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The use of non-invasive brain stimulation in auditory perceptual learning: A review

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ABSTRACT

Auditory perceptual learning is an experience-dependent form of auditory learning that can improve substantially throughout adulthood with practice. A key mechanism associated with perceptual learning is synaptic plasticity. In the last decades, an increasingly better understanding has formed about the neural mechanisms related to auditory perceptual learning. Research in animal models found an association between the functional organization of the primary auditory cortex and frequency discrimination ability. Several studies observed an increase in the area of representation to be associated with improved frequency discrimination. Non-invasive brain stimulation techniques have been related to the promotion of plasticity. Despite its popularity in other fields, non-invasive brain stimulation has not been used much in auditory perceptual learning. The present review has discussed the application of non-invasive brain stimulation methods in auditory perceptual learning by discussing the mechanisms, current evidence and challenges, and future directions.

1. Introduction

Traditionally, the auditory system has been viewed as a genetically determined system largely dependent on critical developmental periods (Hensch, 2005). However, in recent years multiple studies have shown that the auditory system continuously reorganizes itself in response to either lesioning, or to behavioural training via auditory input (Irvine et al., 2001; Irvine, 2018a). In the former, lesion-induced pattern changes of input cause sensory cortices to modify in response. In one study, it was shown in cats that cochlear lesioning resulted in an expanded representation of adjacent cochlear regions (a mechanism further discussed later in this paper) (Rajan et al., 1993). In humans with tinnitus, a similar pattern was found, as magnetoencephalographic (MEG) recordings showed a shift in cortical representation of tinnitus, suggesting pathologically-induced plasticity (Muhlnickel et al., 1998). Alternatively, auditory plasticity has also been shown to result from behavioural training, including learning. This form of learning is called auditory perceptual learning. Perceptual learning has been used as an umbrella term for experience-dependent learning which includes a wide variety of sensory modalities, such as visual, auditory, tactile, taste, and olfaction (Gold et al., 2010). Early studies observed a dramatic improvement in the ability of humans to distinguish between two tactile stimuli on the skin through training (Gibson, 1953, 1969). These changes occurred within days, and therefore too rapid to be caused by an increase in peripheral receptors, instead it was hypothesised that it involved changes in the central nervous system (Gold et al., 2010). For many years, research into perceptual learning has been dominated by visual studies, and only more recently has auditory perceptual learning become a topic of interest (Irvine, 2018b). auditory perceptual learning can be studied using a variety of tasks, including frequency discrimination, interval discrimination, spatial hearing, intensity discrimination, and tone pattern learning (Wright et al., 2009).

Through animal research, various ideas have emerged on the neural and cortical processes that underlie auditory perceptual learning . These studies have particularly focused on auditory frequency discrimination (Polley et al., 2006; Recanzone et al., 1993). A reason being that frequency discrimination is easily applicable to animal models. Animal models have revealed a possible role of map plasticity in the primary auditory cortex (A1) in auditory perceptual learning by showing an increased cortical area of representation in the A1 for behaviourally trained frequencies (Polley et al., 2006; Recanzone et al., 1993). The finding that the auditory system is plastic is promising, especially for

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methods like non-invasive brain stimulation which have been related to the promotion of plasticity in the brain (Huang et al., 2017). Non-invasive brain stimulation is a relatively novel technique used to identify the functional role of specific brain structures, and it can provide valuable information about the relationship between brain and behavior (Cirillo et al., 2017). As perceptual learning can be substantially improved during adulthood through practice, there is scientific interest in the ability to modulate auditory perceptual learning via non-invasive brain stimulation. A handful of studies have used non-invasive brain stimulation for auditory perceptual learning, but with mixed results, possibly due to methodological differences between these studies (Simonsmeier et al., 2018). Overall, there seems to be a lack of consensus in the field on how non-invasive brain stimulation could be applied for auditory perceptual learning. In the current review, we will discuss how non-invasive brain stimulation methods could be used for auditory perceptual learning. A narrative review was chosen in this context because of the sparce literature available on this topic, with this review we would like to provide an overview on what is currently being done and what might be valuable for future studies to focus on. This review begins by providing a concise overview of what is known about the mechanisms of action associated with auditory perceptual learning. Then we will summarize and discuss studies that have used non-invasive brain stimulation to modulate auditory perceptual learning. Lastly, we will discuss the current challenges of applying non-invasive brain stimulation in auditory perceptual learning research, and our recommendations for future research.

