99–103.

Koelsch, S., Schulze, K., Sammler, D., Fritz, T., Müller, K., & Gruber, O. (2009). Functional architecture of verbal and tonal working memory: an fMRI study. *Human Brain Mapping, 30*, 859–873.

Luber, B., Kinnunen, L. H., Rakitin, B. C., Eslsasser, L., Stern, Y., & Lisanby, S. H. (2007). Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: frequency- and time-dependent effects. *Brain Research, 1128*, 120–129.

Mathys, C., Loui, P., Zheng, X., & Schalug, G. (2010). Non-invasive brain stimuation applied to Heschl's gyrus modulates pitch discrimination. *Frontiers in Psychology, 1*, 193.

Mottaghy, F. M., Döring, T., Müller-Gärtner, H. W., Töpper, R., & Krause, B. J. (2002). Bilateral parieto-frontal network for verbal working memory: an interference approach using repetitive transcranial magnetic stimulation. *European Journal of Neuroscience, 16*, 1627–1632.

Müllensiefen, D., Gingras, B., Musil, J., & Stewart, L. (2014). The Musicality of non-musicians: an Index for assessing musical sophistication in the general Population. *PLoS One, 9*, e89642.

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *The Journal of Neuroscience, 28*, 8929–9893.

Romero, L., Walsh, V., & Papagno, C. (2006). The neural correlates of phonological short- term memory: a repetitive transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 18*, 1147–1155.

Rushworth, M. F. S., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience, 4*, 656–661.

Sakurai, Y., Takeushi, S., Kojima, E., Yazawa, I., Murayama, S., Kaga, K., et al. (1998). Mechanism of short-term memory and repetition in conduction aphasia and related cognitive disorders: a neuropsychological, audiological and neuroimaging study. *Journal of Neurological Neuroscience, 154*, 182–193.

Schaal, N. K., Bauer, A.-K. R., & Müllensiefen, D. (2014). Der Gold-MSI: Replikation und Validierung eines Fragbogeninstrumentes zur Messung Musikalischer Erfahrenheit anhand einer deutschen Stichprobe. *Musicae Scientiae, 18*(4), 423–447.

Schaal, N. K., Krause, V., Lange, K., Banissy, M. J., Williamson, V. J., & Pollok, B. (2015). Pitch memory in non-

musicians and musicians: revealing functional differences using transcranial direct current stimulation. *Cerebral Cortex*. http://dx.doi.org/10.1093/cercor/bhu075 (in press).
Schaal, N. K., Williamson, V. J., & Banissy, M. J. (2013). Anodal transcranial direct current stimulation over the supramarginal gyrus facilitates pitch memory. *European Journal of Neuroscience, 38*, 3513–3518.
Schulze, K., Müller, K., & Koelsch, S. (2011). Neural correlates of strategy use during auditory working memory in musicians and non-musicians. *European Journal of Neuroscience, 33*, 189–196.
Schulze, K., Zysset, S., Mueller, K., Friederici, A. D., & Koelsch, S. (2012). Neuroarchitecture of verbal and tonal working memory in nonmusicians and musicians. *Human Brain Mapping, 32*, 771–783.
Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex, 45*, 1091–1096.
Tseng, P., Hsu, T.-H., Muggleton, N. G., Tzeng, O. J. L., Hung, D. J., & Juan, C.-H. (2010). Posterior parietal cortex mediates encoding and maintenance processes in change blindness. *Neuropsychologia, 48*, 1063–1070.
Vines, B. W., Schnider, N. M., & Schlaug, G. (2006). Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. *Neuroreport, 17*, 1047–1050.
Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1*, 73–79.
Williamson, V. J., & Stewart, L. (2010). Memory for pitch in congenital amusia: beyond a fine-grained pitch discrimination problem. *Memory, 18*, 657–669.
Zatorre, R. J., & Belin, P. (2001). Spectral and temporal processing in human auditory cortex. *Cerebral Cortex, 11*, 946–953.

From amusic to musical? – Improving pitch memory in congenital amusia with transcranial alternating current stimulation

Nora K. Schaal[1], Jasmin Pfeifer[2,3], Vanessa Krause[4], Bettina Pollok[4]

1. Department of Experimental Psychology, Heinrich-Heine-University, Düsseldorf, Germany

2. Amsterdam Center for Language and Communication, University of Amsterdam, The Netherlands

3. Institute for Language and Information, Heinrich-Heine-University, Düsseldorf, Germany

4. Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

Running Title: Improving pitch memory in amusia

Corresponding Author:

Nora K. Schaal
Heinrich-Heine-University Düsseldorf
Department of Experimental Psychology
Universitätsstraße 1
40225 Düsseldorf
Telephone: +49 211 81 13863
Fax: +49 211 81 13490
Email: nora.schaal@uni-duesseldorf.de

Abstract

Brain imaging studies highlighted structural differences in congenital amusia, a life-long perceptual disorder that is associated with pitch perception and pitch memory deficits. A functional anomaly characterized by decreased low gamma oscillations (30-40 Hz range) in the right dorsolateral prefrontal cortex (DLPFC) during pitch memory has been revealed recently. Thus, the present study investigates whether applying transcranial alternating current stimulation (tACS) at 35 Hz to the right DLPFC would improve pitch memory. Nine amusics took part in two tACS sessions (either 35 Hz or 90 Hz) and completed a pitch and visual memory task before and during stimulation. 35 Hz stimulation facilitated pitch memory significantly. No modulation effects were found with 90 Hz stimulation or on the visual task. While amusics showed a selective impairment of pitch memory before stimulation, the performance during 35 Hz stimulation was not significantly different to healthy controls anymore. Taken together, the study shows that modulating the right DLPFC with 35 Hz tACS in congenital amusia selectively improves pitch memory performance supporting the hypothesis that decreased gamma oscillations within the DLPFC are causally involved in disturbed pitch memory and highlighting the potential use of tACS to interact with cognitive processes.

Keywords: congenital amusia, memory, pitch, right dorsolateral prefrontal cortex, transcranial alternating current stimulation

1. Introduction

Music is an important trait of human culture. In order to process and understand music, it is essential to be able to perceive and memorize musical material such as musical pitches. Though, about four per cent of the population lack these abilities and have a congenital perception disorder, known as tone-deafness or congenital amusia (Kalmus and Fry, 1980 [1]; Peretz et al., 2003 [2]), which is not caused by insufficient exposure to music, a hearing deficiency or intellectual impairment (Ayotte et al., 2002 [3]). Behavioural research has shown that amusia is linked to pitch perception deficits (Foxton et al., 2004 [4]; Hyde and Peretz, 2004 [5]) and impaired pitch memory (Gosselin et al., 2009 [6]; Tillmann et al., 2009; [7] Williamson et al., 2010 [8]; Williamson & Stewart, 2010 [9]; Albouy et al., 2013 [10]) whereas the visuo-spatial domain is not affected (Williamson et al., 2011 [11]). Recent studies have also indicated deficits in language perception or more specifically intonation perception (Patel et al., 2008 [12]; Liu et al., 2010 [13]; Hamann et al., 2012 [14]).

