NEUROPHYSIOLOGICAL INVESTIGATION OF AUDITORY AUGMENTATION TO FACILITATE OBSERVATIONAL LEARNING OF EVERYDAY ACTIONS

A Thesis Submitted for the Degree of Doctor of Philosophy

By

Fabio Castro

Department of Life Sciences, College of Health, Medicine and Life Sciences

Brunel University London

ABSTRACT

This thesis explores the neurophysiology of auditory augmentation of observed actions, and its effects on motor learning, neural activity, and plasticity. To this end, three studies were conducted. In the first study, we used Transcranial Magnetic Stimulation (TMS) to determine the effects of practising a motor task via sonification of combined action observation and motor imagery (sAOMI) on corticospinal excitability, compared to practising without extrinsic auditory information. In addition, we aimed at probing practice-dependent audiomotor plasticity. To this extent we used a variation of a commonly used method to probe and induce plasticity in humans, auditory paired associative stimulation (aPAS). Practice significantly increased corticospinal excitability, but sonification did not affect it. In addition, while aPAS completed alone significantly modulated corticospinal excitability, when practice primed aPAS, no neuromodulation was found. In a follow-up study, we explored the effects of sAOMI on corticospinal excitability during action observation (AO) or AOMI of the same action, and whether sonification induced audiomotor resonance, which is usually interpreted as development of an audiomotor association. The results corroborated and extended the findings of the previous study: practice increased corticospinal excitability at rest and during AO and AOMI, but sonification did not affect it. In addition, with sonification did not induce an audiomotor association. In a third study, we used electroencephalography (EEG) and other psychophysical measures, including a motor imagery questionnaire and mental chronometry, to assess changes resulting from practising with sonified action observation, followed by motor imagery of the same action. After two practice sessions, performance and kinaesthetic motor imagery vividness significantly improved, and participants' mental chronometry was significantly more aligned with the speed of the observed action, compared to pre-practice measures. Sonification did not induce changes in any measure. EEG analysis revealed that participants who practised with sonification were able to sustain event-related desynchronization (ERD) in the lower alpha band (7-10 Hz) for longer, compared to participants who practices without sonification. No changes in higher alpha (10-12 Hz) or Beta (16-25 Hz) bands were found. Taken together, convergent results from this thesis suggest that sonified action observation has little effect on neurophysiological and behavioural markers of motor imagery ability and performance in healthy individuals. On the other hand, practising with sonified action observation may induce attentional modulations that enhance the learner's ability to sustain action-related attentional processing for longer. We discuss these results in the context of contemporary neurocomputational theories of perception and action.

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LIST OF ABBREVIATIONS

ADM: Abductor Digiti Minimi

AO: Action Observation

AOMI: Combined used of action observation and motor imagery

aPAS: Auditory Paired Associative Stimulation

APB: Abductor Pollicis Brevis Muscle

BCI: Brain-Computer Interfaces

CNS: Central Nervous System

CON: Control Group

EEG: Electroencephalography

FDI: Frist Dorsal Interosseus Muscle

IPL: Inferior Parietal Lobule

LTD: Long Term Depression

LTP: Long Term Potentiation

MI: Motor Imagery

MIQ: Motor Imagery Questionnaire

MP: Mental Practice

MRP: Movement-related Potentials

OL: Observational Learning

PAS: Paired Associative Stimulation

PMv: Ventral Premotor Cortex

PNS: Peripheral Nervous System

PP: Physical Practice

sAO: sonified Action Observation

sAOMI: Sonified combined action observation and motor imagery

SMA: Supplementary Motor Area

SON: Sonification Group

STS: Superior Temporal Sulcus

TMS: Transcranial Magnetic Stimulation

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LIST OF PUBLICATIONS

Articles Published

Castro, F., Osman, L., Di Pino, G., Vuckovic, A., Nowicky, A., & Bishop, D. (2021). Does sonification of action simulation training impact corticospinal excitability and audiomotor plasticity? *Experimental Brain Research*, 1-17. DOI: 10.1007/s00221-021-06069-w

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Manuscript in Preparation

Castro, F., Vuckovic, A., Nowicky, A., & Bishop, D. Electrophysiological Correlates of sonified Observational learning.

INTRODUCTION

This thesis explores how a richer perceptual environment, in the form of auditory augmentation of observed actions, may affect the ability to imagine and learn those actions. Originally developed in sport psychology, the use of action observation (AO) and motor imagery (MI) in clinical sciences has recently been encouraged, validated by studies suggesting that these cognitive activities can induce long-lasting effects on the sensorimotor system and performance. As a learning strategy, however, AO and MI are suboptimal, compared to physical practice (PP), possibly due to the lack of sensory feedback associated with actions. In the series of studies presented in this thesis, we explore whether movement sonification, associated with AO of different actions affects behavioural and neurophysiological indices related to brain activity and learning. Movement sonification refers to a feedback strategy whereby sound is associated with – and modulated by – movement.

This thesis is organised in Five Chapters. In Chapter 1, we will introduce and discuss existing literature on the topic. We begin with an overview of the nature of multisensory processing and its role in creating and maintaining internal representations of body and environment. This provides the conceptual and computational bases to discuss neurophysiology of action simulation. Next, we discuss neurophysiology of sensorimotor learning, and various forms of practice pertinent to this thesis, namely learning with sensory augmentation as well as observational and mental practice. This leads up to three experimental chapters, summarising three studies completed during the Ph.D. Chapter 2 will describe an investigation using Transcranial Magnetic Stimulation (TMS) on the effects of practising with sonification of combined action observation and motor imagery (sAOMI) on corticospinal excitability. In addition, this study presents an investigation on practice-dependent audiomotor plasticity, by using a modified version of a common TMS method to induce and probe plasticity – Auditory Paired Associative Stimulation (aPAS). In Chapter 3, another TMS study will extend the previous chapter, by investigating practice-dependent audiomotor resonance induced by a similar sAOMI practice. In the last experimental chapter, Chapter 4, we focus on sonified action observation (sAO), and its effects on the ability to perform and imagine actions, as well as changes in neural activation after a two-days practice protocol. These three chapters are self-contained, providing a discussion of the topic and results obtained. Chapter 5 will summarise and unify the results from the three experimental chapters, and provide a general discussion on the topic, in light of contemporary neurophysiological and computational theories of action and perception, as well ideas for future investigations.

CHAPTER 1

THE MULTISENSORY NATURE OF MOTOR COGNITION AND LEARNING.

1.1. PERCEPTION AND (SIMULATED) ACTION

This thesis explores auditory augmentation of simulated actions, and its relationship with motor control and learning. Auditory augmentation refers to a class of extrinsic feedback strategies whereby a sound is used to provide information about *hidden* aspects of the environment, aspects of our worldly experience that would be hard to perceive without extrinsic information (Dubus & Bresin, 2013; Schaffert, Janzen, Mattes, & Thaut, 2019; Sigrist, Rauter, Riener, & Wolf, 2013). A fundamental axiom of sensory augmentation is the existence of a link between perception and action, such that an enriched perceptual environment affords individuals with better *internal representations* of the environment, the body and their interaction (henceforth referred to as representations; Sigrist et al., 2013). This, in turn, allows for better sensorimotor processing, leading up to a more stable performance. The first section of this literature review provides a brief description of the computational valence of sensory information for sensorimotor control. After, neuroanatomy and neurophysiology of action observation and motor imagery will be discussed, laying the bases for the second part of the literature review, which discusses their use in sensorimotor learning.

1.1.1. Internal Representations in the Brain

In computational neuroscience, an internal representation refers to a mapping between causes and effects; that is, between an action and the anticipated sensory and environmental states (Sensinger & Dosen, 2020)[1]. While the exact algorithmic processes making up those internal representations and their role in perception and action are under debate (Friston, 2011a; McNamee & Wolpert, 2019; Ostry & Feldman, 2003; Wolpert, 2007), there is agreement that the emergence of behaviour is carried out by a message passing in feedforward and feedback streams, between brain networks involved in decision-making, action preparation and execution (Sensinger & Dosen, 2020). In the context of sensorimotor control, feedforward control acts as a top-down definition of the motor command. Originating from a goal, the brain decides (i.e. predicts) the most appropriate action, given the desired effects, and defines the dynamics of the motor commands that would eventually leave the brain towards muscles (Adams, Shipp, & Friston, 2013; Kriegeskorte & Diedrichsen, 2019). This is also referred to as an inverse model (from effects to causes). Another important consideration in the definition of the motor command is the sensory predictions about the effects of the motor command.

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[1] Depending on the particular field of research, internal representations are also called internal models, and represent a longstanding issue in sensorimotor and cognitive neuroscience (McNamee & Wolpert, 2019).

Indeed, sensory feedback is slow and noisy (Shadmehr & Krakauer, 2008; Shadmehr, Smith, & Krakauer, 2010). Thus, a forward model (from causes to effects) feeds back predictions to the controller, about the sensory consequences of a motor command (Desmurget & Grafton, 2000). This information is taken into consideration in perceptual feedback processing (Blakemore, Wolpert, & Frith, 2000).

One issue with purely feedforward control is that it does not take into consideration real-time environmental contributions to the state of the system (Ostry & Feldman, 2003). This is a major issue, as actions always happen in an ever-changing environment. To complicate things, sensory and motor systems are inherently noisy and delayed, posing challenges to exactly define the set of control command for human-environment interaction (Körding & Wolpert, 2006). Thus, a feedforward stream is integrated with a feedback stream, which provides the controller with important information about the state of the system itself, via interception and proprioception, as well as the environment, via exteroception. Feedforward and feedback streams are interfaced via a comparator, a computational device that estimates the difference (or error) between top-down predictions and bottom-up feedback streams (Körding & Wolpert, 2004; Sensinger & Dosen, 2020; D. M. Wolpert, 2007). The importance of feedback streams for motor control is appreciated in clinical conditions where feedback is not present, especially proprioception and movement-related feedback. These conditions are characterised by very uncoordinated movement (Hermsdörfer, Elias, Cole, Quaney, & Nowak, 2008), and in the case of a lack of proprioception, the inability to control body parts that are not in the visual field (Sacks, 1985). Feedback is also very important for body perception and ownership, which is revealed by research on sensorised prostheses, and their link to body ownership in amputees (Di Pino et al., 2020; Sensinger & Dosen, 2020). Lastly, as will be discussed in Section 2, lack of movement-related feedback may affect the rate of learning during AO and MI (Lepage et al., 2012; Pascual-Leone et al., 1995).

Different versions of computational theories of motor control exist, which provide different takes on the precise nature of the message passing between computational units (Friston, 2011b), as well as how this may be carried out by the brain (Friston, Daunizeau, Kilner, & Kiebel, 2010; Shadmehr & Krakauer, 2008). In recent years, conceptual works have advanced the idea that not only sensory, but also motor processing represent a process of inference (Botvinick & Toussaint, 2012), or active inference, as it has come to be known (Friston, 2005, 2010; Friston et al., 2010). Active inferences stresses that an imperative for the brain is to maintain *computational homeostasis* – stability against environmental perturbation. This is achieved via a process of prediction error minimization (Hohwy, 2016; Limanowski, 2014). That is, the brain tries to infer the hidden causes of sensation (Friston, Mattout, & Kilner, 2011; Kilner, Friston, & Frith, 2007; Palmer, Zapparoli, & Kilner, 2016), and it *behaves as if* it engages in computations similar to Bayesian inferences, actively engaging in hypothesis testing, minimizing the difference between its prior beliefs (predictions) and sensations sampled from the world (Gregory, 1980; Kanai, Komura, Shipp, & Friston, 2015). These inferences are carried out from those internal representations, which can be seen as a computational counterpart of Bayesian prior belief (Palmer, Auksztulewicz, Ondobaka, & Kilner, 2019).

Active inference retains the feedforward and feedback design but stresses the three-dimensionality of the computational processing (c.f. Mumford, 1992), with a different algorithmic arrangement of those streams in controlling actions (Friston et al., 2010). The process of prediction error minimization is carried out by perception and action, which interface internal representations, sensations and the environment. Perception is a process of bottom-up update of internal representations: the brain has internal representation based on prior experience; given certain sensations, the brain tries to infer the hidden causes of those sensations; and the difference between predictions and sensations, also known as *prediction error*, updates these representations. On the other hand, the brain can also change sensation sampled via actions. Given predictions about future sensations, also called *reafferences* (Pinardi et al., 2020a), an action arises as a top-down process of prediction error minimization between predicted, and current sensations (Palmer et al., 2016). Activation of the motor system arises as a result of this delta (Feldman, Ilmane, Sangani, & Raptis, 2014; Friston, Daunizeau, Kilner, & Kiebel, 2010), and depends on the computational equilibrium between sensorimotor prediction and afference (Feldman, 2011)[2]. Thus, internal representations are a mechanism the brain uses to gauge *knowledge* about the world, and the body it inhabits. It should be noted that according to the active inference, this process is recursive, happening at different levels of the computational hierarchy (Hohwy, 2013, 2016). One major consequence of active inference is that, within the right conditions, an enriched perceptual environment, for example via sensory augmentation, affords the possibility to refine these internal representations, allowing for more sophisticated and precise behaviour.

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[2] This view of motor control was originally proposed by Anatol Feldman in the latter part of the 20th century, under the name of 'Equilibrium-Point Hypothesis' (Feldman, 1966), but has extensive point of overlap with the 'Active Inference' account, proposed by Karl Friston and his colleagues (Friston et al., 2010).

How does the brain achieve this? Active inference proposes that inferences are carried out in the brain by a hierarchical structures of areas connected in a relatively stable and stereotyped fashion, as to carry out *information passing* between hierarchically lower levels, which encode physical aspects of the percept – sensations – and computationally higher levels, which encode progressively abstract representations of causality between worldly and bodily states (Kanai et al., 2015; Mumford, 1991, 1992; Shipp, Adams, & Friston, 2013). In the neocortex, neurons are organised in functionally segregated areas, distributed in cortical layers, each of which contains neurons that project and receive inputs from other areas and layers. Connectivity patterns between are ensured by descending connections from higher to lower areas, and ascending pathways from lower to higher areas. Since higher order areas are involved in abstract representation, top-down connectivity is thought to provide predictions about the sensation sampled. On the other hand, since lower order areas represent physical processing of sensations, bottom-up connectivity is thought to project prediction errors between sensations and top-down predictions (Shipp et al., 2013). As the processing travels throughout the hierarchy, unimodal sensations are integrated with other modalities, by a process of multisensory integration. Given sensory redundancy, sensations are integrated and weighted, based on their *epistemic precision* – The ability to decrease representational uncertainty (Mirza, Adams, Friston, & Parr, 2019). Thus, sensory integration is based on a hierarchy of sensory contribution, where hierarchically higher sensory contributions exhibit the least sensory noise, given the context (Körding & Wolpert, 2006). For example, in goal-directed behaviour, vision dominates the sensory hierarchy, and has a fundamental role in movement planning and motor cognition (Sarlegna & Sainburg, 2009). On the other hand, proprioception has been shown to play a fundamental role in motor control, providing valuable information about prediction error during actions (Friston et al., 2010; Polit & Bizzi, 1979). Interestingly, the hierarchy for sensory weighting is not fixed; unavailability of sensory information of one modality quickly results in a sensory re-weighting process. This is the case not only for permanent sensory loss, for example in blindness (Hamilton & Pascual-Leone, 1998), but also for a seemingly simple act of closing one’s eyes (Ben-Simon et al., 2013; Marx et al., 2004, 2003). It should be noted that this computational mechanism is not an exclusive part of active inference. Other theories of sensorimotor control assign the process of weighting sensory sources to the aforementioned comparator (Körding & Wolpert, 2006; Wolpert, 2007).

As sensations are integrated and transferred to hierarchically higher multisensory areas, they progressively lose their physical nature, to become more abstract representations of the interaction between the body and the environment (Hohwy, 2013). At the highest computational level the representation becomes amodal, as it loses its motor or perceptual nature (Friston et al., 2011; Kilner, 2011; Kilner, Friston, & Frith, 2007). This has direct application to sensory augmentation. Given its transitory nature, the goal of an effective sensory augmentation strategy is to integrate the augmented feedback with other sensations, such that they all concur to yield richer representations. This, in turn, affords the ability to make more precise sensorimotor predictions about perception and action. In other words, since an individual does not live in an environment where augmented feedback is constantly present, an effective sensory augmentation strategy should associate the augmented feedback with other sensorimotor characteristics of an action, such that performance improves above and beyond the practice phase. The exact mechanism for this is not completely clear, but evidence suggests that associative plasticity may be the neural underpinning of this integration (Guidali, Carneiro, & Bolognini, 2020; Petroni, Baguear, & Della-Maggiore, 2010). Section 2 and Chapter 2 will further discuss and explore this mechanism in relation to auditory augmentation.

From a neurophysiological point of view, convergence defines brain areas with multisensory characteristics. A simplified model of the influence of multisensory inputs on the behaviour of a single area can be used to clarify this point (c.f. Murray & Wallace, 2011; pp 8). In this model, an area is assumed to receive inputs from other areas, which process two sensory modalities (A and B). Inputs from modality A only will define *unisensory* areas, since the receiving area will contribute to computations within the same modality as its inputs. On the other hand, inputs from both modalities will confer the receiving area multisensory properties; In other words, its computations will spread on two modalities, with a spectrum of possible responses, depending on the distribution of inputs from single modalities. Bimodal areas have equal distribution of inputs from modality A and B, and it will be active during computation of both modalities. In unequal distribution of inputs from both modalities, the integration of inputs may be enough to make the area active for one modality, but not for another one. In this case, the area can be said to be subthreshold. This model highlights one of the most important features of multisensory integration, which is to serve as a *crossroad* from which processing of one modality interfaces with other modalities and together serve as a bottom-up integration of sensations. Studies on animals and humans have identified several areas with multisensory properties, such as superior temporal sulcus (STS; Hein & Knight, 2008), intraparietal Sulcus (IPS; Fogassi et al., 2005), and the premotor cortex (PM; Rizzolatti & Craighero, 2004).

It is, perhaps, not surprising that these areas have been systematically involved in sensorimotor transformations integrating multisensory input in the definition of actions. These areas are part of an established fronto-parieto network underlying action control, as well as simulated actions – Action Observation (AO) and Motor Imagery (MI; Davare, Kraskov, Rothwell, & Lemon, 2011; Hardwick, Caspers, Eickhoff, & Swinnen, 2018; Jeannerod, Arbib, Rizzolatti, & Sakata, 1995), and contain neurons with mirror properties or are part of an 'extended' mirror neurons system (Pineda, 2008). *Mirror neurons* have the special property of contributing to computations of both action and its perception (Rizzolatti & Craighero, 2004). Originally discovered in monkey's promotor cortex (area F5; di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992) mirror neurons are active during execution, as well as during perception of actions, e.g. AO. In addition, *audiomotor mirror neurons* underlie audiomotor transformations, after the discovery of with preferential firing for sound (Keysers et al., 2003; Kohler et al., 2002; Rauschecker & Tian, 2000; Rauschecker, 2011). Since their first discovery, neurons with mirror-like activity have been discovered in other areas of monkeys' brain, such as M1 (Kraskov et al., 2014; Kraskov, Dancause, Quallo, Shepherd, & Lemon, 2009; Vigneswaran, Philipp, Lemon, & Kraskov, 2013). Mirror-like neurons have also been documented in humans. Using single cells recordings, Mukamel, Ekstrom, Kaplan, Iacoboni and Fried (2010) provided the first account of neurons with mirror characteristics in humans, in areas such Supplementary Motor Area (SMA), and parietal lobe. Mirror neurons interface the brain with the environment, inferring the goal of a perceived action (Binkofski & Buccino, 2006; Kilner et al., 2007; Kilner, Friston, & Frith, 2007; Rizzolatti & Sinigaglia, 2016), and today, they are a very widely discussed topic[3].

1.1.2. Neuroanatomy of Simulated and Executed Actions

Throughout the years, a large body of research focussed on the analysis of the network active during either AO, or MI, as well the commonalities between simulated and executed actions, the so-called *functional equivalence* (Holmes & Collins, 2001). fMRI is the technique that has been most frequently used to examine functional equivalence (Jeannerod, 2001). However, whilst affording valuable insights, fMRI has some drawbacks. By nature, it relies on contrasts between experimental conditions of interests (e.g. rest vs MI). Thus, the type of contrast can impact results (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012). In addition, task choice may

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[3] In his book 'Against Empathy. A Case for Rational Compassion', Paul Bloom introduces a variation on Godwin's law, suggesting that, today, the longer a discussion in neuroscience, the easier it will be to end up talking about mirror neurons.

affect brain activity (Caspers, Zilles, Laird, & Eickhoff, 2010; Hardwick et al., 2018), thus representing a further potential confounding variable. Lastly, it has been reported that fMRI studies may be underpowered, thus providing unreliable results (Yarkoni, 2009). Metanalyses based on Activation Likelihood Estimates (ALE) proved to be valuable to overcome these potential confounding variables in neuroimaging studies (Eickhoff et al., 2012, 2009, 2016). Using ALE, studies suggest that the AO network is composed of bilateral ventral and dorsal premotor cortex (PMv and PMd, respectively), bilateral inferior and superior parietal lobules (IPL and SPL, respectively), parieto-occipital areas, pre-supplementary motor area (pre-SMA), and areas within the superior occipital gyrus (Caspers et al., 2010; Hardwick et al., 2018). On the other hand, MI consistently activates PMv, PMd, IPL, SPL, left dorsolateral prefrontal cortex (DLPFC), SMA, but also subcortical regions, such as the basal ganglia (putamen) and the cerebellum (lobule VI;) Hardwick et al., 2018; Hétu et al., 2013). One consistent result from ALE metanalyses is the activity in a fronto-parietal network. Conjunction analysis performed by Hardwick and colleagues suggests that PMv, PMd, IPL, SPL and SMA and pre-SMA are shared between AO, MI and physical execution (PE) of the same action. These results are also consistent with a single study by Filimon, Nelson, Hagler and Sereno (2007), which was among the few studies investigating a common network which may underlie neural representations of during executed and simulated actions. It should be noted, however, that *common* network does not necessarily mean *exact* network, as volume comparison showed that AO and MI activated only half of the voxels activated during PE (Hardwick et al., 2018), with different maxima (the voxel with maximum activity; Caspers et al., 2010; Hardwick et al., 2018; Hétu et al., 2013). In addition, Filimon, Rieth, Sereno and Cottrell (2015) reported that activity in premotor and parietal cortices could be successfully classified by multivariate fMRI analysis, suggesting that even thought a shared core network exists between AO, MI and PE, activity-dependent modulations of brain activity is still in place. Nevertheless, these results are consistent with theoretical accounts of action simulation, suggesting that both AO and MI interact with internal representations, but from different perspectives – AO as bottom-up, and MI as top-down, sensorimotor processing (Vogt, Di Rienzo, Collet, Collins, & Guillot, 2013).

It is interesting to note that Hardwick and colleagues did not report differences in activity in visual areas during AO vs MI, even though their analysis on the AO network reported activity in occipital areas. This may be due to the fact that Hardwick and colleagues did not perform contrasts sub-analysis between AO and different modalities of MI, due to a lack of studies on visual MI (Eickhoff et al., 2009). Visual motor imagery activates visual areas more strongly than kinaesthetic imagery (Guillot et al., 2009). The inability to differentiate between MI modalities may have affected the statistical differences between occipital voxels, thus failing to provide significant difference between AO and MI in these areas. To summarise, premotor and parietal areas can be considered as hierarchically higher areas, active both in perception and action (overt and covert). Consequently, one may speculate that these areas encode internal representations of the interaction between the body and the environment (Kilner & Lemon, 2013; Kilner et al., 2007a).

1.1.3. Investigating Neurophysiology of Visuo- and Audio-Motor Interaction with Transcranial Magnetic Stimulation

While fMRI is used to investigate functional specialization and segregation of brain activity (Friston et al., 2017), in humans, functional neurophysiology can be studied using Transcranial Magnetic Stimulation (TMS), with which is possible to stimulate the brain with a high degree of spatial focality and an excellent temporal specificity (Hallett, 2007; Loporto, Mcallister, Williams, Hardwick, & Holmes, 2011). Methodological development of Transcranial Electrical Stimulation (TES), TMS takes advantage of the magnetic fields produced by electrical current that passes briefly through a coil when the TMS is triggered (cit). The magnetic field produced penetrates the skull painlessly, and induces a intracranial current that activate neurons in underneath the stimulating coil (cit). When applied to M1, TMS allows to record the excitability of the corticospinal tract at rest and during different tasks, by recording motor-evoked potentials (MEPs) from a surface electromyographic (EMG) electrode, placed on the muscle of interest. This provides a physiological measure of the computational state of the sensorimotor system (Bestmann, de Berker, & Bonaiuto, 2015; Bestmann & Duque, 2016). Finally, causal connectivity among other brain areas and M1 can also be studied using double-coil protocols (for a review Neige, Rannaud Monany and Lebon, 2021).

Common output measures of TMS-evoked responses are the amplitude and the latency of the MEPs, which can be taken as an index of the state of the motor system, and provides information on the type of neurons targeted by the TMS pulse (Hallett, 2007). A higher MEP amplitude is taken as a measure of enhanced excitability of the corticospinal tract, which from deep cortical layers of M1 descend towards the muscles (Lazzaro & Ziemann, 2013). On the other hand, the latency of the MEP provides very useful information about which populations of neurons are stimulated by different TMS protocols (Di Lazzaro et al., 2012). Determinants of neurophysiological loci of TMS are, among others, coil orientation and stimulus intensity, which is then reflected in MEPs of different amplitude of latency. When the coil is oriented is a way as to induce posterior-to-anterior current in the brain, a TMS pulse activates corticospinal neurons, which are located in layer 5 of M1 (Di Lazzaro et al., 2012), indirectly, via monosynaptic projection from pyramidal neurons located in superficial layers (Abbruzzese & Trompetto, 2002; Esser, Hill, & Tononi, 2005) The latency of TMS-evoked MEP is 1.5 ms later than the one that can be evoked with transcranial electrical stimulation (TES), which is thought to activate the corticospinal neurons directly, at the axon hillock (Di Lazzaro et al., 2001). Direct, and indirect MEPs are reported as D- and I-waves, respectively. With TMS it is possible to evoke D-waves, but at high stimulation intensities (Di Lazzaro et al., 2004). A TMS pulse evokes different I-waves, which according to their order of arrival are named I1, I2, etc. These I-waves are thought to originate from different cortical structures, such as PMv (Di Lazzaro et al., 2012; Loporto et al., 2013). Changing coil orientation also changes the pattern of stimulation, possibly due to differences in recruitment of excitatory synapses (Di Lazzaro & Rothwell, 2014; Hannah, Rocchi, & Rothwell, 2018). Posterior-to-anterior coil orientation is thought to preferentially recruit I1 (Di Lazzaro et al., 2012). On the other hand, if the coil is rotated as to induce anterior-to-posterior current in the brain, later I-waves are preferentially recruited, possibly originating from cortico-cortical inputs to superficial layers (Di Lazzaro et al., 2001). Finally, if the coil is oriented as to induce latero-medial current in the brain, D-waves are evoked, even at low stimulation intensities, suggesting that this coil orientation has stimulation properties that are similar to TES (Nakamura et al. 1996; Kaneko et al. 1996; Lazzaro et al. 1998).

Taken together, TMS has been a major methodological development in the field of neuroscience and is now a common tool in the field on sensorimotor and cognitive neuroscience. Depending on the specifics of the TMS protocol, different properties of cortico-cortical and corticospinal system can be investigated, allowing us to investigate not only basic neurophysiology, but also brain activity during perception and action (Bestmann et al., 2015). In the following section, the neurophysiology of visuo-and audio-motor interaction will be described, providing propaedeutic notions that will be at the heart of later experimental chapters.

1.1.3.1.Neurophysiology of Visuomotor Interaction

Visuomotor interaction is carried out by a bottom-up dorsal pathway which, from the primary visual area, engages parieto and frontal areas (Goodale, 2011) From the first study on AO using TMS (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995), several studies suggest that when people observe an action, their corticospinal tract becomes active, which is reflected in an increase in MEP amplitude (Vincenzo Di Lazzaro & Rothwell, 2014), although not all studies are consistent with this proposition (c.f. the review by Naish, Houston-Price, Bremner, & Holmes, 2014). This increase in corticospinal excitability is also known as *visuomotor resonance* (Uithol, van Rooij, Bekkering, & Haselager, 2011). Given the high spatial and temporal specificity of TMS; studies have focussed on three main characteristics of visuomotor resonance, namely muscle, temporal and contextual specificity of corticospinal excitability during AO.

Muscle specificity of motor resonance. Studies investigating muscle specificity of motor resonance report that when a person observes an action, there is a muscle-specific activation of the same muscle used to perform the action. Although, several studies investigated this, Naish et al. (2014) argued that not all studies compared motor resonance with EMG during physical execution of the same action. This is important especially for multi-degrees of freedom actions. A series of studies have investigated simple, one degree of freedom movement, like finger adduction/abduction. Romani et al. (2005) reported that when participants observed thumb abduction/adduction, MEPs over the Abductor Digiti Minimi (ADM) muscle were significantly higher than when participants observed a still image of the hand or had their eyes closed. The observation-induced facilitation was not present, however, for the ADM muscle. The opposite was reported when participants observed little finger abduction/adduction. Intriguingly, the same pattern of facilitation was also seen when participants observed impossible movements made with the same muscles, suggesting that motor resonance may have to do more with the coding of the internal representation of the body, rather than exactly simulating the action. A later study extended the original finding by Romani et al. (2005), by reporting that the muscle-specific facilitation was only present when there was a congruence between prime mover activity and the observed action (Urgesi, Candidi, Fabbro, Romani, & Aglioti, 2006). Specifically, First Dorsal Interosseus (FDI) muscle was facilitated only when the palm was oriented downward, while the opposite happened for ADM muscle. This was coherent with electromyography (EMG) activity recorded during the actual execution of the movements. Not all studies have reported muscle-specific facilitation during AO, reporting mixed results. For example Lepage, Tremblay and Théoret (2010) reported an increase in corticospinal excitability during AO of index finger movements, not only in FDI muscle, but also in ADM muscle, which would not normally participate to the action. Similar results were obtained by D’Innocenzo et al. (2017). Somewhat opposite results were reported by Kaneko, Yasojima and Kizuka (2007), who reported a partial muscle-specific facilitation only for FDI during index abduction/adduction, but not for ADM during little finger abduction/adduction.

Temporal specificity of motor resonance. The earliest modulation of corticospinal excitability during AO was reported by Lepage et al. (2010). They collected MEPs at different time points, while participants observed either an index finger abduction/adduction, or a video of a static hand. MEPs during index finger movement observation were significantly higher only when the TMS pulse was delivered between 60 and 90 ms from the onset of the video. This modulation, as discussed earlier, was non-muscle specific. On the other hand, other studies suggests that at later time points (around 200 ms) there is a muscle-specific motor resonance (e.g. Cavallo, Bucchioni, Castiello, & Becchio, 2013). In their model of spatio-temporal AO-dependent motor resonance, Naish et al. (2014) suggests a dual-phase processing, where a first activation, around 100ms, represent non-muscle specific activity depending on attentional processes, followed by a phase of muscle-specific activation based on top-down processing, such as recognition of action correctness and prior intentions.

Contextual specificity of AO-induced motor resonance. Few studies have also investigated context-specific modulation of corticospinal excitability when people observe actions. For example, a series of experiment, Alaerts and colleagues investigated the influence of force requirements on motor resonance. Alaerts et al. (2010) asked their participant to observe two reach-and-grasp-to-lift action. In one action, the object to be lifted was heavy, and the other one light. They collected MEPs during the grasping phase of both movements. When participants observed the lifting of the heavy object, their motor resonance was increased, compared with the observation of the light object. This that during AO, there is a matching between force requirement of the action, and the degree of activation in the observer's motor system. In a following experiment, Alaerts, Swinnen and Wenderoth (2010) instructed their participant to observe three videos, depicting the reach-and-grasp-to-lift of a plastic bottle, of different weight, which was given by the amount of liquid contained in it. They collected MEPs from three muscles, Opponent pollicis, Extensor and Carpi Radialis and Flexor Carpi Radialis. In accordance with their previous experiment, the observation of heavy objects significantly increased MEPs, and this modulation was graded according to the perceived weight of the bottle; That is, observation of the lifting of a full bottle produced MEPs significantly higher that the lifting of a half-full bottle, which in turn produced MEPs significantly larger than observation of empty bottle lifting. This modulation was reported only for Opponent pollicis and Extensor and Carpi Radialis, however.

Other studies on contextual aspects of motor resonance also studied gaze behaviour associated with visuomotor resonance. D'Innocenzo et al. (2017) asked their participants to observe index or little finger abduction/adduction. MEPs were collected from the FDI or ADM muscle. Participants' gaze was modulated by placing a visual cue in different parts of the video. Compared to free viewing condition, MEPs were significantly larger only when the visual cue was placed in the space between the thumb and the index, and this modulation was muscle-unspecific, since this modulation was reported for both FDI and ADM. More recently, Riach, Holmes, Franklin and Wright (2018) reported that the background also affects motor resonance. They instructed participants to observe a sponge squeezing in three different backgrounds, a plain black one, a kitchen sink (congruent with the action) and a background containing non-kitchen-related tools (incongruent with the action). MEPs were collected from the FDI and ADM muscle. When compared to the control condition, a static image of the hand holding a sponge over a black background, MEPs over FDI were significantly higher when the observed action was embedded in a contextually congruent environment, compared to the observation of a static hand image or when the same action was performed on a black background. Different results were obtained for ADM, which did not show the same pattern of modulation of corticospinal excitability but showed a significant modulation for MEPs during the observation of a static image, compared to the observation of the action performed over a black background.

1.1.3.2.Neurophysiology of Audiomotor Interaction

As for visuomotor processing (Goodale, 2011; Milner & Goodale, 2008), audiomotor interactions are also carried out in a similar fronto-parieto network, forming the dorsal stream of auditory processing, which is also responsible for processing of time-varying audiomotor events (Rauschecker & Tian, 2000; Rauschecker, 2011). The engagement of the fronto-parietal network is reflected in action-related *audiomotor resonance*, carried out by audiomotor mirror neurons, mirror neurons with specialised tuning for auditory sensation (Aziz-Zadeh, Iacoboni, Zaidel, Wilson, & Mazziotta, 2004a). In monkeys' premotor cortex (Area F5), a class of mirror neurons with preferential activity not only for observed an action, but also action hearing had been observed (Keysers et al., 2003; Kohler et al., 2002). Keysers and colleagues reported that about half of neurons tested responded to visual or auditory observation of action-related stimuli, while other neurons have preferential activation for either stimuli. This form of audiomotor resonance has been investigated in humans too, by mean of neuroimaging and TMS. Evidence on audiomotor resonance is smaller compared to visuomotor resonance induced by AO (Uithol et al., 2011). However, a few interesting studies highlight how sound can induce audiomotor resonance. When people listened to action sound done with the hands, e.g. Typing on a keyboard or tearing paper, MEPs were higher compared to rest and leg's corticospinal excitability highlighting, as for visuomotor resonance, some form of muscle specificity (Aziz-Zadeh et al., 2004a). Interestingly, audiomotor resonance is induced also by listening action-related words (Tettamanti et al., 2005), with an activation of a fronto-parietal network, thus further corroborating the idea that this network underlies sensorimotor processing related to the representation of the interaction between the body and the environment.

Audiomotor interactions manifest themselves as movement- or sound-oriented. The difference between the two types, according to Bevilacqua et al. (2016), rests in the relationship between sound and action. In *movement-oriented* tasks, the focus is on the action, and the auditory dimension acts as feedback, in the sense that it provides knowledge of results or performance (Scholz et al., 2014). A suitable audiomotor interaction belonging in this class is sonification, which is discussed in later sections, and is the main object of this thesis. On the other hand, in *sound-oriented* tasks the intention is to produce a certain sound, and action is subservient of the auditory dimension. Music is the quintessential sound-oriented action; The goal is to produce a certain note or melody, and the movement pattern producing it is not important. If we observe violinists playing during a concert, it is easy to see that even though they all produce the same note (assuming that this is a requirement of the symphony), the posture of each violinist is different from the one of other colleagues. This is because of the motor redundancy of the motor system (Latash, 2012), which implies that given a certain task, there are more way to fulfil that tasks than necessary. Thus, in sound-oriented tasks, movement is subordinated to the goal of producing a certain sound.