2. Mechanisms of auditory perceptual learning

To discuss how non-invasive brain stimulation could be applied in auditory perceptual learning, it is important to first understand the mechanisms of action associated with auditory perceptual learning. Before perceptual learning can take place, the incoming stimulus first needs to be processed. Auditory input travels first through the outer ear, ear canal, and then eardrum (Saenz et al., 2014). Soundwaves vibrate the eardrum, and these vibrations are then amplified by the auditory ossicles. The amplified waves enter the inner ear, and then the cochlear, see Fig. 1. Filled with fluid, vibrations in the cochlea are picked up by hair cells, converting the waves to electrical signals. The cochlea is also tonotopically organized, with the base tuned to higher frequencies, and decreasing toward the apex, tuned to low frequencies (Hackett, 2015; Musiek et al., 2018; von Bekesy, 1970). After transduction, the signal is transmitted by the cochlear nerve, sending tonotopic projections from the auditory nerve (Peterson et al., 2022). Next, the site of binaural convergence, information is transmitted to the superior olivary complex. The signal then travels to the nuclei of the lateral lemniscus, which itself has two regions: the ventral nucleus, and the dorsal nucleus. The ventral nucleus receives information from the central cochlear nucleus and is not tonotopically organized, however the inferior colliculus, at the roof of the mesencephalon, is organized (in the central nucleus) tonotopically, receiving inputs from the cochlear nuclei, and the superior olivary complex (Musiek et al., 2018). Lastly between the inferior colliculus and the auditory cortex is the thalamic relay, the medial geniculate nucleus. Similar to the inferior colliculus, the ventral division of the medial geniculate nucleus displays tonotopy, and projects to the core areas of the auditory cortex (primary and associated). The auditory cortex is also organized tonotopically, similar to the distribution of the cochlea, with a gradient of neurons preferentially responding to high or low frequencies (Peterson et al., 2022).

Studies that investigate the functional organization of the A1 use electrophysiological measures to map the A1 by identifying the frequency within a neuron's receptive field to which it is maximally sensitive, called the characteristic frequency (CF) (Saenz et al., 2014). Related to this is the so-called 'best frequency', which represents the frequency that evokes the strongest response (Saenz et al., 2014).

Early studies have argued for a role of map plasticity underlying auditory perceptual learning (Polley et al., 2006; Recanzone et al., 1993). For example, Recanzone and colleagues (Recanzone et al., 1993) were one of the first to find an increased cortical area of representation for behaviourally trained frequencies. In the study, monkeys were trained on a frequency discrimination task while tonotopic organization was measured through the recording of the number of neurons in A1 with CFs in the frequency range used during the task. A correlation was found between improvement on the trained frequency in a frequency discrimination task and an increase in the cortical area of representation pertaining to that frequency. Additionally, Polley and colleagues (Polley et al., 2006) also found an expansion of cortical representations for trained frequencies in rats both in A1 and in the suprarhinal auditory field, a secondary higher auditory field. The inclusion of a secondary higher auditory field made it possible to investigate whether tonotopic map plasticity is guided by bottom-up or top-down factors. The expectation was that plasticity in the suprarhinal auditory field would be influenced by top-down factors, whereas reorganization in A1 would indicate bottom-up factors. Additionally, the task was designed in a way