Brain imaging studies have revealed structural and functional brain differences compared to healthy controls, predominantly in the frontal and temporal lobes (Hyde et al., 2006, 2007, 2011 [15, 16, 17] ; Loui et al., 2009 [18]; Albouy et al., 2013 [10]). Using voxel-based morphometry, Hyde et al. (2006) [15] reported reduced white matter concentration in the right inferior frontal lobe in amusic individuals, which was accompanied by more grey matter volume in the same region. In addition, cortical malformations (e.g. thicker cortices) in the right inferior frontal gyrus and right auditory cortex in participants with congenital amusia compared to controls were found (Hyde et al., 2007) [16]. A functional magnetic resonance imaging study revealed abnormal deactivation of the right inferior frontal gyrus and reduced connectivity of this area to the auditory cortex in amusic brains (Hyde et al., 2011) [17]. Further support for a reduced fronto-temporal connectivity in congenital amusia was revealed by Loui et al. (2009) [18] suggesting reduced fiber activity in the right arcuate fasciculus compared to matched controls. A recent study by Albouy et al. (2013) [10] investigated short-term memory for six-tone sequences in congenital amusics using magnetoencephalography and voxel-based morphometry. The study confirmed anomalies of grey and white matter concentrations in the right inferior frontal gyrus. Additionally, the study showed that during the retention of the pitch material the induced low gamma oscillations (30-40 Hz range) in the right dorsolateral prefrontal cortex (DLPFC) were lower in congenital amusics. This result suggests that the impairment in maintaining the pitch information in individuals with congenital amusia might be related to alterations of oscillatory activity in the low gamma range.

Non-invasive brain stimulation such as transcranial magnetic stimulation (TMS), transcranial direct and transcranial alternating stimulation (tDCS, tACS) allows to draw causal involvements of certain brain areas and their function on cognitive performances (e. g. Miniussi et al., 2013 [19] for a review) and have also been used for therapeutic interventions (e.g. Kuo et al., 2014 [20] for a recent review). TACS most likely interferes with ongoing brain oscillations. When stimulation is applied for a longer time period, tACS allows to influence cortical excitability and can lead to neuroplastic reorganisations (Antal & Paulus, 2013) [21]. Previous studies have also shown the potential use to modulate perception and cognitive performances (Herrmann et al., 2013 [22] for a recent review). Helfrich et al. (2013) [23] showed that 10 Hz tACS applied to the parieto-occipital cortex led to an improved performance in a visual target detection task which was traced back to an entrainment of alpha oscillations in the targeted area measured by electroencephalography (EEG). Laczo et al. (2012) [24] applied tACS at different frequencies within the gamma range (40, 60 and 80 Hz) over the primary visual cortex and revealed that only 60 Hz tACS facilitated contrast perception. Furthermore, working memory improved when performance was tested during online theta tACS over bilateral DLPFC compared to post-stimulation testing (Meiron & Lavidor, 2014) [25].

Building on the results by Albouy et al. (2013) [10], who showed decreased low gamma oscillations (30-40 Hz) in the right DLPFC while amusics perform a pitch memory task, the aim of the present study was to investigate whether applying tACS at 35 Hz to the right DLPFC can facilitate pitch memory abilities in congenital amusia. We hypothesized that (i) amusics exhibit a selective impairment in pitch memory compared to controls before stimulation and (ii) that tACS applied with a frequency of 35 Hz to the right DLPFC will improve pitch memory performance in amusics to the level of healthy controls.

2. Material and Methods

2.1 **Participants**

Nine amusics (7 female; age: 24.89 ± 1.33 years (mean ± standard error of the mean, SEM); musical education: 3.22 ± 1.18 years) and eight matched control participants (7 female; age: 23.75 ± 0.70 years; musical education: 3.00 ± 1.25 years) took part in the present study. This modest sample size is common for studies including participants with congenital amusia. One amusic was excluded from the data analysis as she performed more than three standard deviations away above the mean in the pitch memory task. All participants were native speakers of German, right handed, as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971 [26]), and had normal hearing (defined as a mean hearing level of 20 dB or less in both ears), which was assessed by pure tone audiometry at 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz. In addition, exclusion criteria were history or family history of epileptic seizures or any other neurological or psychiatric disorder, metallic implants and drug or alcohol abuse. To be considered as amusic, participants had to score below a cut-off score of 75% on the first four subtests of the Montreal Battery of Evaluation of Amusia (Peretz et al., 2003 [2]); see material for further details) while all controls scored 88% or higher on the same four subtests.. The mean score of the amusic group was 20.26 ± 1.52 for the pitch-based subtests and 24.12 ± 2.86 for rhythm. The results of the control group (pitch-based mean: 27.33 ± 1.36, rhythm mean: 27.06 ± 1.18) differed significantly from the values of the amusic group [$t(16) = 9.79$, $p < .001$ for pitch-based and $t(16) = 2.68$, $p = .018$ for rhythm].

The study was approved by the ethics committee of the Medical Department of the Heinrich-Heine-University in Düsseldorf and prior to the study all participants gave their informed written consent to take part and received a small monetary reimbursement for their participation.

2.2 **Material**

The **Montreal Battery of Evaluation of Amusia** (MBEA, Peretz *et al.*, 2003 [2]) was used to categorize the participants as amusic and normal controls. The MBEA contains six subtests that assess several components of musical perception and memory and is the most widely used tool to diagnose congenital amusia (e.g. Hyde *et al.*, 2006 [15]; Gosselin *et al.*, 2009 [6]; Albouy *et al.*, 2013 [10]). The first three subtests evaluate melodic organization or pitch perception (scale, contour and interval), the fourth and fifth subtests evaluate temporal organisation (rhythm and metre) and the remaining sixth test is a memory test. The amusic participants completed the MBEA for a firm diagnosis twice, once online and once in the laboratory, to ensure that participants were categorized as amusics correctly. In addition, all participants answered a detailed questionnaire about their musical and linguistic background, ensuring that all participants were native speakers of German and that they had no knowledge of Sanskrit, Hindi or any other language written with Devanagari, since this script was used in the visual control task of the main experiment.