1.1.4. Mental Representation of Actions: Motor Imagery

Up to this point, the discussion focussed on how the brain integrates multisensory information and constructs mental representation of the environment and the body it embodies. As highlighted in the introduction, however, actions are another computational mechanism the brain is thought to use to maximise stability of those internal representations. Investigations in the dynamics of actions control suggests that actions have an anticipatory, predictive nature (Feldman, 2006; Friston et al., 2010). In other words, activation of the biomechanical system is the last phenomenological aspect of action control. We could refer to this as motor control

(Morasso, Casadio, Mohan, Rea, & Zenzeri, 2015). On the other hand, predictive computations underlying intentionality, action selection and preparation could be considered as motor cognition (Derosiere & Duque, 2020; Haggard, 2018; Jeannerod, 2001). Those two aspects of action control have also been conceptualised as *overt and covert state* of an action, respectively (Jeannerod, 2001). Interestingly, similar computational and neurophysiological processes underlying processing of an overt action seems to be also in place for motor imagery. (Grospretre, Ruffino, & Lebon, 2016; Lebon et al., 2019; Lotze & Halsband, 2006). This led researchers to hypothesise a functional computational equivalence between executed and imagined actions (Holmes & Collins, 2001; Jeannerod, 2004). This hypothesis is predicated on the idea that everything that is involved in an overt action, except muscular contraction is also involved in motor imagery (Jeannerod, 2004). In order to do this, it is assumed that the brain is able to *simulate* an action off-line, computationally disconnected from the motor system, possibly via a process of inhibition (Guillot, Di Rienzo, MacIntyre, Moran, & Collet, 2012). The process of inhibition during motor imagery is not completely clear, and the area has seen a surge of interest in recently (Neige et al., 2020; Persichetti, Avery, Huber, Merriam, & Martin, 2020). Even though a neural mechanism for this hypothesised disconnection of the motor system from the areas that controls it is not completely clear, it is undoubtedly clear that similarities exist between motor imagery and execution. Converging evidence suggests that the ability to imagine a movement is directly related to the nature and the constraints of action execution, that is the representation of the action (Jeannerod, 2006, pp. 23-44). Furthermore, MI entails similar computational processes underlying motor planning and preparation (Hanakawa, Dimyan, & Hallett, 2008; Lebon et al., 2019) and, as we will see later, MI entails a similar muscle, temporal and contextual specificity of activation. A particular telling evidence in favour of a computational equivalence is a series of studies using movement-related potentials (MRP), electrical potentials recorded using EEG which have been related to sensorimotor processing and preparation to move (Cunnington, Iansek, Bradshaw, & Phillips, 1996; Cunnington, Windischberger, & Moser, 2005). Evidence shows that the initial portion of the MRP, which is related to motor preparation, does not differ during MI and physical execution of ana action (Cunnington et al., 1996). The difference between the two phenomena seems to be in the latter portion, which is instead related to the actual execution of the planned action (Caldara et al., 2004). Taken together, evidence indeed converges on a computational equivalence during the sensorimotor transformation during MI and physical execution of an action.

When talking about similarities during MI and PE, we should note that MI is not a single phenomenon (Hanakawa, 2016). One of the major discriminants of different motor imagery concept is the level of explicitness. *Explicit* motor imagery entails conscious simulation of action, including predicted sensory afferences (Annett, 1995; Kilteni, Andersson, Houborg, & Ehrsson, 2018). On the other hand, *implicit* motor imagery could be defined as unintentional representation of a an action, usually with epistemic purpose, that is to understand what hand is shown, like in mental rotation tasks (Osuagwu & Vuckovic, 2014). In this regard, implicit motor imagery is much similar to action observation, rather than explicit motor imagery (Hanakawa, 2016). Explicit MI can be further subdivided in i) *external visual imagery*, in which people imagine observing an action of themselves, or another person performing the action; ii) *internal visual imagery*, in which it is imagined what one would see if they were performing an action; and iii) *kinaesthetic motor imagery*, which entails imagining sensory consequences of one's body performing the action. These MI perspectives seems to have distinct pattern of connectivity, with kinaesthetic MI being more closely related to physical execution of action, in terms of neural activity (Solodkin, Hlustik, Chen, & Small, 2004).

As for the study of AO, discussed earlier in the text, further evidence of neurophysiology of MI comes from studies using TMS (Grospretre et al., 2016). Imagining an action is associated to a significant increase MEP evoked in muscles involved in the imagined action, compared to rest (Izumi et al., 1995). However, as for AO, MEPs during MI are usually smaller than MEPs during physical execution of the action. The fact that motor imagery modulates M1 excitability, but to a lesser degree compared with physical execution, is in line with the idea that during motor imagery entails similar computation with physical execution of the same action, but a process of inhibition prevents the biomechanical system to execute the action (Stinear, 2010). Recent evidence highlights a possible mechanisms for the reduced MEP amplitude during motor imagery. (Persichetti et al., 2020) used vascular space occupancy (VASO), a novel fMRI technique not based on blood-oxygen-level-dependent (BOLD), to assess the layer-specificity of brain activation during motor imagery. They reported that MI induced activation only in superficial, but not deep layers of M1. In M1, superficial layers contain interneurons and cortico-cortical superficial pyramidal neurons, while deep layers, especially layer 5 contains pyramidal neurons forming the corticospinal tract (Vincenzo Di Lazzaro & Rothwell, 2014). This report is in line with the idea that the computation of an action is in place, for both MI and physical execution of the action, but the output is inhibited. Which mechanisms inhibits the input pyramidal neurons, in not clear yet.

Similarly, to the discussion of AO, Grospretre and colleagues highlight how TMS evidence in favour of a computational equivalence between MI and PE could be clustered according to four types of MI-induced modulation of corticospinal excitability: i) spatial and ii) temporal modulation of MI-induced neural activity, iii) graduality of MI-induced facilitation and, lastly, iv) Contextual modulation of MI-induced facilitation.

Spatial specificity of MI-induced facilitation. Imagining a movement is associated with similar muscle- and hemispheric-specific increase in corticospinal excitability, compare to physical execution of the same action (Facchini, Muellbacher, Battaglia, Boroojerdi, & Hallett, 2002). For example, Fadiga et al. (1999) investigated MEP modulation during flexion and extension of the right arm, and hand closure and aperture. For both movements, MEPs size was increased, compared to rest, and compared to non-motoric dynamic activity, such expansion and shrinkage of geometrical figures. This modulation was evident both in biceps brachii and hand muscles. Corticospinal excitability during motor imagery seems to be related to the prime mover of the movement sequence (Rossini, Rossi, Pasqualetti, & Tecchio, 1999). When participants imagined index finger abduction, the FDI was significantly modulated, compared to ADM. Vice versa, little finger abduction reversed the modulation, since ADM is the prime mover for little finger abduction. Similar results were obtained in lower limbs, where a significant modulation of corticospinal excitability for the right quadriceps, but not for biceps femoris during motor imagery of knee extension was found (Tremblay, Tremblay, & Colcer, 2001).

Temporal specificity of MI-induced facilitation. Early reports found discrepancies in temporal modulation of corticospinal excitability during motor imagery (Abbruzzese, Trompetto, & Schieppati, 1996; Stephan & Frackowiak, 1996). An explanation for these discrepancies may be the fact that investigating temporal aspects of motor imagery is difficult since no overt movement is observable. Thus, TMS pulses may not coincide with MI phase. When TMS pulse and MI phases are controlled, there is evidence of phase-dependent modulation of M1 during actual movement (Stinear & Byblow, 2003). Since those earlier reports, later studies have found ways to control for movement phase during motor imagery. For example Fadiga et al., (1999) used a computer-produced sound to control for the phase of the movement, and found that, for arm flexion extension, MEPs of biceps brachii were modulate only in the flexion phase, while for the hand opening/closing, APB was active only in the closing phase. Similar results were reported for rhythmic wrist movements (Hashimoto & Rothwell, 1999).

1.2. SENSORIMOTOR LEARNING

The brain integrates sensory information to create internal representations of body and environment (Limanowski & Friston, 2020). The structured process of creating new or updating these internal representations can also be seen as motor learning (Wolpert & Flanagan, 2016). Experience has an undoubtedly powerful effect on the conception we have about our body in action and its surroundings. As our bodily experience grows, our internal representations become more precise, which in turn allows us to make better predictions about causal relations between perception and action, between the acting body and the changes it produces on the environment. In past years, different frameworks modelling this relation between past experience, predictions and body-environment interaction have been advanced (Dayan & Cohen, 2011; Latash, 2010; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). All of them seem to agree on the principle that the modulatory influence of experience on performance is a multi-stages process, consisting of a fast and a slows component. During the initial phase of leaning, there is a fast, but not stable performance improvement. As practice progresses, performance becomes more stable, and sees further performance improvement, but at a slower rate, until asymptotic levels, in which case the performer would be considered to 'master' the action. The timing between fast and slow learning is directly related to the nature and the complexity of the task to be leant (Dayan & Cohen, 2011). Performing thumb adduction/abduction as fast as possible, is easier and most likely quicker to learn than a basketball shot (Rosenkranz, Kacar, & Rothwell, 2007; Ziemann, Ilić, Pauli, Meintzschel, & Ruge, 2004). In addition, the extent of sensorimotor integration needed to achieve the tasks is another integral component of the learning process. Naturalistic actions always require a certain degree of multisensory integration, but there are tasks that are multimodal by nature, such as music, and its audio-proprioceptive integration, which allows for a movement pattern that produce a certain note (Munte, Altenmuller, & Jancke, 2002). Perhaps because of the need for the brain to maintain stability of its internal representations, research shows that multisensory training afford better behavioural changes, compared to unisensory training (Shams & Seitz, 2008). Multisensory training can be implemented in different ways. One such ways is to provide augmented external feedback, via sensory augmentation (Sigrist, Rauter, Riener, & Wolf, 2013). One important feature of multisensory learning is that it produces a more complex behaviour by the performer, because the additional sensory inputs are better integrated in the internal representation of the body and the environment, and evoke by contextual stimuli (Bavelier & Neville, 2002; Di Pino, Maravita, Zollo, Guglielmelli, & Di Lazzaro, 2014; Shams

& Seitz, 2008). From a neurophysiological point of view, motor learning, in all its forms, is based on neural plasticity, the functional and structural reorganization of neural substrates affording performance improvements (Di Pino et al., 2014). In motor skill learning, practice-dependent plasticity of the intact central nervous system (CNS) is thought to be mediated by two distinct mechanisms. The fast component is mediated by a combined reduction in the activity of inhibition interneurons and an increase in excitatory neurons, which overall increases cortical excitability (Buonomano & Merzenich, 1998; Jones, 1993). This synergic action brings about an unmasking of silent cortical connections – cortical structures that were already present, but inhibited because lacking of excitatory receptors (Jacobs & Donoghue, 1991) – between the areas involved in the training (Pascual-Leone et al., 1995). In other words, during fast learning components, the brain facilitates performance via a maximization of neural structures already present, but inactive. On the other hand, during the slow phase, *synaptogenesis*, the creation of new synapses, is thought to be the primary mechanisms mediating performance stability (Rosenkranz, Kacar, et al., 2007), leading to a slower improvement and stabilization of performance.

An influential model is spike-timing dependent synaptic plasticity (STDP; Caporale & Dan, 2008), also known as *Hebbian* learning, suggests that if a series of neurons are both active within a particular time window, and if the pattern of activation is sustained in time, the connection between those neurons strengthens (Hebb, 1949). To better clarify this principle, let us imagine that some neurons have weak or no connection with each other. At some point these neurons receive stimuli from other neurons; If those stimuli arrive all within a certain time window, and this stimulation pattern is persistent over time, then some of the originally disconnected neurons will connect with each other or strengthen their originally weak or silent synaptic connection. In this case a new network is formed (or strengthened). When stimuli from the other neurons terminate, the newly formed network will still be in place, although will be silent, and will be activated even if one of the neurons in the network is activated by a certain stimulus. This is because of the reciprocal connections that were formed during the association phase. STDP is manifested via long-term potentiation (LTP) and depression (LTD; Caporale & Dan, 2008), which represent the long-term increase and decrease in synaptic strength between neurons, respectively. It should be noted, however, that if left unchecked, Hebbian plasticity triggers a recurrent strengthening of the systems involved in training, creating the neural unbalances (Abraham, 2008; Di Pino, Pellegrino, Capone, & Di Lazzaro, 2014; Müller-Dahlhaus & Ziemann, 2015; Yee, Hsu, & Chen, 2017). To avoid this, the brain is equipped with the homeostatic mechanisms of synaptic metaplastity, which harmonises LTP/D in the brain (Karabanov et al., 2015). Chapter 2 will further discuss homeostatic metaplasticity, applied to the audiomotor network.

The field of motor learning is vaster than it would be possible to discuss here. For this reason, the remaining of this literature review will highlights feature of sensorimotor learning that will be most useful for this thesis, namely, the influence of sensory augmentation on performance, and the use of AO and MI as a learning strategy.

1.2.1. Learning via sensory augmentation

One interesting form of learning is via sensory augmentation, sensory manipulation strategy whereby a stimulus is used to provide information that would be hard to perceive in normal conditions (Dubus & Bresin, 2013). As all types of extrinsic feedback, the fundamental proposition of sensory augmentation is to afford the user with an enriched perceptual environment, which is then used to create a better internal representation of the environment and body (Sigrist et al., 2013), which in turn would allow for better predictive sensorimotor processing, and a more stable performance. During sensory augmentation of movement, there is a mapping, an association between a sensory stimulus and a *hidden movement characteristic*, a movement aspect that could not, or would be hard to be inferred otherwise. Sensory augmentation is a multifaceted technique, with a plethora of dimensions and determinants, which potentially influence the interaction between perception, action and learning (Sigrist et al., 2013).

Different strategies can be used to provide knowledge of result or performance. With the former we intend feedbacks that represents the end-result of a task, usually with the intent of signalling whether an action was successful or not. For example, in a reaching task, knowledge of results can be provided on whether my finger touched the centre of a screen, as well as how far from the target my movement was. On the other hand, knowledge of performance aims at providing feedback on performance itself, e.g. movement kinematics, regardless of the result (Wulf, Lauterbach, & Toole, 1999; Wulf, Shea, & Lewthwaite, 2010). Sensory augmentation can be administered as concurrently or terminally, with respect of the action (Sigrist et al., 2013). Also known as online feedback, concurrent sensory augmentation provides feedback information as the movement unfolds, while terminal sensory augmentation provides feedback at the end of the movement. Although not always the case, it is easy to see a certain affinity between knowledge of performance and concurrent feedback, and knowledge of result and terminal feedback. An optimal feedback strategy should consider when and what to provide feedback on, but another very important dimension in the definition of sensory augmentation design is the type of feedback provided. On a conceptual level, any sensory modality can be used as sensory augmentation. However, the most used seems to be visual, haptic and auditory modality (Sigrist et al., 2013). Taken together, sensory augmentation is not a single phenomenon, but manifests itself as a multifaceted set of strategies, all applicable to learning, given the right conditions. In this thesis, we used sonification, so further discussions will be based on this.

Sonification describes a real-time auditory augmentation strategy whereby a sound characteristic, e.g. pitch, volume, brightness, waveform, is associated with – and dynamically modulated by – a *silent* movement characteristic, e.g. kinematics, kinetics etc. For example, the pitch of a sound can be associated with the kinematics of a certain action, for example a biceps flexion and extension. As the arm is flexed, the pitch of the sound may decrease, and vice versa, when the arm extends, the pitch can increase. Incidentally, the pitch-kinematics mapping is the most used sonification strategy, as a meta-analysis by Dubus and Bresin (2013) suggests. One of the reasons for the increase in scientific interest towards sonification is its reduced susceptibility to the *guidance effects*, the detriment in performance when the augmented feedback is removed (Dyer, Stapleton, & Rodger, 2017; Dyer, Stapleton, & Rodger, 2015). A study by Ronsse et al. (2011) confirms this. They investigated the effects of visual or auditory augmented feedback on the learning of complex bimanual tasks, in which participants, split in two group, each receiving an auditory augmentation modality, had to learn a complex wrist movement coordination task. Visual feedback was provided showing the relative position of the wrist, with respect of the other, as cursor movement, which auditory augmentation was provided by a low or a high tone associated maximal flexion and extension of the left or right wrist, respectively. Visual feedback induced a faster rate of learning, compared to auditory feedback, but at the end of the training both groups had similar performance levels. Interestingly, however, when extrinsic feedback was removed, the group that trained with visual feedback showed a decrease in performance, compared with the one practising with auditory feedback, which retained their performance. Participants' slower rate of learning matched fMRI data, as the group who trained with auditory feedback showed sustained activation of the dorsolateral prefrontal and orbitofrontal cortex, brain areas that have been involved in attention modulation (Suzuki & Gottlieb, 2013). Thus, Ronsse et al. (2011) suggests that although auditory augmentation may have beneficial long-terms effects, it seems to imply increased attentional demands at the beginning of the practice, in order to create an effective audio-proprioceptive mapping.8

The audiomotor mapping strategy is probably the main methodological consideration that needs to be made in sonification. Dubus and Bresin, (2013) systematically reviewed this, reporting that that pitch is the most frequently used auditory dimension, while kinematics is the most frequently used movement characteristic. This association could be intended as *synthesised*, as pitch change is usually a non-ecologically valid tone. However, some studies suggest that ecologically valid sound, sounds that already have established representative link with environmental events, may bring an advantage, compared to synthesised sound (Dyer, Stapleton, & Rodger, 2015). The supposed advantage of ecologically valid sound over synthesised ones may be an increased intuitiveness of the relationship sound-movement. A very interesting example of this is the sonification strategy created by Vogt et al. (2009). They associated wild forest sounds with arm adduction/abduction such that, as the arm abducted, the sounds localization moved up, from the terrain to the sky (leaves on the floor and wind as lowest and highest spatially localised sounds, respectively). In the field of rehabilitation, sounds of walking on gravel at different speeds, has been used to improve walking speed of people affected by Parkinson's disease (Young, Rodger, & Craig, 2013). On the other hand, as already mentioned, most sonification research is carried out with synthesised sound. Although it may be harder to associate with action, which may partly explain the aforementioned results provided by (Ronsse et al., 2011), synthesised sound provide a great advantage, as they do not rely on already established audiomotor associations and metaphorical translation. This, while increasing its learning time, may open a great deal of learning possibilities.

Research on music, the quintessential example of synthesised audiomotor association, suggests that it is possible to effectively associate a synthesised sound to a movement. Music training induces an enlargement of the representation of the body part associated to the played instrument (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Pantev et al., 1998). Outside the musical domain, there is evidence suggesting that it is possible to associate a simple button press to a tone. Ticini et al. (2011), for example, trained their participants to associate two tones with index or little finger. Practice-dependent changes in neural representation of the movement was probed with TMS over FDI and ADM muscles, prime movers from index and little finger abduction/adduction, respectively. After a very short training, MEPs amplitudes increased, compared to pre-training measures. This increase was tone-muscle specific, as MEPs increased only when the presented tone was congruent with the learned audiomotor mapping. Interestingly, when the audiomotor mapping was reversed, MEP showed opposite effect. Taken together, there is evidence of practice-dependence audiomotor resonance, but the results of Ticini and colleagues suggest that this association is not just a mapping between a movement and a sound, but audiomotor training establishes the association at a hierarchical higher order, such that a sound evokes an audiomotor resonance in body parts that have been previously associated to the sound. This has important implications for the application of sonification to the domain of motor learning.

Sonification is usually done starting from movement-related data (Caramiaux, Françoise, Liu, Sanchez, & Bevilacqua, 2020). However, the fact that the auditory dimension is data-driven, does not represent the *condicio sine qua non* that allows us to call an audio-motor interaction, sonification. The audiomotor mapping strategy must be meaningful and intended to enrich the environment of information, such that people can exploits it to their advantage, to better integrate a (re)action in the person's own sensorimotor system. In other words, it needs to have *epistemic value*, such that it can be integrated and processed with other sensations. A study by Schmitz et al. (2013), highlights this. They asked participants to observe a human-like avatar performing a breaststroke, where the relative distance between the two wrists and the two ankles was sonified. Participants were also asked to judge movement speed. The procedure was carried out in two conditions: In a first one, the mapping between sound and kinematics characterised the movement (congruent), while in another condition, the sound was sham, that is it did not characterise the movement. When participants observed the action with congruent sound, their error judgment was lower compared with action observation with incongruent sonification, thus suggesting a better perceptual judgement. Thus, it seems that congruency in multisensory interaction is a very important requirement for sonification to work (Shams & Seitz, 2008).

Since sonification is carried out using sound in a continuous manner, it shares some characteristics with music. One of which is temporal perceptual dimension. It is known that music is able to interact with movement rhythm (Bigliassi, Karageorghis, Nowicky, Wright, & Orgs, 2018; Bigliassi, Karageorghis, Wright, Orgs, & Nowicky, 2017). Thus, it is not surprising that sonification is able to do so too (Young et al., 2013).This characteristics is very important in sports, where technique has a very important spatiotemporal dimensions. It is perhaps unsurprising that sonification has been applied to a plethora of sports, such as swimming, Karate, Rowing, Ski, German wheel, rifle shooting, cycling and golf (Reviewed by Schaffert, Janzen, Mattes, & Thaut, 2019). Outside sport, sonification has been used as a mean to provide information about movement patterns and kinetics loads (Batavia, Gianutsos, Vaccaro, & Gold, 2001). For example, Petrofsky (2001) sonified electromyography of the two gluteus in patients with Trendelenburg gait following an incomplete spinal cord injury. To improve bilateral control of gait, he defined a system providing an auditory alarm if the activity in the affected leg was reduced, compared to the activity of the unaffected one. After 2 month of home training using this device, participants showed a gait pattern almost similar to a normal one. Recent evidence explored the use of sonification in for stroke rehabilitation. Scholz et al. (2016) designed a protocol where patients were trained to recreate a reference melody with their own movements. As the arm moved in the 3D space allowed, the sound characteristics (brightness, volume, and pitch) varied according to the patients' arm configurations and kinematics, such that they learned to produced melodies that resembled as much as possible the reference melody. This practice regime decreased joint pain and increased movement smoothness, a major problem for stoke patients. Thus, sonification not only provides additional perceptual information on the movement, but ultimately aids its production.

1.2.2. Learning through simulation: the case for action observation and motor imagery

Another important and widely researched area of sensorimotor (re)learning is action simulation, instantiated in observational learning (OL; Buccino, 2014) and mental practice (MP; Ruffino, Papaxanthis, & Lebon, 2017). The two training regimes – indeed the two research areas – which in the past were considered separately by researchers (see the interesting point by Vogt et al., 2013 on this), are now considered complementary methodologies to induce motor learning without or in conjunction of physical practice (PP; Eaves et al., 2016). The complementarity of AO and MI as learning strategies is highlighted in their interaction with internal representations, which has already been discussed in previous sections, such that AO engages with the internal model in a bottom-up fashion, by mapping the observed action and its intentions onto the observer's one, and MI engages in a top-down fashion, as internally-driven generation of sensorimotor prediction about the interactions between the body and the environment (Annett, 1995; Kilteni et al., 2018).

When talking about the use of AO and MI as learning strategies, one inevitably needs to confront with its potential utility in inducing behavioural or neural changes, as well as its relationship with other, already established regimes based on PP. Specifically, one important question is to what extent these cognitive strategies can improve performance, especially if one could simply physically execute the action. This point, was also highlighted by Kraskov (2012), referring to observational learning and its relationship with motor inhibition during AO. Answering this question is the focus of the last portion of this literature review, which will contextualise the importance of using AO and MI in motor learning. As for the discussion of AO and MI, learning via those strategies will be discussed separately, before converging the two methodologies into a unified methodology. When directly comparing these three forms of practice, the literature seems to suggest that learning via AO and MI is suboptimal, compared to PP. With regards to MI, a seminal study suggests that MI may require additional practice sessions, compared to PP training. Pascual-Leone et al. (1995) instructed participants to perform silent piano sequences for five days. Performance changes were evaluated by the number of errors in executing the sequences, as well as through the investigation of neural plasticity via TMS-evoked mapping. Half of participants performed the training solely using motor execution, while the other half could use only motor imagery. TMS results reported no changes in TMS-evoked maps between the groups, since both groups increased the size of the evoked map, without significant difference in performance. On the other hand, behavioural data showed that the performance of the MP group at the end of the 5th day was similar to the one of the PP group on the 3rd day, and the MP group needed an additional practice to reach the performance of the PP group. Similar behavioural results were obtained more recently by Kraeutner et al. (2015), who investigated whether it is possible to learn without physical practice. Participants, divided in PP and MP group, were instructed to practice different sequences on key presses, whereby an implicit sequence of presses was imbedded (and representing 80% of the trials). After the practice, both groups improved their performance, as measured by the relative timing of key presses. However, there was a significant between-group difference in reaction time; That is, the group that practice the task physically has a significant shorter reaction time, compared with the group that practice using MP. Similar results have also been reported for observational learning (Blandin, Proteau, & Alain, 1994). Taken together, it seems that both AO and MI can improve performance, but with less effectiveness, compared to PP. It may be possible that this is due to the lack of proprioceptive feedback, which is fundamental for motor control and learning, and has been stressed by research in the field (Blandin et al., 1994).

This suboptimality, however, should not deter practitioners to use these cognitive strategies in sport and clinical practice. Indeed, there is also evidence of equivalence of learning effects, in both AO and MI, and these will be discussed in later sections. In addition, OL and MP seem to involve similar neural dynamics, with respect of general aspect of learning. Beside equivalent behaviour of the TMS-evoked M1 map reported by Pascual-Leone et al. (1995), Avanzino et al. (2015) reported that both MP or PP practice was able to occlude the LTP-like effect of a PAS intervention, completed after the session (See Introduction of Chapter 2 for a discussion on occlusion of LTP-like plasticity). Interestingly, in their research, both groups improved performance, but only PP modulated corticospinal excitability, compared to pre-training conditions. Similar results were obtained by Lepage et al. (2012), who investigated occlusion of LTP-like plasticity after training sessions of either performing thumb abductions as fast as possible, or observing it. This hints to the possibility of integrating these forms of learning with more conventional execution-based protocols. For example, AO and MI may find application in the field of telemedicine, which has seen an expansion in recent times (Minghelli et al., 2020).

Mental Practice. The use of MP is not new, as it was originally developed in the field of psychology (Driskell, Copper, & Moran, 1994), where different models have been advanced over the years (Guillot & Collet, 2008; Holmes & Collins, 2001). In recent years, however, different authors highlighted its usefulness in neurorehabilitation (Abbruzzese, Avanzino, Marchese, & Pelosin, 2015; Di Rienzo, Collet, Hoyek, & Guillot, 2014; Malouin, Jackson, & Richards, 2013; Mulder, 2007). One interesting important feature of MP, over PP, is the fact that MP does not induce neuromuscular fatigue, since movement is inhibited (Rozand, Lebon, Papaxanthis, & Lepers, 2014). This makes MP an attractive choice for clinical sciences, where neurological condition may imply an inability to sustain prolonged rehabilitation. Its application, however, need to strike a balance between executed and imagined trails. Proprioceptive feedback is fundamental for learning (Ostry & Gribble, 2016), and studies found that the combination of physical and mental practice benefitted performance more than the two together (Grospretre et al., 2016). On the other hand, prolonged MI session induce mental fatigue, with decreased accuracy (Rozand, Lebon, Stapley, Papaxanthis, & Lepers, 2016). Thus, in practical contexts one would need to determine the highest number of MI that it is possible to perform, without causing mental fatigue. If MI trials are fewer than optimal, performance may not benefit from MP (Allami, Paulignan, & Brovelli, 2008). Gentili, Han, Schweighofer and Papaxanthis (2010) found that after 60 trials, attention decreased.

Even though MP does not cause mental fatigue, studies have shown that it has small effect on strength development. A four weeks fingers strength training induced a 22% and 30% significant increase in strength for MP and PP group, respectively (Yue & Cole, 1992). Similar results were obtained by Ranganathan, Siemionow, Liu, Sahgal, & Yue (2004). Interestingly

Leung, Spittle and Kidgell (2013), reported a differences between performance and corticospinal excitability enhancement. After 3 weeks of strength training for biceps curl, either executed or imagined, increased strength, but PP resulted in more than double the strength enhancement, compared to the group who used MP. Interestingly, no changes in corticospinal excitability were found. This differential effect of strength training on performance and corticospinal excitability may be due to a computational equivalence of MP and PP, and the behavioural difference could be explained by the lack of movement in MP. Different studies suggests that the initial improvement in strength at the beginning of a training is due to neural adaptations, while muscle hypertrophy is responsible for later improvements (Sale, 2008). However, strength training also induces different changes in muscle properties, notwithstanding the sensory reafference during PE, and this may be responsible for the significant difference in strength improvement between the groups. In other words, the evidence on the use of MI for strength training suggests that MP can induce significant changes in behavioural and neural activity that could be explained by a modulation of top-down processes of action preparation and control. In line with this, a recent metanalysis by Palic (2018) reported that MP improved maximum voluntary contraction, but this effect was small, compared to PP. While this is important for athletes, MP for strength training has important applications in clinical context. People with neurological disfunctions shows a decrease in strength, compared to healthy individuals, and while the aetiology may be varied, the use of MI may be able to alleviate this, and improve performance (Di Rienzo et al., 2014; Giuliani, 1995).

The effectiveness of MP in neurorehabilitation was also suggested by recent metanalyses, further highlighting MP as a valuable tool in the practitioner's rehabilitative toolbox, in a variety of contexts. For example, Nicholson, Watts, Chani and Keogh (2019) suggested that older adults may benefit from MP, who show an improvement on a variety of tests measuring mobility and balance. This, associated to the ease of MP on the neuromuscular system, makes it an attractive way to maintain the brain active while experiencing low mobility, to be associated with normal physiotherapy. Other studies show that MP could also be a valuable addition in stroke. A systematic review found that combined mental and physical practice improved gross motor function, as compared to PP alone (Machado, Carregosa, Santos, Manoel, & Melo, 2019). Nevertheless, more studies are needed to further validate MP as a therapeutic route. Recent metanalyses highlight a high uncertainty on the effectiveness of MP as a rehabilitative tool for walking after stroke (Silva et al., 2018).

Observational learning. While mental practice involves simulation of predicted sensation associated with actions, OL involves using other's behaviour to model the action to be learnt. This learning strategy is well grounded in the neurophysiology of mirror neurons and action observation, which was discussed in earlier sections, involving visuomotor mapping of the observed characteristics of the action. Of interest is the fact that OL does not imply only instructions on *what* to do, but *how* to do it too. Mattar and Gribble (2005) asked their participants to observe videos of a person reaching clockwise to different targets, in a force-field environment, which are heavily used in motor control research field to study internal models and motor memories (Kawato, 1999; Körding & Wolpert, 2004). Participants were assigned to either i) a group that observed clockwise reaching to various targets in a novel force-field environment, ii) a group who observed the opposite action, counter-clockwise reaching, or iii) a group that did not observe any action. Observation of clockwise action induced an improvement in performance, compared to no observation or counter-clockwise actions, which was the group who performed worse. This suggests that AO produced specific adaptation, by developing a motor memory of the observed action containing, among others, the neuromechanical predictions about sensory consequences of the observed action. In other words, OL induce specific implicit modulation in sensorimotor memories of the observer, and this acts as a visual guidance on how to perform the action (c.f. Holmes & Calmels, 2008 for a similar point on the application of OL in sport). The bottom-up visuomotor guidance afforded by OL suggests that one of the benefits of AO may be implicit learning. Indeed, observing an actor performing sequential actions yield an improvement of performance, but does not produce explicit knowledge of the sequence (Bird, Osman, Saggerson, & Heyes, 2005; Breslin, Hodges, & Williams, 2009; Vinter & Perruchet, 2002). This hints to an important application of AO in learning for people with mental health disorders, especially anxiety (Rathus, Reber, Manza, & Kushner, 1994), and may be a great advantage for certain population, such as elderly people.

OL is not a new method in motor learning research, as it is common practice in learning new skills in sports (Ste-Marie et al., 2012). In recent years, however, its use has been extended to rehabilitation (Buccino, 2014), for example stroke, and Parkinson's disease (Abbruzzese et al., 2015). Recent studies suggest that OL could represent an important integrative component supporting PP. For example, studies explored the use of OL as a tool to maintain the sensorimotor system during post-surgical immobilization. OL could represent a strategy to contain loss of muscle properties, as well as a decrease in neural activity usually associated with immobilization (Bassolino, Campanella, Bove, Pozzo, & Fadiga, 2014), and could contribute towards maintaining internal representations of the body active, especially when paired with traditional physiotherapy (Bellelli, Buccino, Bernardini, Padovani, & Trabucchi, 2010). Recent metanalyses suggests that OL can have an influence on the outcome, and thus speed-up the rehabilitation process in stroke (Zhang et al., 2019) and musculoskeletal pain (Suso-Martí, La Touche, Angulo-Díaz-Parreño, & Cuenca-Martínez, 2020). Buchignani et al. (2019) reported that OL induced significant improvements in both upper and lower limb, with a larger effect size in the latter, thus corroborating the use of OL as addition to normal rehabilitation. It is interesting to note that these behavioural changes are associated with a reorganization of sensorimotor structures. In post-stroke rehabilitation, 4 weeks of OL yielded significant improvement in motor performance, compared to normal rehabilitation, and these improvements were retained up to 8 weeks after the end of the rehabilitation protocol (Ertelt et al., 2007). These behavioural improvements were also associated with increased activity in PMv, SMA and STS, key areas for visuomotor transformation and motor control (Davare et al., 2011). Taken together, OL could represent an interesting low-cognitive strategy to activate the sensorimotor system and induce changes in performance and brain activity, which ultimately should induce a quicker functional recovery (c.f. Bellelli et al., 2010)

Combined Use of AO and MI. Even though AO and MI are related to internal representations of an action, and their use in learning is encouraged, some studies reported that the benefits of those learning strategies are not equivalent. Studies directly comparing OL and MP report different level of effectiveness for different conditions, such that one strategy may be better than the other in different conditions (Bassolino et al., 2014). Starting from this consideration, authors have advanced the idea that AO and MI are complementary to each other, and performed simultaneously (Eaves, Behmer, & Vogt, 2016; Vogt et al., 2013). This proposition rests on the assumption that the brain is able to represent different potential action, and then, through a process of competition resolution, the most appropriate action, given external and internal states (Cisek & Kalaska, 2010). When applied to action simulation, the *dual simulation hypothesis* proposed by Eaves et al. (2016) suggests that top-down processes underlying MI, and bottom-up sensorimotor mapping of AO can be carried out simultaneously. One very attractive feature of this hypothesis is that the content of what is imagined vs observed has observable effects on neural activity. Indeed, the hypothesis suggests that according to the content of AO and MI, the evoked representations can facilitate or compete for neural substrates that carry out these sensorimotor processing. To investigate this, studies usually contrast AOMI of different contents, and measure a variety of neurophysiological indices. Usually, three versions of AOMI are investigated. In congruent AOMI, the imagined action is the same of the observed one, while in coordinative AOMI, the imagined action may differ from the observed one with respect of the perspective with which the action is observed. On the other hand, in conflicting AOMI the imagined action is not compatible with the observed action, thus instantiating a processing conflict between AO and MI.

Until recently, most of the studies investigating AOMI focussed on congruent AOMI. Neuroimaging studies found that congruent AOMI induces a more extended activation in areas already active during AO and MI. It should be noted, however, that the AOMI network in not the additive result of combining AO and MI (c.f. taube), as it retain unique neural signatures. Different studies reported difference between AOMI and AO and MI alone in cerebellum, BA7, left M1 and left cingulate cortex, SMA, putamen, thalamus, as well as frontal and parietal areas. (Berends, Wolkorte, Ijzerman, & Van Putten, 2013; Macuga & Frey, 2012; Nedelko, Hassa, Hamzei, Schoenfeld, & Dettmers, 2012). In addition, EEG studies also suggest that congruent AOMI also induces activity in the dorsolateral prefrontal cortex, which may be suggestive of an attentional shift from externally-to internally-induced simulation of sensorimotor characteristics of the action (Eaves et al., 2016). The facilitatory effect of congruent AOMI results in facilitation of corticospinal excitability, compared to AO and MI alone (Bruton, Holmes, Eaves, Franklin, & Wright, 2020; Meers, Nuttall, & Vogt, 2020; Sakamoto, Muraoka, Mizuguchi, & Kanosue, 2009; Wright et al., 2018) although recent evidence suggests that this increase is mainly driven by MI (Meers et al., 2020), which is in line with an attentional shift from external to internal sensorimotor processing suggested by Eaves and colleagues (2016). It is interesting to note that recent evidence also finds support for a processing competition when the AO and MI are not congruent. Bruton et al. (2020) reported that corticospinal excitability during congruent AOMI was significantly higher than conflicting AOMI, and interviews revealed that participants found harder to perform conflicting AOMI. A more active brain may induce better learning and plasticity beyond the one afforded by AO and MI alone. Several studies found increased learning outcome in sport (Romano-Smith et al., 2018; Taube et al., 2015; Wright et al., 2018) and clinical contexts (Friesen, Bardouille, Neyedli, & Boe, 2017; Marshall, Wright, Holmes, Williams, & Wood, 2020; Marusic et al., 2018; Scott, Emerson, Dixon, Tayler, & Eaves, 2019; Wang, Wong, Sun, Chu, & Tong, 2018). Taken together, behavioural and neuroscientific evidence confirm the idea that AO and MI lie on a continuum of internal representation of actions, but from different perspective (cit). It also highlights that AOMI is not just a conjunction of two distinct activities, but a unique phenomena, which lies in the same continuum of AO, MI and PE (c.f. Taube et al., 2015).

1.3. CONCLUSIONS

Taken together, it could be argued that AO and MI, while being suboptimal learning strategies compared to PP, are better than no practice (Grospretre et al., 2016; Ruffino et al., 2017). Since they are less susceptible to neuromuscular fatigue (Rozand et al., 2014), their application to clinical activities can be impactful, and should be encouraged. In addition, under the right conditions, combining AO and MI may be preferable to using the two strategies alone, and could afford better learning and practice-dependent plasticity. On the other hand, it could be hypothesised that the lack of sensory feedback associated to actions, the sensory re-afference, may be one of the causes for the suboptimality of these cognitive strategies, compared to PP. This aspect is fundamental to the effective development of these cognitive-sensory-motor learning strategies. Provision of sensory information during training has been shown to be very important for learning (Laaksonen et al., 2012; Ostry & Gribble, 2016), and could represent an important addition to the use of AO and MI in clinical sciences.