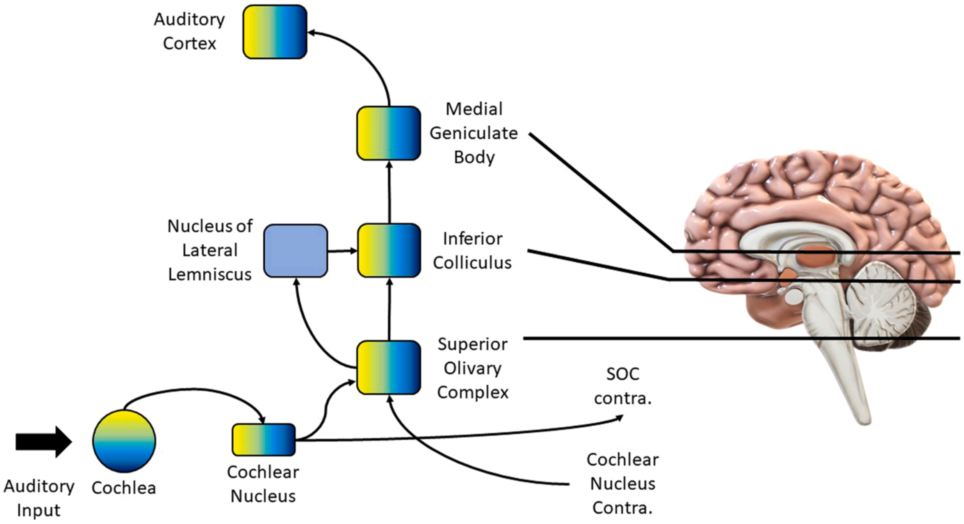


Fig. 1. Central auditory pathway. Auditory input first travels through the auditory canal where it reaches the inner ear. Through the auditory nerve, the sound reaches the brain, where it travels along the central auditory pathway. The auditory information is transmitted through a series of nuclei before it reaches the auditory cortex.

to observe whether the type of stimulus that was attended to, could influence the magnitude of the respective cortical area. These studies found an increased cortical area of representation in A1 for behaviourally trained frequencies. However, there are also several studies that have failed to find map plasticity associated with improved auditory perceptual learning (Brown et al., 2004; Thomas et al., 2020; Witte et al., 2005). A number of models for auditory plasticity have emerged over the years. The Weinberger model by Weinberger and colleagues (Weinberger, 2007) highlighted the importance of sensory structures in memory and associative learning. Although, associative learning is different from perceptual learning, the two concepts are closely related. Through classical conditioning studies, Weinberger and colleagues (Weinberger, 2004) initially proposed a model with multiple key brain structures in associative receptive field plasticity, including the nucleus basalis, the amygdala, the brainstem, and the magnocellular medial geniculate nucleus. With their model they showed auditory plasticity in many of these structures, making the field switch from only focusing on plasticity in A1 to looking at subcortical structures. The nucleus basalis and its cholinergic projections is especially important in long-term plasticity according to the Weinberger model (Weinberger, 2007). Suga and colleagues (Suga et al., 2003) agreed on the importance of the nucleus basalis in plasticity but also proposed in their alternative model which included the descending auditory system, suggesting that plasticity that develops in the association cortex is relayed via the amygdala to the inferior colliculus, which then promotes plasticity in A1. (Suga et al., 2003; Weinberger, 2007) Bajo and colleagues (Bajo et al., 2010) further stressed the role of the descending auditory pathways, by showing that lesions in these pathways did not affect sound-localization in ferrets but did severely affect localization learning. Their results indicated that descending projections from A1 is responsible for learning and that concurrent plasticity might occur subcortically. Therefore, a shift in the literature occurred of only focusing on plasticity in A1 to also observing plasticity in subcortical structures. This was further investigated by Edeline and colleagues (Edeline et al., 2011), they stimulated the locus coeruleus – a small brainstem structure with noradrenergic projections – paired with a tone frequency while recording cells both in the auditory cortex and the auditory thalamus. They observed plasticity in both the cortex and the thalamus because of locus coeruleus-tone pairing, indicating plasticity at the thalamic and cortical level and the importance of the locus coeruleus-noradrenergic pathway in promoting auditory plasticity. In the work of Shore and colleagues (Shore et al., 2006), another structure in the brainstem, the cochlear nucleus, has been highlighted as having an important role in auditory plasticity (Koehler et al., 2013; Shore et al., 2006). The cochlear nucleus' principal output are fusiform cells, and a hyperactivity in these cells has been suggested to be related to tinnitus, a phantom auditory perception (Dehmel et al., 2012; Koehler et al., 2013; Stefanescu et al., 2015).