We also included a **pitch detection** and a **pitch direction task** to determine perceptual pitch discrimination thresholds in order to ensure that the pitch intervals for the pitch memory task would be supra-threshold for all participants. The task parameters and procedures were based on the tasks also used in Williamson & Stewart (2010) [9]. Both tasks were two alternative forced choice AXB paradigms using an adaptive two-up-one-down staircase procedure. A trial consisted of three tones, each 600 ms in length. The task was to identify the target tone that was different to the other two tones. The target tone was with equal probability either in the first or the last position. When participants gave two consecutive correct answers, they advanced a level. When they made one mistake, they went one level down. Each change of level was called a reversal. Each task ended after 15 reversals. For the pitch detection task, the two non-target tones were steady state tones of 500 Hz. The target tone was a pitch glide, either upwards or downwards, randomly distributed, centred around 500 Hz. For the pitch direction task, all tones were glides centred around 500 Hz. The target tone was a glide in the opposite direction to the non-target glides. The direction of target and non-target glides was distributed randomly but equal. The target glide was initially set to range 6 semitones. Every time participants advanced a level, the pitch range was reduced; when participants made a mistake the pitch range was increased. In order to increase the sensitivity, variable pitch ranges or steps were employed. For the first 5 reversals, the range comprised a change of 1 semitone. For reversals 6-9, a change of 0.2 semitones and for reversals 10-15 a change of 0.05 semitones was used. The last 10 trials were averaged to compute the perceptual threshold of each participant. The two tasks were included to ensure that participants had a perceptual threshold below 4 semitones so that the pitch contrasts in the pitch span tasks were well above their thresholds. This was important because the span task should measure the memory abilities of the participants, which should not be confounded by pitch discrimination problems.

The main tACS experiment consisted of two tasks: An **auditory short-term memory span task** and a **visual short-term memory span task**. Both tasks followed the same two alternative forced choice design with an adaptive two-up-one-down staircase procedure. The procedure and the tone stimuli for the auditory task were adapted from Williamson and Stewart (2010) [9]. The stimuli were ten sine tones with a duration of 500 ms (including 20 ms fading in and fading out) each with fundamental frequencies ranging from 262 to 741 Hz in whole tone steps and they were created in Praat (Boersma & Weenink 2014 [27]). For the auditory task, an initial silence duration of 500 ms was followed by two successive tone sequences of equal length and the task was to indicate whether the two sequences were the same or different. The interval between every tone of a sequence was 383 ms and the interval between the two sequences of a trial was 2 s. The participant responded via mouse click and each trial ended with 2 s of pink noise in order to diminish any auditory traces before the next trial started (adopted from Williamson and Stewart 2010 [9]).

The stimuli for the visual memory span task were ten Devanagari letters presented in black on a white background. Each letter was also presented for 500 ms. Devanagari letters instead of e.g. numbers, as in Williamson and Stewart (2010) [9], were selected to ensure that participants would have no phonological representation, which could be influenced by the tACS. This control task was chosen in order to ensure that the set-up was as similar as possible to the pitch span task but required only visual memory. The letters were ranked according to similarity by ten participants in a previous pilot study. Some letters share greater similarity with each other than others, reflecting, as closely as possible, the relation of the auditory stimuli. For the visual task, a blank screen was initially presented for 500 ms followed by two sequences of Devanagari letters that were presented sequentially. The interval between every stimulus of a sequence was 383 ms and the interval between the two sequences of a trial was 2 s, exactly the same as in the auditory task. Each trial ended with the presentation of a black and white checkerboard for 2 s in order to diminish any visual traces after the participant responded via mouse click.

The selection of tones or letters, respectively, for a sequence followed a constrained random sampling without replacement: Adjacent tones had to differ by at least two tones. Adjacent letters had to be at least two steps apart in their ranking. The two sequences in a trial were either identical or the position of two tones/letters was reversed in one of the sequences. In addition, the first and the last item were never switched, except in sequences of two or three tones. Identical and non-identical trials occurred with the same probability. The participant's task was to determine whether the sequences were same or different (Figure 1). For the auditory task, sequences consisted of only two tones at the beginning. For the visual task, sequences initially consisted of four letters as pilot studies had shown that the visual task was slightly easier than the auditory task. The sequence length increased after two consecutive correct answers from the participant and decreased after one incorrect answer. Each task was terminated after four incorrect answers. The span, indicating the individual memory load participants can hold in mind, for each task was calculated by averaging the last ten trials.

- Insert figure 1 approximately here -

2.3 **Neuronavigation and tACS parameters**

Neuronavigation (Localite GmbH, Sankt Augustin, Germany) was used to identify the right DLPFC. The procedure began by measuring characteristic head landmarks of each participant using predefined points (i.e. inion and nasion; left and right pre-auricular points;

most posterior and superior points). The individual head coordinates were then mapped on a standard brain. Finally, a target with the MNI coordinates x=45, y=31, z=25 (Albouy et al., 2013 [10]) was set as target area (Figure 2). The position of the corresponding entry was then marked on the participants scalp with a skin-friendly highlighter. Two 5 cm x 5 cm electrodes covered in saline-soaked sponges were used. One electrode was placed over the target area and the second electrode was adjusted over the left supraorbital area. TACS was applied for a maximum of 20 minutes with 5 seconds fade in and fade out with a current intensity of 1 mA (DC-Stimulator Plus, NeuroConn, Germany). The current density under the electrode was 0.04 mA/cm^2. Two stimulation frequencies were tested in each amusic in separate sessions which were at least 1 week apart: The target frequency was 35 Hz and the control frequency 90 Hz. Participants were blind for the stimulation frequency applied. Six participants reported a slight flickering in the left eye, predominantly for the 35 Hz stimulation, but were informed that the flickering can occur depending on individual sensibility which can differ on a daily basis.

- Insert figure 2 approximately here -

2.4 **Procedure**

Amusic participants completed three sessions in the laboratory. After having completed the online-version of the MBEA with a score indicating amusia, the participant was invited to take part in the present study. In session 1, the participants completed the MBEA a second time to confirm the perceptual disorder and also filled in a questionnaire about their musical and linguistic background. Participants completed the pitch detection and direction at the beginning of session 2. Otherwise, sessions two and three were identical in their set up which is described in the following (see Figure 3). The participants were tested for their pitch and visual memory at baseline and during tACS. The stimulation frequencies (35

Hz vs. 90 Hz) were counterbalanced across participants. For baseline testing the participants completed the pitch span and visual span task in counterbalanced order in both sessions (e.g. if a participant started with the pitch span in session two, the same participant started with the visual span in session three). After baseline testing, neuronavigation was performed to mark the right DLPFC as stimulation target on the scalp and the electrodes were adjusted. After 2 minutes of stimulation, the participants completed the two memory tasks (pitch and visual span) in the same order as for the baseline testing. The stimulation ended after 20 minutes. In two sessions the participant over lasted the stimulation by completing the second task 3 minutes after the stimulation had stopped. The electrodes were removed and participants filled in a short questionnaire about the two tasks. Sessions two and three were completed one week apart.

- Insert figure 3 approximately here -

In order to compare performances of the amusic participants with normal musical perception and memory abilities, controls, matched by age, gender and musical training in the past, were also tested. The controls completed the pitch detection and pitch direction task as well as the pitch and visual span task (the latter two in counterbalanced order) in one session. Controls did not receive tACS. The control participants also completed the MBEA, either in the same testing session after the two memory tests or in an individual pretesting session.

Participants completed all tasks on a Windows 7 Lenovo Thinkpad Laptop with a mouse attached to it. All tasks were implemented in Praat (Boersma & Weenink 2014 [27]) and the sessions took place in a soundproof booth. The auditory stimuli were presented via closed dynamic headphones (Beyerdynamic, DT 770 M, 80 Ohm) at a comfortable level for the participants.