To this purpose, one underexplored research areas is sensory augmentation of covert actions. In past years, limited research has been carried out on feedback provision during AO. For example, in a series of studies Bisio and colleagues explored the use of peripheral nerve stimulation (PNS) in motor learning. When AO of index-thumb opening and closing movements and PNS (delivered at the closing phase) were combined, this produced a post-intervention increase in corticospinal excitability, and this lasted up to 45’ after the intervention. On the other hand, PNS and AO alone did not result in significant modulation of corticospinal excitability (Bisio et al., 2015). In a follow-up study (Bisio, Avanzino, Biggio, Ruggeri, & Bove, 2017) reported that AO+PNS shared overlapping neural substates with TMS-induced LTP, assessed with Paired Associative Stimulation (PAS), a protocol that associates a TMS pulse to a sensory stimulus, typically PNS. Both PAS and AO+PNS induced significant increase in corticospinal excitability when done alone, but if PAS followed AO+PNS, corticospinal excitability decreased, exhibiting metaplasticity, a sign of an overlap in neural substrate of practice (see next chapter for more on this). Another interesting route to augment learning is based on AO and MI is sonification. Limited research on *sonified action observation* (sAO; Mezzarobba et al., 2018) suggests that provision of auditory augmentation to healthy and clinical populations, may be beneficial for perceptual judgment and performance

(Mezzarobba et al., 2018; Schmitz et al., 2013). Schmitz and colleagues instructed their participants to observe a human-like avatar performing a breaststroke, where the relative distance between the two wrists and the two ankles was sonified. Participants were also asked to judge movement speed. The procedure was carried out in two conditions: In a first one, the mapping between sound and kinematics characterised the action (congruent condition), while in another condition, the sound did not characterise the action (incongruent condition). Congruent sAO induced a lower judgment error about movement speed, compared to incongruent sAO. This performance improvement was also associated to an enhanced activation of superior and medial posterior temporal regions, as well as bilateral activation of the insula. On the other hand, incongruent sAO showed an enhanced activation in left inferior temporal cortex, left operculum, left Broadman Area 6 (BA6), and Inferior Parietal Lobule (IPL). Interestingly, functional connectivity analyses using Superior Temporal Sulcus (STS) as region of interest, showed that activity in this region during congruent sAO increased connectivity with basal ganglia, thalamus and frontal regions – all areas involved in motor control (Hardwick et al., 2018) – whereas incongruent sAO did not show the same extent of connectivity strength. This reinforces the importance of audiomotor mapping, which has been discussed in previous sections of the literature review. In this case, the results provided by Schmitz et al. (2013) shows that optimal auditory feedback, in conjunction with AO, is able to engage the sensorimotor system in a way as to aid action-related computations. More recently, Mezzarobba et al. (2018) explored the influence of sAO on freezing of gait in people with Parkinson’s disease. Their participants engaged in either an experimental rehabilitation protocol, based on sonification, or in a standard protocol for Parkinson’s disease rehabilitation. The experimental protocol, which lasted 3 months, was based on sAO and subsequent physical imitation of 8 different walking actions (e.g., turning around), where movement velocity was mapped to a pitch change. At the end of the protocol, participants treated with sAO improved on a variety of clinical measures, compared with standard training, but this performance improvement was still evident after 1 and 3 months from the end of the training protocol.

To further explore sonification of covert actions, in the next chapters we present three studies that were carried out on a healthy cohort. In the first study, we assess the effects of sonification of combined action observation and motor imagery on corticospinal excitability and audiomotor plasticity (Chapter 2). We then follow up on this with a study on the effects of sAOMI on the development of practice-dependent audiomotor resonance in Chapter 3. Lastly, in Chapter 4 we explore the effects of sAO on neural activity and attention. In Chapter 5, we conclude with a general discussion of the main findings from the three studies, and their implications to scientific and practical contexts.

CHAPTER 2

DOES SONIFICATION OF ACTION SIMULATION TRAINING IMPACT CORTICOSPINAL EXCITABILITY AND AUDIOMOTOR PLASTICITY?

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ABSTRACT

Sonification is a sensory augmentation strategy whereby a sound is associated with, and modulated by, movement. Evidence suggests that sonification could be a viable strategy to maximize learning and rehabilitation. Recent studies investigated sonification of action observation, reporting beneficial effects, especially in Parkinson's disease. However, research on simulation training – a training regime based on action observation and motor imagery, in which actions are internally simulated, without physical execution – suggest that action observation alone is suboptimal, compared to the combined use of action observation and motor imagery. In this study, we explored the effects of sonified action observation and motor imagery on corticospinal excitability, as well as to evaluate the extent of practice-dependent plasticity induced by this training. Nineteen participants were recruited to complete a practice session based on combined and congruent action observation and motor imagery (AOMI) and physical imitation of the same action. Prior to the beginning, participants were randomly assigned to one of two groups, one group (9 participants) completed the practice block with sonified AOMI, while the other group (10 participants) completed the practice without extrinsic auditory information and served as control group. To investigate practice-induced plasticity, participants completed two auditory paired associative stimulation (aPAS) protocols, one completed after the practice block, and another one completed alone, without additional interventions, at least 7 days before the practice. After the practice block, both groups significantly increased their corticospinal excitability, but sonification did not exert additional benefits, compared to non-sonified conditions. In addition, aPAS significantly increased corticospinal excitability when completed alone, but when it was primed by a practice block, no modulatory effects on corticospinal excitability were found. It is possible that sonification of combined action observation and motor imagery may not be a useful strategy to improve corticospinal, but further studies are needed to explore its relationship with performance improvements. We also confirm the neuromodulatory effect of aPAS, but its interaction with audiomotor practice remain unclear.

2.1. INTRODUCTION

Motor imagery (MI) and Action Observation (AO), introduced in the literature review, can be effectively integrated in a practice protocol, to improve performance in sport and clinical contexts (Abbruzzese et al., 2015). In some cases, such as following neurological injury or immobilization, simulated training is the only possible route to maintain the sensorimotor system active (Abbruzzese et al., 2015; Bassolino et al., 2014). Studies explored whether it is possible to augment mental simulation of actions, with external feedback, with encouraging results (Bisio et al., 2017, 2015; Mezzarobba et al., 2018; Schmitz et al., 2013). In the present study we aimed at extending the study of sonified action simulation, by investigating whether motor imagery could have an incremental effect on sAO. Recent evidence suggests that during MI, the brain also simulates the sensory consequences of the imagined movement (Kilteni et al., 2018), and a copy of the motor command (efference copy) is treated as a sensory afference and integrated with others sensory modalities (Pinardi et al., 2020b). Thus, it is conceivable that the spatiotemporal information about an action obtained during AO and sonification, along with the simulated one during MI, would all converge to a better integration of a multisensory internal models. This would be in line with the dual simulation hypothesis, suggesting that congruent sensorimotor representations would facilitate the simulation of the action, and potentially afford plasticity (Eaves, Riach, Holmes, & Wright, 2016). Thus, the first aim of this study was to investigate whether sonified AOMI (sAOMI) of a right-hand battery pinching would enhance motor cortex excitability. To investigate it, we compared practice-related changes in peak-to-peak amplitude of the motor-evoked potentials (MEPs) in two groups of participants undergoing a practice block based on AOMI. For one group, AOMI was enriched with sonification (SON group) and the other without extrinsic auditory information (CON group).

A secondary aim of this study was to gain information about audiomotor plasticity arising from the interaction between sonification, action observation and motor imagery (sAOMI) practice. To do so, we took advantage of the inter-dependency between practice and neuroplasticity, i.e. the propensity of the nervous system to change its structure and function with experience (Di Pino, Maravita, Zollo, Guglielmelli, & Di Lazzaro, 2014). At the synaptic level, motor skill learning is associated with modulation of the synaptic strength, based on spike-timing-dependent plasticity (STDP; For a review see Caporale & Dan, 2008), also called Hebbian learning (Hebb, 1949). This stimulus association, repeated in time, allows for the strengthening of the synapses within the circuitry involved in training. The strengthening of synaptic interaction is named long-term potentiation (LTP); the converse is known as long-term depression (LTD; Dayan & Cohen, 2011; Malenka & Bear, 2004). The involvement of LTP/D process in learning was first studied in non-primate animal models, through in vitro studies (Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998). However, using TMS, it is possible to observe similar effects non-invasively in humans (Cirillo et al., 2016; Ziemann et al., 2004). A popular experimental method to assess Hebbian learning is Paired- Associative Stimulation (PAS), a non-invasive brain stimulation protocol whereby a sensory or motor stimuli are paired with TMS pulses. In its original formulation, Stefan, Kunesch, Cohen, Benecke, & Classen (2000) paired peripheral nerve stimulation with TMS pulses; either LTP or LTD was induced, according to the interstimulus interval (ISI) between medial nerve stimulation and the TMS pulse, (see Carson & Kennedy, 2013 for a review on the topic). Specifically, if sensory stimulation is adjusted so that the afferent signal arrives at M1 at the same time as the TMS pulse, then LTP-like plasticity is induced (PAS_{LTP}), which is reflected in an increase of Motor-Evoked Potential (MEP) after the PAS intervention. On the other hand, if the afferent stimulus arrives at M1 after the TMS pulse, then LTD-like plasticity is induced (PAS_{LTD}), with a resultant decrease in corticospinal excitability (Carson & Kennedy, 2013). For PAS interventions, the term 'LTP/D-like plasticity' is preferred because, as Ziemann, Ilić, Pauli, Meintzschel, & Ruge, (2004) noted, although the results of PAS are similar to non-primate experiments (Rioult-Pedotti et al., 1998), currently there it is still unclear whether the mechanisms underpinning the observed effects of PAS are actually LTP/D.

Using PAS interventions, significant progress has been made in the understanding of the neural underpinnings of plasticity developed at different phases of motor learning, i.e. fast (intra-session) and slow (inter-session) phases (Dayan & Cohen, 2011). Ziemann et al. (2004) were among the first to confirm the original proposition of Pascual-Leone et al. (1995), which suggested that the initial phase of learning, so-called fast learning, is modulated by an "unmasking" of silent cortical connectivity. This was suggested by the fact that, when Ziemann et al. (2004) applied a PAS intervention after a motor practice session, increases in corticospinal excitability usually seen for the PAS_{LTP} were occluded. Indeed, after motor practice both PAS_{LTP} and PAS_{LTD} decreased participants' corticospinal excitability. The results by Ziemann et al. (2004) and others (Jung & Ziemann, 2009; Rosenkranz, Kacar, et al., 2007) provide evidence for a causal relationship between motor practice and cortical connectivity. That is, if we assume that LTP/D-like plasticity and motor learning share the same mechanisms, then both can induce an unmasking of silent cortical connectivity. It should be noted, however, that the repetition of these protocols over time may result in synaptic imbalances within the brain. To prevent this, the brain is equipped with different methods to maintain homeostasis of synaptic weighting. Specifically, research on plasticity reveals that the ability to induce synaptic plasticity is based on the history of the previous synaptic activity (Cooper & Bear, 2012; Suppa et al., 2017). A history of high synaptic activity is thought to prevent further induction of LTP, whereas a history of low synaptic activity facilitates it (Müller, Orekhov, Liu, & Ziemann, 2007; Ziemann et al., 2004). This homeostatic mechanism is come to be known as homeostatic metaplasticity (plasticity of plasticity), and it is thought to be based on the Bienenstock-Cooper-Munro theory of bidirectional synaptic plasticity (BCM; Bienenstock, Cooper, & Munro, 1982; Cooper & Bear, 2012). In practice, this means that if motor practice and LTP-like mechanisms induced by PAS share the same network, then we should see an interaction of those two protocols, so that the training session, which is thought to result in high levels of synaptic activity in the neural circuitry involved in the training, shifts the threshold for further induction of LTP, concomitantly decreasing the threshold for the induction of LTD (Rosenkranz, Kacar, et al., 2007; Ziemann et al., 2004). Thus, if PAS_{LTP} is performed after motor practice, a decreased ability of the PAS protocol to produce further LTP, and an enhanced ability to induce LTD-like results, should be evident (Jung & Ziemann, 2009; Müller-Dahlhaus & Ziemann, 2015; Müller et al., 2007). It is also interesting to note that similar interactions are obtained not only with motor practice, but also when two PAS protocols are sequential to each other (Müller et al., 2007).

In its original formulation, PAS intervention was designed to test LTP-like plasticity in motor system, with electrical stimulation of peripheral nerves. In recent years, however, variation of the original PAS methodology, by associating different types of sensory and motor stimuli to the TMS pulse, suggest that associative plasticity may be a more general principle of brain organization (Suppa et al., 2017). For example, Thabit et al. (2010) paired TMS pulses with ballistic thumb abduction, while Mrachacz-Kersting, Kristensen, Niazi, & Farina, (2012) designed a protocol in which TMS pulses were paired with MI of right foot dorsiflexion. Outside the sensorimotor system, Suppa and colleagues provided evidence of associative interaction within the visuomotor circuitry (Suppa, Li Voti, Rocchi, Papazachariadis, & Berardelli, 2015), while more recently, Ranieri et al. (2019) reported that the visual system too exhibits associative Hebbian-like modulation of excitability. Taken together these studies suggests that PAS is able to modulate corticospinal excitability, and that this modulation is sensitive to the ISI of the pairing. Interestingly, there is evidence that also the audiomotor pathway exhibits Hebbian plasticity. Sowman, Dueholm, Rasmussen, & Mrachacz-Kersting (2014) investigated the use of auditory stimuli paired with TMS stimulation delivered over M1. They reported that after auditory PAS (aPAS), corticospinal excitability increased by 48% immediately post-intervention and 65% increase after 15 minutes from the aPAS intervention. In this study, we employed aPAS to study the temporal interaction between a sAOMI practice and LTP-like plasticity of the audiomotor pathway artificially induced by a non-invasive neuromodulatory protocol. To do so, we administered aPAS to our participants after a practice session based on AOMI and compared the induced changes of motor cortex excitability with the ones induced in the same subject by aPAS alone performed on a different day.

2.2. METHODS

2.2.1. Participants

Twenty-two self-reported neurologically and psychiatrically healthy right-handed young adults (Table 1; 8 females; age: M 25.67, SE 2.08) were recruited for this study. None of them reported completing any formal musical training. Participants completed the Edinburgh Handedness Inventory to assess their hand dominance (EHI; Oldfield, 1971). In addition, participants completed a TMS safety screening questionnaire (Rossi, Hallett, Rossini, & Pascual-Leone, 2009, 2011). Finally, participants' vividness of MI was assessed using the Motor Imagery Questionnaire 3 (MIQ-3; Williams et al., 2012). Two participants dropped out after the first session. In addition, one more participant's data were discarded due to compromised M-wave recording. Those participants were excluded, leaving nineteen participants to be included in the analysis. Nine participants were assigned to the SON group, and the remaining ten were assigned to the CON group. The study was approved by the Brunel University London College of Health, Medicine and Life Sciences Research Ethics Committee and data collection was in accordance with the principles of the Declaration of Helsinki.

Table 1 – Participant's Demographic Data by Group

	SON		**CON**	
	Mean	**SEM**	**Mean**	**SEM**
Age (years)	25.67	2.08	25.27	2.01
EHI Score	9.57	0.74	7.71	0.74
Body Weight (kg)	74.78	5.76	66.73	3.26
Body Height (cm)	171.56	3.93	172.55	2.32
Internal visual imagery	5.39	0.41	5.73	0.36
External Visual Imagery	5.97	0.29	5.64	0.32

Kinesthetic Imagery	5.11	0.48	5.45	0.44

2.2.2. Experimental Design

Figure 1a provides a chronological representation of the experimental design. The experiment consisted of two sessions, completed in fixed order on two separate days. The second session was completed after at least seven days, to prevent carryover influences of the aPAS on the first session (Ziemann et al., 2004). In the first session, participants completed an aPAS protocol alone. This session served as a baseline for comparison with data from the second session. Corticospinal excitability was assessed before (PRE) and after (POST) the aPAS protocol. The second session was designed to assess the influence of sonification on corticospinal excitability, and audiomotor plasticity arising from the training. Participants completed a practice block composed of congruent AOMI followed by either MI or PE of the same action (see later for more details). In this practice session, participants were randomly assigned to two groups: SON group engaged in sAOMI, while CON completed the session without extrinsic auditory information. After the practice, participants completed another aPAS protocol, which allowed us to investigate the audiomotor-induced plasticity arising from the training. In the second session, corticospinal excitability was measured at three time points: Before (PRE) and after (POST 1) the practice block, and after the aPAS session (POST 2).

2.2.3. Combined Action Observation and Motor Imagery Practice

During the second experimental session, both groups completed a single AOMI practice block, comprising 96 trials for a total duration of approximately 30 minutes. Trials were split into six blocks, with a one-minute break in between the blocks, to allow the participant to relax. Figure 1b depicts a schematic representation of the stimuli presentation during each trial. Participants first observed the action and were asked to concurrently imagine executing the same action using kinaesthetic motor imagery. During AOMI, SON group listened to the sonification sound, while CON group did not hear any extrinsic sound. After that, a blue cross appeared for 1 second, notifying them to get ready, after which an icon indicated that they should either imagine (thought bubble icon) or imitate (battery icon) the action. After this, participants pushed the ‘enter’ button on a numeric keypad, to terminate the trial, and rest for 5 seconds, after which a new trial begun, by showing another blue cross. Ten trials in each block required the participants to engage in MI; the remaining ones required them to perform the action (PE). We chose to add physical execution trials, because we sought to design a practice protocol that was as similar as possible to one that would be carried out in applied settings. It has been argued that, although it is possible to learn an action using just MI (Kraeutner et al., 2015), physical execution of an action remains a fundamental component in motor learning (Mulder, Zijlstra, Zijlstra, & Hochstenbach, 2004). Previous research has highlighted the benefits of execution trials in mental practice (Ruffino et al., 2017), and evidence from clinical studies show that people that who cannot execute movements, such as in spinal cord injury, can attempt at perform it, with beneficial effects for performance (Mateo et al., 2015)MI and PE trials were fully randomized; PE occurring 25% of trials.

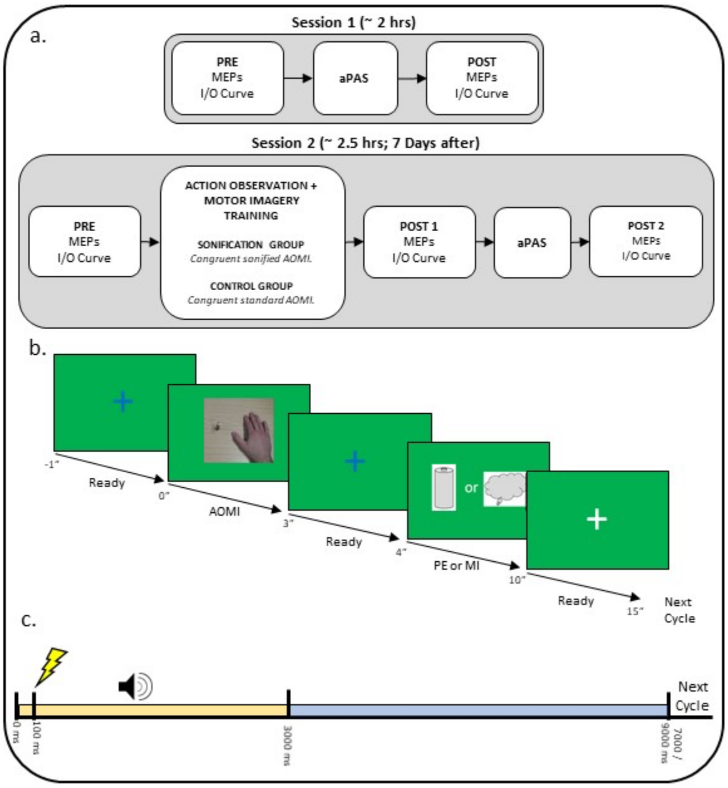

Figure 1 – Schematic representation of the experimental design. **a.** Participants visited the laboratory on two non-consecutive sessions. Session 1 was designed to investigate the effect of aPAS on corticospinal excitability. On the second session, participants engaged in a single practice block, followed by another aPAS protocol, to investigate the interaction between practice and PAS. Measures of corticospinal excitability on the first visit were obtained before and after the completion of the aPAS protocol. For the second visit, corticospinal excitability was measured at 3 timepoints: before the training (PRE), after the training (POST1) and after the aPAS (POST2). **b.** Schematic representation of the practice session. Participants first observed a blue cross, representing a 'ready' cue, then engaged in AOMI; the SON group heard the sonification sound concurrently. After this, another blue cross appeared, after which participants either imagined (MI; cloud icon) or executed (PE; battery icon) the same action. When a white cross appeared, participants did nothing for a 5 s period. **c.** Details of the aPAS protocol. For each audiomotor training, the TMS pulse was delivered 100 ms after the onset of the sound. The sound lasted for 3 s (yellow box). The audiomotor training were delivered every 4-6 s (blue box)

2.2.4. Task and Sonification Process

Participants observed an actor pinching a battery with his right thumb and index finger, an action that was either sonified (SON) or not (CON)[4]. Sonification was performed using a frame-by-frame strategy. Raw videos were recorded using a Sony HDR-TD30, and images were acquired at 25 frames per second, at a resolution of 1920 x 1080 pixels. The raw files were exported in the free video editing software *Hitfilm express 2017* (FXHOME Limited, UK) for sonification. We chose to sonify the distance between the thumb and the index finger. The sonification sound chosen was a synthesized pitch, which was created in the opensource software *Audacity*. The sound was first created and then matched with the video in *Hitfilm express 2017* (FXHOME Limited, UK). We chose a synthetized sound because we were interested in exploring the potential use of non-action sound, auditory stimuli that do not evoke audiomotor resonance per se. Research shows that these sounds can be effectively associated to the representation of an action (L. Ticini et al., 2011). In addition, our audiomotor mapping is the most used in sonification research, as per a recent systematic review (Dubus & Bresin, 2013)

2.2.5. Assessment of corticospinal excitability

To measure changes in corticospinal excitability as a result of the intervention and aPAS, we investigated changes in peak-to-peak amplitude MEPs of the first dorsal interosseous (FDI) muscle, a muscle that was involved in the action. TMS pulses were delivered at 130% of individual's resting motor threshold (rMT). In addition, we investigated the input-output relationship of MEPs (IO curve). For this test, MEPs were collected at the intensities of 80%, 90%, 100% (rMT), 105%, 110%, 120%, 130%, 140% and 150% of rMT. A total of 90 pulses were randomly delivered, 10 per stimulation intensity. The IO curve assesses differential recruitment of different motor units with increasing stimulation intensity (Carroll, Riek, & Carson, 2001; Devanne, Lavoie, & Capaday, 1997). Both MEP and IO curve data were collected because the latter may be necessary when the protocol implies measuring corticospinal excitability across multiple days, as is more robust to possible confounds, such as intertrial changes in coil position and orientation (P. M. Rossini et al., 2015).

Participants sat on a chair in front of a 24" LCD monitor (model XL2430-B, BENQ) at a viewing distance of one meter. They were instructed to position their arms and elbows on the

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[4] Link to the video

table, keeping their hands in a pronated and relaxed position. Muscle activity was monitored throughout the experiment. Participants were continuously reminded to relax as much as possible, and not to move during the stimulation periods. TMS responses were delivered using a Magstim 200 delivering monophasic pulses (Magstim Company, Whitland, UK), using a 70 mm figure-of-eight stimulation coil, oriented as to induce posterior-to-anteriror current. MEPs were collected using Ag/AgCl electrodes (Kendall, Covidien, Canada) arranged in a bipolar, belly-tendon montage. To reduce skin resistance, participants' skin area was shaved (if necessary), abraded using an abrasive paste and cleaned using isopropyl alcohol swabs. After the preparation of the participant, the hotspot for TMS stimulation was found. Hotspot identification began by placing the coil 5 cm lateral and 1 cm anterior to the individually defined apex. From this position, the hotspot was defined as the coil position and orientation that evoked MEPs of the largest amplitude at the same stimulation intensity. The position was marked on the scalp with a soft-tip pen, to allow repositioning of the TMS coil after the breaks. Subsequently, the resting motor threshold (rMT) was determined using adaptive threshold hunting technique (Ah Sen et al., 2017; Awiszus, 2011). This allowed us to determine the rMT with a reduced number of TMS pulses, thereby improving participants' comfort, and reducing total testing time. During all periods of TMS stimulation, participants were asked to direct their visual attention to a fixation cross at the centre of a screen and to count down from 200 to 0 (Kumpulainen et al., 2014). At the end of each session, FDI M-waves were collected to normalize MEPs across participants. This was done using peripheral magnetic stimulation of the ulnar nerve, which was obtained by placing the TMS coil on the elbow, between the olecranon and the medial epicondyle, with the coil handle perpendicular to the direction of the ulnar nerve, to induce current flow in the nerve with the monophasic stimulator (Lampropoulou, Nowicky, & Marston, 2012). To determine M-max, we collected 5 evoked M-waves responses from intensities ranging from 20% to 70% of the maximum stimulator output, with incremental steps of 10%. Surface electromyography and evoked responses were recorded using Signal (v. 6, CED, UK) and amplified at a gain of 1000 and sampled at 4kHz. To reduce the influence of external artefacts, an online band-pass filter (5 to 2000 Hz) was applied. TMS was applied through synchronized stimulus presentation, using TTL output triggers generated by E-Prime software (v 3.0; Psychology Software Tools, Pittsburgh, PA), and sent to the magnetic stimulator.

2.2.6. Auditory Paired-Associative Stimulation (aPAS)

The aPAS protocol (Figure 1c) consisted of 200 audiomotor pairings, each of which consisted of an auditory stimulus and a TMS pulse. The protocol was controlled using E-Prime, which was used to time the TMS pulse in relation to the auditory stimulus. The pairing auditory stimulus was a pre-recorded sound of fingers typing on a computer keyboard, and the TMS pulse was delivered 100 ms after the sound onset, with stimulus intensity set at 120% rMT. The auditory stimulus was played for 3000ms. The interstimulus interval (ISI) between sound onset and TMS pulse was chosen in accordance with previous research on aPAS (Sowman et al., 2014). The pairs of stimuli were delivered with a random interval between 4000 and 6000 ms. The pairings were organized in four blocks of 50 pairings each, with one minute of rest between blocks. Auditory stimulation was delivered via in-ear earphones. Sound volume was adjusted for each participant so that it was comfortable to hear the sound, without perceived distortions. During the protocol, participants were asked to direct their gaze to a white fixation cross on the screen, and to pay attention to the sound. Prior to the beginning of the protocol, the sound was played, and all participants successfully reported to recognize the action sound.

2.2.7. Data and Statistical Analysis

MEPs Analysis. All data were stored on an external drive for offline analysis. For each trial, MEPs peak-to-peak amplitude and background EMG levels were calculated using a custom-made script in Signal software (CED, v 6.05; UK), and then exported to Microsoft Excel for further analysis. Muscle activity prior to the TMS pulse was calculated as a root mean square of background EMG during the 100 ms prior to the TMS pulse. Trials with background EMG levels greater than 300 µV were excluded from MEPs analysis. With this threshold, less than 1% of the total number of MEPs were removed from the analysis. Raw MEPs were normalized and expressed as a percentage of the maximal evoked muscle response (M_{max}), obtained for each participant at the end of each testing session, using the following formula (henceforth, MEPs will refer to normalized, not raw, MEPs):

$$Normalised\ MEP = 100 * \frac{MEP}{Mmax} \qquad [1]$$

We chose this normalization method because M_{max} is thought to thought to be stable across time, as it represents the maximal activation of the α motoneuron pool, in this case evoked by peripheral magnetic stimulation (Lampropoulou et al., 2012; Palmieri, Ingersoll, & Hoffman, 2004). Thus, this gave a stable comparison for MEPs, which are influenced by different activities (Bestmann et al., 2015; Klein-flu, Nobbs, Pitcher, & Bestmann, 2013).

IO Curve Analysis. The relationship between TMS stimulation and MEP response, was investigated by fitting a 4 parameter Boltzmann sigmoid function over the MEPs of the 9 stimulation intensities. Peak-to-peak amplitude and bgEMG was calculated using the same script. We averaged MEPs for each stimulation intensity. Curve fitting was performed using the built-in sigmoid curve fitting features of Signal software (CED, v 6.05, UK). The fitting was done using the following equation:

$$MEP(I) = \frac{MEPmax - MEPmin}{1 + e\frac{\mathrm{I}50 - 1}{s}} \tag*{[2]}$$

Where MEP_{max} and MEP_{min} are the maximum and minimum asymptote, respectively; I_{50} is the stimulus intensity needed to evoke MEPs that are 50% of $\mathrm{MEP}_{\mathrm{max}}$, and s is the slope of the curve. Curve fitting with Boltzmann equation provided several parameters, which were then used to characterize changes in corticospinal excitability as a result of protocol intervention (Carroll et al., 2001; Devanne et al., 1997). In addition to the parameter in the equation above, another index was calculated, slope I_{50}, which represented the slope of the ascending phase of the curve at I_{50}, which was calculated according to the following formula:

$$Slope\ I50 = \frac{m * MEPmax}{4} \tag*{[3]}$$

Where m is the slope parameter of the Boltzmann sigmoid function.

Statistical Analysis. Statistical analysis was carried out in SPSS. Outliers in the data were assessed using z scores. Values greater than ± 2.99 were considered outliers and discarded from the analysis. Data distribution was assessed via the Shapiro-Wilk test. A paired-sample t-test was used to assess statistical differences in rMT between sessions, while an independent t-test was used to assess group difference in rMT in the second visit. The same tests were also used to assess between groups differences in vividness of motor imagery, by analysing the three output of the MIQ questionnaire, internal visual imagery (IVI), external visual imagery (EVI) and kinaesthetic motor imagery (KI). Lastly, between-days changes in $\mathrm{M}_{\mathrm{max}}$ were calculated using a paired-sample t-test. Some of the indices were not normally distributed ($p > 0.05$), so non-parametric statistical analyses were used instead. Homogeneity of variance was assessed using Levene's test for equality of variances. To assess the effects of aPAS alone (on experimental session 1), we performed non parametric test on pre- and post-aPAS MEPs.

Wilcoxon signed-rank test was used to assess statistical differences on IO curve indices. To assess the effects of the practice block on corticospinal excitability, and its priming effect for aPAS, we performed a mixed ANOVA with factors TIME and GROUP. TIME factor had three levels – pre-training, post-training (post 1) and post-aPAS (post 2), and GROUP two (SON and CON). In addition, we also analysed the percentage change of corticospinal excitability after the two session. To this end, we performed a mixed ANOVA with factors 'TIME' (two levels: 'aPAS D1' and 'aPAS D2') and GROUP (two levels, SON and CON). For IO curve indices, six parameters were analysed, MEPmax, MEPmin, MEP range, slope, I50 and slope I50. For each of these indices an individual Sphericity of covariance was assessed with Mauchly's test of sphericity. In case of violation of sphericity, Greenhouse-Geisser epsilon adjustment was used. Bonferroni correction was applied for post hoc comparisons.

2.3. RESULTS

There were no significant differences in rMT between the first (38± 5 %) and the second visit (38 ± 4 %), $t(19) = 0.151$, $p = 0.882$. In addition, there were no statistically significant differences in rMT between the SON (37 ± 4 %) and CON group (38 ± 4 %) on the second visit, $t(17) = -0.612$, $p = 0.55$. The MIQ-3 analysis showed no significant differences between the groups in self-reported vividness of Internal Visual Imagery ($t(19) = -0.49$, $p = 0.63$), External Visual Imagery ($t(19) = 0,62$, $p = 0.54$), or Kinaesthetic Imagery ($t(19) = -0.36$, $p = 0.72$). No statistically significant differences were found in Mmax between the first (11.38 ± 4.22 mV) and the second (11.70 ± 4.52 mV) visits, as assessed using a Wilcoxon signed-rank test ($z = -0.181$, $p = 0.856$).

2.3.1. Session 1: Effects of aPAS on corticospinal excitability

Figure 2 and Table 2 provide a summary of the results for the first session. The aPAS protocol induced a significant increase in peak-to-peak MEP size (Figure 2a), as compared with pre-aPAS measure: $z = 3.058$, $p = 0.002$). Figure 2d reports the IO curve fitting with Boltzmann function. Analysis on the indices arising from curve fitting reported a significant increase in MEP_{max} ($z = 2.495$, $p = 0.013$; Figure 2b), slope of the fitted curve ($z = 2.012$, $p = 0.44$, Figure 2c), and range of MEP responses ($z = 2.535$, $p = 0.11$). No significant differences were found for MEPmin ($p = 0.136$), I_{50} ($p = 0.390$), and the slope at I_{50} ($p = 0.601$).

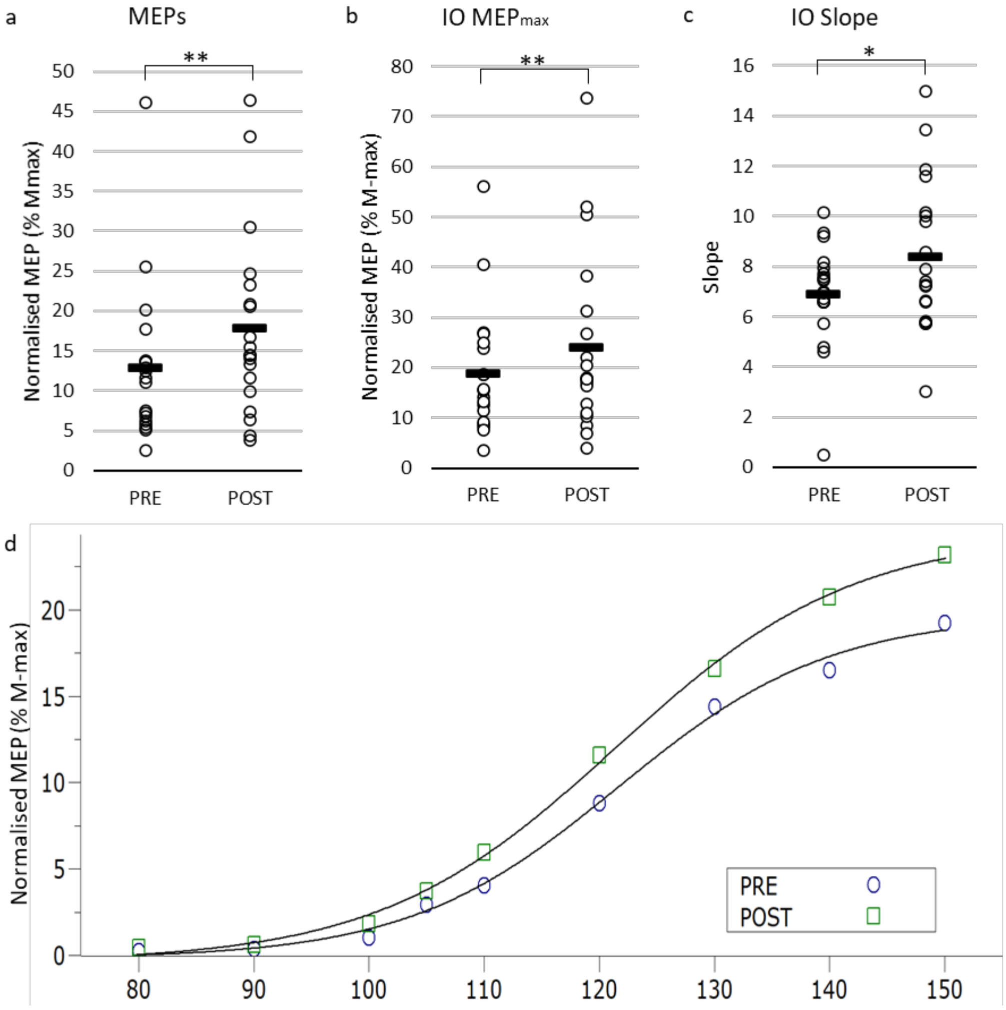

Figure 2 – Corticospinal excitability measures before and after aPAS. On the first visit both SON and CON completed the same protocol, so the data shown represents the group average of both groups (n=21) a. MEPs collected at 130% rMT, b. MEPmax of the IO curve sigmoid fitting; c. Slope of the IO curve sigmoid fitting; d. Sigmoid fitting of the 9 IO curve stimulation intensities for pre- and post-aPAS. White circles represent individual data, while black rectangles represent group means. *: $p < 0.05$; **: $p < 0.01$.

Table 2 – Descriptive Statistics for Corticospinal Excitability Measures – Visit 1 [All participants; n=19]. MEPs were normalised as percentage of Mmax

						95% Confidence Interval	
		Mean	Median	SD	SEM	Lower	Upper
			MEPs at 130% rMT				
MEP	Pre	12.89	11.63	9.89	2.27	8.13	17.67
	Post	17.9	14.45	11.63	2.66	12.3	23.5
			IO Curve				
MEP_{min}	Pre	0.15	0.10	0.39	0.09	-0.04	0.34
	Post	-0.20	-0.12	0.90	0.21	-0.63	0.23
MEP_{max}	Pre	18.76	15.53	12.67	2.91	12.65	24.86
	Post	23.94	17.68	18.06	4.14	15.23	32.64
I_{50}	Pre	120.03	119.38	6.02	1.38	117.13	122.94

	Post	118.69	117.95	8.12	1.86	114.78	122.60
Slope	Pre	6.89	6.98	2.10	0.48	5.88	7.90
	Post	8.39	7.41	3.03	0.70	6.93	9.85
MEP Range	Pre	18.61	15.17	12.75	2.93	12.46	24.76
	Post	24.14	18.29	18.71	4.29	15.12	33.16
Slope I_{50}	Pre	1.05	0.51	1.75	0.40	0.20	1.89
	Post	0.74	0.45	0.52	0.12	0.49	0.99

2.3.2. Session 2: Effects of AOMI training practice on corticospinal excitability and practice-dependent plasticity

Figure 3 and Table 3 provide a summary of the main results for the second session. There was a main effect of 'TIME' on peak-to-peak MEP amplitude: F(2,34) = 7.397, $p = 0.002$, $\eta 2_p$= 0.303. No interaction TIME x GROUP on peak-to-peak MEP amplitude was found: F(2,34) = 0.972, $p = 0.389$, $\eta 2_p$= 0.054. Post hoc analysis using Bonferroni correction revealed that MEP mean amplitude significantly increased after the training, as compared with pre-training values ($p = 0.015$, Figure 3a). No significant changes were found between POST1 and POST2, suggesting that post-training aPAS did not significantly change corticospinal excitability. For the analysis of the parameters IO curve (Figure 3b) arising from the Boltzmann fitting, a mixed ANOVA reported no main effects of TIME, nor TIME x GROUP interaction for any parameter ($p > 0.05$).