Another leading hypothesis that should be mentioned in relation to perceptual learning and plasticity is the expansion-renormalization model for plasticity and learning (Reed et al., 2011). Reed and colleagues (Reed et al., 2011) applied nucleus basalis stimulation through a surgical implant while presenting rats with a frequency discrimination task. This was based on findings that nucleus basalis stimulation paired with tone presentations leads to stimulus-specific tonotopic map expansions in A1 and the secondary auditory cortex possibly by mimicking nucleus basalis activity during periods of arousal (Froemke et al., 2007; Kilgard et al., 1998; Puckett et al., 2007). The results showed cortical map plasticity to be associated with learning, but not as much with performance. Reed and colleagues (Reed et al., 2011) made this distinction by using nucleus basalis stimulation-tone pairing to cause auditory map expansions before discrimination learning to assess learning. Performance was assessed by pairing nucleus basalis stimulation with tones in rats that had already learned the task. They found that the nucleus basalis stimulation-tone pairing enhanced tone frequency discrimination learning. No difference in discrimination ability was found between the paired group and the control group after they had already learned the task, indicating that performance on a well-learned task could not be further improved through nucleus basalis stimulation-tone pairing, specifically for the low tone group. Based on this finding, the expansion-renormalization model for plasticity and learning was formulated (Reed et al., 2011). Unlike the earlier hypothesis that suggested that improved frequency discrimination is due to large scale cortical map reorganization, this model has suggested that improved frequency discrimination may be due to a temporary increase of a cortical representation only for the duration of the task. After learning is complete, the map is hypothesised to return to its "normal" organization. Although this model is more generally applicable to learning and plasticity, in this instance it will be discussed in relation to auditory perceptual learning. According to the expansion-renormalization model, the process of auditory perceptual learning consists of two stages. In the expansion stage, neuromodulators are repeatedly released during the discrimination of a target frequency. Due to the release of these neuromodulators, the cortical map expands by increasing the number of neural circuits related to that frequency. After map expansion, the neural circuits associated with the stimulus will be more easily available. According to this model, after learning is complete, the map will return to its "normal" organization. Froemke and colleagues (Froemke et al., 2013) have shown results in favor of the expansion-renormalization model. They studied neural activity in rats in vivo by applying nucleus basalis stimulation paired with tone presentations. Indeed, the findings indicate that nucleus basalis stimulation-tone pairing induced increased excitation of the paired input, while decreasing excitation for the stimuli that originally evoked the largest response. This finding argues for an optimization of the underlying neural circuits as a response to the trained frequency. Interestingly, they also recorded long-term changes and observed that inhibition at the paired input recovered and returned to its default organization.

The findings discussed up to here are a brief representation of what has been done in the field so far, for a full review on the mechanisms underlying auditory perceptual learning see Irvine and colleagues (Irvine, 2018b). Overall, there seems to be a lack of agreement between studies on the mechanisms related to auditory perceptual learning, but the majority agrees that neural plasticity is involved.

3. Non-invasive brain stimulation and auditory perceptual learning

The finding that the auditory system is plastic is promising, especially for methods like non-invasive brain stimulation which have been related to the promotion of plasticity in the brain (Huang et al., 2017). Non-invasive brain stimulation is a relatively novel technique used to identify the functional role of specific brain structures (Cirillo et al., 2017).

Most studies investigating non-invasive brain stimulation in relation to auditory perceptual learning have used transcranial electrical stimulation. Transcranial electrical stimulation is a non-invasive, cost-effective, highly tolerable, and convenient method (Hoy et al., 2010). There are three types of transcranial electrical stimulation that are most commonly used: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). tDCS applies a weak direct electrical current to the scalp through two or more electrodes, either in an anodal or cathodal fashion (Woods et al., 2016). The effects of tDCS are believed to occur due to the manipulation of ion channels or a shift in the electrical gradients across the neural membrane (He et al., 2020). Motor studies have shown that when an anodal electrode was applied over the primary motor cortex, it enhanced corticospinal excitability, whereas the cathodal electrode diminished it (He et al., 2020; Nitsche et al., 2005). From these observations in the motor cortex, it was concluded that anodal stimulation enhances cortical excitability, whereas cathodal stimulation supressed it. In contrast, tACS applies a sinusoidal current to the scalp and is believed to induce frequency dependent effects through modulation of endogenous oscillations in the brain (He et al., 2020). Similar to tACS, tRNS also uses alternating currents, but with tRNS the stimulation frequency continuously changes within a spectrum of oscillations.

There are a few studies that have used non-invasive brain stimulation to investigate its effects on auditory perceptual learning. The stimulated brain area is mostly the A1 because of its intuitive relation to auditory learning.