3. Results

3.1 **Pretests**

The thresholds for the pitch detection and direction tasks confirmed that all amusics (mean scores: 0.44 for pitch detection and 0.89 for pitch direction) as well as controls (mean scores: 0.36 for pitch detection and 0.19 for pitch direction) had thresholds substantially below 4 semitones. Table 1 gives an overview of mean group thresholds and independent-samples t-tests reveal a significant difference between amusics and controls for the pitch direction task [$t(14) = 2.27$, $p = .039$] but no significant difference in the pitch detection task [$t(14) = 0.25$, $p = .804$]. These findings are in accordance with the results reported by Williamson and Stewart (2010) [9].

- Insert table 1 approximately here -

3.2 **Main tACS experiment: Amusics**

Table 2 summarizes the span performances for the pitch and visual span tasks at baseline and during the 35 Hz and 90 Hz tACS condition.

- Insert table 2 approximately here -

When comparing baseline performances of the pitch span task and the visual span control task, paired-samples t-tests reveal significant differences for the amusics at baseline in both testing blocks (p-values < .002) confirming the selected memory impairment for musical material and not memory in general (Williamson et al., 2011) [11].

A repeated measures analysis of variance (ANOVA) with pitch span scores as the dependent variable and *time* (baseline vs. online stimulation) and *stimulation* (35 Hz vs. 90

Hz) as the within-subject variables revealed no significant effect of *time* [$F(1, 7) = .272$, $p = .618$, $\eta_p^2 = .037$] , but a significant effect for *stimulation* [$F(1, 7) = 8.66$, $p = .022$, $\eta_p^2 = .553$] and a significant *time*stimulation* interaction [$F(1, 7) = 6.17$, $p = .042$, $\eta_p^2 = .468$]. In order to investigate the significant *time*stimulation* interaction paired-samples t-tests with Bonferroni corrections were conducted for the baseline and online tACS comparisons for both stimulation conditions. Comparing the results in the 35 Hz condition, the paired-samples t-test revealed a significant improvement in pitch memory performance [$t(7) = 3.55$, p = .018] whereas the comparison in the 90 Hz stimulation condition did not show a significant effect [$t(7) = .41$, $p = .696$] (Fig. 4). Baseline performances in both session correlated significantly [$r = .75$, $p = .031$ and did not differ significantly [$t(7) = 1.93$, $p = .095$].

A repeated measures ANOVA for the visual control task with the visual span scores as the dependent variable and *time* (baseline vs. online stimulation) and *stimulation* (35 Hz vs. 90 Hz) revealed non-significant results for both main effects [*time*: $F(1, 7) = 1.34$, $p = .285$, $\eta_p^2 = .161$; *stimulation*: $F(1, 7) = 1.01$, $p = .348$, $\eta_p^2 = .126$] and the interaction [$F(1, 7) = 0.98$, $p = .355$, $\eta_p^2 = .123$] indicating that both stimulation conditions had no effect on the control task. Results are summarized in figure 4.

- Insert figure 4 approximately here -

In this context it is important to note that six participants reported a slight flickering in the 35 Hz stimulation condition. Thus, we cannot rule out the possibility that phosphenes induced by this stimulation frequency might have masked a visual memory deficit in amusic participants, But, comparing visual memory performances during 35 Hz tACS of the participants who reported phosphenes and the ones who did not, did not reveal a difference between participants – at least on a descriptive level, weakening the assumption that phospehenes might have affected the present results.

3.3 **Comparing memory performances of amusics and controls**

The control participants showed a mean pitch span performance of 5.4 tones (SD = 1.57) and a mean visual span performance of 6.82 symbols (SD = 1.17). For comparisons between amusics and controls we calculated overall average baseline performances for the amusic participants for each task (pitch and visual), respectively as they performed the baseline memory tasks twice ($\frac{baseline\ 1+baseline\ 2}{2}$). Independent t-tests comparing baseline performances between the groups (amusic vs. control) reveal a significant difference for the pitch memory task [$t(14) = 2.19$, $p = .046$] (Fig. 5) but no significant difference for the visual control task [$t(14) = 1.67$, $p = .118$]. When comparing the 35 Hz tACS pitch memory performance of the amusics with performance of the controls, independent-samples t-tests show that performances do not differ significantly anymore [$t(14) = 1.08$, $p = .298$] (Fig. 5). This result highlights that 35 Hz tACS to the right DLPFC in amusics leads to a comparable performance to individuals with 'normal' pitch memory suggesting that modulating the function of the right DLPFC at 35 Hz in amusics has the potential to overcome the perceptual dysfunction.

- Insert figure 5 approximately here -

4. Discussion

The present study investigated whether the decreased low gamma oscillations in the right DLPFC during pitch memory in congenital amusia is causally involved in the pitch memory deficit typical for this perceptual disorder. To this end, tACS with a frequency of either 35 or 90 Hz was applied to the right DLPFC while participants with congenital amusia performed a pitch memory recognition task, as well as a visual control task. The results show that pitch memory improved significantly in congenital amusia when 35 Hz tACS was applied while a stimulation effect was neither found on the visual control task nor when applying tACS at 90 Hz. The present result is in accordance with our hypothesis to find a significant improvement after 35 Hz on the pitch memory task as Albouy et al. (2013) [10] showed decreased low gamma oscillations during pitch memory, which is impaired in congenital amusia. The visual control task was not affected, which is also in line with previous research (Williamson et al., 2011 [11]). This result supports the hypothesis that the affected function of the right DLPFC in congenital amusia is a key factor of the perceptual disorder. But, it is important to note that the study concentrated on investigating the function of the right DLPFC in amusics only as it is based on the study by Albouy et al. (2013) [10]. We do acknowledge that other brain areas that have been shown to be abnormal in amusics such as the inferior frontal gyrus and the auditory cortex (Hyde et al., 2006, 2007, 2011 [15, 16, 17]; Loui et al., 2007 [18]) are also relevant for the neural basis of this congenital disorder.

4.1 **Functional significance of the right DLPFC and gamma oscillations for memory in general**

The present result fits well into previous research, which revealed a close association of the DLPFC and memory functions. Numerous functional imaging studies have highlighted the activation of the DLPFC during recognition and working memory (e.g. McDermott et al., 2000 [28]; Narayanan et al., 2005 [29]) and also non-invasive brain stimulation has been used frequently to investigate the involvement of the DLPFC for memory processes (see Brunoni & Vanderhasselt, 2014 [30] for a recent review). It has also been shown that gamma oscillations in the inferior frontal lobes are closely linked to auditory and visual memory processes (Howard et al., 2003 [31]; Kaiser et al., 2003 [32]). A review from Jensen et al.

(2007) [33] highlights the general association of gamma oscillations with memory and attention.