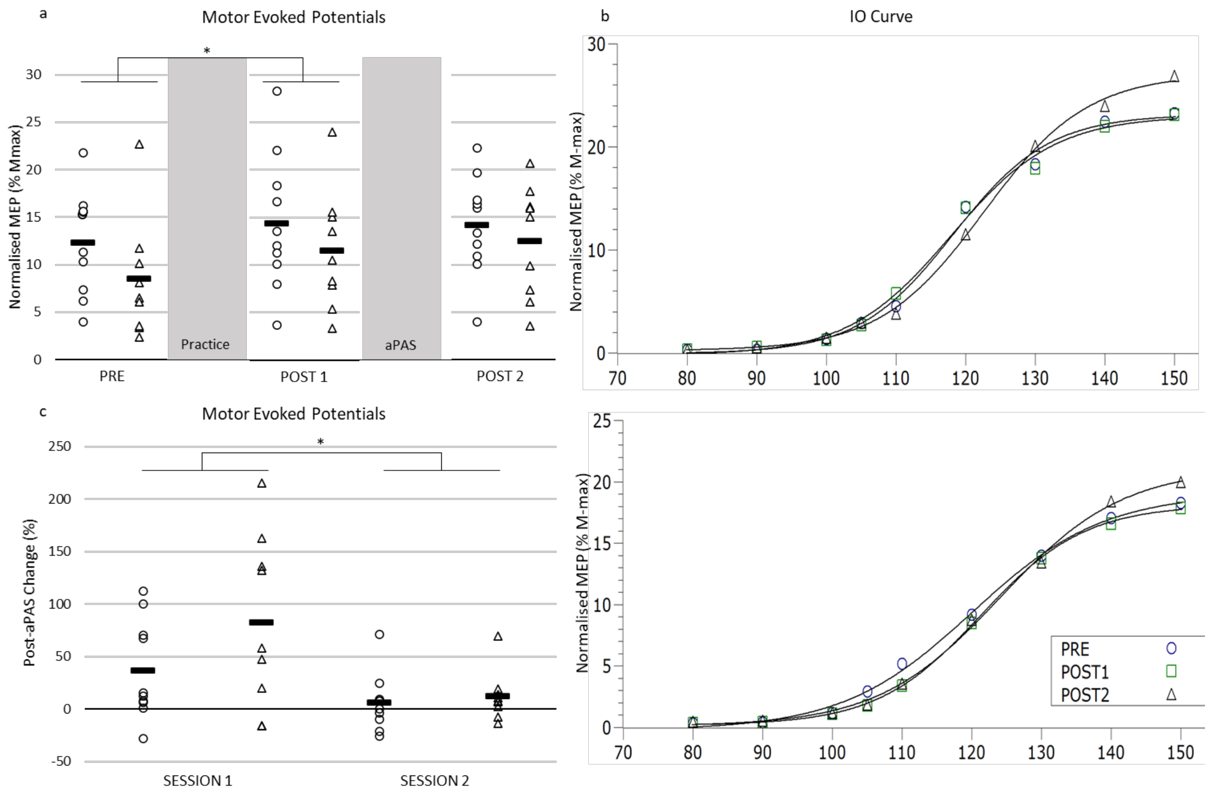

Figure 3 – Second visit. MEPs were collected at three time points: Before the practice session (PRE), after the practice session (POST 1), and after the aPAS (POST 2). **a.** Corticospinal excitability on the second visit for SON and CON groups. **b.** Sigmoid fitting of the 9 IO curve stimulation intensities for PRE and POST 1 and POST2 for CON group (upper panel) and SON group (lower panel). **c.** Between-days effects of aPAS on corticospinal excitability. In session 1 aPAS was the only intervention, while on session 2, aPAS was administered after the practice block. Circles and triangles represent individual values for SON and CON group, respectively. Black rectangles represent group means. * $p < 0.05$.

Table 3 – Descriptive Statistics for Corticospinal Excitability Measures – Visit 1 [CON group n= 10; SON group n=9)]. MEPs were normalised as percentage of Mmax

						95% CI	
		Mean	Median	SD	SEM	Lower	Upper
SON Group							
MEPs at 130% rMT							
MEP	Pre	12.34	13.3	5.51	1.74	8.41	16.28
	Post 1	14.35	12.79	7.11	2.25	9.26	19.42
	Post 2	14.18	14.68	5.26	1.66	10.4	17.92
IO curve							
MEP$_{min}$	Pre	-0.11	-0.03	0.83	0.28	-0.74	0.53
	Post 1	0.33	0.23	0.66	0.22	-0.18	0.83
	Post 2	0.31	0.40	1.11	0.37	-0.54	1.16
MEP$_{max}$	Pre	19.37	19.44	7.27	2.42	13.79	24.96
	Post 1	18.01	16.80	6.86	2.29	12.74	23.28

	Post 2	20.03	14.34	8.70	2.90	13.34	26.71
I_{50}	Pre	118.38	119.52	4.65	1.55	114.81	121.96
	Post 1	120.46	118.85	3.54	1.18	117.74	123.18
	Post 2	120.11	119.19	5.46	1.82	115.91	124.31
Slope	Pre	7.82	7.85	1.93	0.64	6.33	9.30
	Post 1	6.62	6.91	1.58	0.53	5.41	7.83
	Post 2	6.06	6.05	2.51	0.84	4.13	7.99
MEP Range	Pre	19.48	18.73	7.66	2.55	13.59	25.37
	Post 1	17.68	16.44	6.74	2.25	12.51	22.86
	Post 2	19.72	14.46	8.78	2.93	12.97	26.47
Slope I_{50}	Pre	0.64	0.70	0.21	0.07	0.48	0.80
	Post 1	0.72	0.69	0.35	0.12	0.45	0.99
	Post 2	0.97	0.70	0.61	0.20	0.50	1.44
CON Group							
MEPs at 130% rMT							
MEP	Pre	8.29	6.51	6.26	2.09	3.48	13.10
	Post 1	11.50	10.49	6.29	2.10	6.66	16.34
	Post 2	12.50	15.03	5.92	1.97	7.95	17.05
IO curve							
MEP_{min}	Pre	-0.01	0.17	0.67	0.21	-0.49	0.47
	Post 1	-0.10	0.10	1.00	0.32	-0.82	0.61
	Post 2	0.50	0.46	0.64	0.20	0.05	0.95
MEP_{max}	Pre	17.12	13.90	12.67	4.01	8.05	26.18
	Post 1	17.51	15.32	11.21	3.54	9.49	25.53
	Post 2	20.50	18.79	12.95	4.09	11.24	29.77
I_{50}	Pre	121.08	119.68	5.11	1.62	117.42	124.74
	Post 1	119.86	119.52	7.11	2.25	114.77	124.95
	Post 2	122.89	122.00	8.41	2.66	116.87	128.91
Slope	Pre	9.20	9.08	3.02	0.96	0.64	0.07
	Post 1	8.02	7.25	2.65	0.84	6.12	9.91
	Post 2	6.95	8.29	3.11	0.98	4.73	9.17
MEP Range	Pre	17.13	13.52	13.03	4.12	7.81	26.45
	Post 1	17.62	15.37	11.40	3.61	9.46	25.77
	Post 2	20.00	18.13	12.99	4.11	10.71	29.29
Slope I_{50}	Pre	0.53	0.38	0.47	0.15	0.19	0.87
	Post 1	0.58	0.50	0.43	0.14	0.28	0.89
	Post 2	1.82	0.65	3.76	1.19	-0.87	4.50

2.3.3. Between-days Effects of aPAS

Both groups showed a decrease in aPAS effect on the second visit, compared to the first one, expressed as a post-aPAS percentage change in MEP peak-to-peak amplitude (Figure 3c, Table 4). A mixed ANOVA revealed a main effect of TIME on percentage change of MEP peak-to-peak amplitude following the aPAS on the two experimental sessions: F(1,17) = 8.183, p = 0.011; $\eta 2_p$ = 0.325. No interactions TIME x GROUP were found: F(1,17) =1.275, p = 0.274; $\eta 2_p$ = 0.07.

Table 4 – Descriptive statistics for the effect of aPAS on corticospinal excitability expressed as a percentage change for the first and second session (CON group n= 10; SON group n=9).

						95% CI	
		Mean	**Median**	**SD**	**SEM**	**Lower**	**Upper**
Session 1	SON	36.44	13.62	47.40	14.99	2.53	70.35
	CON	82.41	57.96	82.63	27.54	18.90	145.93
Session 2	SON	5.98	3.89	27.29	8.63	-13.54	25.50
	CON	12.21	7.48	23.77	7.92	-6.06	30.49

2.4. DISCUSSION

This study was carried out to investigate the effects of sonification of combined action observation and motor imagery on corticospinal excitability. To this purpose, we trained participants to engage in a practice block comprising congruent AOMI, MI and execution of the same action. The experimental group received sonification during AOMI, while a control group received no sonification. An additional aim of this study was to investigate audiomotor plasticity arising from such training. To do so, we used a variation of an established method to investigate neural plasticity, auditory paired-associative stimulation.

2.4.1. Combined Action Observation and Motor Imagery Training and Effect of Sonification

The primary aim of this project was to investigate the effects of auditory augmentation of AOMI on corticospinal excitability. To this end, participants completed a single practice session based on AOMI, MI and physical execution of the same action. In addition, a SON group received auditory augmentation during AOMI. Sonification yielded no significant facilitation of corticospinal excitability, compared to training without sensory augmentation. Although we are not aware of studies exploring the effects of sonification of corticospinal excitability, neuroimaging and behavioural studies have shown that observing a sonified action induces better movement-related perceptual judgments, a more active engagement of the sensorimotor system during AO (Schmitz et al., 2013), as well as superior performance and rehabilitative outcomes in people with Parkinson's disease (Mezzarobba et al., 2018). It is possible that sonification did not exert its enriching function during AOMI because the task was straightforward to perform or imagine, rendering the auditory information redundant. There is evidence suggesting that corticospinal excitability is influenced by the vividness of MI (Lebon, Byblow, Collet, Guillot, & Stinear, 2012). Thus, even though the task was straight forward, it may not necessarily mean that it was easy to imagine. However, MIQ results suggest that our participants were, on average, good imagers (c.f. Marchesotti, Bassolino, Serino, Bleuler, & Blanke, 2016; Vuckovic & Osuagwu, 2013), thus further decreasing the value of sensory augmentation. Given the need for accurate coil localization, we were restricted on actions that could be used in this study. Future studies should explore sonification of simulated action using a more ecologically valid action accordingly.

Another possible reason for the lack of effect of sonification on corticospinal excitability may be due to interactions between AO, MI, and external auditory feedback. Recent investigations suggest that combined usage of AO and MI affects attentional processing and mental effort (Bruton et al., 2020; Meers et al., 2020). Studies show that during AOMI, there is a reallocation of attention between externally-evoked to internal simulation of the kinaesthetic predicted sensation arising from the action (Eaves et al., 2016). Studies investigating corticospinal excitability during various forms of AOMI support this view. Bruton, Holmes, Eaves, Franklin and Wright (2020) assessed corticospinal excitability, eye movement and behavioural data while participants engaged in congruent, coordinated, and conflicting AOMI. Congruent AOMI, as used in this study, resulted in significantly higher MEPs and reduced mental effort. Relevant to the present study, however, is the fact that participants reported increased attentional demands during conflicting AOMI, and MEPs were significantly lower than during congruent AOMI. Even though research on sonification suggests that an optimal audiomotor mapping decreases attentional demands and cognitive load of the task (Dyer et al., 2017), and improves performance (Sigrist et al., 2013), there is also evidence suggesting that, compared to other sensory augmentation strategies, sonification may represent an additional attention weight on people, especially early in the training regime (Ronsse et al., 2011). In our study, we used congruent AOMI, which has been shown to require less mental effort, but the addition of sonification may have resulted in comparable increases in attentional demands, thereby negating potential facilitative effects of the former. Further studies are needed to confirm this hypothesis.

Regardless of sonification, however, statistical analysis revealed a practice effect that agrees with the available literature on practice-related neuromodulation. Thus, the training exerted its modulatory effect. Motor learning, with or without sensory augmentation, is characterized by an increase in corticospinal excitability, as measured by TMS (Jung & Ziemann, 2009; Rosenkranz, Kacar, et al., 2007; Ziemann et al., 2004). It is thought that the initial phase of learning, the within-session fast learning, is based on an unmasking of silent connections, which are based on LTP-like mechanisms (Pascual-Leone et al., 1995). Studies show that even very simple movements, such as repeated thumb abduction/adduction, produce measurable changes in corticospinal excitability, in line with LTP-like plasticity (Rosenkranz, Williamon, & Rothwell, 2007; Ziemann et al., 2004). This mechanistic view of motor learning also applies to more cognitive forms of motor learning, such as AO and MI, as evidence shows that similar plasticity-related modulation of corticospinal excitability are obtained when PAS follows a practice session of observational or mental practice (Avanzino et al., 2015; Lepage et al., 2012). In addition, engaging in AOMI may be better than AO and MI alone (Marshall, Wright, Holmes, Williams, & Wood, 2020; Marshall et al., 2019), as it has been linked to increased neural activity (Bruton et al., 2020; Eaves et al., 2016; Wright et al., 2018), thus could potentially influence the rate of practice-dependent plasticity (Eaves, Riach, Holmes, & Wright, 2016). To our knowledge no research has been done on this. Taken together, our results confirm that practising the pinching of a small object – in this case, a battery – induces an increase in corticospinal excitability of the FDI muscle. The fact that only MEPs, but not the IO curve parameters, exhibited modulation effects suggests that any learning effect was probably small.

In this study, we focussed on sonification of congruent AOMI, which has been the most studied form of AOMI. However, future studies should also explore the effects of sonification of other types of AOMIs such as coordinative and incongruent AOMI (Eaves, Riach, Holmes, & Wright, 2016; Vogt, Di Rienzo, Collet, Collins, & Guillot, 2013). Under the dual simulation hypothesis, when the observed and imagined action are not congruent, there is a representational conflict, which results in a lower corticospinal excitability, and an increase in attentional demand to complete the task (Bruton et al., 2020; Meers et al., 2020). However, these forms of dual representation of action can still be used in motor (re)learning and should be further explored. Considering that AOMI implies a change in focus between externally- top internally-driven action simulation (Eaves, Behmer, & Vogt, 2016; Eaves, Riach, Holmes, & Wright, 2016), sonification could be used to integrate multimodal representation of a complementary aspect of an imagined action. In a hypothetical scenario, a person could imagine performing an action, while simultaneously observing the same action from another point of view and listening to auditory augmentation. Future studies, however, need to further explore whether this hypothesis could have real application to the field of motor (re)learning.

Our discussion regarding the effectiveness, or lack thereof, of sonification for simulation training remains somewhat speculative, given the inconclusive findings. Indeed, the sample size was limited, thus affecting our ability to conclusively discuss the impact of sAOMI for action simulation. Further studies, with a larger sample size, are needed, to further explore this area. Different studies have highlighted the importance of AO and MI for rehabilitation regimes, and its fundamental role in neurological conditions (Abbruzzese et al., 2015; Marshall et al., 2020; Mulder, 2007) and immobilization (Bassolino et al., 2014). Under the right conditions, sonification could represent important strategy to maximize learning in clinical conditions, such as stroke survivors (Scholz, Rhode, Großbach, Rollnik, & Altenmüller, 2015; Scholz et al., 2016, 2014), but could also be a viable sensory substitution strategy for conditions such as deafferentation (Danna & Velay, 2017; Danna et al., 2015). Lastly, further development of sonification research may find application in the field of brain-computer interfaces, by affording strategies to improve embodiment of non-body objects, such as neuroprostheses (D’Alonzo, Mioli, Formica, Vollero, & Di Pino, 2019; Di Pino et al., 2014, 2020), an issue that crucial for optimal development of the field (Makin, De Vignemont, & Faisal, 2017).

2.4.2. The Effect of aPAS on corticospinal excitability.

On the first visit, we evaluated the effects of aPAS on corticospinal excitability. aPAS produced an increase in MEPs immediately post aPAS, compared to pre-aPAS measures. In addition, for the IO curve parameters resulting from the Boltzmann curve fitting, we observed a significant increase in the maximum evoked potential, as well as a significant shift to the left of the slope of the curve, which is usually interpreted as an increase in corticospinal excitability (Rosenkranz, Kacar, et al., 2007). A significant increase in the range of the evoked potentials is also consistent with the increase in MEP_{max}. Our results confirm those of Sowman et al. (2014), who first reported associative LTP-like plasticity within the audiomotor domain by associating a speech sound (the word ‘Hey’) to TMS delivered over the FDI muscle. In our experiment, we used a similar protocol, except that the sound associated to the TMS pulse was a keyboard typing action sound. We used this sound because we stimulated the FDI muscle, which is a prime mover for this action. Our results, however, are very similar to those obtained by Sowman and colleagues. Thus, together with this previous study, our findings suggest that the association of an action sound, regardless of the effector, to a TMS pulse delivered 100 ms after the sound onset at 120% of the individually defined rMT yields a robust modulatory effect on corticospinal excitability.

From a mechanistic point of view, PAS is based on spike-timing-dependent plasticity (STDP). One of the key features of STDP is associativity; that is, its modulating effects are based on the timing of arrival of the two stimuli on the target neuron (Suppa et al., 2017). In most of PAS interventions, an interstimulus interval of 25ms is usually chosen to induce LTP-like plasticity (Carson & Kennedy, 2013; Ranieri et al., 2019; Stefan et al., 2000). We based our protocol on an already published literature on associative plasticity in the audiomotor domain (Sowman et al., 2014). 100 ms from a stimulus onset also coincides with the N100 component of the ERP waveform, which is thought to be related to stimulus-dependent arousal (Naatanen, Kujala, & Winkler, 2011; Nash & Williams, 1982). There is evidence that the auditory N100 is influenced by habituation. Indeed, Löfberg and colleagues reported that, when the same auditory stimulation is delivered in trains of four – one per second – corticospinal excitability is increased only for the first stimulus in each train; subsequent TMS pulses yield decreases in corticospinal excitability, suggesting an habituation effect (Löfberg, Julkunen, Kallioniemi, Pääkkönen, & Karhu, 2018; Löfberg, Julkunen, Pääkkönen, & Karhu, 2014). Nevertheless, we did not find evidence of habituation, as our results confirm that aPAS is a robust technique for modulating corticospinal excitability, consistent with Hebbian learning. In addition, evidence from visuomotor PAS confirms a modulation of corticospinal excitability with an interstimulus interval of 100 and 120 ms (Suppa et al., 2015). Taken together this raise the possibility that the interstimulus interval for cross-modal PAS may be around 100ms. Further studies are needed, however, to confirm this hypothesis.

2.4.3. Occlusion of LTP-Like plasticity after training

A secondary aim of this study was to gain information on the interaction between sonification and plasticity. To this end, both SON and CON group underwent an additional aPAS protocol after the training session. Evidence suggests that PAS and practice-dependent plasticity share similar neural mechanisms, such that the priming of practice affects the modulatory effects of PAS. Specifically, studies suggest that both motor skill learning and PAS-induced associative plasticity result from a modulation of synaptic strength and weight within the network targeted by the intervention, and this is based STDP (Caporale & Dan, 2008). Evidence also shows that if two LTP-inducing protocol are done in succession, the first protocol interferes with the effect of the second. This form of metaplasticity – plasticity of plasticity - can be induced with two excitatory PAS (Müller-Dahlhaus et al., 2015; Müller et al., 2007) or by priming a PAS with a practice block (Rosenkranz, Kacar, et al., 2007; Stefan et al., 2006; Ziemann et al., 2004).

In our study, both CON and SON performed the same protocol, except for auditory augmentation during AOMI. Considering that in the first session we confirmed the sensitivity of aPAS to audiomotor plasticity, we wanted to explore the interaction between sonification and aPAS, which is designed to test audiomotor connectivity. This could provide evidence of practice-dependent cross-modal interaction. Post-aPAS measures of corticospinal excitability, however, did not report any neuromodulation, compared with post-practice measures for both groups. In addition, for both SON and CON group, the effect of aPAS completed after the practice was lower than the one completed in the first session, and no differences between the group were found. It is possible that the effect of sonification on learning was small, and that the execution component of the training block masked any effect of sonification. The auditory cortex and M1 do not have direct connections (Cammoun et al., 2015) and, as for the visual processing (Milner & Goodale, 2008), auditory processing engages two pathways, a ventral and a dorsal one (Rauschecker & Tian, 2000), with the dorsal pathway being responsible for audiomotor integration (Baumann et al., 2007). It is thought that an auditory stimulus engages the motor system via the dorsal route (Rauschecker, 2011), which from the thalamus, engages the parietal cortex, where it is integrated with visual and other stimuli (Tanaka & Kirino, 2018), to create a multisensory perception (Gottlieb, 2007). As highlighted earlier in the text, if a practice block is followed by PAS protocol, an interaction between the two protocols is evident (Rosenkranz, Kacar, et al., 2007; Stefan et al., 2006;Ziemann et al., 2004). MEPs are a motor phenomenon (Hallett, 2007; Terao & Ugawa, 2002) and, as such, it is possible that the physical execution portion of the training produced a ceiling effect in terms of LTP in M1, so as to mask any effect of sonification on the interaction between practice and aPAS.

Another possible explanation for our aPAS results could be methodological. It is also possible that the temporal spacing between the practice block and subsequent aPAS session influenced participants' attention levels. There is evidence that the interaction between LTP-like neuromodulatory protocols are sensitive to the spacing between those two protocols (Müller-Dahlhaus et al., 2015). While plasticity arising from motor learning is long-lasting (Dayan & Cohen, 2011), the spacing between our two protocols may have affected the level of attention during aPAS. This view is supported by evidence that participants' level and focus of attention affect the outcome of PAS (Kamke et al., 2012; Kamke, Nydam, Sale, & Mattingley, 2016; Stefan, Wycislo, & Classen, 2004). That is, it is possible that participants may have been unable to sustain high level of attention to the protocol, or worst may have been in a state of drowsiness. However, drowsiness is associated with a decrease in corticospinal excitability (Salih et al., 2005). The fact that after the practice block the effect of aPAS on corticospinal excitability was smaller than the session completed in isolation may be evidence of a suboptimal level of attention to the aPAS stimuli. To mitigate loss of attention, future studies should explore the optimal length of an aPAS protocol, to suggest the minimum number of audiomotor pairing that still neuromodulate corticospinal excitability. It is possible that a shorter aPAS protocol may allow participants to better sustain the practice block and the aPAS protocol. For example a longer break between practice block and post-practice aPAS may be longer, to give participants time to relax, and be more predisposed to the protocol. Lastly, future studies should investigate the neural aftereffects of aPAS to gain evidence on the interaction between the practice block and aPAS, for example with combined TMS-EEG (Hallett et al., 2017; Ilmoniemi & Kičić, 2010; Rogasch & Fitzgerald, 2013)

To the best of our knowledge, we are the first to explore audiomotor metaplasticity. Our results extend the findings of Sowman et al. (2014), with regard to the effects of aPAS on corticospinal excitability of hand muscles. However, we acknowledge that our study would have benefitted by a larger sample size. Future studies are needed to further explore this protocol. Plasticity is thought to be the underlying neural substrate of learning, and measuring the neuromodulation resulting from the learning process is fundamental for the development of new tools and strategies to maximize learning, and more studies are needed to further elucidate the neuromodulatory effects of aPAS. The development of aPAS may provide an effective test to assess audiomotor connectivity, which may provide, in turn, mechanistic evidence for clinical deficits, as well as the link between the deficit and interventions, via occlusion of LTP-like plasticity (Rosenkranz, Kacar, et al., 2007; Ziemann et al., 2004). Further, aPAS may also represent an intervention tool. Recent studies highlighted the potential therapeutic benefits of using PAS in neurological conditions such as stroke (Silverstein et al., 2019) or incomplete spinal cord injury (Ling, Alam, & Zheng, 2020); Along those lines, aPAS may represent a viable intervention for audiomotor conditions, such as stuttering (Sares, Deroche, Ohashi, Shiller, & Gracco, 2020). To achieve this, future studies should confirm the optimal ISI. Since PAS is based on STDP (Caporale & Dan, 2008), the timing of the arrival of volleys at M1 is crucial.

2.5. CONCLUSION

In the present study we investigated the effects of sAOMI on corticospinal excitability, and its neuromodulatory role when paired with aPAS. After a training practice based on sAOMI and Physical execution of the action, corticospinal excitability was not modulated, compared to pre-practice measures. In addition, our results confirm previous evidence that aPAS alone modulates corticospinal excitability, evidenced by post-aPAS increases in MEP amplitudes. However, its effects on homeostatic metaplasticity are unclear, and future studies with a larger participant pool may provide more robust evidence of the effects of sonification on action simulation training and audiomotor metaplasticity.

CHAPTER 3

SONIFICATION OF COMBINED ACTION OBSERVATION AND MOTOR IMAGERY: EFFECTS ON CORTICOSPINAL EXCITABILITY

ABSTRACT

Action observation and motor imagery were suggested to be valuable strategies for motor learning. Their simultaneous use (AOMI) increases neural activity, with related benefits for motor learning, compared to the two strategies alone. In this study, we explored how sonification influences AOMI. Twenty-five participants completed a practice block based on AOMI, motor imagery and physical execution of the same action. Participants were divided into two groups: An experimental group that practiced with sonification during AOMI (sAOMI), and a control group, which did not receive any extrinsic feedback. Corticospinal excitability at rest and during action observation and AOMI was assessed before and after practice, with and without sonification sound, to test the development of an audiomotor association. The practice block increased corticospinal excitability in all testing conditions, but sonification did not affect this. In addition, we found no differences in action observation and AOMI, irrespective of sonification. These results suggest that, at least for simple tasks, sonification of AOMI does not influence corticospinal excitability. In these conditions, sonification may have acted as a distractor. Future studies should further explore the relationship between task complexity, value of auditory information and action, to establish whether sAOMI is a valuable for motor learning.

3.1. INTRODUCTION

The previous study explored the effects of a practice block based on sAOMI, MI and PP on corticospinal excitability, measured at rest. In addition, we also investigated the links between practice and audiomotor plasticity. Taken together, the results suggested that sonification did not affect corticospinal excitability, measured at rest. Its effects on internal simulation of an action, however, are unknown. In this study, we explored the effects of practising with sAOMI on audio- and visuo-motor resonance. Chapter 1 reviewed the literature on audio- and visuo-motor resonance, suggesting that AO, MI and PE share spatial, temporal, and contextual equivalence of corticospinal excitability (Grospretre et al., 2016; Naish et al., 2014). A similar forms of motor resonance has also been found for action sound (Aglioti & Pazzaglia, 2011), although the topic is less explored. Action sounds resonate in the brain by activating the neuronal representation of the same effector used in the action that is heard (Aziz-Zadeh, Iacoboni, Zaidel, Wilson, & Mazziotta, 2004b). In addition, hearing action words, seems to resonate within the listener brain (Tettamanti et al., 2005). Taken together, sensorimotor resonance may be seen as a process of internal representation of an action, which allows a person to infer the state of the environment and the interaction with others (Cattaneo & Rizzolatti, 2015; Shipp et al., 2013; Uithol et al., 2011). Crucially, this resonance is specific to the experience of a person, such that observing actions that are not in our daily experience, or performed by robot does not resonate to the same level as an action performed by a person (Aglioti, Cesari, Romani, & Urgesi, 2008; Press, 2011).

Interestingly, audiomotor resonance seems to follow the same patter, as it has been reported for both naturalistic and synthetised sound, after an association period (Launay, Dean, & Bailes, 2016; Ticini, Schütz-Bosbach, & Waszak, 2017; Ticini et al., 2011). In the context of this thesis, the development of an audiomotor resonance between a sonification and the observed and practiced action may suggest that auditory information provided by sonification has been successfully integrated in the observer’s internal representations. To investigate this, we designed a between-groups protocol in which healthy participants completed a single session of training based on AOMI, MI and physical execution of the same action. Before and after the practice, corticospinal excitability was assessed at rest and during AO and AOMI, to gain insights into neural activity induced by auditory information and practice. In addition, we tested AO and AOMI with and without sonification sound, to assess the development of practice-dependent audiomotor associations.

3.2. METHODS

3.2.1. Participants

Twenty-five self-reported neurologically healthy, right-handed young adults were recruited for this study (Table5). Participants were randomly assigned to either the experimental group (SON, 12 participants), which completed the practice block with sonification, or the control group (CON, 13 participants), who did not receive auditory augmentation during the practice. Prior to the beginning of the experiments, participants completed the Edinburgh Handedness Inventory (Oldfield, 1971) to assess their degree of right-handedness, and were asked to complete a safety screening questionnaire, to assess potential contraindication for the use of TMS (Rossi et al., 2009, 2011). To assess baseline MI ability, participants completed a motor imagery questionnaire (Williams et al., 2012). At the end of the study, each participant received a £20 Amazon gift card.

Table 5 – Demographic data, by Group

	SON		**CON**	
	Mean	**SEM**	**Mean**	**SEM**
Age (years)	26.22	3.08	24.44	2.10
EHI Score	8.89	0.76	9.67	0.33
Body Weight(kg)	72.78	5.99	67.89	4.73
Body Height (cm)	173.11	3.28	167.12	3.08
Internal visual imagery	5.28	0.47	5.75	0.33
External Visual Imagery	5.67	0.28	5.98	0.28
Kinesthetic Imagery	5.33	0.44	5.58	0.33
rMT	41.11	2.18	37.33	1.26

3.2.2. Experimental Design

Figure 4a depicts a schematic representation of the experimental procedure. In a single-session, we tested corticospinal excitability before and after a practice block, based on congruent and combined AOMI, MI and physical execution of the same action (see ‘AOMI practice block’). Assessment of corticospinal excitability, before and after the intervention, was carried out by measuring motor-evoked potentials (MEPs) while participants were at rest, while observing the practiced action, or while they imagined the action they concomitantly observed. These tests were conducted without auditory augmentation. After the practice block, participants completed the same tests, but engaged in AO and AOMI tests twice, the first one without, and the second one with auditory augmentation. We tested this to assess whether SON group developed an audiomotor resonance following the sonification training. The audiomotor condition was always completed after the silent condition, as there is evidence that even a short audiomotor pairing can establish an association. In all tests, participants had a similar posture depicted in the video, composed of holding of a foam a ball with their right hand (Figure 5a). This congruency between participants' posture and observed action was needed as there is evidence that this type of congruence affects motor resonance (Zimmermann, Toni, & de Lange, 2013); The same happens during MI (Saimpont, Malouin, Tousignant, & Jackson, 2012; Vargas et al., 2004).

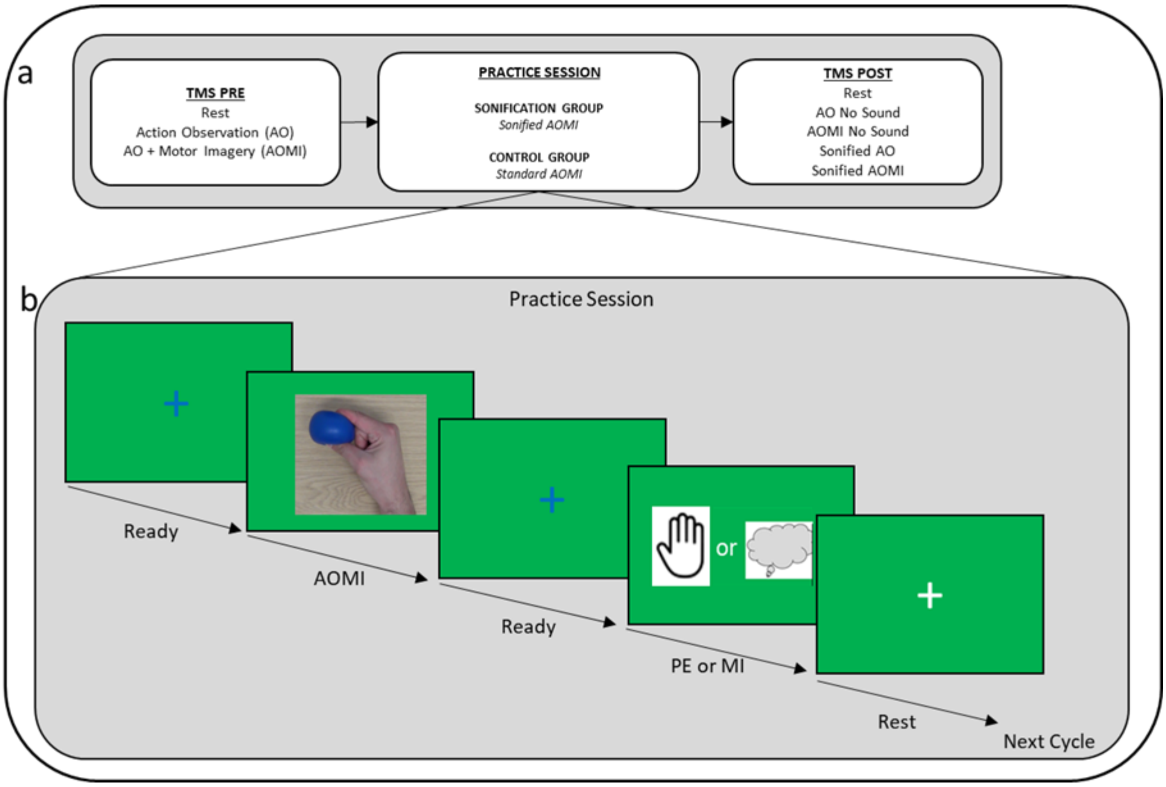

Figure 4 – **a.** Schematic representation of the experimental design. In a single session, corticospinal excitability measures were collected before and after a practice block. These measures were collected at rest and during AO and AOMI. After the practice, motor-evoked potentials (MEPs) were collected twice during AO and AOMI, with and without sound. **b.** Schematic representation of stimuli presentation during the practice block. At the beginning of the cycle, participant observed a blue cross ('get ready' cue). After one second, the video of an actor's hand squeezing a foam ball appeared. Participants were instructed to pay attention to the video, while at the same time imagining themselves performing the action. SON group also received auditory augmentation during AO. After the video, another blue cross appeared, after which participants were asked to either imagine the action they just saw (MI; bubble icon), or physically execute the same action (PE; hand icon). Participants were asked to press a button with their left hand when they completed the simulated of or executed action, thus triggering a rest period (white cross) for 5 seconds.

3.2.3. Combined Action Observation and Motor Imagery Practice

The practice block consisted of combined and congruent AOMI, followed by MI and physical execution of the same action. The single-session training comprised 48 trials, for an average duration of 30 minutes. Trials were divided into three blocks of 16 stimuli each, with one minute of rest between blocks. Figure 4b depicts the practice structure and stimuli presentation. Participants first observed, while concurrently imagining the kinaesthetic feelings associated with the action they observed, from a first-person perspective (kinaesthetic imagery). In this phase, the SON group listened to the sonification sound too, and they were asked to pay attention to information that this sound may have provided with respect to the action. After the AOMI phase, a blue cross appeared, cuing participants to prepare for the next phase, in which they had to either imagine the same action (bubble icon appeared on the screen) or had to physically imitate the same action (hand icon). Executed trials represented 25% of the total trials and were fully randomised. At the end of either MI or PE, participants had to press a button with their left hand to rest for 5 seconds. We chose to include executed trials because we aimed at an ecologically valid training regime, and usually, physical execution remain an integral part of a learning regime, and without it, motor learning is suboptimal, even if the action is imagined (Mulder et al., 2004). In addition, recent evidence suggests that the inclusion of physical execution induces both behavioural and neural benefits (Ruffino et al., 2017).

3.2.4. Task and Sonification Process

Participants observed and imagined an action in which an actor squeezed a foam ball with their index and thumb finger, viewed from a first-person perspective[5]. The action lasted about 3 seconds. The sonification process was performed using a frame-to-frame strategy. Raw videos were recorded at 25 frame per seconds using a Sony HDR-TD3, at a resolution of 1920 x 1080. Sonification was performed using the open-source *Audacity* software, by synthetising a pitch of the same duration of the action. Raw videos and synthetised sound were then exported in the free video editing software *Hitfilm express 2017* (FXHOME Limited, UK), where sound and video were manually synchronised. Sonification consisted of increasing or decreasing the volume of the tone according to the force visibly applied to the ball: as the ball was compressed, the volume of the tone increased, and diminished as the force decreased and the ball expanded back to its original shape. We chose this audiomotor association because it is among the most commonly used mapping in sonification research (Dubus & Bresin, 2013). We chose a

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[5] Link to the video

synthetised sound because we were also interested in the effects of sonification on audiomotor resonance. We deemed unlikely that such a tone would be able to induce audiomotor resonance per se. However, after audiomotor practice, these type of sounds can induce activity in the motor system, after an audiomotor association has been established. (Launay, Dean, & Bailes, 2016; Ticini, Schütz-Bosbach, & Waszak, 2017; Ticini, Schutz-Bosbach, Weiss, Casile, & Waszak, 2011).