Mathys and colleagues (Mathys et al., 2010) investigated the effects of cathodal and anodal tDCS applied to the Heschl's gyrus on a pitch direction discrimination task. In this task, participants were asked to indicate whether a second tone was higher or lower than the first. Before the stimulation was applied, the participants engaged in a practice session without tDCS. A day later, three tDCS sessions took place each with a day in between. In the stimulation groups, participants received stimulation over the right or left Heschl's gyrus, and results showed that cathodal tDCS on the Heschl's gyrus interferes with pitch direction discrimination ability. More specifically, they found a greater contribution to this interference by the right Heschl's gyrus compared to the left. Although an inhibiting effect was found during cathodal stimulation, no significant effects were found in the anodal stimulation group. Mathys and colleagues (Mathys et al., 2010) used *offline* stimulation in their study, meaning the stimulation was not delivered during the task, but before or after. In this case, stimulation was delivered before the task. Similarly, Loui and colleagues (Loui et al., 2010) applied offline cathodal tDCS to the superior temporal gyrus and the inferior frontal gyrus before a pitch matching task, chosen because this skill is impaired in tone-deaf people (Loui et al., 2008). Participants were presented with a pure tone and were asked to reproduce the tone by humming. Stimulation was delivered on four separate days for 20 min over four target regions: the left posterior superior temporal gyrus, left posterior inferior frontal gyrus, right posterior superior temporal gyrus, and right posterior inferior frontal gyrus. The fifth day, sham stimulation was applied. After each stimulation session, the participant engaged in the pitch matching task. They found a disruption in pitch matching after cathodal tDCS was delivered to the left posterior inferior frontal gyrus. Additionally, they report that stimulation over the right posterior superior temporal gyrus produced marginal disruptions in pitch matching. There were no effects of stimulation found on the right posterior inferior frontal gyrus and left posterior superior temporal gyrus. In contrast, Tang and Hammond (Tang et al., 2013) used *online* stimulation, meaning the stimulation was delivered during the task. Participants were trained on a frequency discrimination task for two days. Anodal or sham tDCS was applied over the right auditory cortex only on the first day of testing but not on the second day. They found that anodal tDCS applied over the right auditory cortex impaired frequency discrimination. The authors argued that this was due to tDCS affecting temporal coding, shown through the result of a decreased frequency selectivity – a measure related to place coding – at 2000 Hz but not at 1000 Hz. Temporal processes seem to play a dominant role at lower frequencies, whereas place processes are more dominant at higher frequencies (Johnson, 1980). Similarly, Matsushita and colleagues (Matsushita et al., 2015) found a disruption in pitch discrimination learning when anodal tDCS was applied over the right temporal cortex. Participants were trained on a micromelody pitch discrimination task for three consecutive days. The task consisted of a pair of micromelodies, and the participant was asked to indicate whether the two items were the same or different. On the first day, the baseline performance was measured without applying tDCS. The next day, participants received tDCS while performing the same task as on the first day. On the third day, the participant performed the task again without receiving any tDCS. The sample was divided in three groups: the anodal group, the cathodal group, and the sham group. Cathodal tDCS did not have a significant effect on pitch discrimination learning. When replicating their initial study, Matsushita and colleagues (Matsushita et al., 2021) found the same result that applying anodal tDCS over the right auditory cortex disrupts pitch learning. Furthermore, they recorded electrophysiological data through MEG. MEG was recorded before, during, and after tDCS. MEG data showed that tDCS to the left or right auditory cortex induced an ipsilateral decrease in N1m amplitude during stimulation. In conclusion, this study showed a significant association between pitch threshold changes and the degree of decrease of N1m induced by tDCS in the right auditory cortex.