4.2 **Pitch memory in amusics compared to healthy controls**

In order to compare the memory performances of congenital amusics with individuals who have an intact music perception, the present study also included matched controls. The comparison of the two groups at baseline showed that amusics, compared to controls, show a selective impairment in pitch memory. On the visual control tasks no group differences were found. This is in accordance with previous studies, which have shown that congenital amusics show impaired pitch memory whereas spatial memory abilities are not affected (Tillmann et al., 2009 [7]; Williamson & Stewart, 2010 [9]; Williamson et al., 2011 [11]). Most importantly, when comparing the performance of the pitch memory task of amusics when receiving 35 Hz tACS and the performance of controls, a non-significant result was revealed. This finding shows that the memory deficits of amusics can be overcome by modulating the functionality of the right DLPFC by tACS at 35 Hz and it provides further support that the right DLPFC is a key brain area for pitch memory (Albouy et al., 2013 [10]; Jerde et al., 2011 [34]; Zatorre et al., 1994 [35]). It would be desirable for future studies to investigate the reverse situation and to see whether suppressing the activity of the right DLPFC with cathodal transcranial direct current stimulation in musically intact individuals would lead to a decline in pitch memory and maybe also pitch perception deficits. In this regards, Loui et al. (2010) [36] showed that cathodal transcranial direct current stimulation over the inferior frontal and superior temporal regions led to a deterioration of performance in a pitch matching task in healthy individuals but memory functions were not examined in this study.

4.3 **Limitations**

Although the data reveals evidence for the assumption that tACS at 35 Hz applied over the right DLPFC overcomes the pitch memory deficit in congential amusia, the following limitations need to be considered.

As the study did not include neurophysiological recordings like EEG or magnetoencephalography (MEG), the interpretation of how the 35 Hz tACS affected the function of the right DLPFC is limited. Based on previous research which has shown that applying tACS with a specific frequency can lead to an entrainment of the ongoing oscillations with the induced frequency (Zaehle et al., 2010 [37]; Helfrich et al., 2014 [23]), we would like to argue that entrainment is also the key mechanism our results are based on. By applying the frequency of 35 Hz to the right DLPFC of amusics, we strongly believe that an entrainment of the ongoing neural oscillations with the externally applied 35 Hz frequency occurred. As Albouy et al., 2013 [10] have shown that an increase in low gamma oscillations in the right DLPFC was found in healthy controls during pitch memory, it is likely that we have externally induced this increase in amusics and that the facilitation of pitch memory is the result of the entrainment of 35 Hz oscillations.

Furthermore, it is notable that the baseline performance in the 35 Hz stimulation condition was descriptively, but not statistically significant, lower than the baseline performance of the 90 Hz tACS session. Thus, we cannot exclude the possibility that during 90 Hz tACS further improvement did not occur simply due to a ceiling effect.

Additionally, amusic participants completed the span tasks twice in each session and one might suggest that practice effects could also account for the improvement in pitch memory in the 35 Hz stimulation condition. But as we counterbalanced the order of stimulation (35 Hz vs. 90 Hz) and we do not find any improvement in the 90 Hz session when participants performed the pitch span task the second time during stimulation, we would like to argue that practice effects are fairly unlikely. Also, the results of the visual control task support the claim that practice effects are not present in these task paradigms using this experimental set-up.

Finally, also the results of the visual control task should be discussed here in the limitation section. The aim of the control task was to create a task which does not allow participants to use any form of auditory phonological representations and is identical to the pitch span task in its procedure and memory parameters. As the application of 35 Hz tACS is more likely to provoke phosphenes as shown by a recent study (Turi et al., 2013 [38]) and as reported by two thirds of our sample, we cannot rule out completely that this may have affected our results. It is theoretically possible that the 35 Hz stimulation improved visual memory as well but the sensations of phosphenes compensated for this effect. But as the comparison between the ones who reported a slight flickering and the ones who have not does not show any disadvantages for the group with the visual sensation, we would argue that the phosphene sensation does not interfere with memory performances and a potential facilitatory effect of tACS on also the visual memory task in the present experiment.

4.4 **Conclusion**

In sum the present study reveals that affected pitch memory abilities in congenital amusia can be facilitated by applying tACS at 35 Hz to the right DLPFC. No modulation effects were found on a visual memory task or when applying 90 Hz stimulation. Therefore, the study reveals first evidence for a causal link between the dysfunction of the right DLPFC as indicated by reduced low gamma oscillations and pitch memory deficits in congenital amusia. Additionally, the results show that modulating the function of the right DLPFC with tACS can overcome the congenital disorder.

Funding

This work was supported by the Netherlands Organisation for Scientific Research (grant numbers 322-75-004) to J.P. B.P. is grateful for financial support by a grant from the DFG (PO806-3) and a grant from Heinrich-Heine-University (9772558).

References

[1] Kalmus, H., and Fry, D. B. (1980). On tune deafness (dysmelodia): frequency development, genetics and musical background. *Ann Hum Genet*, 43, 369-382.

[2] Peretz, I., Champod, A. S., and Hyde, K. (2003). Varieties of Musical Disorders: The Montreal Battery of Evaluation of Amusia. *Ann N Y Acad Sci*, 999, 58-75.

[3] Ayotte, J., Peretz, I., and Hyde, K. (2002). Congenital Amusia: A group study of adults afflicted with a music-specific order. *Brain*, 125, 238-251.

[4] Foxton, J.M., Dean, J.L., Gee, R., Peretz, I., and Griffiths, T.D. (2004). Characterization of deficits in pitch perception underlying 'tone deafness'. *Brain*, 127, 801-810.

[5] Hyde, K., and Peretz, I. (2004). Brain that are out of tune but in time. *Psychol Sci*, 15, 356-360.

[6] Gosselin, N., Jolicoeur, P., and Peretz, I. (2009). Impaired Memory for Pitch in Congenital Amusia. *Ann N Y Acad Sci*, 1169, 270-272.

[7] Tillmann, B., Schulze, K., and Foxton, J. M. (2009). Congenital amusia: a short-term memory deficit for non-verbal, but not verbal sounds. *Brain Cogn*; 71, 259-264.

[8] Williamson, V. J., McDonald, C., Deutsch, D., Griffiths, T. D., and Stewart, L. (2010). Faster decline of pitch memory over time in congenital amusia. *Adv Cogn Psychol*, 6, 15-22.

[9] Williamson, V. J., and Stewart, L. (2010). Memory for pitch in congenital amusia: beyond a fine-grained pitch discrimination problem. *Memory*, 18, 657-669.

[10] Albouy, P., Mattout, J., Bouet, R., Maby, E., Sanchez, G., Aguera, P.-E., Daligault, S., Delpuech, C., Bertrand, O., Caclin, A., and Tillmann, B. (2013). Impaired pitch perception and memory in congenital amusia: the deficit starts in the auditory cortex. *Brain*, 136, 1639-1661.

[11] Williamson, V. J., Cocchini, G., and Stewart, L. (2011). The relationship between pitch and space in congenital amusia. *Brain Cogn*, 76, 70-76.