3.2.5. Assessment of Corticospinal Excitability

Assessment of corticospinal excitability was done by collecting MEPs from the right first dorsal interosseous (FDI) muscle. For each condition, twenty-five MEPs were collected, with a stimulation intensity of 130% of the individually defined resting motor threshold (rMT). Participants sat on a chair in front of a 24” LCD monitor, at a viewing distance of one meter. In rest condition, TMS pulses were delivered while participants directed their visual attention at a fixation cross, at the centre of the screen, and engaged in a secondary, non-motoric activity, consisting of a countdown from 200 to 0 (Kumpulainen et al., 2014). During AO and AOMI tests participants kept an arm configuration congruent with the action (figure 5a), and TMS pulses were delivered when the video depicted the maximal squeezing phase (figure 5c). TMS monophasic pulses were delivered using a Magstim 200 (Magstim Company, Whitland, U.K.), using a 70 mm figure-of-eight stimulation coil, oriented to induce posterior-to-anterior current. Muscle responses were collected using Ag/AgCl electrodes arranged in a bipolar, belly-tendon setup. Participants’ skin area was shaved (if needed), abraded using an abrasive paste and cleaned using isopropyl alcohol swabs. After the preparation, and before any test, the hotspot for TMS stimulation was determined as coil position that evoked MEPs of the largest amplitude, at the same intensity, and then marked on participants scalp with a soft-tip pen. rMT was estimated, using adaptive threshold hunting technique (Ah Sen et al., 2017; Awiszus, 2011), which allowed us to determine rMT with a reduced number of TMS stimulations, thereby improving participants’ comfort. At the end of the experiment, we collected the maximum evoked muscle twitch (M_{max}) evoked by peripheral magnetic stimulation at the FDI muscle. This was done by placing the TMS coil on participants’ right elbow, between the olecranon and the medial epicondyle, with the coil handle perpendicular to the direction of the ulnar nerve, to induce current flow in the nerve with the monophasic stimulator (Lampropoulou et al., 2012). To determine M_{max}, we collected five evoked responses for responses ranging between 20% and 70% of the maximum stimulus output, in incremental steps of 10%. Surface electromyography (EMG) and evoked responses were recorded using Signal (v.6, CED, UK) and amplified at a gain of 1000 and sampled at 4 kHz. To reduce the influence of external artefacts, an online band-pass filter (5 to 2000 Hz) was applied. TMS pulses were delivered through synchronized stimulus presentation, using TTL output triggers generated by E-Prime software (v 3.0; Psychology Software Tools, Pittsburgh, PA), and sent to the magnetic stimulator.

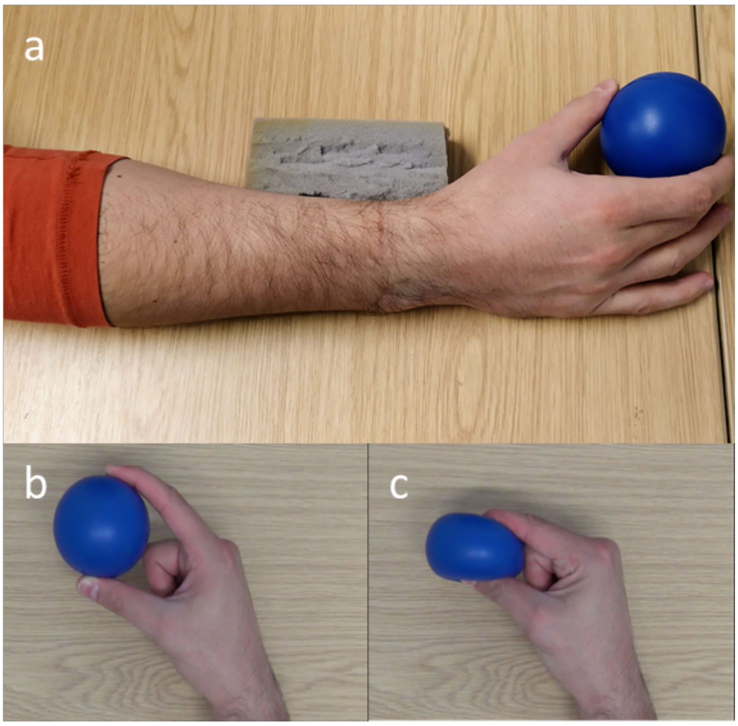

Figure 5 – **a.** Arm configuration during TMS testing and practice block. Participants were instructed to keep their hands on a table and hold a ball, which rested on the table, in their hands, and participants were asked to relax as much as possible and avoid muscle contractions. To further improve their comfort, a foam mat was placed under their forearm. **b.** The initial video frame; **c.** The point in the video at which TMS pulses were delivered (maximal compression).

3.2.6. Data and statistical Analysis

MEPs Analysis. Peak-to-peak MEP amplitude and background EMG were calculated for every trial using a custom-made script in Signal software (CED, v6.05; UK). For background EMG, we calculated the root mean square of muscle activity during 100 ms prior to the TMS pulse. MEPs were normalised and expressed as percentage of M_{max}, using the following formula:

$$Normalised\ MEP = 100 * \frac{MEP}{Mmax} \tag{1}$$

We chose this normalization method according to the rationale that M_{max} measures the maximum possible contraction, and it is thought to be stable against transient changes in excitability (Palmieri et al., 2004). In addition, this normalization method is commonly used to express spinal excitability (Palmieri et al., 2004). Unless otherwise specified, in later sections MEPs will refer to normalized, not raw, values.

Post-Training Audiomotor Resonance. To assess audiomotor resonance arising from the sonification practice, we calculated the percentage change between pre- and post-practice raw MEP values. For both AO and AOMI, we compared pre- with post-practice completed with or without sonification sound.

$$MEP\_ns = 100 * \frac{Pre - Post\ no\ Sound}{Pre} \qquad [2]$$

$$MEP\_s = 100 * \frac{Pre - Post\ Sound}{Pre} \qquad [3]$$

Both CON and SON completed this. Since CON was not exposed to the sound during the training, we did not expect modulation of corticospinal excitability with sound, so it was used as control for SON.

Statistical Analysis. Statistical comparisons were carried out using SPSS (v). Outliers were assessed using z-scores; values greater than ± 2.99 were considered as outliers and removed from the analysis. Data distribution was assessed with the Shapiro-Wilk test. Handedness and MIQ results were analysed using nonparametric tests. For the analysis of corticospinal excitability changes between pre- and post-practice at rest and during AO and AOMI, we ran a mixed ANOVA with factors TIME (2 levels, pre and post) and GROUP (2 levels, SON and CON). For the analysis of audiomotor resonance during AO and AOMI, we run a mixed ANOVA with factors SOUND (2 levels, sound and no sound) and GROUP (SON and CON).

3.3. RESULTS

Table 5 provide a summary of anthropometric data between SON and CON. There were no significant between-group differences in handedness (z = -0.748, p = 0.454), rMT (z = 0.906, p = 0.365). No significant differences were found for Internal visual imagery (z = -0.164, p = 0.870), external visual imagery (z = -0.301, p = 0.764) and kinaesthetic imagery (z = -0.164, p = 0.870). There were no significant differences in bgEMG levels between AO and rest (p > 0.05). Engaging in AO did not result in a significant modulation of corticospinal excitability, compared to resting conditions. On the other hand, engaging in AOMI resulted in a significant increase in corticospinal excitability, compared to rest (z = 2.44, p = 0.015). However, bgEMG analysis revealed significantly differences in muscle activity between AOMI and rest (z = -2.731, p = 0.006).

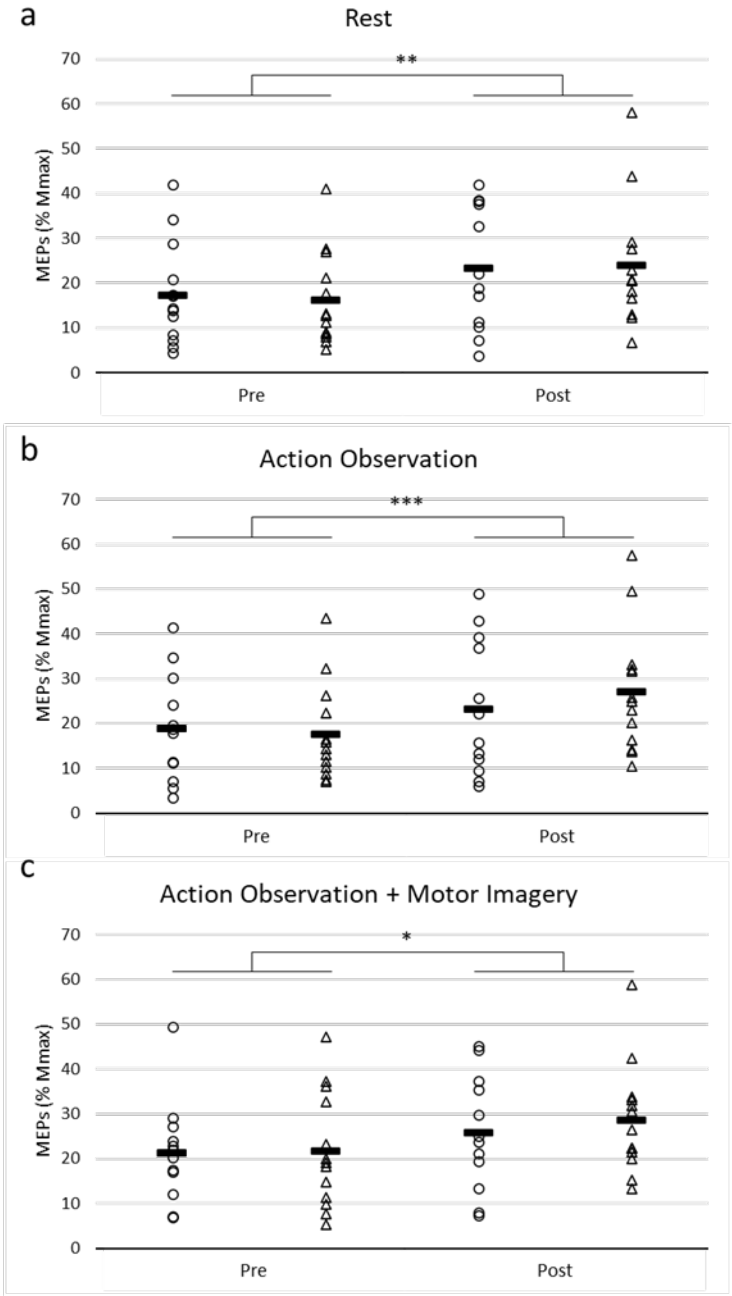

Figure 6 – Corticospinal excitability measures before and after the practice block, measured at rest (a), during Action Observation (b), and during combined action observation and motor imagery (AOMI, c). Circle represents SON group (12 participants), while the triangles represent CON groups (13 participants). Black bars represent group-level means. *: $p < 0.05$: **: $p < 0.01$; ***: $p < 0.001$

3.3.1. Effects of practice on corticospinal excitability at rest and during AO and AOMI

Practice effect was assessed by comparing MEPs before and after the practice, at rest, as well as during AO and AOMI (Table 6). There were no significant differences in bgEMG levels in all three condition ($p > 0.05$). At rest (Figure 6a), there was a main effect of TIME on MEPs amplitude: $F(1, 23) = 15.03$; $p = 0.001$, $N^2_p = 0.395$. No TIME x GROUP interaction was detected: $F(1, 23) = 0.289$; $p = 0.596$, $N^2_p = 0.012$. During AO (Figure 6b), there was a main effect of TIME on MEPs amplitude: $F(1,23) = 27.450$; $p < 0.001$; $N^2_p = 0.544$. There was a trend towards significance for the interaction TIME x GROUP: $F(1,23) = 3.509$; $p =0.074$; $N^2_p = 0.132$. Lastly, during AOMI (Figure 6c) there was a main effect of TIME on MEP amplitude: $F(1,23) = 7.742$; $p = 0.011$; $N^2_p = 0.252$. No TIME x GROUP interactions were found: $F(1,23) = 0.311$; $p = 0.582$; $N^2_p = 0.0.13$.

Table 6 – Descriptive Statistics for corticospinal excitability measures. MEPs are expressed as percentage of M_{max}.

						95% CI	
		Mean	Median	SD	SEM	Lower	Upper
				Control			
Rest	Pre	17.01	12.94	10.41	3.00	10.40	23.63
	Post	25.29	20.73	13.33	3.85	16.81	33.76
AO	Pre	18.55	15.22	10.77	3.11	11.71	25.39
	Post	27.47	25.46	14.46	4.17	18.28	36.65
	Sound	24.45	21.93	14.58	4.21	15.18	33.71
AOMI	Pre	21.89	18.71	13.46	3.88	13.34	30.44
	Post	29.73	28.50	12.02	3.47	22.09	37.36
	Sound	28.60	26.16	14.90	4.30	19.13	38.07
				Sonification			
Rest	Pre	17.38	13.92	12.48	3.76	9.00	25.77
	Post	21.83	18.82	13.61	4.10	12.69	30.97
AO	Pre	17.69	17.88	12.00	3.62	9.63	25.75
	Post	21.97	15.59	15.26	4.60	11.72	32.22
	Sound	20.14	17.26	12.67	3.82	11.62	28.65
AOMI	Pre	20.49	20.17	11.64	3.51	12.67	28.31
	Post	24.73	23.75	12.97	3.91	16.02	33.45
	Sound	23.68	22.42	14.35	4.33	14.04	33.33

3.3.2. Effects of sonification on audiomotor resonance after practice

After the practice block, we collected MEPs during AO and AOMI with and without sonification sound (Table 7). MEPs with sound were always collected last. We compared these with Pre-practice measures, to explore whether sonification induced an audiomotor association. During AO (Figure 7a), a rmANOVA revealed no statistical differences for SOUND, F(1,22) = 1.834, p = 0.189, N^2_p = 0.077, and no SOUND x GROUP interactions were found: F(1,22) = 0.014, p = 0.906 N^2_p = 0.001. Similarly, during AOMI (Figure 7b) there were no significant main effect of SOUND, F(1,22) = 0.385, p = 0.541, N^2_p = 0.017. No SOUND x GROUP interaction emerged: F(1,22) = 0.281, p = 0.601, N^2_p = 0.013.

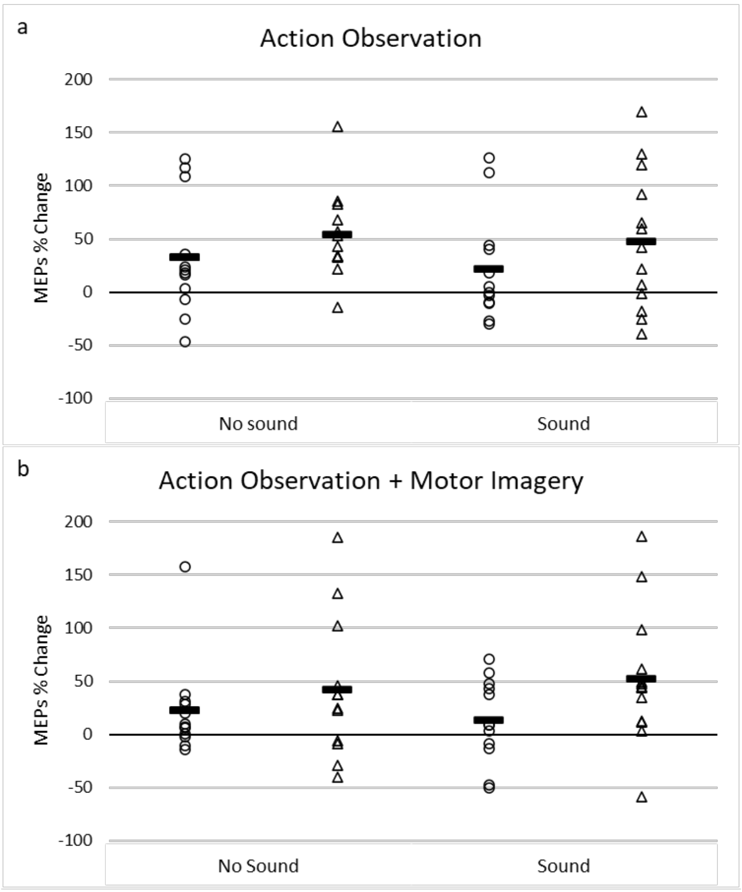

Figure 7 – re-post percentage change comparisons on the influence of auditory stimulation while engaging in AO (a) and AOMI (b). After the practice block, we measured corticospinal excitability during AO and AOMI in two conditions, with and without sonification sound. The No sound condition represents comparisons between pre and post-no sound, while the Sound condition represents comparisons between and post-sound. For both AO and AOMI, no significance differences were found between the SON group (12 participants; circles) and CON group (13 participants; triangles). Black bars represent group-level means.

Table 7 – Descriptive Statistics for percentage change in between pre and post-practice, measured with and without sonification sound

	95% CI

		Mean	Median	SD	SEM	Lower	Upper
		Control					
AO	Sound	46.04	42.40	66.10	19.93	1.63	90.44
	No Sound	60.62	53.10	37.81	11.40	35.22	86.02
AOMI	Sound	44.07	44.72	52.44	15.81	8.85	79.30
	No Sound	48.63	37.35	66.67	20.10	3.83	93.42
		Sonification					
AO	Sound	22.13	2.46	50.99	14.72	-10.26	54.53
	No Sound	32.48	19.59	55.87	16.13	-3.02	67.97
AOMI	Sound	13.22	8.67	39.34	11.36	-11.77	38.21
	No Sound	22.63	8.42	45.69	13.19	-6.40	51.66

3.4. DISCUSSION

The aim of this study was to investigate the effects of sAOMI on corticospinal excitability. Participants completed a practice block composed of AOMI, motor imagery and execution of the same action. SON group received auditory augmentation during AOMI, while CON group did not receive any extrinsic auditory stimulation.

3.4.1. Effects of sAOMI on corticospinal excitability

At the end of the practice block, participants' corticospinal excitability was significantly higher than pre-training measures at rest, as well as during AO and AOMI. However, we did not find significant differences between the two groups. The fact that corticospinal excitability after the practice block increased in both groups is in line with literature suggesting that, among other effects, practice induces changes in corticospinal excitability, due to an unmasking of silent cortico-cortical connections (Dayan & Cohen, 2011; Rosenkranz, Kacar, et al., 2007; Ziemann et al., 2004), resulting in long-term potentiation of circuits involved in practice. This neural mechanism was shown to be involved not only in physical practice, but also observational and mental practice (Avanzino et al., 2015; Lepage et al., 2012).

With regard to sonification, our results seem to be in contrast with existing literature on sAO, which suggest that observing an action with congruent sonification induces a more precise perceptual judgment about movement speed in healthy population, associated with an increased activation in areas involved in sensorimotor transformations and motor control (Schmitz et al., 2013). In addition, sAO was associated with significant improvement of a variety of measures of freezing of gait in people with Parkinson's disease (Mezzarobba et al., 2018). Lastly, research on movement sonification generally reports that congruent sonification has beneficial effects in inducing changes in performance (Schaffert et al., 2019; Sigrist et al., 2013). Some differences between our study and others may explain this disparity. First, in our study we used sonified congruent AOMI to deliver auditory augmentation. Compared to AO or MI alone, AOMI induces increased neural activity, as measured with fMRI (Macuga & Frey, 2012), and EEG (Eaves, Behmer, & Vogt, 2016), which is ultimately reflected in increased corticospinal excitability, compared to AO and MI alone (Bruton et al., 2020; Meers et al., 2020; Sakamoto et al., 2009; Wright, Wood, Eaves, et al., 2018). Interestingly, changing the relation between the content of the imagined and observed action seems to influence MEP amplitude and attentional measures. To explore this, studies usually contrast three forms of AOMI: congruent, coordinative, and conflicting. In the first one, the observed and imagined action has the same content, while in coordinative AOMI it may be the same but from a different perspective, or a complementary action which may assist the other. On the other hand, in conflicting AOMI the observed and imagined actions are different and not compatible with each other. Recently, Bruton et al. (2020) reported that corticospinal excitability was lower in conflicting AOMI, compared to congruent AOMI. Interestingly, engaging in coordinative and conflicting AOMI also increased attentional demands and cognitive efforts, compared to congruent AOMI.

The fact that engaging in different forms of AOMI is associated with different neurocognitive signatures is in line with a representationalist framework originally developed by Cisek and Kalaska (2010), but later adapted to action simulation by Eaves et al. (2016), suggesting that the brain represents different potential actions and, through a process of competition resolution, it interfaces with the environment, selecting the most appropriate one, given prior intentions, predictions and sensations sampled (c.f. Bestmann & Duque, 2016; Derosiere & Duque, 2020 for an account of action preparation and competition resolution). Applied to AOMI, the dual simulation hypothesis developed by Eaves et al. (2016) suggests that the brain is able to represent observed and imagined actions simultaneously and, according to their content, may either facilitate one another or compete for neural resources. It is possible that sonification could have played a similar role in sensorimotor computations to coordinative and conflicting AOMI. That is, it is possible that, even though sonification had a clear reference to the action, it competed with bottom-up and top-down representations evoked by AO and MI, respectively. Even though research on sonification generally reports a reduction in cognitive load (Dyer, Stapleton, & Rodger, 2015), A study by Ronsse et al. (2011), suggests that compared to visual augmentation, sonification induces a slower rate of learning at the beginning of a coordinative bimanual task practice, and induced increased activity in the dorsolateral prefrontal cortex, a brain area widely involved in attentional processing (Gottlieb, 2012; Suzuki & Gottlieb, 2013). Interestingly, at the end of the training, performance was significantly improved, compared to visual augmentation, in line with accounts of beneficial effects of sonification (Schaffert et al., 2019; Sigrist et al., 2013).

Another potential difference with other studies on sonification, which reconciles with the previous point, is the ball squeezing task used in this study. This is akin to many common daily tasks, which people without movement disorders can perform with little effort. However, research show that MI vividness, the ease with which people create mental images, affects corticospinal excitability, thus suggesting that even though a task is easy to perform, it may not necessarily mean that it is easy to imagine. However, MIQ results suggests that, on average, our participants were 'good imagers' (Marchesotti et al., 2016; Vuckovic & Osuagwu, 2013). Thus, it is possible that this action was simple to internally simulate, and sonification did not exert its augmenting influence. In this study, we focussed on congruent AOMI, but it is possible that sonification may have beneficial effects on other forms of AOMI. Especially with coordinative AOMI, sonification could be associated to a complementary aspect of an observed action, while a person engages in MI. To the best of our knowledge this question remains unanswered.

A similar point can be made for the lack of corticospinal excitability during AO. Both groups increased corticospinal excitability after the practice, and SON group showed a lower level of corticospinal excitability, compared to CON group, although this difference was not significant. Different studies suggests that, within the right condition, AO requires relatively low cognitive effort, especially when compared to MI (Nota, Chartrand, Levkov, Montefusco-Siegmund, & DeSouza, 2017). However, neural activity during AO is modulated by different factors, which is some cases increases cognitive effort. Different studies showed that visual attention influences corticospinal excitability during AO. For example, corticospinal excitability is higher when directing gaze to the primary focus of the action (D'Innocenzo et al., 2017; Gandevia & Rothwell, 1987; David J. Wright, Wood, Franklin, et al., 2018). In addition, the congruency of the background with the observed action seems to influence motor resonance (Riach et al., 2018). Other studies investigated the influence of distractors on AO-evoked MEPs. For example Puglisi, Leonetti, Cerri and Borroni (2018) reported that, if participants observed the video of an action in peripheral vision, instead of directing gaze directly to the most salient portion of the video, corticospinal excitability was virtually abolished. However in the same setup, if the video depicted impossible movements, which are known to increase corticospinal excitability (Romani et al., 2005), motor resonance was re-established. These results suggests that when gaze behaviour is suboptimal, bottom-up mapping of sensorimotor characteristics into the observer's own brain is also suboptimal and requires more computational difficulty to perform. Although in our study we used a different paradigm, the results by Puglisi and colleagues suggest that cognitive load influences corticospinal excitability.

As mentioned, this lack of modulation of sonification may be due to interaction between task complexity and cognitive load induced by sonification (c.f. Ronsse et al., 2011), which acted as a distractor and competed with computational resources. If the action was very simple to imagine for the participants, and the sonification did not exert its augmenting effects, it may have acted as a distractor for the mapping of the observed action into participants' own sensorimotor system. Future studies, with a larger sample size, are needed to further explore and add robustness to the relationship between the value of an augmented sensory information and action simulation.

3.4.2. Effects of Sonification of Audiomotor Association

After the practice block, we tested corticospinal excitability during AO and AOMI twice, with and without sonification sound. Both groups did not show significant differences in corticospinal excitability. For CON, no corticospinal excitability change was expected, as the sonification sound was novel to them. On the other hand, SON practiced with sAOMI, so the development of an audiomotor association could be expected. Action sounds interact with the sensorimotor system, similarly to AO, by mapping the sound into the listener's own sensorimotor system, through a process of multisensory convergence (Aglioti & Pazzaglia, 2011). Even though action and non-action sounds are thought to be processed differently (Pineda et al., 2013), it is possible to associate a non-action sound to a motor response. Music is a chief example for this: Listening to the sound of a practised piece activates brain areas responsible for physical execution of the same action (Baumann et al., 2007; Lahav, Saltzman, & Schlaug, 2007). In addition, it has been reported that it is possible to associate a sound with a simple button press. Ticini et al. (2011) trained participants to press two buttons, one with the index and the other with the little finger, which were associated to two different tones. After the training, playing the sounds evoked increased MEPs in the fingers used to press the button during the association practice. Interestingly, when the setup was reversed, so as to reverse the relationship between muscle and button, the pattern of corticospinal excitability was reverse too, such that it preserved the audiomotor relationship developed during the practice. This suggests that the association is not just tone-muscle, but or higher order, associating the sound to the goal of the action. More recently, Ticini, Schütz-Bosbach and Waszak, (2017) reported that when the association was established, a training of equal time inducing opposite association was not enough to dissociate the audiomotor resonance developed during the training.

In this study, we used a synthetised sound, and the audiomotor association – volume of a sound associated with perceived kinetics – is a common audiomotor mapping in sonification research (Dubus & Bresin, 2013). However, our results are in line with a possible interference of sonification for sensorimotor computations underlying action simulation. Sensory information are thought to be processed in early sensory cortices, which deal with the physical nature of the stimulus, and then integrated by higher order areas, for example a fronto-parietal network including ventral premotor cortex and posterior parietal cortex (Rizzolatti & Sinigaglia, 2010), where they are integrated into the representation of the body and the outside environment, which are thought to be used to make top-down predictions about perception and actions (K. Friston et al., 2011; James M Kilner et al., 2007). Research on auditory distractors processing during movement suggest a modulating activity in a fronto-parietal network which resolves the conflict (Bigliassi et al., 2018) and allows performance to be carried out without detrimental effects. In this study, if sonification did not exert its augmenting effect, possibly because the task was too simple, it is possible that the sound was not fully integrated the visual stimuli and predictions about the sensory consequences of the imagined action. Furthermore, the tasks used in this study were simulated, and not executed, and as mentioned earlier, changes in content or relationship between AO and MI may influence cognitive effort and performance (Bruton et al., 2020; Meers et al., 2020). Our discussion on the relationship between sonification sound and action simulation remains, however, somewhat speculative, and future studies are needed to further explore this area. Specifically, our study used a relatively easy tasks to perform, and a more complex task may induce different results. In addition, a larger sample size would add robustness to the analysis.

3.5. CONCLUSIONS

The purpose of this study was to explore whether sonification of combined action observation and motor imagery (sAOMI) influenced corticospinal excitability, and whether a practice block based on sAOMI, MI and physical execution of the same action influenced the establishment of an audiomotor association. Our results suggest that, at least for simpler tasks, sonification does not influence corticospinal excitability and, on the contrary it may act as a distractor, preventing an audiomotor association from being developed. Future studies are needed to further explore the relationship between auditory augmentation and action simulation, to establish the optimal audiomotor mapping to maximise neural activity and practice-dependent plasticity.

CHAPTER 4

ELECTROPHYSIOLOGICAL CORRELATES OF SONIFIED OBSERVATIONAL LEARNING

ABSTRACT

Motor imagery and action observation have been suggested to be valuable addition to training regimes. Recent investigations explored whether it is possible to augment these cognitive activities, with provision of external sensory feedbacks. In this study, we explore the use of sonified action observation, a sensory augmentation strategy whereby sound is associated with – and modulated by actions. We recruited participants to complete a two-days protocol where they practiced a sequential imagery task. The training protocol was based on action observation, with subsequent motor imagery of the same action. Prior to the beginning of the training, participants were randomly allocated to either an experimental group (SON), which observed the action with sonification, or a control group (CON), which did not receive external feedback. To measure performance, we used a variety of psychophysical measures, and electroencephalography (EEG). Practice significantly decreased the number of errors in sequential performance, and decreased imagination, but not execution time. EEG analysis revealed differences in ERD in lower alpha (7-10 Hz) frequency band, suggesting that SON group was able to sustain ERD for longer, compared to CON group. This points to a beneficial effect of audiomotor association on the internal representation of the action during motor imagery. However, no changes in neural activity were found in higher alpha (10-13 Hz) and beta (16-25 Hz), suggesting that the training did not change neural activity associated with MI of the movement. We discuss these results and possible implications.

4.1. INTRODUCTION

The previous two studies explored sonification of action observation and motor imagery of simple short actions. Taken together, sAOMI did not yield additional advantages over normal AOMI on measures of corticospinal excitability and audiomotor plasticity. We contextualised these results as a possible interference of sonification on the sensorimotor processing underlying representation and simulations of the observed and imagined action. This may also partly explain why after practice for SON group, engaging in AO and AOMI with the sound did not modulate corticospinal excitability, a sign of the development of an audiomotor resonance. In addition, the practice blocks in the previous experiments had a practical component which, when associated to the simplicity of the actions, may have further decreased the value of sonification. Lastly, physical execution of the action may have masked the interaction between sonification and homeostatic metaplasticity in Chapter 2. On the other hand, previous research on sAO points towards a beneficial effect of auditory augmentation on mental representation of actions, evident in both perceptual and motor domains (Mezzarobba et al., 2018; Schmitz et al., 2013).

To account for possible confounding variables from previous chapters, in this study, we explored whether a protocol based on sAO and subsequent MI of the same action could improve MI abilities and performance in healthy participants. To this end, we used a variety of behavioural and neurophysiological measures commonly used in imagery research (Collet, Guillot, Lebon, MacIntyre, & Moran, 2011). In addition to performance measures, we used mental chronometry, which assesses temporal congruency between imagined and executed movement, the so-called *mental travel effect* (Collet et al., 2011). Studies suggest that people with good motor imagery ability should maintain congruent movement timing during MI, compared with execution of the same action, and it has been shown to be a reliable method to assess the temporal characteristics of MI in healthy and clinical population (Collet et al., 2011; Malouin, Richards, Durand, & Doyon, 2008; Marchesotti et al., 2016). A second behavioural measure to assess the effects of sonification was the motor imagery questionnaire, a commonly used method of assessing motor imagery vividness – How easily people can imagine a variety of actions. Various version and types have been suggested, to account for different imagery perspectives or populations. In this study, we used the third version of the Motor imagery questionnaire (MIQ-3; Williams et al., 2012).

In this study we were also interested in neural signatures of this intervention, and to this end we used EEG to assess changes in neural oscillations before and after practice. Studies with EEG highlighted that MI has a specific neural signature, evident via an increased activity in the alpha (8-13 Hz) and beta (13-30 Hz) frequency bands, spatially located over sensorimotor areas, which is also known as mu rhythm (Han Yuan & Bin He, 2014 for a review on the topic). The mu rhythm has been extensively used in BCI investigations because of its comparable oscillatory behaviour during various motor-related activities, including motor execution (Pfurtscheller, Neuper, Andrew, & Edlinger, 1997), motor imagery (Marchesotti et al., 2016; Pfurtscheller, Neuper, Flotzinger, & Pregenzer, 1997), action observation (Frenkel-Toledo, Bentin, Perry, Liebermann, & Soroker, 2013) and perception of action sounds (Pineda et al., 2013; Tsuchida, Ueno, & Shimada, 2015). When an individual engages in these sensorimotor activities, the oscillatory power over sensorimotor areas decreases, relative to rest, in a phenomenon called *event-related desynchronization* (ERD). Studies on the physiology of ERD suggests that this oscillatory power decrease is a short-lasting phenomenon, lasting for about two seconds, and is due to task-related activation of different sets of neurons (Cassim et al., 2000; Nam, Jeon, Kim, Lee, & Park, 2011).

4.2. METHODS

4.2.1. Participants

Twenty-nine self-reported neurologically healthy, right-handed adults were recruited for this study (Table 8). Participants were randomly assigned to either an experimental group, which completed practice with sAO (SON), or a control group, which did not receive extrinsic auditory augmentation (CON). Prior to the first visit, right-handedness was confirmed using the Edinburgh Handedness Inventory (Oldfield, 1971). At the end of the protocol, participants received a £10 Amazon voucher. Seven people dropped out from the study after the first session, so their data was not included in the analysis. The remaining 22 participants were included in the analysis (11 participants per group, SON: 5 females, 6 males; CON: 8 females, 3 males). The study was approved by the Brunel University London College of Health, Medicine and Life Sciences Research Ethics Committee and data collection was in accordance with the principles of the Declaration of Helsinki.

Table 8 – Demographic Data, by Group

	CON		**SON**	
	Mean	SEM	Mean	SEM
Age (Years)	23	1.464	27	3.89
Height (cm)	169.38	4.563	173.8	3.994
Weight (kg)	65	5.244	72.6	4.51
EDI	90	3.896	91.5	4.153

4.2.2. Experimental Design and Procedure

Figure 8 provides a schematic representation of the experimental design. Participants visited the laboratory on two consecutive days. On the first visit, participants completed pre-practice tests, which included mental chronometry, and an EEG test, in which they were asked had to imagine the same action that was later practised (see section 'Motor Imagery Task'). After the tests, participants completed the first practice session. On the second visit, next day, participants completed the second practice session, followed by post-practice tests, which included again mental chronometry and EEG test. Each visit lasted approximately 3 hours. To screen how vividly participants created mental images, and to measure the practice-induced changes in self-reported measures of MI vividness, the day before and after the two visits, participants completed the motor imagery questionnaire (MIQ; Williams et al., 2012).

4.2.3. Motor Imagery Questionnaire

To screen how vividly participants created mental images, and to measure the practice-induced changes in self-reported measures of MI vividness, participant completed a motor imagery questionnaire (MIQ; Williams et al., 2012; Appendix E). This was carried out the day before and after the two visits to the lab. The MIQ comprises 12 actions to be firstly executed slowly, and then imagined according to three perspectives: i) internal visual imagery (IVI), what participant would see in first person if they executed the action; ii) external visual imagery (EVI), what participants would see if they or someone else executed the action; and iii) kinaesthetic motor imagery (KI), what participants would feel if they executed the action. After the imagery, they were asked to rate, on a scale ranging from 1 (not at all) to 7 (completely easy), how vividly they could imagine the movement.

4.2.4. Mental Chronometry

At the beginning of the first visit, and after the practice on the second visit, participants completed the mental chronometry test. They first observed, then executed, and lastly imagined two actions, one that was practised during the training, and a second one, which was not practised and thus was specific to the mental chronometry session only. The former consisted of a person rearranging construction block toys on a board with the right hand (LEGO; Figure 9), while the latter consisted of a reach-and-grasp-to-drink action (RAG), in which an actor reached and grasped a cup, mocked drinking from it, and put it back on the table. During this test, no auditory feedback was provided for neither of the two groups. The rationale for including a second, non-practised action was to assess the generality of learning effect; A more congruent completion time between executed and imagined tasks for both actions would suggest a transfer of MI learning. The two movements were segregated in two consecutive blocks. In each block, participants initially watched each action five times, then executed and imagined those movements for ten trials (five executed, five imagined). Onset and offset of movement and imagined times were determined by pressing a button, with the left hand. Participants' performance was assessed by their blocks in displacement error. For the trial to be considered correct, the blocks needed to be displaced in the correct order, to the correct location on the board (Figure 9).

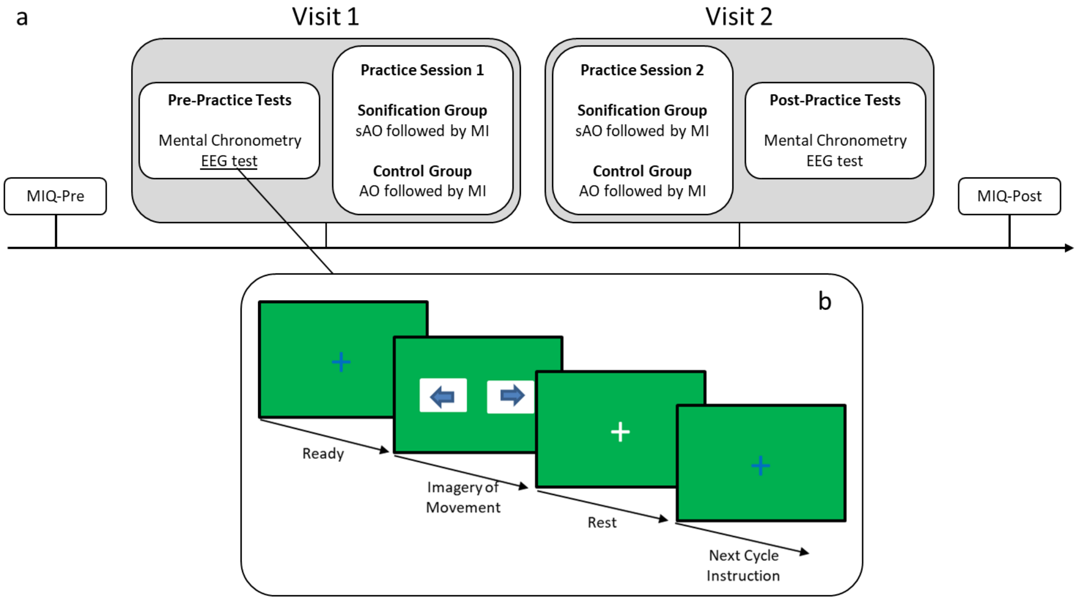

Figure 8 – **a.** Schematic representation of the Experimental Design. Participants visited the lab on two consecutive days. On the first visit, they completed the mental chronometry test and the EEG test, followed by the first practice session. On the second visit, participants completed the second practice session, followed by post-practice mental chronometry and EEG test. The day before and after the two visits, participants completed the Motor Imagery Questionnaire (MIQ). **b.** Schematic representation of

the stimulus presentation during the EEG test. A blue cross ('get ready') appeared one second before the MI period, which lasted 8 seconds. For each block, MI could be performed either with the right or left hand. After MI, participants rested (white cross), until a new cycle begun.