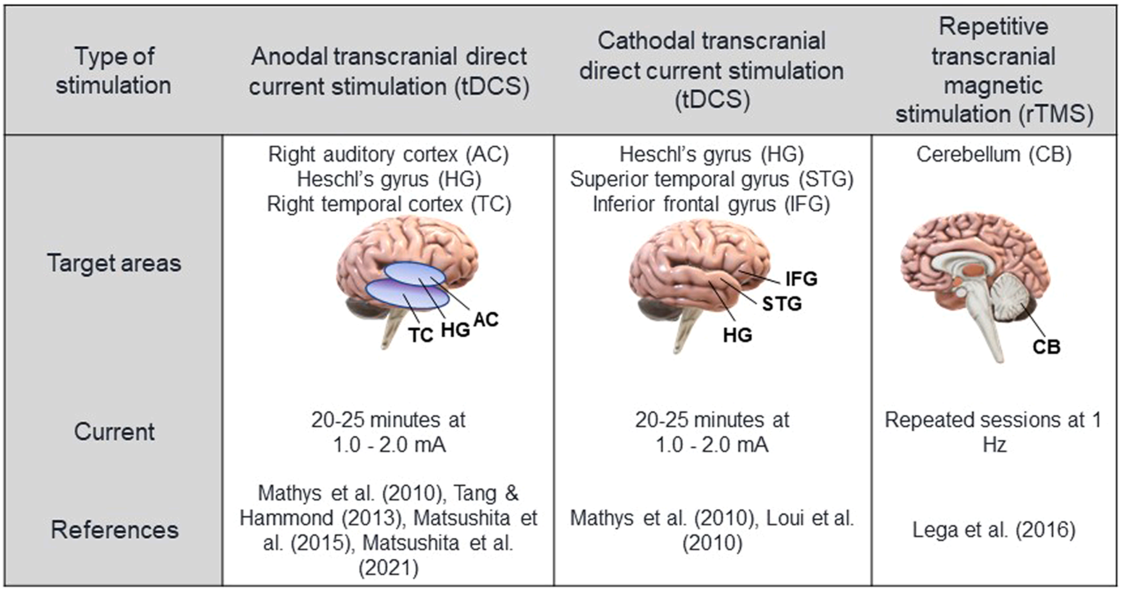
Lega and colleagues (Lega et al., 2016) used another type of non-invasive brain stimulation, transcranial magnetic stimulation (TMS), to look at the role of the cerebellum in pitch and timbre discrimination. TMS uses magnetic stimulation to deliver single pulse, double pulse, online repetitive pulse, or offline repetitive pulse to the brain (Parkin et al., 2015). The effect of the stimulation on cortical activity is dependent on the type of pulse. For example, single pulse displays excitatory effects, whereas repetitive pulse has an inhibitory effect (Parkin et al., 2015). Lega and colleagues (Lega et al., 2016) applied offline repetitive TMS at 1 Hz to the right cerebellum expecting an inhibiting effect on performance. Participants performed two tasks – a pitch discrimination and a timbre discrimination task – before and after they received TMS. They found that offline repetitive TMS at 1 Hz impaired pitch discrimination ability but not timbre discrimination. These results show a possible association between the subcortical cerebellum and pitch discrimination ability.

So far, studies investigating the effects of non-invasive brain stimulation on auditory perceptual learning produced mixed results. On one hand, cathodal tDCS on the right auditory cortex – specifically, Heschl's gyrus – has shown to disrupt pitch discrimination performance (Mathys et al., 2010). On the other hand, anodal tDCS that is thought to have an excitatory effect on the brain, displayed the same disruptive effect (Matsushita et al., 2015, 2021; Tang et al., 2013). Other brain regions that have been linked to auditory perceptual learning are the left posterior inferior frontal gyrus and the cerebellum (Lega et al., 2016; Loui et al., 2010). Interestingly, none of the studies using non-invasive brain stimulation led to an improvement in performance on an auditory perceptual learning task. An overview of the stimulated areas and non-invasive brain stimulation techniques used in auditory perceptual learning studies can be found in Fig. 2.

4. Challenges and future directions

The conflicting results found in studies applying non-invasive brain stimulation to auditory perceptual learning could be explained by methodological differences. The first difference lies in the use of offline stimulation versus online stimulation. So far, no studies have examined the effects of online versus offline stimulation in auditory perceptual learning directly. However, a study investigating the effect of online versus offline transcranial electrical stimulation in visual perceptual learning found that offline stimulation applied to the primary visual cortex increased visual perceptual learning whereas online tDCS did not improve performance (Pirulli et al., 2013). Although visual perceptual learning and auditory perceptual learning have different underlying mechanisms both are based on experience-dependent learning. Therefore, future research may benefit from further exploring online and offline stimulation in auditory perceptual learning.