[12] Patel, A., Wong, M., Foxton, J., Lochy, A., and Peretz, I. (2008). Speech intonation perception deficits in musical tone deafness (congenital amusia). *Music Percept*, 25, 357-368.

[13] Liu, F., Patel, A. D., Fourcin, A., and Stewart, L. (2010). Intonation processing in congenital amusia: Discrimination, identification and imitation. *Brain*, 133, 1682-1693.

[14] Hamann, S., Exter, M., Pfeifer, J., and Krause-Burmester, M. (2012). Perceiving Differences in Linguistic and Non Linguistic Pitch: A Pilot Study With German Congenital Amusics. Proceedings of the 12th International Conference on Music Perception and Cognition (ICMPC) and 8th Triennial Conference of the European Society for the Cognitive Sciences of Music (ESCOM), 398-405.

[15] Hyde, K., Zatorre, R. J., Griffiths, T. D., Lerch, J. P., and Peretz, I. (2006). Morphometry of the amusic brain: a two-site study. *Brain*, 129, 2562-2570.

[16] Hyde, K., Lerch, J. P., Zatorre, R. J., Griffiths, T. D., Evans, A. C., and Peretz, I. (2007). Cortical Thickness in Congenital Amusia: When Less Is Better Than More. *J Neurosci*, 27, 13028-13032.

[17] Hyde, K., Zatorre, R. J., and Peretz, I. (2011). Functional MRI Evidence of an Abnormal Neural Network for Pitch Processing in Congenital Amusia. *Cereb Cortex*, 21, 292-299.

[18] Loui, P., Alsop, D., and Schlaug, G. (2009). Tone deafness: a new disconnection syndrome? *J Neurosci*; 29, 10215-10210.

[19] Miniussi , C., Harris, J. A., and Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. *Neurosci Biobehav Rev*, 37, 1702-1712.

[20] Kuo, M.-F., Paulus, W., and Nitsche, M.A. (2014). Therapeutic effects of non-invasive Brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *NeuroImage,* 85, 948-960.

[21] Antal, A., and Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Front Hum Neurosci*, 7:317.

[22] Herrmann, C. S., Rach, S., Neuling, T., and Strüber, D. (2013). Transcranial alterning current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci*, 7: 279.

[23] Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., and Herrmann, C. S. (2014). Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation. *Curr Biol*, 24, 333-339.

[24] Laczó, B., Antal, A., Niebergall, R., Treue, S., and Paulus, W. (2012). Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. *Brain Stim*, 5, 484-91.

[25] Meiron, O., and Lavidor, M. (2014). Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. *Clin Neurophysiol*, 125, 77-82.

[26] Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9, 97-113.

[27] Boersma, P., and Weenink, D. (2014). Praat: doing phonetics by computer [Computer program]. Version 5.3.63, retrieved 25 January 2014 from http://www.praat.org/

[28] McDermott, K. B., Jones, T. C., Petersen, S. E., Lageman, S. K., and Roediger H. L. (2000). Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: An event-related fMRI study. *J Cogn Neurosci*, 12, 965-976.

[29] Narayanan, N. S., Prabhakaran, V., Bunge, S. A., Christoff, K., Fine, E. M., and Gabrieli, J. D. E. (2005). The role of the prefrontal cortex in the maintenance of verbal working memory: An event-related fMRI analysis. *Neuropsychology*, 19, 223-232.

[30] Brunoni, A.R., and Vanderhasselt, M.-A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain Cogn*, 86, 1-9.

[31] Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., Schulze-Bonhage, A., and Kahana, M. J. (2003). Gamma Oscillations Correlate with Working Memory Load in Humans. *Cereb Cortex*, 13, 1369-1374.

[32] Kaiser, J., Ripper, B., Birbaumer, N., and Lutzenberger, W. (2003). Dynamics of gamma-band activity in human magnetoencephalogram during auditory pattern working memory. *NeuroImage*, 20, 816-827.

[33] Jensen, O., Kaiser, J., and Lachaux, J.-P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci*, 30, 317-324.

[34] Jerde, T. A., Childs, S. K., Handy, S. T., Nagode, J. C., and Pardo, J. V. (2011). Dissociable systems of working memory for rhythm and melody. *NeuroImage*, 57, 1572–1579.

[35] Zatorre, R. J., Evans, A. C., and Meyer, E. (1994). Neural mechanisms underlying melodic perception and memory for pitch. *J Neurosci*, 14, 1908–1919.

[36] Loui, P., Hohmann, A., and Schlaug, G. (2010). Inducing Disorders in Pitch Perception and Production: a Reverse-Engineering Approach. *Proceedings of Meetings on Acoustics*, 9: 50002.

[37] Zaehle, T., Rach, S., and Herrmann, C. S. (2010). Transcranial Alternating Current Stimulation Enhances Individual Alpha Activity in Human EEG. *PLoS ONE*, 5: e13766

[38] Turi, Z., Ambrus, G. G., Janacsek, K., Emmert, K., Hahn, L., Paulus, W., and Antal, A. (2013). Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during transcranial alternating current stimulation. Restorative *Neurol Neurosci*, 31(3), 275-285. doi: 10.3233/rnn-120297

Table 1 – Group thresholds for the pitch detection and direction tasks in tones with the standard error of mean.

	Pitch detection	Pitch direction
Amusics	0.44 ± 0.22	0.89 ± 0.31
Controls	0.36 ± 0.22	0.19 ± 0.03

Table 2 – Overview of pitch and visual span performance of amusics. Displayed are mean scores and the standard error of mean.

	Pitch – 35 Hz	Visual – 35 Hz	Pitch – 90 Hz	Visual – 90 Hz
Before tACS	3.61 ± 0.36	5.84 ± 0.59	4.28 ± 0.53	6.01 ± 0.45
During tACS	4.64 ± 0.52	5.28 ± 0.42	4.38 ± 0.52	6.11 ± 0.54

Figure Legends

Figure 1
Two examples of trials for the span memory tasks. Tones (pitch span) and Devanagari letters (visual span) were presented in succession and in both examples the second and third item are in reversed position and therefore the answer 'different' would be correct.