4.2.5. Motor Imagery Task

To assess practice-induced changes in brain activity, before the first and after the second practice session we collected EEG data while participants imagined the LEGO action. They sat on a chair and looked at a 24" LCD monitor, at a viewing distance of one metre, and they were instructed to rest their arms and elbows on the table, while maintaining their hand pronated, in a relaxed position. Participants imagined the action 120 times, 80 times with the right hand and 40 times with the left. However, only MI with the right hand was analysed, as left-hand motor imagery was included only to mitigate the manifestation of anticipatory lateralization of responses. The number of trials were split into eight blocks, containing 10 right hand and 5 left hand movements, presented in randomised order. Between each block, a 1-minute rest period was allowed. At the completion of each block, they were asked to report their levels of attention, alertness, and mental fatigue, via three Likert scales ranging from 0 to 10.

Figure 8b shows the stimulus presentation sequence. First, a blue cross notified participants that the MI task was about to begin. One second later, an arrow appeared, to identify the hand with which the MI the LEGO action should be performed. Participants were instructed to imagine the action using kinaesthetic motor imagery. MI phase lasted for 8s and participants were instructed to imagine only when the arrow was present, and to repeat the MI of the movement in a continuous way, for as long as the arrow was present. After an inter-trial interval (randomised duration; range 4-6 s), the blue cross appeared again, beginning a new cycle.

4.2.6. Mental practice

On both sessions, participants completed two mental practice sessions, based on AO and MI. At the beginning of the cycle, a blue cross ('get ready' cue) appeared for one second, after which participants observed videos of the LEGO action. SON group observed the video with sonification sound, while CON group did not receive extrinsic auditory feedback. After AO phase, participants were asked to imagine the same action for 8 seconds, using kinaesthetic perspective. For both SON and CON group, participants were instructed to keep temporal congruency between the movement speed in the video and their motor imagery speed. Each session comprised 60 trials, which took an average duration of 30-40 minutes to complete To aid the learning process, another video was presented every 4 trials, depicting only thumb and index finger aperture/closure[6]. SON group observed this video with movement sonification, while CON group observed this video silently. The rationale for this video was to provide SON with information regarding the relationship between the auditory components and the motor components of the action (see the section ‘Task and Sonification’ for more details on the sonification). Similarly, for CON, these videos represented an opportunity to focus on various components of the action.

4.2.7. Sonification Reports

At the end of the study, participants in SON group were asked to complete a sonification report, a custom-made questionnaire created to collect participants’ views on the sonification process. The questionnaire was composed of five questions: A first open question asked participants to write overall their thoughts on the practice (*Please, could you tell me your thoughts on the sound accompaniment that you heard during the practice?*) The second question (*How did you find the sound, in terms of its pleasantness?*) was directed at investigating how participants perceived the sound, in terms on its pleasantness. The third question (*To what extent did the sound help you to imagine performing the movement as you practised it?*) was directed at investigating to what extent sonification influenced the practice sessions. The fourth question (*To what extent, during the 'motor imagery task', did you imagine the sound in synchrony with the imagined movement?*) was directed at exploring whether participants imagined the sound concomitantly with the movement. This was important information within which the EEG data could be contextualised. The last question (*To what extent, do you think that the sound improved your ability to imagine the movement?*) was directed at exploring the perceived effectiveness of sonification as a sensory augmentation strategy. Participants responded to Question 2-5 via, a Likert scale spanning from 0 (*Not at all*) to 10 (*Completely*), as well as an open box where participants could provide more details.

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[6] Link to the video

4.2.8. Task and Sonification

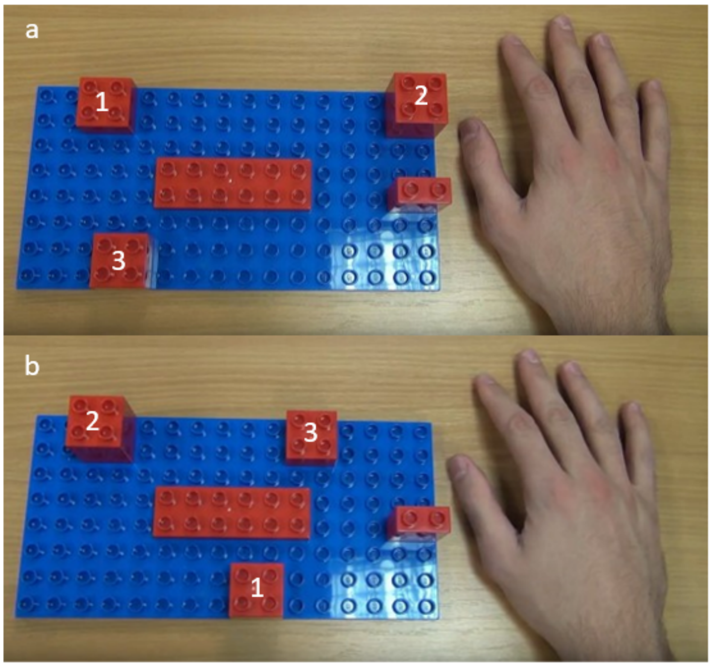

Figure 9 – Initial (a) and final (b) configuration of the construction blocks toys on the board. Number represents the order of sequential displacement.

The action tested in mental chronometry and MI task, as well as practised during the MI practice sessions, depicted a person moving construction blocks toys with their right hand (LEGO[7]; Figure 9). The video showed the hand of a male actor picking up blocks with their thumb and index finger from a base board, before repositioning them on the board. The video was shot from 1st person perspective; that is, the video showed the scene as participants would see it if they were performing the action.

Raw videos were recorded using a Sony HDR-TD30, and images were acquired at 25 frames per seconds, at the resolution of 1920 x 1080 pixels. The raw files were exported in the free video editing software *Hitfilm express 2017* (FXHOME Limited, UK). Sonification was done using a frame-to-frame manual strategy. Two movement characteristics were sonified: the grasping, and the trajectory of the blocks as they were moved to another location on the board. Sounds were synthesised and elaborated in the opensource software *Audacity*. For the block grasping, a pitch increase was associated with the aperture between the tips of the thumb and forefinger of the actor's right hand, whilst a pitch decrease was associated with the fingers closure. The trajectory of the block was sonified with a synthesized 'swoosh', which was created starting from a synthesized pink noise, to which a 'fade in' and 'fade out' was applied

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[7] Link to the video

to the first and the last half of the track, respectively. This created a bell-shaped-like sound profile, which was preferred to a constant tone, as it resembles the bell-shaped velocity profile of limb movements (Atkeson & Hollerbach, 1985). The sounds, once created, were uploaded to the video editing software, and were matched in duration and onset to the finger-thumb aperture and the block displacement. At the end of the process, the congruency between sound and images was checked.

4.2.9. EEG setup

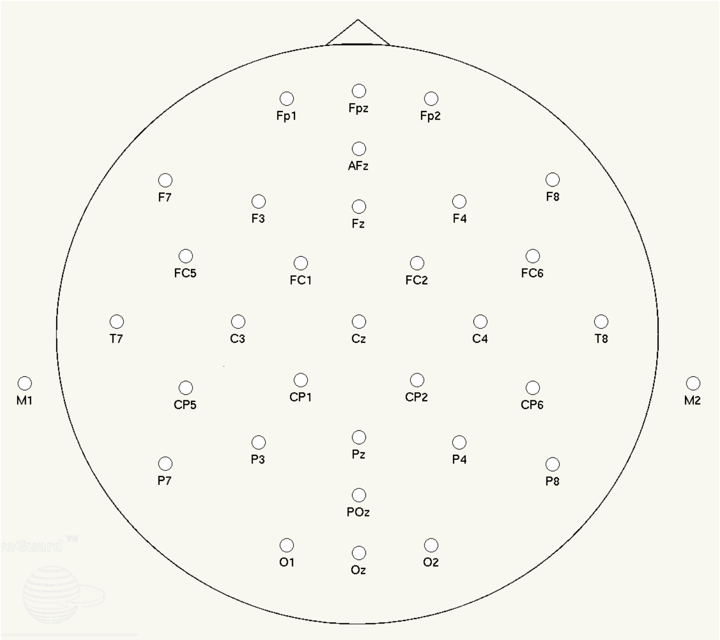

Figure 10 – Spatial arrangement of the EEG electrodes, based on the 10-20 international standard.

EEG was recorded using a 32-channel system (eego sport; ANT Neuro; Figure 10), and an EEG cap (waveguard original; ANT Neuro) covering the whole head, with Ag/AgCl electrodes, organized according to the 10-20 International system guidelines (Homan, Herman, & Purdy, 1987). The electrodes were filled with electrode gel (Onestep Cleargel, H + H Medizinprodukte GbR, Germany), to reduce impedance between the scalp and the electrode, which was kept below 10 kΩ, as the international guidelines for EEG research suggest (Keil et al., 2014). The signal was amplified at a gain of 1000 and sampled at 500 Hz. To reduce the influence of external artefacts, an online band-pass filter (0.5-100 Hz) was applied. Data was collected with reference to the CPz electrode and re-referenced during the off-line analysis to the average of the two mastoids electrodes (M1, M2). EEG data was synchronized with stimulus presentation, using triggers from the software E-Prime (Psychology Software Tools, Pittsburgh, PA). A trigger was sent to the EEG software at the appearance of the arrow, which instructed the participant to imagine the action.

4.2.10. DATA ANALYSIS

EEG analysis. EEG data was analysed offline using the MATLAB toolbox EEGLAB (v14; Delorme & Makeig, 2004). In chronological order, the signal was re-referenced to the average of the two mastoid electrodes (M1 and M2), then band-passed filtered between 2 and 45 Hz. Continuous files were manually inspected to remove evident artefacts, such as electrode movements or large muscle contractions. Eye movements, and other stereotyped noise components were removed using independent component analysis (ICA). Even though the standard procedure for eye blink and movements removal suggests this to be done using electrooculography (EoG; Croft and Barry, 2000), ICA was shown equally accurate in artifact removal, with comparable result as EoG (Chaumon, Bishop, & Busch, 2015; Hoffmann & Falkenstein, 2008). It should be noted, however, that one limitation of removing artefactual components using ICA, is that this process is, among other things, highly subjective. In order to make this process as objective as possible, independent components (ICs) were analysed using the EEGLAB toolbox ADJUST (‘Automatic EEG artefact Detection based on the Joint Use of Spatial and Temporal features’; v 1.1.1; Mognon, Jovicich, Bruzzone, & Buiatti, 2011). This algorithm uses temporal and spatial regularities of common EEG artefacts to categorise artefactual components in an automatic way. ADJUST considers four artefact classes: three oculars (eye blink, vertical and horizontal movements), and a more generic artefact, which represent a discontinuity from the signal dynamic. The categorization of the ICs was done using the combination of five temporal and spatial indices: i) Spatial Average Difference (SAD); ii) Spatial Eye Difference (SED); iii) Generic Discontinuities spatial Features (GDSF); iv) Maximal Epoch Variance (MEV); and v) Temporal Kurtosis (TK). Artefactual ICs were thus categorised as follow:

- Eye blink: SAD + TK;
- Vertical eye movements: SAD + MEV;
- Horizontal eye movements: SED + MEV;
- Generic Discontinuities: GDSF + MEV

Figure 11 shows the graphical interface of ADJUST, and typical components that were removed. Cleaned data was epoched with reference times spanning from -4 to 8 second with respect to the MI trigger. At the end of the pre-processing, trials were manually inspected singularly to check if they still contained noise. Noisy trials were discarded. Changes in event-related spectral dynamics was calculated at a group level for the following electrodes: FC1, FC5, C3, T7, CP1, CP5 and P7. In addition, for the alpha and beta frequency bands, we calculated scalp distribution of the signal across the whole epoch (topoplots), but also for the first and second half of the epoch.

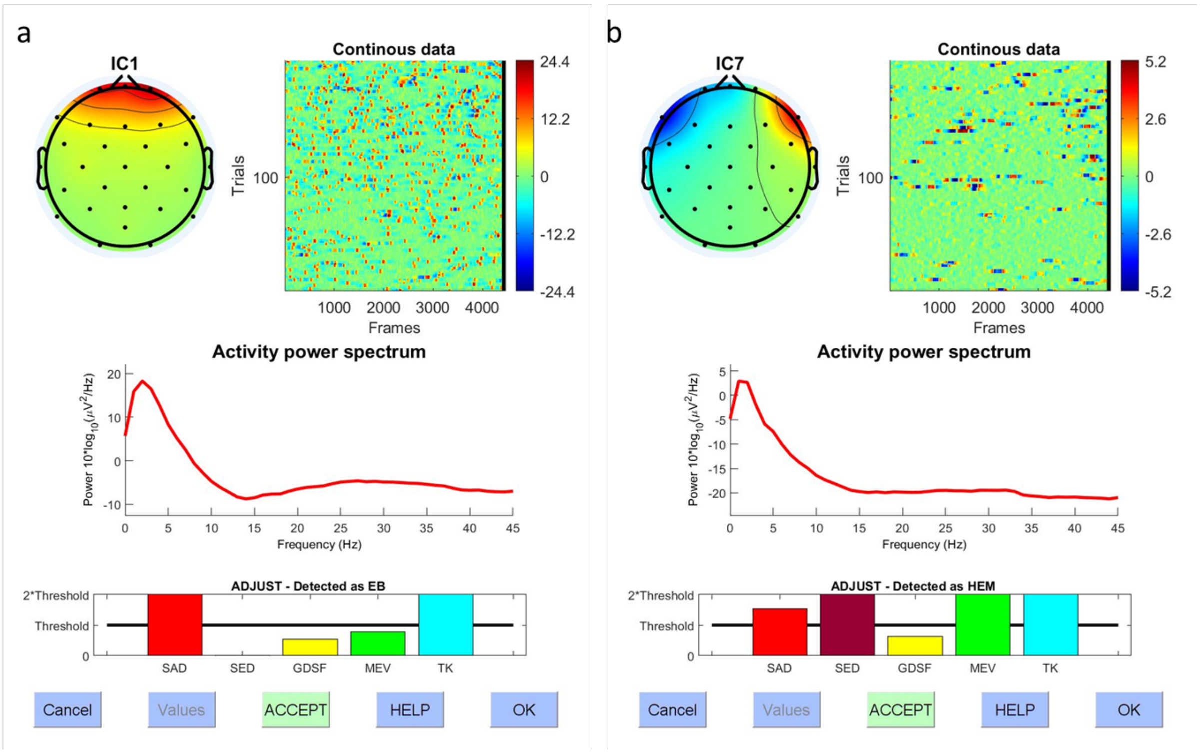

Figure 11 – An example of components that were removed, as identified as eye blink (a) and horizontal eye movement (b)

Statistical Analysis. Statistical analysis of behavioural data was completed using SPSS. Outliers in the data were assessed using z-scores. Value greater than ± 2.99 were considered outliers and discarded from the analysis. Normality distribution was assessed via the Shapiro-Wilk test ($p > 0.05$). A mixed ANOVA with factors ‘TIME’ (2 levels, pre- and post-practice) and ‘GROUP’ (SON and CON) was used to assess within- and between-group differences between pre-and post-training behavioural measures. Assumption of Homogeneity was assessed via Levene’s test of homogeneity of variance. EEG statistical analysis was conducted in EEGLAB. Nonparametric permutation statistics was used to assess within- and between-group differences. False Discovery Rate (FDR) was used to correct for multiple comparisons, which was set at $p < 0.05$.

4.3. RESULTS

4.3.1. Displacement Errors

All participants' task performance improved, as indicated by fewer errors in blocks' displacement (Table 9; see Figure 9 for the beginning and end configuration of the LEGO blocks). There was a significant main effect of 'TIME'; F(1,19) = 32.89, $p = 0.0001$, η^2_p= 0.634, but no significant interaction 'TIME x GROUP' F(1,19) = 0.41, $p = 0.529$, $\eta^2_p = 0.021$.

4.3.2. Motor Imagery Questionnaire

After the practice, participants' self-reported vividness scores, as assessed by the MIQ, improved for all three subscale scores (Table 12; Figure 12). There was a significant main effect of 'TIME' on external visual imagery: F(1,19) = 4.90; $p = 0.039$, $\eta^2_p = 0.205$, and kinaesthetic imagery F(1,19) = 9.16; $p = 0.007$, $\eta^2_p = 0.325$, but not for internal visual imagery: F(1,18) = 1.32, $p = 0.266$, $\eta^2_p = 0.068$. No 'TIME x GROUP' interaction was found for any of the three subscale scores: External visual imagery F(1,19)= 0.098, $p = 0.758$, $\eta^2_p = 0.005$; Internal visual imagery F(1,18) = 0.47, $p = 0.500$, $\eta^2_p = 0.026$; Kinaesthetic imagery F(1,19) = 0.969, $p = 0.337$, $\eta^2_p = 0.049$.

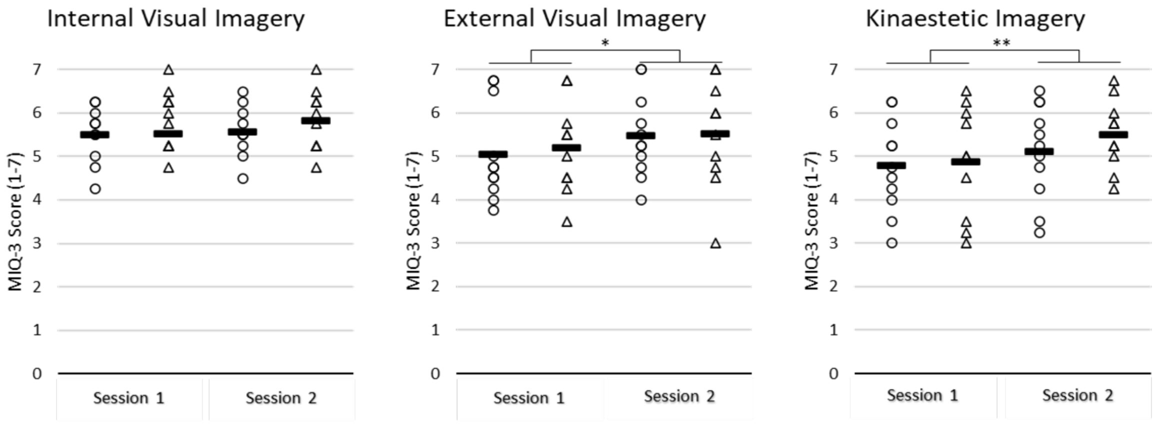

Figure 12 – Inter-individual changes in MIQ-3 subscores. White circles represents SON, while white triangles represent CON. *$p < 0.05$; ** $p < 0.001$

Table 9 – Descriptive statistics for performance, Motor Imagery Questionnaire and Verbal Report.

						95% Confidence Interval	
		Mean	Median	SD	SEM	Lower	Upper
			Performance (Displacement Error)				
SON	D1	3	5	2.74	1.23	-0.40	6.40
	D2	0	0	0	0	0	0
CON	D1	2.14	1	2.41	0.911	-0.09	4.37
	D2	0.14	0	0.378	0.143	-0.21	0.49

			MIQ - Internal Visual Imagery				
SON	D1	5.70	5.75	0.48	0.22	5.10	6.30
	D2	5.70	5.50	0.41	0.18	5.19	6.21
CON	D1	5.32	5.25	1.30	0.49	4.12	6.52
	D2	5.64	5.25	0.76	0.29	4.94	6.35
			MIQ - External Visual Imagery				
SON	D1	5.80	6.50	1.20	0.54	4.30	7.30
	D2	6.05	6.25	1.02	0.46	4.78	7.32
CON	D1	5.11	5.50	1.09	0.41	4.10	6.11
	D2	5.32	5.50	1.26	0.48	4.15	6.49
			MIQ - Kinaesthetic Imagery				
SON	D1	4.65	4.25	1.10	0.49	3.29	6.01
	D2	4.85	5.00	1.21	0.54	3.35	6.35
CON	D1	5.18	5.00	1.21	0.46	4.06	6.30
	D2	5.79	5.75	0.67	0.25	5.17	6.40
			Verbal Reports - Alertness				
SON	D1	6.92	7.10	1.15	0.51	5.50	8.34
	D2	8.10	7.90	1.04	0.46	6.81	9.39
CON	D1	6.91	6.40	1.57	0.59	5.46	8.37
	D2	8.13	7.60	1.52	0.58	6.72	9.54
			Verbal Reports - Mental Fatigue				
SON	D1	4.18	4.90	1.26	0.57	2.61	5.75
	D2	4.12	4.00	2.24	1.00	1.34	6.90
CON	D1	3.69	4.40	2.08	0.79	1.76	5.61
	D2	1.91	2.50	1.50	0.57	0.52	3.31
			Verbal Reports - Attention				
SON	D1	6.96	7.50	1.48	0.66	5.12	8.80
	D2	7.60	7.60	0.80	0.36	6.61	8.59
CON	D1	7.11	6.50	1.32	0.50	5.89	8.34
	D2	8.24	7.90	1.30	0.49	7.04	9.45

4.3.3. Mental Chronometry

Mental chronometry was used to assess mental travel effect, for both the LEGO action, which was practised during the practice, and RAG action, which was not practised at all. For the LEGO movement (Table 10; Figure 13a), results showed that practice decreased both execution and imagery times. There was a main effect of TIME for motor imagery F(1,19) = 4.66, p = 0.04, , η^2_p = 0.197 but no interaction TIME x GROUP: F(1,19) = 0.001, p = 0.982, , η^2_p = 0.000027. For motor execution during the LEGO action, there was no main effects of TIME: F (1, 20) = 3.22; p = 0.088, , η^2_p = 0.138, and no interaction 'TIME x GROUP': F(1,20) = 0.89, p = 0.357, , η^2_p = 0.043. For the reach-and-grasp-to-drink action (Table 10; Figure 13b), both groups improved their mental chronometry scores. For motor imagery, there was a main effect of TIME: F(1,19) = 9.54, p = 0.006, η^2_p = 0.334, but no interaction TIME x GROUP: F (1,19) = 0.15, p =0.698, η^2_p = 0.008. For motor execution, there was no main effect of TIME: F (1,19) = 2,70, p = 0.117, , η^2_p = 0.125, and no TIME x GROUP interaction: F (1, 19) = 0.26, p = 0.618, , η^2_p = 0.013.

Table 10 – Descriptive statistics for Mental Chronometry for LEGO and RAG action, Values expressed in ms.

						95% Confidence Interval	
		Mean	Median	SD	SEM	Lower	Upper
			LEGO - Motor Execution				
SON	D1	9102.64	8892.40	1910.60	854.45	6730.32	11474.96
	D2	8991.40	8681.40	1327.62	593.73	7342.94	10639.86
CON	D1	9824.00	10372.20	1877.67	709.69	8087.45	11560.55
	D2	8607.06	8787.40	829.63	313.57	7839.78	9374.34
			LEGO - Motor Imagery				
SON	D1	10820.44	10235.00	3746.01	1675.27	6169.15	15471.73
	D2	8322.16	8162.60	1383.11	618.54	6604.81	10039.51
CON	D1	9345.63	9072.20	2660.69	1005.65	6884.90	11806.36
	D2	8276.43	8119.60	991.11	374.60	7359.81	9193.05
			Reach-and Grasp - Motor Execution				
SON	D1	5798.48	5476.80	1141.34	510.42	4381.32	7215.64
	D2	5165.48	4942.60	947.46	423.72	3989.06	6341.90
CON	D1	5706.86	5598.80	812.99	307.28	4954.97	6458.75
	D2	5388.94	5402.60	633.71	239.52	4802.86	5975.03
			Reach-and Grasp - Motor Imagery				
SON	D1	6129.28	5442.60	2074.18	927.60	3553.85	8704.71
	D2	5261.72	4761.60	2001.80	895.23	2776.15	7747.29
CON	D1	5356.45	5293.00	741.98	280.44	4670.23	6042.66
	D2	4951.73	4842.00	648.22	245.00	4352.23	5551.23

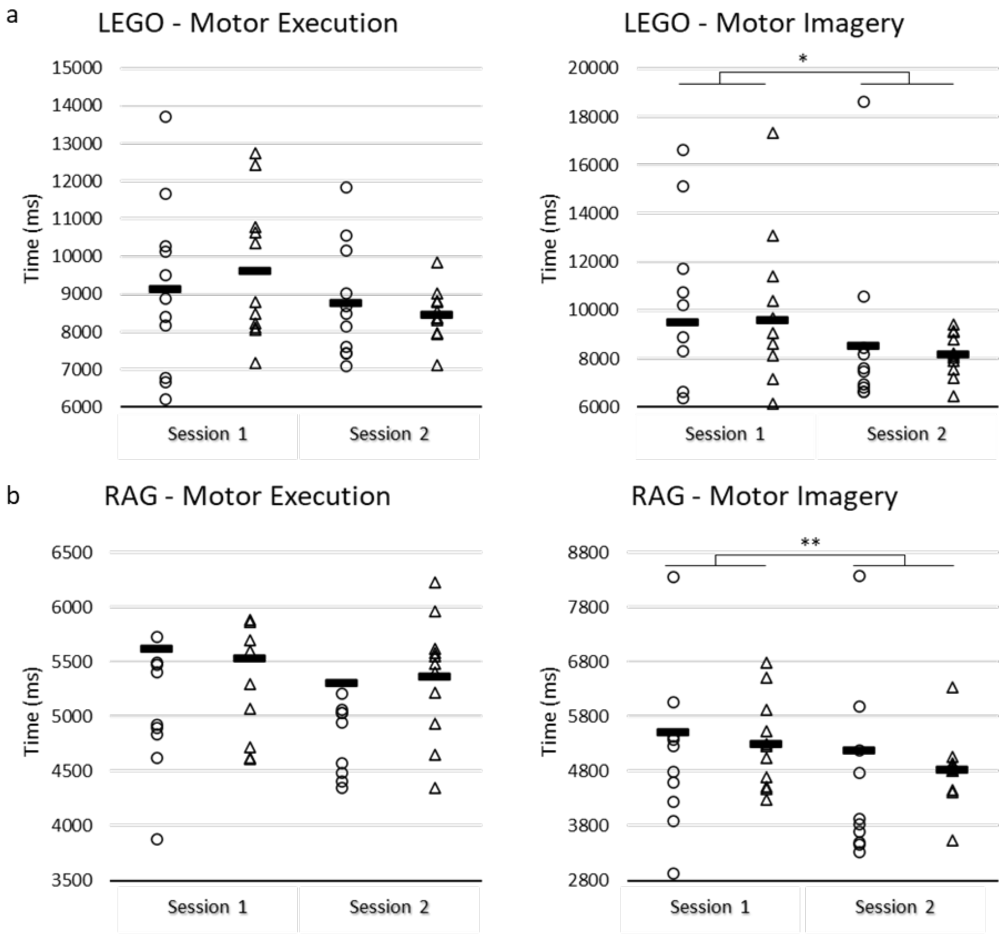

Figure 13 – Inter-individual changes in mental chronometry for LEGO and RAG action, for both motor imagery and execution. White circles represent SON, while white triangles represent CON. $*p < 0.05$; $** p < 0.001$

4.3.4. Verbal Reports

During the motor imagery task, at the end of each block, participants were asked to report their level of attention, alertness, and mental fatigue (Table 11). For attentional level, there was a main effect of TIME: $F(1,20) = 11.82$, $p = 0.003$, $\eta^2_p = 0.371$, but no TIME x GROUP interaction was found: $F(1, 20) = 3.28$, $p = 0.085$, $\eta^2_p = 0.141$. For mental fatigue, there was a main effect of TIME: $F(1,20) = 12.16$, $p = 0.002$, $\eta^2_p = 0.378$, but no TIME x GROUP interaction was found: $F(1, 20) = 0.392$, $p = 0.538$, $\eta^2_p = 0.019$. For alertness level, there was a main effect of TIME: $F(1, 20) = 17.08$, $p = 0.001$, $\eta^2_p = 0.461$, but no TIME x GROUP interaction was found: $F(1, 20) = 0.791$, $p = 0.253$, $\eta^2_p = 0.065$.

4.3.5. Sonification Reports

At the end of the second session participants were asked to fill in a questionnaire (see appendix_ for the questionnaire and Table 11). Since only the SON group received this questionnaire, we did not perform any statistical analysis. Participants reported a moderate pleasantness of the sonification sound, shown by the score to question number 1: *How did you find the sound, in term of its pleasantness?* (mean score: 5.5 ± 1.9; 0 highly unpleasant, 10: highly pleasant). Sonification helped participant to imagine LEGO action during the training sessions, as shown by the high score to question number 3: *To what extent did the sound help you to imagine performing the movement as you practiced it?* (mean score: 7.1 ± 1.8; 0 not at all, 10 completely). In addition, there was a positive effect on the self-reported efficacy of sonification on the improvement of motor imagery ability, as reported by the high score on question number 5: *To what extent, do you think that the sound improved your ability to imagine the movement?* (mean score: 7 ± 2.6; 0 not at all, 10 completely). Lastly, participants reported that during the motor imagery task, where EEG data was collected, they imagined the sonification sound in synchrony with the motor imagery of the LEGO movement, as shown by the high score for question number 4: *To what extent, during the MI task, did you imagine the sound in synchrony with the imagined movement?* (mean score: 7.3 ± 2.8; 0 not at all, 10 completely).

Table 11 – Caption: The table summarises the responses to the sonification report, which was completed after the end of the training protocol on the second session. Not all participants responded to all questions.

	Q1: Please, could you tell me your thoughts on the sound accompaniment that you heard during the training?
S1	Good use of sound- clearly changed as hand opened/closed to pick up object.
S7	The sounds were stimulating and refreshing. They had fairly extreme tones and so they were fairly easy to remember.
S9	It seemed to fit the movement fairly well. It wasn't particularly annoying or pleasant- though the end where the hand lifts off is quite high pitched and piercing.
S14	It helped to make the image more vivid in my mind as I could associate it with the movement.
S20	Simple and not completely distracting. Not uncomforting sounds.
S18	There was interference (white noise) between the actual clear sounds which distracted me. I didn't like the sound because of the pitch or timbre acoustic.
S22	The white noise was something that I wouldn't hear in my head- could not imagine. It would have been nice for the sound to evolve during the exercises.
S16	The second accompaniment really helped me picture the movement better as it enabled me to focus on the movement of the hand not just moving the blocks around.
	Q3: To what extent did the sound help you to imagine performing the movement as you practised it? If YES, then in what ways?
S1	It helped with speed of movement when hand was opening and closing.
S7	It enabled me to use sound/ memory association. It enabled me to gain actual cognitive purchase towards the visual image. It created a 'pairing'.

S9	It helped me to imagine the opening/ closing the hand as necessary and how fast to move. The white noise while the block was moving was a little hard to distinguish where it should start or stop but generally the sound was helpful.
S14	I could associate sounds with specific points of the movement.
S20	Timing the pick-up of the Lego pieces to the sound
S18	At a subconscious level. there may be some anchoring of the sound to the movement. I can hear the sound to the movement.
S22	It helped me regulate time and think about secondary loud movement that I sometimes discarded.
S16	Made me focus on the hand movement before, during and after, picking up each block
Q4: To what extent, during the 'motor imagery task', did you imagine the sound in synchrony with the imagined movement? If YES, then in what ways?	
S1	I imagined the hand opening and closing as the sound changed pitch.
S7	For example: the first sound made a 'dropping/ diving/ lowering' inference/ This allowed me to remember that the first motion/ movement was to bring the Lego piece downwards (it should drop).
S9	I imagined it as per the video
S14	As I put the blocks down in my head, the sound would accompany it.
S22	I reproduced the sound in my head as I was doing the movement connecting the part with fingers, the white noise with arm and silence with grip on the Lego.
S16	I synchronised the sound with when I pick up and put down each block.
Q5: To what extent, do you think that the sound improved your ability to imagine the movement? If YES, then in what ways?	
S1	The sound assisted my ability to imagine the timing of the movement
S7	In the same way as above, second also in that, it offered time segmentation- chunks of execution.
S9	Helped with training and the extent to close/open the hand.
S14	It made it more rhythmic and smooth in my head.
S20	Ability to imagine the movement might have been easier if I had a conscious awareness of the sound.
S18	Did help me to anchor the movement to some extent but it was still distracting. The lack of sound assisted in relief and I thought the task became easier without the sound.
S16	The sound helped me imagine the movement as I could copy that as well as the trying to copy the video.

4.3.5. Electrophysiological Data

We investigated changes in participants neural activity during the MI task, before and after practice with time-frequency analysis, and topographic maps built on all 31 channels. Time frequency analysis reported that the ERD begun around 500 ms after the motor imagery cue. Thus, any further analysis begun from that time stamp. Electrodes over the left hemisphere showed signs of ERD, with intensity changing depending on the electrodes and day, in the frequency bands around 7-12 Hz, and 16-25 Hz (Figure 14). When corrected for multiple comparison, via false discovery rate (FDR) correction, time-frequency maps did not show any significant differences between the groups and between days. However, a visual inspection of those maps suggested that on the second session, SON was able to sustain ERD for longer, compared to CON group the alpha frequency band, evident for all electrodes analysed. In addition, the ERD was more pronounced in the first 2 seconds of the motor imagery period. To gain a visuo-spatial illustration of brain activity over a certain epoch, we created topomaps from the signal of all 31 channels. Firstly, we inspected the topomaps for the whole motor imagery period (500-8000 ms). We were interested in three frequency bands, which shoed ERD in the time-frequency maps, lower (7-10 Hz) and higher (10-12 Hz) alpha, as well as beta (16-25 Hz) frequency band, which are discussed below. We split the analysis of the alpha frequency band because it has been suggested that lower alpha frequency band is related to attentional processes, while upper alpha frequency band relates more to the actual execution or imagery of the movement (Pfurtscheller, Neuper, & Krausz, 2000a).

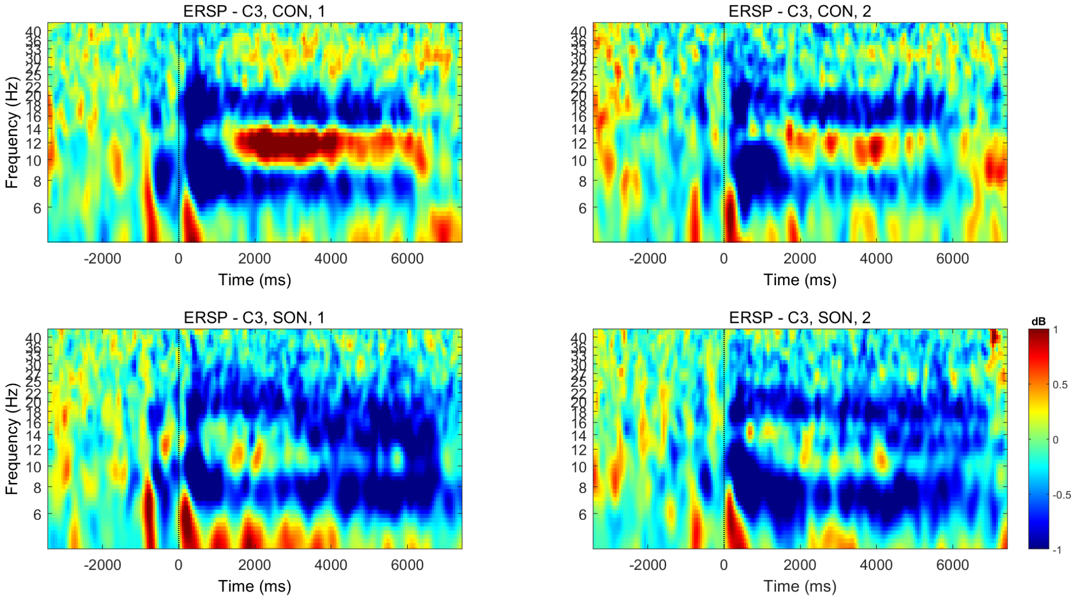

Figure 14 – Group-level time-frequency analysis for the electrode C3. Correction for multiple comparisons did not report significant difference between the group. However, from visual inspection it is possible to appreciate how, in the second session, CON is less able to sustain ERD as the epoch progresses

Lower Alpha (7-10 Hz). During the first session, both groups had ERD localised over sensorimotor as well as occipital electrodes (Figure 15a,b,c). This activation was bilateral, and SON group showed a more pronounced ERD than CON group. During the second session, both groups had a more localised activity over the left sensorimotor electrodes, contralateral to the imagines action. CON group showed a more focussed activity over C3,CP1, CP5 and P3, whereas SON had a more widespread activity on the left hemisphere. Correction for multiple comparison revealed that, compared to the first, during the second complete session CON had a significantly lower activity over CP5, Pz, POz, CP2, CP6, P4, P8 and O2 (Figure 15a; p > 0.05, FDR corrected). After, we inspected topographical maps for the first (Figure 15b; 500 – 4000 ms) and the second (Figure 15c; 4000 – 8000 ms) half of the motor imagery period. The analysis showed that in the second session, CON showed a focussed activity over the left sensorimotor electrodes already in the first half of the epoch (500-4000 ms), with a significant decrease in ERD for the electrode POz, compared with SON. In the second half of the epoch, however, CON showed an ERS over the left sensorimotor and occipital electrodes, with significant changes in activity in the electrodes C4, CP1, CP2, CP6, Pz, P4, P8, POz and O2 (p >0.05, FDR corrected). No significant difference between the groups, nor interaction between EEG session and groups were found.