Another crucial difference is whether a study used stimulation of learning or stimulation of test performance. In a stimulation of learning paradigm, the subject participates in a learning phase first while receiving stimulation before or during this phase, concurrently the participant is tested on a learning outcome measure (Simonsmeier et al., 2018). In contrast, in stimulation of test performance, participants receive brain stimulation before or during their performance on a test without any learning phase beforehand. Simonsmeier and colleagues (Simonsmeier et al., 2018) argues for an underestimation of the beneficial effects of transcranial electrical stimulation due to a lack of differentiation in studies between stimulation of learning and stimulation of test performance. With their meta-analysis, they showed that



Type of stimulation	Anodal transcranial direct current stimulation (tDCS)	Cathodal transcranial direct current stimulation (tDCS)	Repetitive transcranial magnetic stimulation (rTMS)
Target areas	Right auditory cortex (AC) Heschl's gyrus (HG) Right temporal cortex (TC)	Heschl's gyrus (HG) Superior temporal gyrus (STG) Inferior frontal gyrus (IFG)	Cerebellum (CB)
Current	20-25 minutes at 1.0 - 2.0 mA	20-25 minutes at 1.0 - 2.0 mA	Repeated sessions at 1 Hz
References	Mathys et al. (2010), Tang & Hammond (2013), Matsushita et al. (2015), Matsushita et al. (2021)	Mathys et al. (2010), Loui et al. (2010)	Lega et al. (2016)

Fig. 2. Schematic overview of studies. Overview of non-invasive brain stimulation applied in auditory perceptual learning studies.

transcranial electrical stimulation in the learning phase is more effective than transcranial electrical stimulation in the test phase on a variety of cognitive tasks. When looking at the studies mentioned here, half of the studies used stimulation of learning (Matsushita et al., 2015, 2021; Tang et al., 2013) and the other half stimulation of test performance (Lega et al., 2016; Loui et al., 2010; Mathys et al., 2010). What could also be considered is the type of stimulation that is used. The studies discussed above that used transcranial electrical stimulation, all used tDCS. Considering the methodological differences between the three types of transcranial electrical stimulation, it is important to evaluate which one suits the current modality best. Although no studies have directly investigated the effects of tACS on auditory perceptual learning, there are some studies that looked at the effects of tACS on auditory cortex excitability (Hyvärinen et al., 2018; Wang et al., 2021, 2023). Wang and colleagues (Wang et al., 2021) investigated the effects of tACS on the auditory cortex by using the auditory steady-state response (ASSR) – a measure used to assess activity in the auditory pathway – and found that tACS had an inhibitory effect on 40 Hz ASSR, implying that tACS might modulate cortical activity in the auditory cortex. In contrast, Van Doren et al. (2014) found that temporal tRNS increased the power of the 40 Hz ASSR. These studies indicate that not only tDCS can modulate cortical activity in the auditory cortex, but tACS and tRNS also seem to do so. Therefore, future studies may benefit from using tACS and tRNS in relation to auditory perceptual learning. Furthermore, another suggestion has been offered for the conflicting results in transcranial electrical stimulation studies. Namely, it has been proposed that the effects of transcranial electrical stimulation might be more likely to be due to stimulation of peripheral nerves in the skin and not only by direct stimulation of the cortex (Asamoah et al., 2019). The hypothesis of peripheral nerve stimulation has been supported by a study by Vöröslakos and colleagues (Voroslakos et al., 2018) who showed that only 25 to 50 percent of the applied current reaches the brain due to the high electrical resistance of the skull. Indeed, our research group has found an enhancing effect on learning and memory when delivering stimulation to the greater occipital nerve (Luckey et al., 2022, 2020; Vanneste et al., 2020). By using occipital nerve stimulation, the locus coeruleus-noradrenaline pathway might be activated via the peripheral nervous system (Bear et al., 1986; Martins et al., 2015; Vanneste et al., 2020). The locus coeruleus- noradrenaline pathway has shown to promote arousal through the influence of the nucleus of the solitary tract (McIntyre et al., 2012). Concurrently, arousal has shown to improve frequency discrimination by reducing noise correlations (Downer et al., 2015; Lin et al., 2019). Animal studies have shown that pairing perceptual learning with stimulation of the locus coeruleus in rats enhanced auditory perceptual learning through the release of noradrenaline in the auditory cortex (Glennon et al., 2019; Martins et al., 2015). They found that activation of the locus coeruleus paired with pure tones led to long-term responses in formerly silent cells indicating plasticity. Behaviourally, an accelerated learning rate for a new tone in the rats that received locus coeruleus stimulation compared to the control group was observed. These studies suggest that the locus coeruleus plays an important role in auditory perceptual learning, and by using occipital nerve stimulation, the locus coeruleus might be activated in humans (Vanneste et al., 2020). These findings also tie in with the earlier discussed study by Edeline and colleagues (Edeline et al., 2011) in which they found plasticity in the auditory thalamus as a result of locus coeruleus stimulation (Bajo et al., 2010; Edeline et al., 2011). A similar pathway exists for other peripheral nerves including the vagus nerve, in which stimulation increases the noradrenergic release from the locus coeruleus, and in some studies has been associated with increased retention performance and consolidation (Ghacibeh et al., 2006; Jacobs et al., 2020). Vagus nerve stimulation has also been shown to act on the basal forebrain from projections of the nucleus of the solitary tract, which further suggests that the basal forebrain-aCh system can be activation via vagus nerve stimulation, as it has been shown that vagus nerve stimulation evoked activity of the cholinergic axons in the auditory cortex (Mridha et al., 2021). Other pathways that have been stimulated transcutaneously are the trigeminal and dorsal column pathways to the dorsal cochlear nucleus by Wu and colleagues (Wu et al., 2015). They used transcutaneous electrical stimulation of the face and neck in rats to activate these pathways combined with an auditory stimulus. They observed long-lasting changes in the firing rates of the fusiform cells as a result of the stimulation, indicating stimulus time dependent plasticity in these cells.