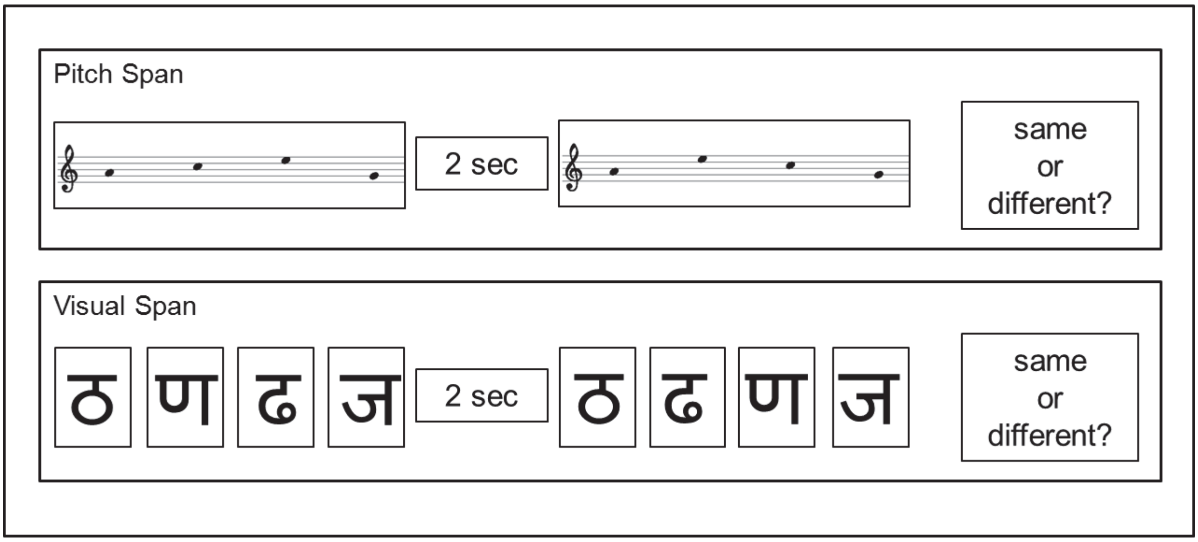
Figure 2
Using neuronavigation the targeted area of the right DLPFC was defined by the MNI coordinates x=45, y=31, z=25 (Albouy et al., 2013).

Figure 3
Timeline of the two tACS sessions for the amusic participants. After being diagnosed with congenital amusia in the first session, amusics returned to session two and three (one week apart) for the stimulation and received either 35 Hz or 90 Hz tACS in counterbalanced order.

Figure 4
35 Hz tACS led to a significant facilitation of pitch memory performance in congenital amusia. Furthermore, the data reveal that at baseline amusics showed a selective impairment in pitch memory as the pitch and visual performances at baseline were significantly different. Error bars represent the standard error of mean.

Figure 5
Baseline performances between the amusics and controls differed significantly on the pitch span task, whereas this difference is not significant anymore during 35 Hz stimulation. Please note that in amusics baseline overall performance was averaged across the two baselines of the 35 and 90 Hz stimulation sessions. Error bars represent the standard error of mean.

Figure 1



Pitch Span
2 sec
same
or
different?
Visual Span
ठ ण ढ ज
2 sec
ठ ढ ण ज
same
or
different?