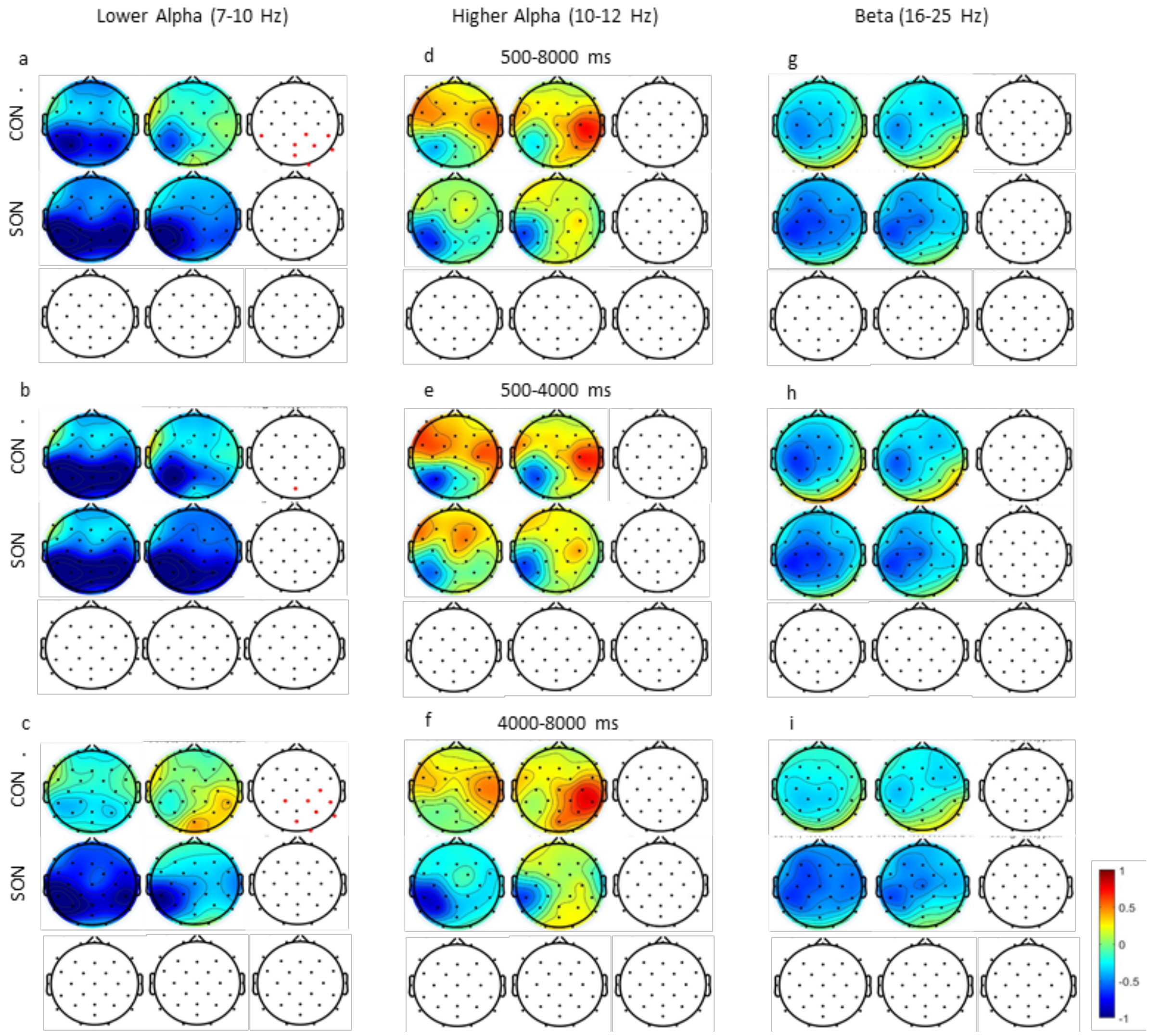

Figure 15 – EEG topoplots showing oscillatory activity during the motor imagery task. Three frequency bands were analysed: Lower (7-10 Hz) and higher (10-12 Hz) alpha, and beta (16-25 Hz). For each frequency band, we analysed the whole epoch (a, d, g), as well as the first (b, e, h) and second (c, f, i)

halves of the epoch. Red Dots represents statistically significant comparisons for each electrode (FDR corrected).

Beta (16-25 Hz). Time-frequency maps showed that participants showed ERD over the beta frequency band, with a ranger of 16-25 Hz. Beta frequency band topomaps (Figure 15g,h,i) showed a generalised pattern of ERD over frontal, central and fronto-central electrodes, which was focussed on central electrodes (Figure 15g). On the first visit, the two groups had similar pattern, although SON was able to sustain a slightly more intense ERD. The analysis of the two halves of the epoch, revealed that SON was able to sustain ERD longer than the CON group (Figure 15h). On day two, the pattern of ERD/D did not change, although the activation was more focussed over left hemisphere. No significant difference between the groups, nor interaction between EEG session and groups were found.

4.4. DISCUSSION

The aim of this study was to explore whether practising with sAO and subsequent motor imagery improved participant's performance and motor imagery ability. We assessed performance changes using a variety of psychophysical tests and EEG to record brain activity during motor imagery before and after practice. Both SON and CON showed a training effect on performance, but no differences between the groups was found, as both groups significantly reduced the number of errors in displacement of LEGO blocks after the training. In addition, both groups improved the mental chronometry test, for both LEGO and RAG actions, but only for motor imagery, and not execution. Lastly, both groups showed improvements in internal visual and kinaesthetic imagery, as assessed with MIQ. EEG analysis revealed no differences in higher alpha (10-12 Hz) and beta (13-16 Hz) in either groups. On the other hand, in lower alpha frequency band (7-10 Hz), SON group was able to sustain ERD over the whole MI epoch. Conversely, CON was not able to sustain ERD over time, which is in line with previous research on MI and alpha frequency band (Nam et al., 2011).

4.4.1. Effects of Sonification on Performance

The LEGO action used in this study was a sequential displacement of construction toy blocks. For the trial to be considered as correct, blocks needed to be displaced in a correct temporal sequence, to the correct location. After the practice session, both groups significantly decreased their displacement errors. These results are in line with the use of AO as visual guidance, in which the sensorimotor characteristics of the action are mapped into the observer's own sensorimotor brain, improving the representation of the action (Holmes & Calmels, 2008; Mattar & Gribble, 2005; Ste-Marie et al., 2012). However, no significant changes in execution time were found. It should be noted that for LEGO action, participants showed, on average, a fairly congruent execution time with the target before the training, so it is possible that, being to a near asymptotic performance level, the practice-induced improvement level was smaller (Dayan & Cohen, 2011). On the other hand, MI timing, which was slower than execution before practice showed a significant improvement. Similar results were found for the RAG action: Physical performance did not show significant changes, and remained slower than the target, but MI showed a more congruent mental travel effect. For the RAG action, the lack of significant modulation in execution time is to be expected since this action was not practiced. Taken together, these results suggests that even though prior to practice our participants could be considered as 'good imagers' (Lebon et al., 2012; Marchesotti et al., 2016; Vuckovic & Osuagwu, 2013), our training protocol produced a further improvement in MI ability. This view is also supported by the MIQ results, which showed an improvement for internal visual and kinaesthetic imagery, thus suggesting an improvement in MI vividness. With regards to the MIQ, we wish to note that the questionnaire was completed away from the lab, and this somehow mines the validity and the controllability of the data. This decision was taken due to time constraints. EEG data collection requires a high number of trials, due to the need to improve signal-to-noise ratio, and one visit lasted approximately three hours. During pilot tests, participant found difficult to maintain suitable levels attention during post-practice MIQ. Thus, we chose to exclude the questionnaire from laboratory protocol under the rationale that its inclusion would have put participants under additional cognitive stress, which would have inevitably meant a suboptimal performance, thus mining the quality of the data in any case. Nevertheless, these results are in accordance with a general improvement of performance after the training.

Our finding that sonification did not exert its additive effect on performance is in disagreement with previous research on the effects of sAO on performance. Schmitz et al. (2013) reported that sonification of the relative distance between the wrists and ankles in a breaststroke action was associated with significantly more accurate judgment about movement speed. When sonification was congruent with the observed action, there was an increased recruitment of movement-related brain areas, including the basal ganglia, very important for action control (Park, Coddington, & Dudman, 2020). In another study, Mezzarobba et al. (2018) reported that sonification of eight daily activity had beneficial effects on a variety of performance-related indices of freezing of gait in people with Parkinson's disease. Our study differentiates from other studies in at least two aspects, namely the action choice, and the use of sAO to prime motor imagery, with no physical execution during practice. We chose a sequential action in which blocks needed to be displaced to another location. A more naturalistic action may have engaged our participants more. Other studies have used sonification of daily actions, such as walking (Young et al., 2013) or sport actions (Schaffert et al., 2019). It is possible that a more ecologically valid action would have resulted in a more perceived usefulness of practice. However, other studies using non-ecologically valid actions, such as bimanual wrist flexion-extension (Dyer, Stapleton, & Rodger, 2017; Ronsse et al., 2011) or arm abduction/adduction (Vogt et al., 2009) reported beneficial effects of sonification on performance which, however, was provided in real time with the physically executed action. Thus, the contribution of task choice in the practice remains unclear.

4.4.2. Effects of Sonified Action Observation on Neural Activity

During the motor imagery task, we collected EEG before and after the two practice sessions, while participants imagined the LEGO movement. We analysed three frequency bands, which are thought to be differentially involved in different cognitive activities. After each task block, participants reported levels of attention, alertness, and mental fatigues. After the second practice session, participants reported significantly lower levels of mental fatigue, and a significant higher level of attention and alertness, which is suggestive of a decrease in participants' perceived effort in performing the task, compared to the first session. This is in line with changes in behavioural performance, and it is usually associated with motor skill learning(Dayan & Cohen, 2011).

4.4.2.1. Effects of sonification on attention

During MI, lower alpha (7-10 Hz) frequency band is thought to represent a more widespread activity due to attentional processes (Pfurtscheller, Neuper, & Krausz, 2000b). Activity in both groups focussed on centro-parietal regions. Parietal regions are a major hub for multisensory integration and, among others, is involved in spatio-motor mapping (Fogassi et al., 2005; Rizzolatti & Sinigaglia, 2010). In our study, the action was a sequential pinching and displacement of blocks which, compared to simple hand movements usually used in EEG studies (Marchesotti et al., 2016), requires this kind of processing. Our results show that after the second practice session SON group was able to sustain ERD over the MI epoch, and a more widespread activity over the left hemisphere, compared to CON group, who showed a significantly more lateralised activity over the left hemisphere (contralateral to the MI), and less ability to sustain ERD in time (figure 15). There is evidence that imagining a continuous task is associated with ERS as MI progresses, after the first second, compared to a discrete task (Cassim et al., 2000; Nam et al., 2011), and the fact that after the training CON group was able to sustain ERD for about 4 seconds is probably due to the spatio-motor requirements of the task. On the other hand, after the practice SON group showed higher and more prolonged ERD, with a more widespread activity over the left hemisphere. Since both groups practised and imagined the same action, the difference in ERD may be an effect of sonification on participants' ability to focus their attention on the action, possibly due to spontaneous auditory imagery associated with the spatio-temporal processing of MI, which allowed them to prolong neural activity for longer, compared to CON group. This view reconciles well with the results of the sonification questionnaire, which SON group completed after the second practice. On average, participants responded that they engaged in auditory imagery to a high extent (average 7, with 10 being the maximum). It should be noted, however, that no significant changes in brain activity were found in temporal lobes in either group. This, however, is in line with the results of a study by Kitahara, Hayashi, Kondo Yano (2017), in which participants had to either imagine foot dorsiflexion either alone, or in association with auditory imagery of drum control. Engaging in auditory imagery improved the classifier for foot motor imagery but did not significantly change the topographical activity. One major difference in our study is that participants were not instructed to the engage in auditory imagery, so it is possible that spontaneous auditory imagery may have helped to imagine the action.

Taken together, these results are in line with research on sonification. As all instances of sensory augmentation, sonification shifts people's focus of attention, by drawing attention to aspects of the action that would be hard to perceive otherwise (Schaffert et al., 2019; Sigrist et al., 2013; Young et al., 2013), and the beneficial effects heavily rely, among other things, on the interpretation of the augmenting stimulus with respect of the to-be-augmented characteristics (Sigrist et al., 2013). From sonification reports, participants reported that after the training, the association was in place, and perceived it as beneficial. In our study, we chose to focus on the perceived distance between the index and the thumb, by associating a synthesized pitch change, and the displacement of the block, which was associated with a synthetised swoosh. (see 'task and sonification' section). These audiomotor associations have been reported to be very common in sonification research (Dubus & Bresin, 2013).

These results have potential application in neurorehabilitation of neurological condition such as stroke and traumatic brain injury which, among others, show a reduced ability to sustain attentional control over time (Zhao et al., 2018). It is possible that sonification may improve the ability to sustain sensorimotor attention, thus improving proprioceptive predictions associated with motor planning (Brown, Friston, & Bestmann, 2011). In addition, sonification could represent a potential treatment with patients with visual neglect, a condition characterised by suboptimal multisensory integration and attention (Parr & Friston, 2018). The speculation that sonification was associated to spatio-motor processing may represent one way to optimise rehabilitation for this neurological condition (Zhao et al., 2018). Future studies are needed to provide evidence for the potential application of sonification to those conditions.

4.4.2.2. Effects of sonification on motor imagery ability

While lower alpha pertains to attentional processes, higher alpha and beta are thought to represent motor-related activity underlying the mental representation and simulation of the action (Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes, 1999). In this study, neither group showed modulations in these frequency bands. This is contrasts with behavioural results showing a practice effect. This is somewhat an unexpected result. Motor imagery training has been shown to modulate neural activity in theta, alpha and beta, with a more focussed activation over sensorimotor areas (Erfani & Erfanian, 2004; Weber & Doppelmayr, 2016; Zabielska-Mendyk, Francuz, Jaśkiewicz, & Augustynowicz, 2018). In our study, activity was already focussed over sensorimotor electrodes, especially in higher alpha frequency band. Even though previous studies have shown that sequential learning induces practice-related changes (Kraeutner, Gaughan, Eppler, & Boe, 2017; Kraeutner et al., 2015), it is possible that overall the sequence was too easy and, along the high MI vividness of our participants, the practice was challenging enough to reduce the number of displacement errors, and inducing changes in MI vividness, but not to induce changes in neural activity.

4.4.3. Study Limitations and Future Direction

In addition to possible methodological issue discussed so far, this study has further limitation. The main one was the high dropout rate, and the resulting limited sample size. One of the reasons for this was the overall length and effort required by the participant for this study. The whole protocol took approximately three hours to complete, most of which required the participant to be seated on a chair, with their hands on the table. Even though we made sure that participants had enough time to relax and stretch, there were times where they had to engage in MI, for long period time, such as the motor imagery task, which run for approximately 35 minutes. Research on mental practice suggests that, despite the fact that MI does not induce neuromuscular fatigue (Rozand et al., 2014), it is a highly demanding cognitive activity, and affects MI accuracy (Rozand et al., 2016). It is possible that clearer results could be obtained by simplifying and shortening the protocol. Future studies should explore this hypothesis with a shorter and simpler protocol.

4.5. CONCLUSION

In conclusion, our results suggest that sonified action observation does not affect behavioural indices reflecting execution or motor imagery of a sequential task. On the other hand, our results suggest that sonification may induce changes in attentional demands which are in line with the role of sonification as external guidance. Sonification, like all sensory augmentation strategies, is designed to attract people' attention to the audiomotor association, and our results suggest that this strategy may be beneficial for the development of strategies allowing people to sustain neural activity for longer, for example in BCI. However, more studies are needed to explore sonified action observation in clinical populations.

CHAPTER 5

GENERAL DISCUSSION

5.1. INTRODUCTION

Previous research on mental simulation of actions suggests that AO and MI may be an effective addition to traditional physical practice (Abbruzzese et al., 2015; Collins & Carson, 2017). Given recent events, it could also represent a particularly interesting tool for telemedicine, especially in remote areas and in condition where free movement of people may be limited, or physiotherapy practices closed (Minghelli et al., 2020). In these conditions, physical therapists could use AO and MI to maintain activity of the patient's sensorimotor system. Different recent metanalyses suggest that such strategies could be effective in inducing changes in behaviour and plasticity (Nicholson et al., 2019; Silva et al., 2018). On the other hand, studies on the effectiveness of MI and AO seem to suggest that these forms of cognitive action are suboptimal, compared to PP (Kraeutner et al., 2015). Specifically, the lack of sensory reafference due to the absence of physical movement may adversely affect the rate of learning and resulting neuroplasticity (Bisio et al., 2015; Blandin et al., 1994; Mulder et al., 2004).

Sensory augmentation may represent an important feedback, which can be used to *augment* AO and MI. In this thesis, we explored sonification, an auditory augmentation strategy whereby a sound is associated with – and modulated by – movement (Dubus & Bresin, 2013). Previous research suggests that sAO has beneficial effects on perceptual judgment and increases neural activity in sensorimotor networks in healthy people (Schmitz et al., 2013). In addition, it reduces freezing of gait in people with Parkinson's disease (Mezzarobba et al., 2018). In this thesis, we were interested in extending these reports by investigating neural correlates of sonification of simulated actions. In addition, a second topic of this thesis was to explore whether sonification of combined and congruent AO and MI could be effective. Previous research on action simulation suggest that AO and MI can be considered as complementary, and its combined use, within the right conditions, induces an increased activity over the sensorimotor system and corticospinal excitability (Bruton et al., 2020; Eaves et al., 2016). In agreement with this, recent studies show that combining AO and MI induces higher rates of (re)learning, compared to the use of AO and MI singularly (Marshall et al., 2020; Romano-Smith et al., 2018; Sun, Wei, Luo, Gan, & Hu, 2016; Wright, Wood, Eaves, et al., 2018). We were interested in extending this framework to the interaction between visual, auditory, and motor system. To this end, we designed a series of experiments, using a variety of behavioural and neurophysiological techniques. In the following section, we discuss the main conclusions of this investigation and highlight their implication for future research and their practical applicability.

5.2. SUMMARY OF THE MAIN FINDINGS

Three studies were carried out for this thesis, presented in Chapters 2, 3 and 4. In Chapter 2 we investigated the effects of sonification of combined AOMI on corticospinal excitability. Participants completed a practice block based on AOMI, MI and physical execution of the same action. In addition to practice effects on corticospinal excitability we also explored audiomotor plasticity arising from the practice. To this end, we used a variation on a commonly used method to probe and induce plasticity, Auditory Paired Associative Stimulation (aPAS), based on pairing a sound with a TMS pulse. Participants completed aPAS alone (7 days before the practice) and after a practice block. Practice induced a significant increase in corticospinal excitability, compared to pre-practice measures, but sonification did not exert augmentative effects. aPAS, when completed alone, significantly improved corticospinal excitability, but when primed by the practice block, it did not induce any modulatory effect for both groups. A follow up study was designed to further investigate the relationship between sonification, practice and action simulation. In Chapter 3, we investigated the effects of a similar practice, with a different action, on corticospinal excitability and audiomotor resonance. Participants completed a similar practice block based on the same paradigm. Before and after the practice block, we measured corticospinal excitability at rest and during AO and AOMI. In addition, after the practice, we measured corticospinal excitability during sAO and sAOMI. We did this to investigate whether SON group developed an audiomotor resonance specific to the sonification sound. In line with the results of the previous study, practice induced a significant improvement of corticospinal excitability in both groups, but sonification did not influence this. This was the case for corticospinal excitability at rest, during AO and AOMI. Interestingly, after the practice block, we found no differences in corticospinal excitability between normal and sonified AO and AOMI, for both groups. While the results of CON may be expected, as the sound was new to them, the results of SON group suggests that sonification did not develop an audiomotor resonance. We interpreted these results as a possible interference of sonification on top-down and bottom-up processing of internal representations of the practised action; It is possible that sonification failed to interact with the action, which may have been too simple, and did not add contextual value or could have acted as a distractor, competing with attentional resources, and interfering with action simulation. A further point of consideration was the fact that in our practice blocks, the action was physically executed, and this may have influenced or masked the effect of sonification on corticospinal excitability and aPAS induced modulation.

In Chapter 4 we used EEG to explore neural and behavioural signatures of sAO practice. We choose EEG, instead of TMS, because of the multidimensionality of its signal. Indeed, different domains of the oscillatory signal characteristics of electrophysiological techniques (EEG and MEG) can be analysed, such as time, frequency, power, space, and phase of oscillations (Cohen, 2014; pp. 15). We choose a popular method in MI and BCI research, event-related (de)synchronization (ERD/S), in time-frequency domain, which is thought to arise as a result of firing of different sets of neurons, which lose their coordinative oscillatory behaviour at rest (Buzsaki, 2006; Buzsáki, Anastassiou, & Koch, 2012; Hipp, Engel, & Siegel, 2011). Different studies have used converted EEG signals as input to control BCIs (Lotte et al., 2018; Wang et al., 2018). In this study, we also used a different task, which was a longer, continuous goal-directed action. Lastly, we removed PE from practice. To measure behavioural changes following practice, we used mental chronometry, a popular method to assess similarities between executed and imagined action (Guillot, Hoyek, Louis, & Collet, 2012; Marchesotti et al., 2016), as well as changes in MI vividness, using MIQ (Williams et al., 2012). After practice, both groups improved vividness of kinaesthetic and visual imagery, and decreased their mental chronometry, but sonification did not exert its additive effects. On the other hand, EEG analysis revealed that, after practice, SON was able to sustain ERD in the lower alpha frequency band (7-10 Hz) for longer, compared to CON group, which instead showed a reduced ability to sustain ERD, in line with studies on continuous MI tasks. No significant changes in higher alpha and beta were found. In the last portion of this thesis, we will discuss the implication of our findings, and contextualise them within the existing literature.

5.3. IMPLICATIONS OF THE RESEARCH FINDINGS

5.3.1. Attention, Multisensory Processing, and the Value of Information

A *fil rouge* that run throughout this thesis is the role of attentional processing underlying action simulation, and its relationship with auditory augmentation. Computationally, attention can be seen as a mechanism to maximise precision of sensory information, creating and maintain stable internal representations of the body and its surrounding environment (McNamee & Wolpert, 2019; Wolpert, 1995). As mentioned at the beginning of Chapter 1, the brain behaves as if it creates and modulates internal representations of the body it inhabits and the surrounding environment, which are then used to make predictions about sensation sampled by peripheral sensors, as well as changing those sensation via actions (Friston et al., 2010). This is done by a hierarchical circuitry which includes, amongst others, frontal and parietal areas. These areas have been constantly involved in motor cognition and control, as they are part of the grasping circuit (Davare et al., 2011; Jeannerod et al., 1995), as well as the action observation and imagery network (Filimon et al., 2007; Hardwick et al., 2018; Simos et al., 2017).

Under predictive coding theories, computations are made to maximise epistemic evidence of regularities about body and surrounding environment. In other words, the brain acts as a '*contextual forager*', to use the rhetoric of Mirza, Adams, Friston and Parr (2019); It is actively engaged in perception and action. However, since sensory information contains both signal and noise (Körding & Wolpert, 2006), the brain needs to establish which sensory sources are most informative, given the context. This could also be conceptualised as the *epistemic value* of sensory information, where sensory inputs are weighted according to their ability to resolve sensorimotor uncertainty (Friston et al., 2015). Thus, it is thought that the brain weights different sources based on their expected precision. For example, different studies highlight how vision has dominance in computing goal-directed actions, but proprioceptive information is fundamental to the development of motor commands (Sarlegna & Sainburg, 2009). This sensory hierarchy is not fixed, but is continually interfaced with contextual information from the environment; sensory deprivation, even transient, results in a sensory reweighting, which facilitates other sensory channels (Marx et al., 2004, 2003). Within this context, attention acts as a *spotlight* that determines which information is processed.

A practical example of this is gaze behaviour and AO. Now classic studies on gaze behaviour suggests that ocular movements are made as to maximise the foveal sampling of salient portions of visual stimuli (Parr, Corcoran, Friston, & Hohwy, 2019). This also explains the relationship between gaze behaviour and AO. Several studies highlight how mapping of sensorimotor characteristics of an action in the observer's own sensorimotor system is modulated by attention and contextual information. When attention is pulled away from salient characteristics of the action, for example via exogenous manipulation (D'Innocenzo et al., 2017; Puglisi, Leonetti, Cerri, & Borroni, 2018; Wright et al., 2017) motor resonance is reduced. This suggests that visual information about observed actions are used by the observer to make sensorimotor predictions about what is happening in the outside environment, thus maintaining a stable representation of it (Friston et al., 2011; Kilner et al., 2007; Shipp, Adams, & Friston, 2013). A similar process happens during auditory perception, where perception of auditory stimuli is modulated by their salience (Barascud, Pearce, Griffiths, Friston, & Chait, 2016; Southwell et al., 2017).

Historically, attentional gain has been investigated in the context of perception, but a similar mechanism has been suggested for preparation of goal-directed actions. Previous studies highlighted the importance of proprioception for action execution (Graziano, 1999; Sarlegna & Sainburg, 2009). Brown, Friston and Bestmann (2011) suggested that this may be due to attentional gain towards expected proprioceptive reafferences during action preparation, which are used to bias action choices (Cisek & Kalaska, 2010), and this would be in line with the role of proprioception in the definition of a 'motor command' (Sarlegna & Sainburg, 2009). Using EEG, in Chapter 4 we found that sonification helped participants to sustain ERD in lower alpha (7-10 Hz) frequency band for longer. Previous research suggests that lower alpha frequency band is involved in sensorimotor attentional processing (Pfurtscheller et al., 2000b). MI of rhythmic movements are characterised by a sharp decrease of ERD early in the MI period, followed by a return to the baseline (Cassim et al., 2000; Nam et al., 2011; Neuper & Pfurtscheller, 2010), which is in line with the results of CON group in Chapter 4. The fact that the SON group was able to sustain ERD for longer may be suggestive of an audiomotor association developed during sAO practice. This audiomotor association may have allowed participants to better simulate proprioceptive reafferences in a more consistent way, possibly associating it to auditory imagery of the sonification sound (c.f. Kitahara et al., 2017). It is tempting to speculate that sensory predictions involved in auditory imagery were associated to action-related simulation of predicted proprioceptive information in somatosensory and motor areas, inducing a more sustained ERD. This would happen even with an easy-to-execute action, which likely would not have benefitted from practice with sensory augmentation, and this would be in line with the absence of significant changes in higher alpha and beta frequency bands in Chapter 4.

In Chapters 2 and 3, no influence of sonification on corticospinal excitability was found for SON, compared to CON group. It should be noted that MEPs are a much less sophisticated index of sensorimotor motor activity, as a variety of technical (Rossini et al., 2015) and physiological (Bestmann et al., 2015; Bestmann & Duque, 2016) processes can influence its amplitude; thus, we were not able to discern the influence of attention-related process from computations underlying MI and AO. While it is possible that a similar process was in place, the fact that in Chapter 3 corticospinal excitability was not modulated by sound during AO and AOMI, together with the results at rest in both Chapters 2 and 3, suggests that sAOMI may underlie different computational mechanisms. This view is supported by evidence of a differential sensorimotor processing underlying AO, MI and AOMI (Bruton et al., 2020; Eaves et al., 2016; Eaves et al., 2016; Meers et al., 2020; Vogt et al., 2013). Under the dual simulation hypothesis, bottom-up and top-down processes of AO and MI, respectively, can be represented simultaneously. However, MI seems to 'drive' corticospinal excitability during AOMI (Meers et al., 2020), and this seems to be induced by attentional shifts, from the externally-induced visuomotor mapping of AO, to internally-induced simulation of kinaesthetic characteristics of the imagined action (Eaves et al., 2016; Eaves et al., 2016). At a computational level, this may be favourable, compared to sAO, as simulation of kinematic characteristics of the action is much closer to computations underlying executed actions. In this case, the simulated proprioceptive information could have been effectively associated to the sonification sound. However, the tasks that we chose may have been not complex enough for sonification to add value to the percept. It could be speculated that if internal models of the actions practised by participants during the first two studies were already 'precise' (with low degree of computational uncertainty), then sonification may have not added epistemic value to the sAOMI, resulting in little sensorimotor gain to the internal representation of the action. This is also what happens at later stages of training, at near-asymptotic levels of performance (Dayan & Cohen, 2011).

Taken together, our results are in line with the idea of perception as *saliency* and is coherent with theories of sensory augmentation, which propose to provide information that, in normal condition the brain cannot sample, such in the case for silent movement characteristics (Dubus & Bresin, 2013; Sigrist et al., 2013). At a computational level, sensory information arising from the augmented association should provide the brain with important epistemic information which are integrated into the internal representation of perception and action, and its relationship with the environment. However, if the action chosen is too simple, then sensory augmentation becomes ineffective, or worse, can act as a distractor.

5.3.2. Can Sonification be Effective for Action Simulation?

Recently, the use of AO and MI in rehabilitation practices has been widely popularised and encouraged, and its use may be a valuable addition to traditional rehabilitation regimes. These forms of cognitive practice engage the sensorimotor system in a largely overlapping way, albeit from different perspectives (Eaves et al., 2016; Vogt et al., 2013). Nevertheless, the lack of sensory reafference could be a concern, and may explain the reason for the suboptimality of action simulation, compared to physical practice (Blandin et al., 1994; Mulder et al., 2004). Sensory feedback is thought to be a fundamental aspect of learning, and it needs to be considered when designing (re)learning protocols (Ostry & Gribble, 2016). In this regard, sensory augmentation could represent an innovative way of augmenting cognitive simulation of action. Sonification is a particularly interesting strategy because, by nature, auditory information is not essential to goal-directed action planning, for which vision has primacy (Sarlegna & Sainburg, 2009). This relative independence of auditory processing in motor control may explain why sonification is less susceptible to the *guidance effect*, the performance detriment usually seen when feedback, usually visual, is removed (Dyer et al., 2017; Dyer et al., 2015). To the best of our knowledge, most research on sonification has been delivered in real-time, as the movement unfolds (Dubus & Bresin, 2013). Auditory information is then matched with movement re-afference, and integrated into the person's neural representation of body and environment (Effenberg, Hwang, Ghai, & Schmitz, 2018). This convergence, once associated with the action, provides auditory guidance for the movement, providing knowledge of results or performance, in a similar way as AO does for visual information (Holmes & Calmels, 2008). As a result, sonification induces better performance, compared to non-sensory augmentation or compared to other sensory augmentation strategies (Dyer et al., 2017; Ronsse et al., 2011; Sigrist, Rauter, Marchal-Crespo, Riener, & Wolf, 2014). In some cases, sonification can also act as sensory replacement, to replace lost or impaired sensory information, for example where proprioceptive afferents have been damaged by injury or illness (Danna & Velay, 2017; Danna et al., 2015).

In this thesis, we investigated a variation of this protocol, namely whether sonification can be delivered online, but associated to simulated actions. Since sonification requires a motor dimension, we associated it to AO. In a model of effectiveness of sensory augmentation based on task complexity, (Sigrist et al., 2013) suggest that sonification is most efficient when associated to simpler actions. However, our results seem to contradict this view, as we used simple actions of increasing complexity, which are summarised and compared with each other in table 12. None of these actions were able to induce changes in neural activity or performance, compared to normal practice without auditory augmentation. In hindsight, the tasks chosen for these studies were, perhaps, too simple, and sonification did not exert its augmenting effects, as mentioned in previous sections. In addition, participants in all three studies were healthy young people with no neurological conditions. It is possible that the same actions would have been more effective with a different population. Limited research on Parkinson's disease suggests that sAO may be effective for improving freezing of gate, with long term retention of these improvements (Mezzarobba et al., 2018). Taken together, sonification of covert actions have the potential to be effective strategy for (re)learning, but further studies are needed to evaluate its effectiveness to clinical populations.

Table 12 - Table summarising the tasks employed in the three experimental chapters. Physical and auditory dimension represent the movement-related characteristics to which the auditory feedback (auditory dimension) was associated to. Chapter 2 and 3, only one movement characteristics was sonified, while in chapter 4 we sonified two movement characteristics.

	Chapter 2	**Chapter 3**	**Chapter 4**
Task	Pinching of a battery with right thumb and index finger (link to the video)	Squeezing a foam ball with the right thumb and index finger (link to the video)	Rearrangement of toy construction blocks with right thumb and index finger (link to the video)
Sonified characteristics	1	1	2
Movement Characteristic	Distance between index and Thumb	Exerted pressure	i) Distance between index and Thumb; ii) Block Displacement
Auditory Characteristics	Pitch increase / decrease	Sound intensity increase / decrease	i) Pitch increase / decrease; ii) Synthetised ‘swoosh’

5.3.3. Plasticity, Metaplasticity and Multisensory Interaction

PAS, aPAS and stability of a neural network. Experience modulates internal representations, and this is also seen at a neural level, where experience modulates synaptic strength of the neural network involved in a particular experience (Müller-Dahlhaus & Ziemann, 2015). Thus, plasticity is the enabling mechanism of motor learning in sport and clinical contexts (Dayan & Cohen, 2011). Long-term Potentiation and Depression (LTP/D) are at the core of plasticity, and LTP is a major contributor to sensorimotor learning (Kumpulainen et al., 2014). Since the discovery of the neuromodulatory effect of TMS, a plethora of brain stimulation protocols have been developed to modulate brain circuitry, under the rationale that an *upregulated* brain would result in improved behaviour. One of these is paired-associative stimulation (PAS). The repetitive association of sensory stimulation and TMS pulse is thought to strengthen the sensorimotor pathway associated to the stimulation. In its original formulation, PAS consisted of a medial nerve stimulation, associated to a TMS pulse over M1. Over the years, different variations of this have been proposed.

Of particular relevance to this thesis, is the fact that auditory paired associative stimulation (aPAS) has been proposed as a intervention to target the audiomotor pathways (Sowman et al., 2014). In Chapter 2, we deployed aPAS to investigate the interaction between sonification and LTP-like plasticity. Our results corroborated the original finding of Sowman and colleagues, suggesting that pairing a sound and a TMS pulse with 100 ms interstimulus interval (ISI) induces a significant increase of corticospinal excitability when completed alone. Interestingly, when we compare our results with those of Sowman and colleagues, it seems that the type of sound does not matter: A word 'Hey' or a more effector-specific action sound – a keyboard typing sound – were equally able to modulate corticospinal excitability of the FDI muscle. 100 ms coincides with the N100, which is an ERP component that is usually associated with unconscious sensory processing (Naatanen et al., 2011), and this may suggest that in order for aPAS to be effective as a neuromodulatory protocol, it does not need to be meaningful, but merely engage with the audiomotor pathway, with the right stimulation order. Nevertheless, further developments of this protocol are needed, to be able to define its neurophysiological effects, and assess whether it can be applied to neurological conditions characterised with audiomotor disfunctions.

In Chapter 2, we also explored the extent to which a practice block based on sonification influenced metaplasticity in the audiomotor domain. Contrary to what we found for the effect of aPAS completed alone, when a practice block *primed* the same aPAS protocol, no modulation of corticospinal excitability was found for both CON and SON groups. In addition, neuromodulation afforded by aPAS after the practice was significantly lower, compared to the same protocol, completed alone, seven days before. One interesting feature of aPAS, which set it apart from other, more conventional, forms of plasticity-inducing techniques is the fact in aPAS, there is an interaction between auditory and motor system, but the outcome measure of the protocol is measured at the level of the motor cortex. Extensive research on the relation between M1 and motor learning suggests that practice induces long-lasting modification to the intrinsic properties of M1 (Rosenkranz, Kacar, et al., 2007; Ziemann et al., 2004; Ziemann & Siebner, 2008). Considering that the practice included a physical execution component, it is possible that this may have been enough to modulate M1, consequently masking the effect of any audiomotor interactions induced by aPAS. Further studies are needed to validate this hypothesis, and to further explore whether audiomotor practice can interfere with aPAS protocol.

Metaplasticity: A possible treatment? In Chapter 2, we deployed metaplasticity to assess how audiomotor practice primed aPAS. However, the opposite logic can be used as strategy to maximise practice-induced plasticity. Based on the BMC theory of sliding windows, history of synaptic activity modulates subsequent ability to induce further modulations of synaptic strengths (Cooper & Bear, 2012; Ziemann & Siebner, 2008). If an LTP-inducing protocol is paired with another LTP-inducing protocol, such as that employed in Chapter 2, the history of high synaptic activity of the first one interacts with the second one, triggering homeostatic mechanisms that result in the second protocol to induce LTD. Conversely, a history of low synaptic activity increases the probability of subsequent induction of LTP (Jung & Ziemann, 2009; Müller et al., 2007). In other words, if practice is primed by PAS_{LTD}, performance and plasticity may be improved beyond practice only. If optimally developed, this could represent an efficient and innovative tool to neuromodulate and enhance practice-dependent plasticity, with clear and potentially impactful application to rehabilitation. In a hypothetical scenario, a person would perform an LTD-inducing rTMS protocol prior to a rehabilitation session. Considering that neuromodulatory protocols are usually relatively short, the addition of this component would not impact the timeframe of traditional rehabilitation. Before this protocol could have practical application, however, several basic neurophysiological and clinical studies should be undertaken to explore and define optimal parameters. For example, the timing between neuromodulation and practice, as well as the number of sessions needed to obtain appreciable results is still unknown. Lastly, Research on this topic used very simple movements, such as finger or wrist movements (Jung & Ziemann, 2009). Future research should explore the applicability of this protocol to daily and more ecologically valid actions.

5.4. LIMITATIONS AND OPPORTUNITIES FOR FUTURE RESEARCH

This series of investigations has some limitations. First, in hindsight, additional behavioural evidence for the effects of sonification was warranted. This limits our ability to discuss possible behavioural changes resulting from sonification. In addition, even though we found coherence among results of the three experimental studies, a larger sample size may have added more robustness to our results, thus being more informative for the discussion. On the other hand, another limiting factor for our discussion on the effectiveness of sonification of covert actions is task choice, and its relationship with the population studied. In all three studies, we focus on a healthy, young population, with no known neurologic conditions. For this population, simple hand movements may have been easy to perform, thus limiting the effect of sonification. In hindsight, more convoluted actions may have been more challenging, with possible repercussions for neural activity and plasticity.