To conclude, both anodal and cathodal tDCS applied to the auditory cortex disrupt auditory perceptual learning (Mathys et al., 2010; Matsushita et al., 2015, 2021). Additionally, rTMS to the cerebellum also showed a disruption in auditory perceptual learning (Lega et al., 2016). The mechanisms underlying the disruption are unclear. There are major differences in the application of stimulation in these studies. While some studies used online stimulation, others used offline stimulation with wide variety in the amount of stimulation sessions. It may improve future research in auditory perceptual learning to establish a protocol to be used in non-invasive brain stimulation studies by using knowledge from other fields. In addition, most studies thus far have applied stimulation to the auditory cortex. However, there are many studies that show plasticity in the auditory system starts subcortically (Bajo et al., 2010; Carcagno et al., 2011; Edeline et al., 2011; Lega et al., 2016; Wu et al., 2015) Therefore, we suggest future research to not only target the A1 but also focus on the subcortical structures in the auditory pathway, including the cochlear nucleus, the locus coeruleus, or the nucleus basalis as a way to stimulate plasticity and possibly enhance auditory perceptual learning. In humans, these subcortical structures could be activated non-invasively through the use of peripheral nerve stimulation. This might enhance our understanding of the auditory pathways and the subcortical structures involved with auditory perceptual learning. A further understanding could be useful in auditory disorders, for example in speech disorders, tinnitus, or for cochlear implant users.

5. Conclusion

The different techniques used in research related to auditory perceptual learning have all contributed substantially to a better understanding of the neural mechanisms underlying perceptual learning. From these studies, it has become clear that synaptic plasticity is key in understanding auditory perceptual learning. Research in animal models have shown an association between tonotopic map plasticity in the A1 and improved frequency discrimination. By using non-invasive brain stimulation, cortical activity can be modulated and promoted which has provided the field with further understanding of the brain areas involved with auditory perceptual learning. Although non-invasive brain stimulation seems to have these enhancing effects in other domains, in the auditory domain the effect seems to be mostly disruptive. However, many methodological differences have been found between these studies and there is not only a pressing need for more studies in this area, but also more agreement in the application of non-invasive brain stimulation in auditory perceptual learning studies – with regards to the timing of stimulation, the type of stimulation, and the stimulated brain area. We suggest exploring peripheral nerve stimulation for subcortical structures to understand more about the auditory pathways. From these studies, a better understanding of the mechanisms of auditory perceptual learning in humans can be established which will be relevant for understanding how perceptual learning occurs.

CRediT authorship contribution statement

Yvette Grootjans: Writing – original draft, Writing – review & editing. **Gabriel Byczynski:** Writing – review & editing. **Sven Vanneste:** Writing – review & editing.

Declaration of Competing Interest

None.

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