Figure 2

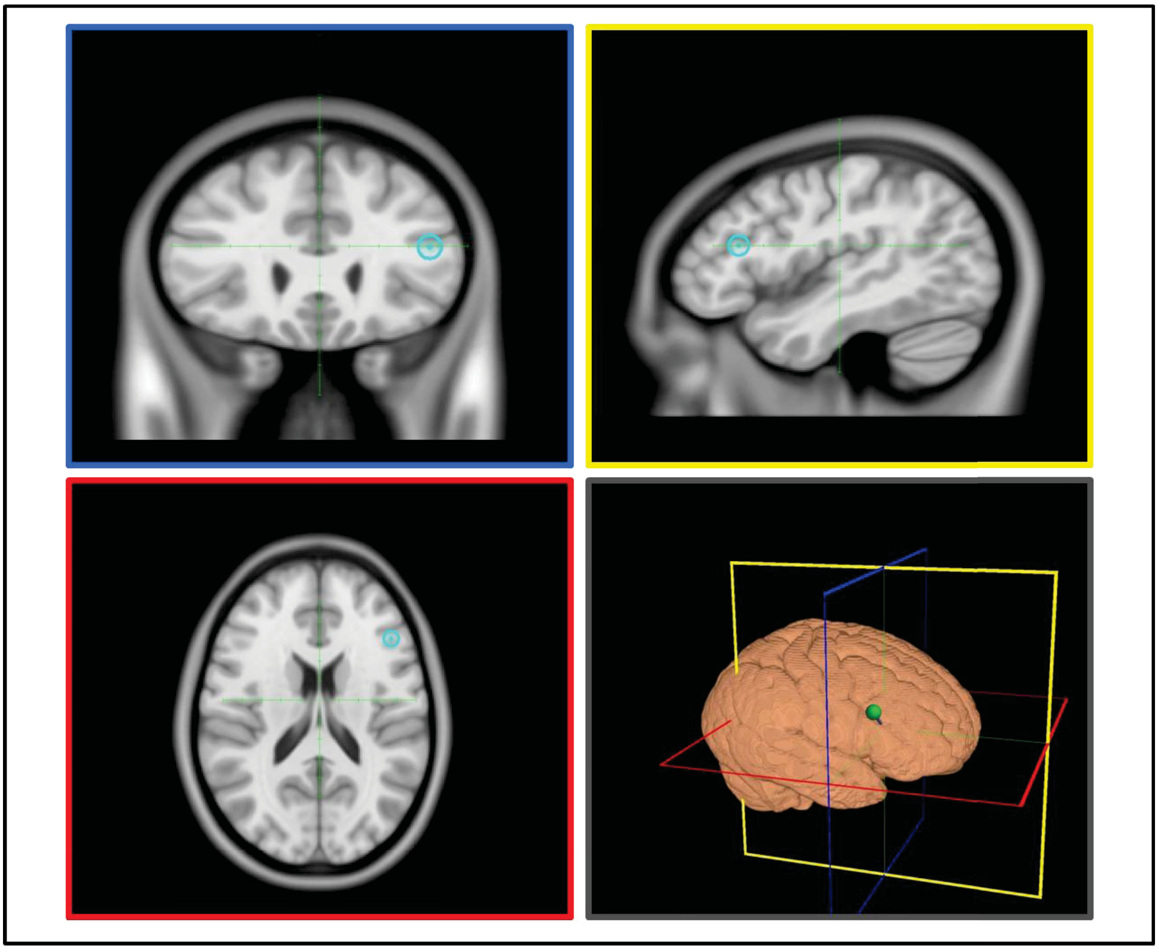


Figure 3

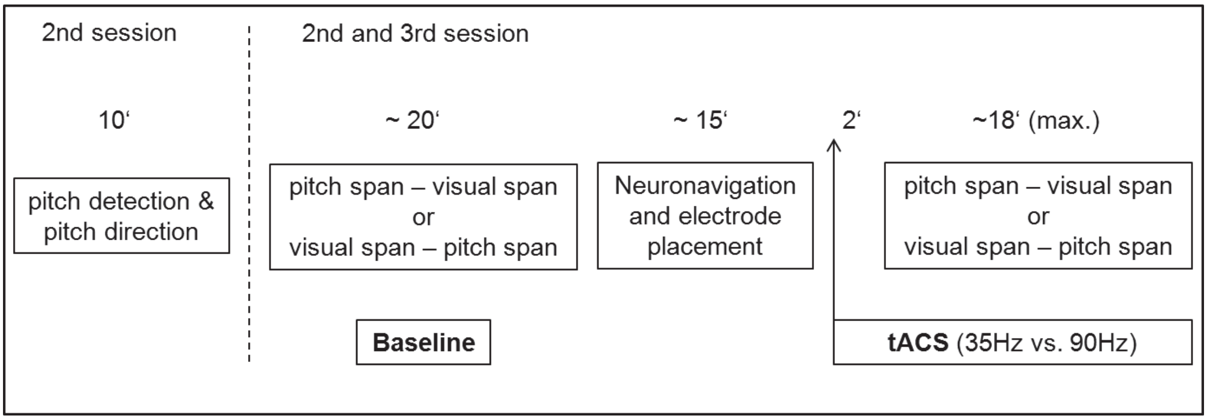
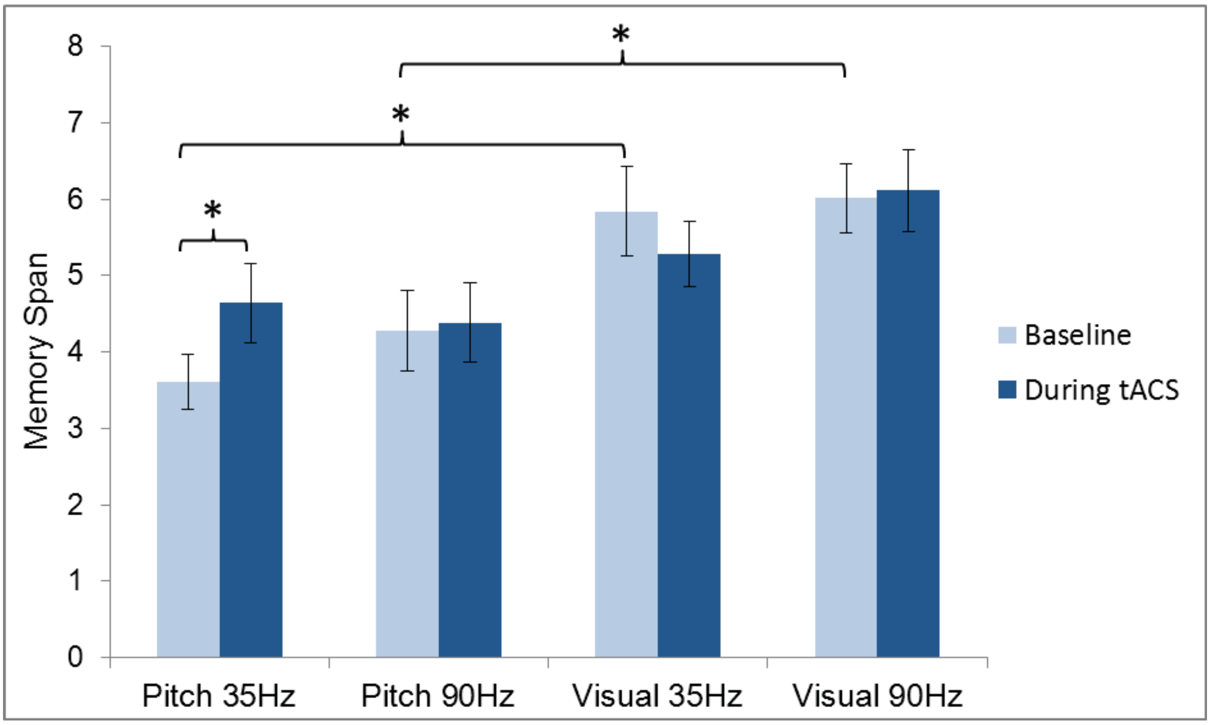
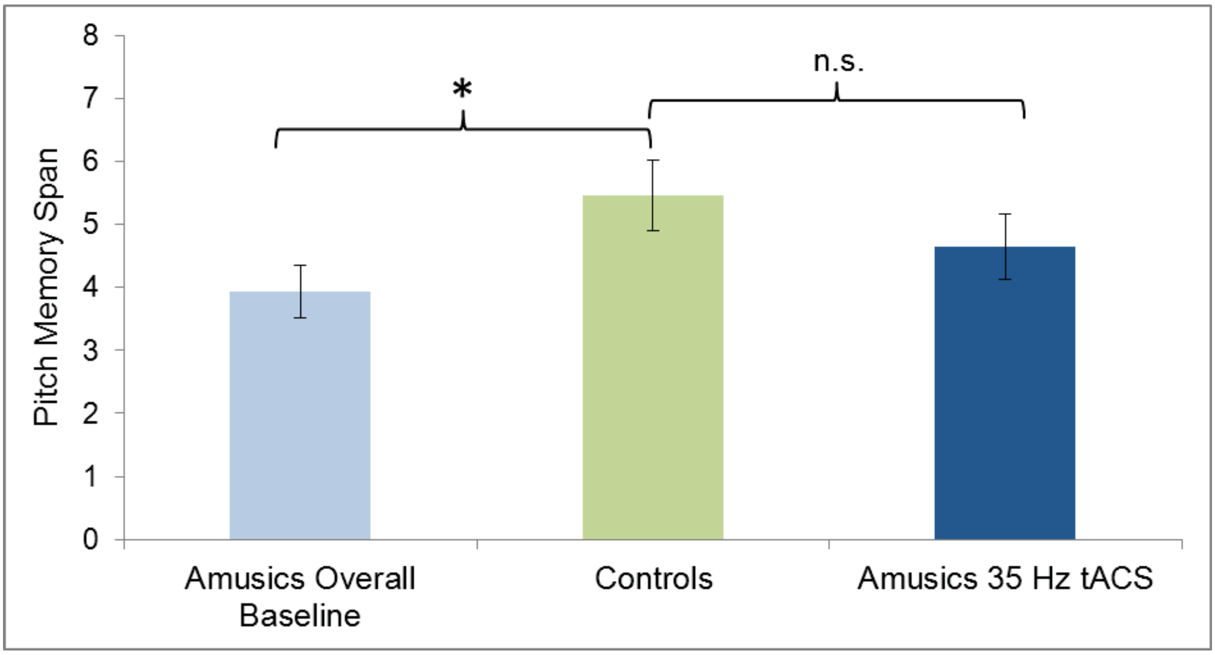

2nd session
2nd and 3rd session
10‘
~ 20‘
~ 15‘
2‘
~18‘ (max.)
pitch detection & pitch direction
pitch span – visual span or visual span – pitch span
Neuronavigation and electrode placement
pitch span – visual span or visual span – pitch span
Baseline
tACS (35Hz vs. 90Hz)

Figure 4



8
7
6
5
4
3
2
1
0
Memory Span
*
*
*
Pitch 35Hz
Pitch 90Hz
Visual 35Hz
Visual 90Hz
Baseline
During tACS

Figure 5



Pitch Memory Span
8
7
6
5
4
3
2
1
0
*
n.s.
Amusics Overall Baseline
Controls
Amusics 35 Hz tACS