On the other hand, it should be noted that participants' primary task of the three studies presented in this thesis was not to execute an action, but to imagine it. Even though the consensus is that MI entails a similar neural dynamic to PE, the vividness with which one can imagine an action mediates its efficacy. When MI vividness is accounted for, studies have consistently reported differences between poor and good imagers. Neural activity, measured with EEG, is closer to the one during PE (Toriyama, Ushiba, & Ushiyama, 2018), and good imagers show higher corticospinal excitability (Lebon et al., 2012; Moriuchi, Nakashima, Nakamura, Anan, & Nishi, 2020) and EEG-related BCI performance (Marchesotti et al., 2016; Vuckovic & Osuagwu, 2013), compared to poor imagers. Crucially, even extremely simple movements, such as hand clasping, are affected by MI vividness (Marchesotti et al., 2016). Given this, in our opinion it was reasonable to use simpler movements, which people with no neurological conditions could perform easily, but they may not imagine it as easily as performing it, and to hypothesise that sonification would have improved vividness.

5.5. GENERAL CONCLUSIONS

This thesis explored the effects of sonified action observation of daily actions on neural activity, motor imagery and performance of those actions. Taken together, our results suggest that the extrinsic feedback provided by sonification modulated sensorimotor attentional processing associated with imagining actions, but did not improve performance and imagery ability, compared to practising without extrinsic feedback. Above all, this thesis highlights the need for careful consideration of audiomotor mapping and the cognitive demands associated with observing and imagining actions. Sonified action observation is still an underexplored area. Whether online (live demonstrations) or offline (via videos), action observation has long been considered an important learning strategy, providing visual guidance not only on what to do, but also how to do it. Extending this external guidance to multimodal stimuli may represent a valuable tool in the practitioner's toolbox for augmenting learning and neurorehabilitation and complementing traditional protocols that are based on physical execution. To fulfil this potential, future studies should explore the link between sensory augmentation and its epistemological effects on internal representations of the body and surrounding environment. In addition, studies with clinical populations are needed, to elucidate the potentially augmentative effect of sAO in individuals for whom physical movement and/or visual perception are impaired.

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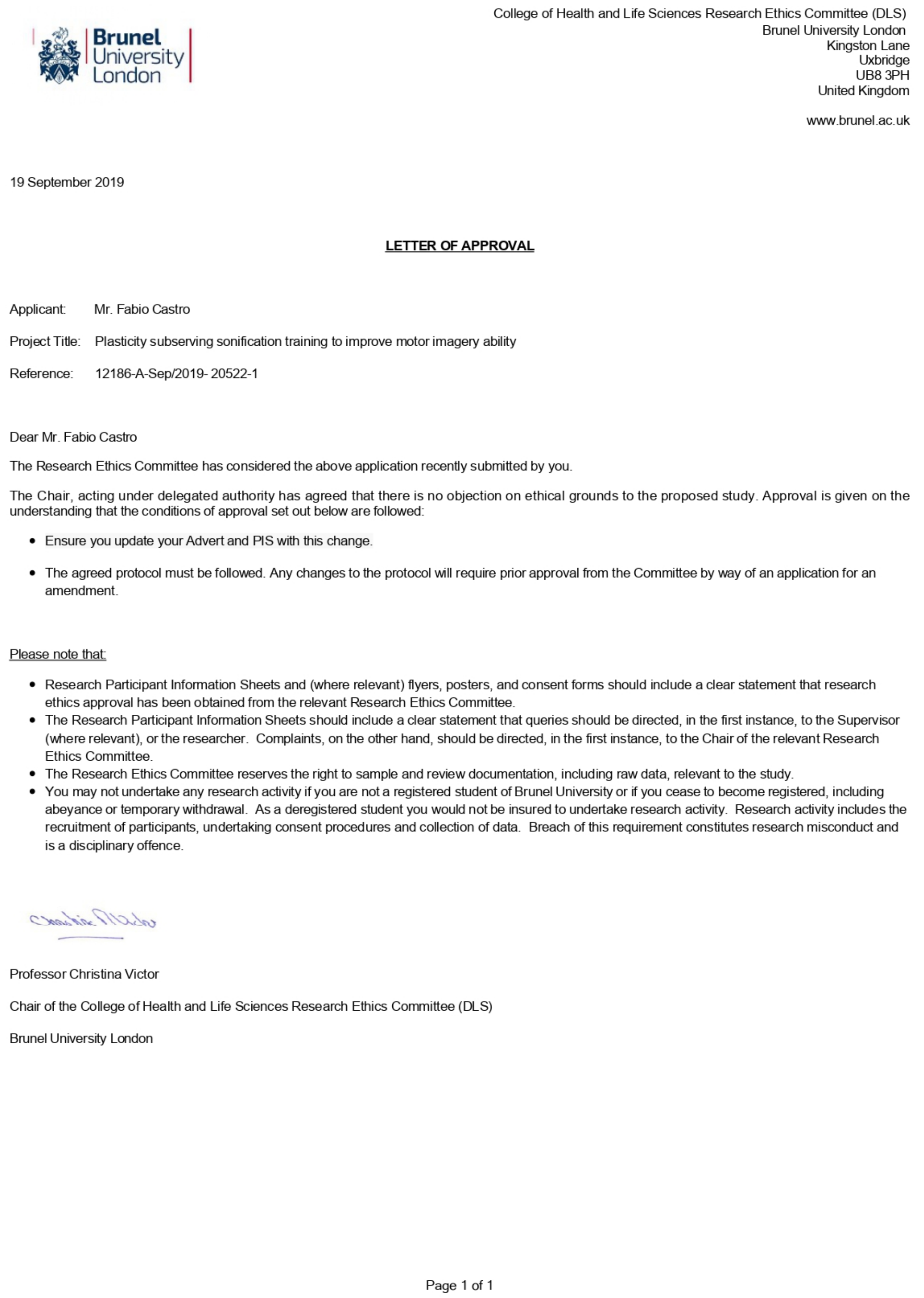
APPENDICES

APPENDIX A– Research Ethics Committee Approval For Study 1



College of Health and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

www.brunel.ac.uk

19 September 2019

LETTER OF APPROVAL

Applicant: Mr. Fabio Castro

Project Title: Plasticity subserving sonification training to improve motor imagery ability

Reference: 12186-A-Sep/2019- 20522-1

Dear Mr. Fabio Castro

The Research Ethics Committee has considered the above application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- Ensure you update your Advert and PIS with this change.
- The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.
- You may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Christina Victor

Chair of the College of Health and Life Sciences Research Ethics Committee (DLS)

Brunel University London

Page 1 of 1

APPENDIX B – PARTICIPANT INFORMATION SHEET FOR STUDY 1

A

College of Health and Life Sciences
Department of Life Science

PARTICIPANT INFORMATION SHEET

Crossmodal plasticity following sonified action observation + motor imagery: a paired-associative stimulation study.

An invitation to participate

You are invited to participate in this study on the effects of sonification on cortical reorganization. This information sheet provides an overview of the study and what is involved, if you decide to participate. Please take your time to carefully consider the information provided. We are happy to discuss any concerns or queries you may have. If you would like more information, please feel free to contact us by e-mail, as provided below. Thank you for taking the time to read this.

What is the purpose of the study?

Observing someone's movements or Imagining the same action has been shown to activate similar motor areas in the brain as the actual execution of the same action This is very important for motor learning and rehabilitation, because it provides different ways for a person to improve performance and learn new skills. In a previous study we investigated whether motor imagery can be improved with the use of sonification, a sensory augmentation strategy that associates a sound to a movement. However, in order to establish whether this strategy can be successfully used as a rehabilitation strategy, we need to investigate the reorganization of the brain following a sonification training.

The aim of this study is i) to investigate the changes neural connections between the auditory and motor areas of the brain and ii) to monitor changes in brain motor cortical area activity after a sonification training.

To do this, we will use a non-invasive stimulation technique called Transcranial Magnetic Stimulation (TMS), which uses magnetic fields to stimulate the brain cortex in a safe, and painless way.

Why have I been invited to participate?

You have been Invited because you meet the inclusion criteria, and you do not have any contraindication to any TMS procedure (assessed via the TMS safety screening questionnaire). Specifically, you should be a neurological healthy (self-reported) male or female within the required age group (18-35 years old). In addition, you should be right handed (this will be assessed via the use of a handedness questionnaire).

Do I have to take part?

It is entirely up to you, whether you would like to participate or not in this study. Participation is voluntary, and you are free to withdraw at any point, with no repercussions. If you decide to participate, you will be first need to complete a medical screening for safe participation in this study using non-invasive brain stimulation, and then provide written consent form.

What will happen to me if I take part?

If you decide to participate in the study, you will visit Brunel University London (MSCB005, Mary Seacole Building, Brunel University Campus) on two separate and non-consecutive days. The two visits will be at least one week apart. Figure 1 provides a schematic representation of the series of tests that you will complete. The total estimated time to completion of the first visit is a maximum of 1-and-a-half hours, while the second visit will be completed in an estimated maximum of 2-and-a-half hours. On the first visit we will assess your brain activity before and after an association protocol called auditory paired-associative stimulation (aPAS), where we will pair a sound with TMS stimulation. This test will require you to remain seated, without excessive movements for the whole stimulation period, which will comprise 2 blocks of 7 minutes each. This may feel somewhat dull to you. However, you will be given plenty time to relax and move around the room during the breaks. On the second visit, we will once again assess your brain activity using TMS, before and after both aPAS and sonification training, in which you will watch videos of a movement and, imagine the same movement at the same time. As for the previous visit, the aPAS test may be somewhat dull, but you will have plenty time to relax and move around the lab in between these periods.

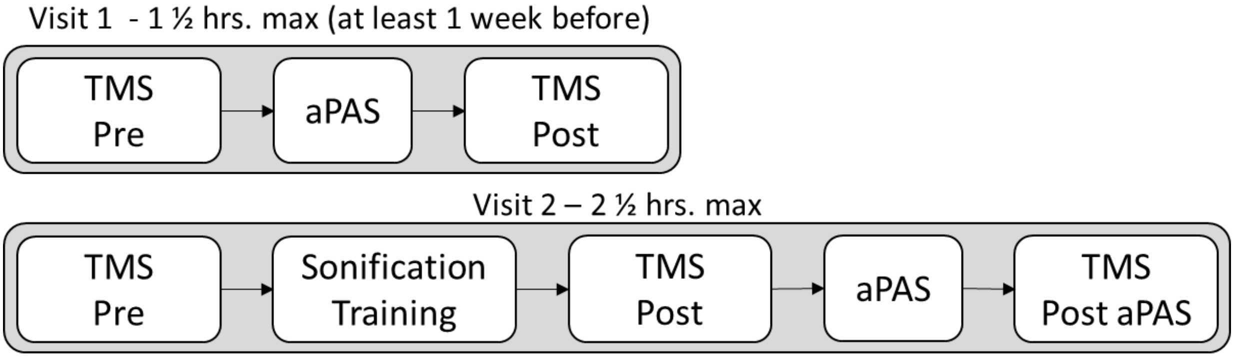


Figure 16 - If you decide to participate in the study, then you will visit Brunel University London on two non-consecutive days, and will complete these steps

What is TMS and EMG?

Transcranial Magnetic Stimulation, or TMS, is used to investigate connections between the brain and muscles. This is a non-invasive and painless method of brain stimulation which has been used safely for at least 25 years throughout research labs to study both healthy and neurologically impaired voluntary control of movement. Using a commercially available device, a small, hand-held electromagnetic coil is placed over the motor area of the brain (at the top of your head). When the device is activated, a brief (1 millisecond) magnetic stimulation is generated and through electromagnetic induction, a small number of brain cells in the motor are send signals through the anatomical pathways connecting the brain to the spinal cord and ultimately to the muscles.

Each time a TMS pulse is applied to the scalp, the signals generated by the brain stimulation result in a tiny painless twitch in relaxed muscle which can be recorded and measures using surface electromyography (sEMG). The use of self-adhesive recording electrodes positioned on the skin over the muscle of interest picks up the small electrical signals generated by nerves and muscle fibres, initiating movement.

What do I have to do?

You will be asked to refrain from consuming any alcohol in an 8-hour period before attending the session. You will also be asked not to apply any moisturisers or ointments over the skin where electrodes will be placed on the day of the experiment. Before you can participate in this study we will give you a medical screening form which is required for non-invasive brain stimulation studies of this nature, to determine whether it is safe for you to participate. Then you will be asked to sign a consent form for your voluntary participation. During testing and the aPAS and intervention protocols, you will simply be asked to relax while we will apply TMS over your scalp to activate the motor area of your brain to monitor changes in brain activity. You will also wear surface electrodes to monitor muscle activity in your hand. During the sonification training, you will be asked to observe a video of a hand squeezing a ball, and at the same time imagining yourself performing the same movement.

As sitting for an extended duration may be uncomfortable, you will be able to let us know when you wish to move around without affecting the conduct of the session. It is very important to us that you do not experience any discomfort, and also that you are happy to continue. If not just let us know and we will stop immediately.

What are the possible disadvantages and risks of taking part?

TMS, sEMG are both safe techniques and without any known long-term risk. They have been used in research and clinical settings for over 25 years. We are required to use a health screening before written consent for known contraindications for TMS in compliance with safe conduct of TMS based research. Although TMS is painless and a non-invasive procedure, the activation of muscles during TMS, may cause some brief discomfort but you should not feel any pain at all. If at any time you experience any irritation, pain or become uncomfortable or anxious, please let us know and we will discontinue the session. Some additional side effects have been reported following TMS, such as syncope (fainting) during participation, or transient hearing changes due to the clicking sound of the electromagnet. However, the incidence of both of these is extremely rare in healthy participants for this type of TMS based study. Should you feel anxious or unwell at any time during the session, just let us know and we will stop. Some mild skin irritation can also occasionally arise from the electrode adhesive when fixed to the skin during sEMG, however again this is very rare. Mild headaches may sometimes occur following TMS as a result of either the stimulation, or from its positioning over the scalp for an extended period of time. We will follow up in one or two days to ask you about any symptoms that you may have experienced after your participation in this study.

Will my taking part in this study be kept confidential?

Any information about you obtained in the study will be confidential, and the data will be anonymized. All paper files and experimental data will be encripted and kept in safe, restricted computer files and locked cabinets. No details about you, as a participant, will be shared with anyone, and you will not be identified in any way. Only summary information will be provided in any related publications of the findings. The data may also be presented at relevant academic conferences. The data of this study will be retained in compliance with university regulations by the researchers for a maximum of five years, and the data will be kept on encrypted/password protected devices. Confidentiality may be broken during instances of legal or ethical investigations.

What are the possible benefits of taking part?

There are no direct benefits of taking part in this study. That said, you may learn more about this type of research in participating, and about your ability to imagine performing movements!

What if something goes wrong?

During the course of the session you will be monitored for possible side-effects and should you have any concerns or worries or become anxious for whatever reason we will discontinue the procedure. However, if you are harmed due to someone's negligence, then you may have grounds for legal action (please see 'What are the indemnity arrangements?' below).

What will happen to the results of the research study?

Results from the study will contribute to a doctoral thesis. The findings may inform other future studies, and also be published in relevant scientific journals. If you wish to receive a report summary of the study, then let us know and we will provide this by email.

What are the indemnity arrangements?

Brunel University London holds insurance policies, which apply to this study. If you can demonstrate that you experienced harm as a result of your participation in this study, you may be able to claim compensation. Please contact Professor Peter Hobson, Chair of the

University Research Ethics Committee (Peter.hobson@brunel.ac.uk) if you would like further information about insurance arrangements which apply to this study.

Who has reviewed the study?

This study will be reviewed and approved by the College of Health and Life Sciences Research Ethics Committee, at Brunel University London.

Passage on the University's commitment to the UK Concordat on Research Integrity

Brunel University is committed to compliance with the Universities UK Research Integrity Concordat. You are entitled to expect the highest level of integrity from our researchers during the course of their research.

CONTACTS FOR FURTHER INFORMATION ABOUT THE STUDY

Fabio Castro (Main Researcher),

Tel.: +44(0)7453659069;

Email: fabio.castro@brunel.ac.uk

Dr. Daniel Bishop (First Supervisor),

Tel.: +44(0)1895267513;

Email: daniel.bishop@brunel.ac.uk

Dr. Alexander Nowicky (Second Supervisor),

Tel.: +44(0)1895268813;

Email: alexander.nowicky@brunel.ac.uk

CONTACT FOR COMPLAINTS AND QUESTIONS ON THE WAY THE RESEARCH WAS CONDUICTED

Professor Christina Victor, Chair College of Health and Life Sciences Research Ethics Committee christina.victor@brunel.ac.uk

APPENDIX C – INFORMED CONSENT FORM

College of Health and Life Sciences

Department of Life Sciences

Brunel University London

CONSENT FORM

The participant should complete the whole of this sheet		
	Please tick the appropriate box	
	YES	NO
Have you read the Research Participant Information Sheet?		
Have you had an opportunity to ask questions and discuss this study?		
Have you received satisfactory answers to all your questions?		
Who have you spoken to?		
Do you understand that you will not be referred to by name in any report concerning the study?		
Do you understand that you are free to withdraw from the study:		
• at any time?		
• without having to give a reason for withdrawing?		
Do you agree to take part in this study?		
Signature of Research Participant:		
Date:		
Name in capitals:		

Researcher name:	Signature:
Supervisor name:	Signature:

APPENDIX D – TMS SAFETY QUETIONNAIRE

College of Health and Life Sciences

Department of Life Sciences

TMS Safety Questionnaire

Confidential

Please answer the following health related questions. You should only complete this screen if you know that you are fit and healthy. If you answer yes to any of these questions then you should not participate in the study.

Please circle your responses

I feel unwell today.	Yes No
I suffer from dizziness/ severe or frequent headaches.	Yes No
I have fainted or passed out one or more times in the last year.	Yes No
I have a low heart rate (bradycardia, less than 55 bpm) and/ or low blood pressure.	Yes No
I have had one or more anxiety/panic episodes in last year.	Yes No
I am on prescribed medication.	Yes No
I have an orthopaedic condition in my arms (injury to my joints).	Yes No
I have a medical condition.	Yes No
I have a heart condition and /or have a cardiac pacemaker.	Yes No

I have a respiratory problem other than asthma.	Yes No
I have a dermatological condition and /or I am allergic to medical adhesives (plasters or others).	Yes No
I have a (metal) prosthesis or implant in my body.	Yes No
I have had a neurosurgical procedure (operation to the skull).	Yes No
I have an aneurysm clip in my head.	Yes No
I have a neurological condition (including epilepsy).	Yes No
I have had a seizure and/or suffered from a traumatic head injury.	Yes No
I am pregnant.	Yes No
I have musculoskeletal dysfunction in my arms.	Yes No
I use hearing aids and/or have cochlear implants.	Yes No
I have hearing difficulties in one or both of my ears.	Yes No
I am not able to wear or listen to music using headphones or earplugs.	Yes No

If you have answered **NO** to all of the above questions then you may participate in the TMS sonification study. Your participation is entirely voluntary. You may withdraw at any time for any or no reason. If you have any concerns then you should speak to one of the study supervisors.

I understand the information provided for me and agree to participate in this study and give my consent.

I understand that I can withdraw from participation at any time without any consequence.	Yes No
I have had adequate an explanation of the technique and risks of TMS and sEMG application.	Yes No

Name: _________________________ Signature: ______________________ Age: ________

Date: _____/________/___________

Witness: ____________________________ Signature: ______________

APPENDIX E – MOTOR IMAGERY QUESTIONNAIRE (MIQ)

Movement Imagery Questionnaire-3

Full Questionnaire with Instructions

Instructions

This questionnaire concerns two ways of *mentally* performing movements which are used by some people more than by others, and are more applicable to some types of movements than others. The first is attempting to form a visual image or picture of a movement in your mind. The second is attempting to feel what performing a movement is like without actually doing the movement. You are requested to do both of these mental tasks for a variety of movements in this questionnaire, and then rate how easy/difficult you found the tasks to be. The ratings that you give are not designed to assess the goodness or badness of the way you perform these mental tasks. They are attempts to discover the capacity individuals' show for performing these tasks for different movements. There are no right or wrong ratings or some ratings that are better than others.

Each of the following statements describes a particular action or movement. Read each statement carefully and then actually perform the movement as described. Only perform the movement a single time. Return to the starting position for the movement just as if you were going to perform the action a second time. Then depending on which of the following you are asked to do, either (1) form as clear and vivid a visual image as possible of the movement just performed from an internal perspective (i.e., from a 1st person perspective, as if you are actually inside yourself performing and seeing the action through your own eyes), (2) form as clear and vivid a visual image as possible of the movement just performed from an external perspective (i.e., from a 3rd person perspective, as if watching yourself on DVD), or (3) attempt to feel yourself making the movement just performed without actually doing it.

After you have completed the mental task required, rate the ease/difficulty with which you were able to do the task. Take your rating from the following scale. Be as accurate as possible and take as long as you feel necessary to arrive at the proper rating for each movement. You may choose the same rating for any number of movements "seen" or "felt" and it is not necessary to utilize the entire length of the scale.

RATING SCALES

Visual Imagery Scale

1	2	3	4	5	6	7
Very hard to see	Hard to see	Somewhat hard to see	Neutral (not easy nor hard)	Somewhat easy to see	easy to see	Very easy to see

Kinesthetic Imagery Scale

1	2	3	4	5	6	7
Very hard to feel	Hard to feel	Somewhat hard to feel	Neutral (not easy nor hard)	Somewhat easy to feel	easy to feel	Very easy to feel

1. STARTING POSITION: Stand with your feet and legs together and your arms at your sides.

ACTION: Raise your right knee as high as possible so that you are starting on your left leg with your right leg flexed (bent) at the knee. Now lower your right leg so you are once again standing on two feet. The action is performed **slowly**.

MENTAL TASK: Assume the starting position. Attempt to **feel** yourself making the movement just observed without actually doing it. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

2. STARTING POSITION: Stand with your feet and legs together and your arms at your sides.

ACTION: Bend down low and then jump straight up in the air as high as possible with both arms extended above your head. Land with both feet apart and lower your arms to your sides.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from an **internal perspective**. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

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3. STARTING POSITION: Extend the arm of your non-dominant hand straight out to your side so that it is parallel to the ground, palm down.

ACTION: Move your arm forward until it is directly in front of your body (still parallel to the ground). Keep your arm extended during the movement, and make the movement **slowly**.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from an **external perspective**. Now rate the ease/difficulty with which you were able to do this mental task and the angle the image was observed from (see additional sheet provided for full list of different angles)

Rating: __________

4. STARTING POSITION: Stand with your feet slightly apart and your arms fully extended above your head.

ACTION: **Slowly** bend forward at the waist and try and touch your toes with your fingertips (or, if possible, touch the floor with your fingertips or your hands). Now return to the starting position, standing erect with your arms extended above your head.

MENTAL TASK: Assume the starting position. Attempt to **feel** yourself making the movement just observed without actually doing it. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

5. STARTING POSITION: Stand with your feet and legs together and your arms at your sides.

ACTION: Raise your right knee as high as possible so that you are starting on your left leg with your right leg flexed (bent) at the knee. Now lower your right leg so you are once again standing on two feet. The action is performed **slowly**.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from an **internal perspective**. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

6. STARTING POSITION: Stand with your feet and legs together and your arms at your sides.

ACTION: Bend down low and then jump straight up in the air as high as possible with both arms extended above your head. Land with both feet apart and lower your arms to your sides.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from **an external perspective**. Now rate the ease/difficulty with which you were able to do this mental task and the angle the image was observed from (see additional sheet provided for full list of different angles)

Rating: __________

7. STARTING POSITION: Extend the arm of your non-dominant hand straight out to your side so that it is parallel to the ground, palm down.

ACTION: Move your arm forward until it is directly in front of your body (still parallel to the ground). Keep your arm extended during the movement, and make the movement **slowly**.

MENTAL TASK: Assume the starting position. Attempt to **feel** yourself making the movement just performed without actually doing it. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

8. STARTING POSITION: Stand with your feet slightly apart and your arms fully extended above your head.

ACTION:: **Slowly** bend forward at the waist and try and touch your toes with your fingertips (or, if possible, touch the floor with your fingertips or your hands). Now return to the starting position, standing erect with your arms extended above your head.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from an **internal perspective**. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

9. STARTING POSITION: Stand with your feet and legs together and your arms at your sides.

ACTION: Raise your right knee as high as possible so that you are starting on your left leg with your right leg flexed (bent) at the knee. Now lower your right leg so you are once again standing on two feet. The action is performed **slowly**.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from **an external perspective**. Now rate the ease/difficulty with which you were able to do this mental task and the angle the image was observed from (see additional sheet provided for full list of different angles)

Rating: __________

10. STARTING POSITION: Stand with your feet and legs together and your arms at your sides.

ACTION: Bend down low and then jump straight up in the air as high as possible with both arms extended above your head. Land with both feet apart and lower your arms to your sides.

MENTAL TASK: Assume the starting position. Attempt to **feel** yourself making the movement just performed without actually doing it. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

11. STARTING POSITION: Extend the arm of your non-dominant hand straight out to your side so that it is parallel to the ground, palm down.

ACTION: Move your arm forward until it is directly in front of your body (still parallel to the ground). Keep your arm extended during the movement, and make the movement **slowly**.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from an **internal perspective**. Now rate the ease/difficulty with which you were able to do this mental task.

Rating: __________

12. STARTING POSITION: Stand with your feet slightly apart and your arms fully extended above your head.

ACTION: **Slowly** bend forward at the waist and try and touch your toes with your fingertips (or, if possible, touch the floor with your fingertips or your hands). Now return to the starting position, standing erect with your arms extended above your head.

MENTAL TASK: Assume the starting position. Attempt to **see** yourself making the movement just observed from an **external perspective**. Now rate the ease/difficulty with which you were able to do this mental task and the angle the image was observed from (see additional sheet provided for full list of different angles)

Rating: __________

Movement Imagery Questionnaire-3

Response Form Only
(if Instructions and Items are read to participants)

After you have completed the mental task required, rate the ease/difficulty with which you were able to do the task in the space provided below. Take your rating from the provided scale. Be as accurate as possible and take as long as you feel necessary to arrive at the proper rating for each movement. You may choose the same rating for any number of movements "seen" or "felt" and it is not necessary to utilise the entire length of the scale.

RATING SCALES

Visual Imagery Scale

1	2	3	4	5	6	7
Very hard to see	Hard to see	Somewhat hard to see	Neutral (not easy nor hard)	Somewhat easy to see	easy to see	Very easy to see

Kinesthetic Imagery Scale

1	2	3	4	5	6	7
Very hard to feel	Hard to feel	Somewhat hard to feel	Neutral (not easy nor hard)	Somewhat easy to feel	easy to feel	Very easy to feel

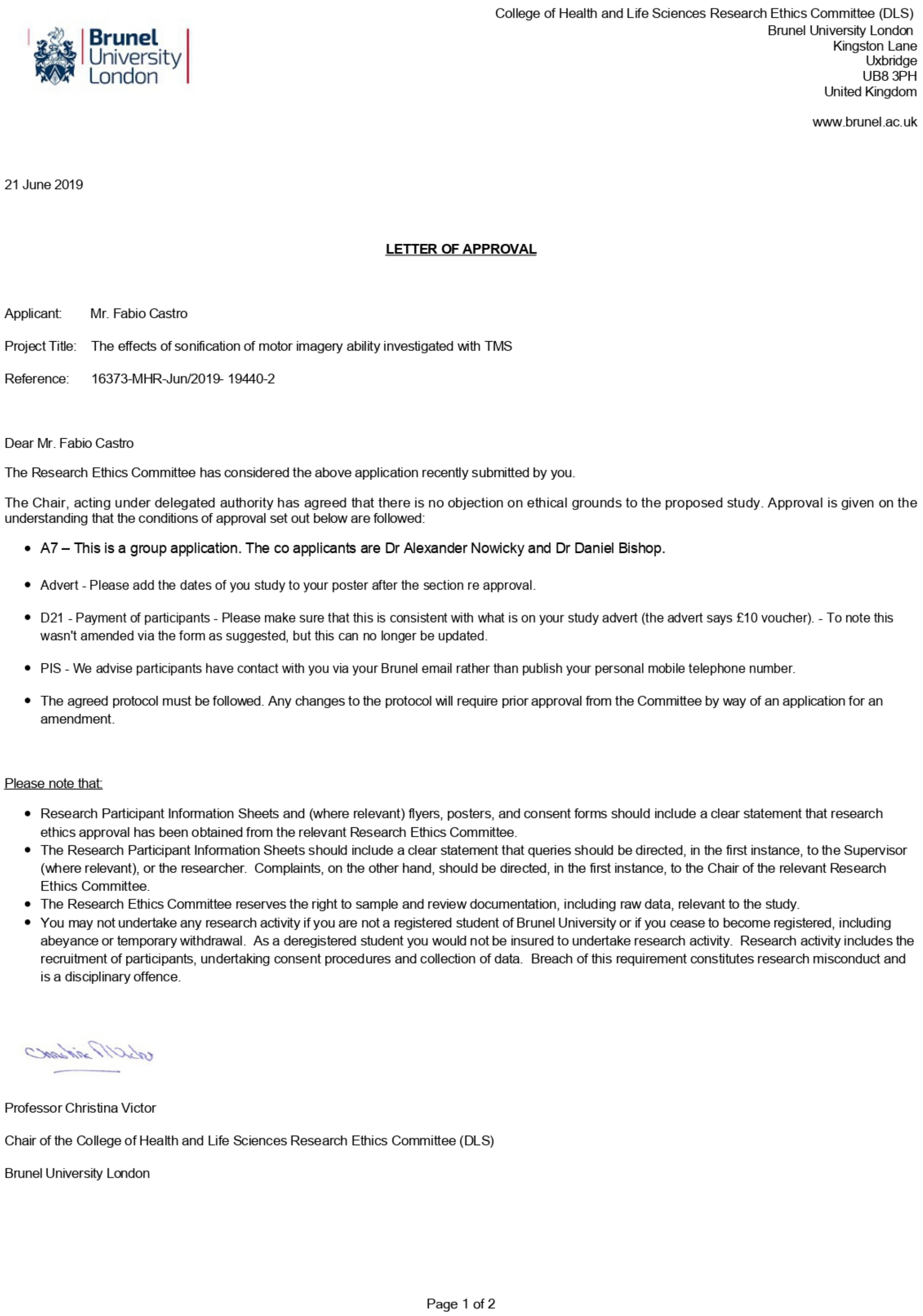
1) Knee lift	Rating: ____	7) Arm movement	Rating: ____
2) Jump	Rating : ____	8) Waist Bend	Rating: ____
3) Arm movement	Rating:____	9) Knee lift	Rating:____
4) Waist Bend	Rating: ____	10) Jump	Rating: ____
5) Knee lift	Rating: ____	11) Arm movement	Rating: ____
6) Jump	Rating:____	12) Waist Bend	Rating:____

Movement Imagery Questionnaire-3

Instructions for Scoring

Subscale	**Items**
Internal Visual Imagery	Item 2 + Item 5 + Item 8 + Item 11/4
External Visual Imagery	Item 3 + Item 6 + Item 9 + Item 12/4
Kinesthetic Imagery	Item 1 + Item 4 + Item 7 + Item 10/4

APPENDIX F – RESEARCH ETHICS COMMITTEE APPROVAL FOR STUDY 2



Brunel University London

College of Health and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

www.brunel.ac.uk

21 June 2019

LETTER OF APPROVAL

Applicant: Mr. Fabio Castro

Project Title: The effects of sonification of motor imagery ability investigated with TMS

Reference: 16373-MHR-Jun/2019- 19440-2

Dear Mr. Fabio Castro

The Research Ethics Committee has considered the above application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- **A7 – This is a group application. The co applicants are Dr Alexander Nowicky and Dr Daniel Bishop.**
- Advert - Please add the dates of you study to your poster after the section re approval.
- D21 - Payment of participants - Please make sure that this is consistent with what is on your study advert (the advert says £10 voucher). - To note this wasn't amended via the form as suggested, but this can no longer be updated.
- PIS - We advise participants have contact with you via your Brunel email rather than publish your personal mobile telephone number.
- The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.
- You may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Christina Victor

Chair of the College of Health and Life Sciences Research Ethics Committee (DLS)

Brunel University London

APPENDIX G – PARTICIPANT INFORMATION SHEET FOR STUDY 2

College of Health and Life Sciences
Department of Life Sciences

PARTICIPANT INFORMATION SHEET

THE EFFECTS OF SONIFICATION ON MOTOR IMAGERY ABILITY AND ACTION OBSERVATION INVESTIGATED VIA TRANSCRANIAL MAGNETIC STIMULATION

An invitation to participate

You are invited to participate in this study on the effects of sonification on cortical reorganization. This information sheet provides an overview of the study and what is involved, if you decide to participate. Please take your time to carefully consider the information provided. We are happy to discuss any concerns or queries you may have. If you would like more information, then please feel free to contact us by e-mail, as provided below. Thank you for taking the time to read this.

What is the purpose of the study?

Observing someone's movements or imagining the same action has been shown to activate similar motor areas in the brain as the actual execution of the same action. This is very important for motor learning and rehabilitation, because it provides different ways for a person to improve performance and learn new skills. In a previous study we investigated whether motor imagery can be improved with the use of sonification, a sensory augmentation strategy that associates a sound with a movement. The aim of this study is to assess changes in brain's motor cortical activity before and after an audio-motor training. To do this, we will use a non-invasive stimulation technique called Transcranial Magnetic Stimulation (TMS), which uses magnetic fields to stimulate the brain cortex in a safe, and painless way.

Why have I been invited to participate?

We are recruiting participants, and you have been invited because you meet the inclusion criteria, and you do not have any contraindication with regard to the TMS procedure (assessed via the TMS safety screening questionnaire). Specifically, you should be a neurologically healthy male or female within the age range 18-40 years. In addition, you should be right-handed (assessed via a questionnaire).

Do I have to take part?

It is entirely up to you, whether you would like to participate or not in this study. Participation is voluntary, and you are free to withdraw at any point, with no repercussions. If you decide to participate, you will first need to complete medical screening for safe participation in this study using non-invasive brain stimulation, and then provide your written consent.

What will happen to me if I take part?

If you decide to participate in the study, then you will visit Brunel University London to engage with a series of tests, which are depicted in figure 1. In chronological order, you will engage in baseline TMS tests, followed by the intervention protocol, which will be different according to the group you will be allocated to. After the intervention, post-intervention measures of corticospinal excitability will be collected. The assessment of corticospinal excitability, before and after the intervention, will be done by collecting motor-evoked potentials (MEPs) from you first dorsal interosseous (FDI) muscle during relaxation (TMS_REST), during observation of an action (TMS_AO) and during the observation of an action in concomitance with imagination of the same movement (TMS_AO+MI).

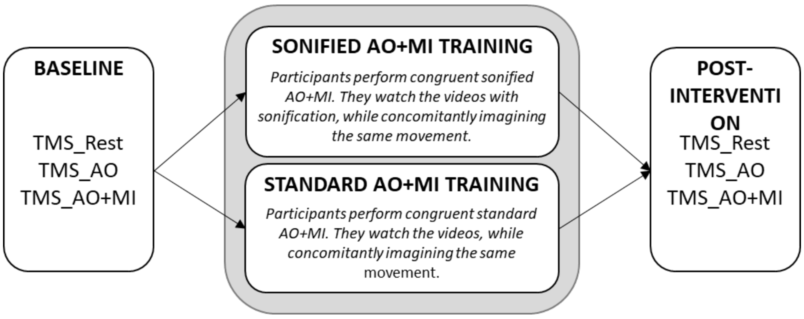


Figure 17 – The picture depicts the series of tests that you will engage on. 'AO+MI': Action observation in concomitance of motor imagery; 'TMS_REST': TMS during relaxation; 'TMS_AO': TMS during the observation of an action; 'TMS_AO+MI': TMS during the observation of an action in concomitance of motor imagery

At the end of the procedure, we will stimulate your ulnar nerve, to elicit the maximum muscle excitability. To do so, we will apply stimulation at the elbow (the ulnar nerve is located on the posterior aspect of the elbow) with 5 pulses per intensity, ranging from 25% to 60-70% of maximum stimulus output (standard unit of intensity of the stimulator device used for this project).

What is TMS and EMG?

Transcranial Magnetic Stimulation, or TMS, is used to investigate connections between the brain and muscles. This is a non-invasive and painless method of brain stimulation which has been used safely for more than 25 years in research labs worldwide, to study both healthy and impaired voluntary control of movement. Using a commercially available device, a small, hand-held electromagnetic coil is placed over the motor area of the brain (at the top of your head). When the device is activated, a brief (1 millisecond) magnetic stimulation pulse is generated and, via electromagnetic induction (where electrical currents are generated in magnetic fields), a number of cells in the motor areas of the brain send signals through the spinal cord to the muscles.

Each time a TMS pulse is applied to the scalp, the signals generated by the brain stimulation result in a tiny painless twitch in relaxed muscle which can be recorded and measures using surface electromyography (sEMG). The use of self-adhesive recording electrodes positioned on the skin over the muscle of interest picks up the small electrical signals generated in muscle fibres.

What do I have to do?

You will be asked to refrain from consuming any alcohol in an 8-hour period before attending the session. You will also be asked not to apply any moisturisers or ointments over the skin where electrodes will be placed on the day of the experiment. Before you can participate in this study we will give you a medical screening form, which is required for non-invasive brain stimulation studies of this nature, to determine whether it is safe for you to participate. Then you will be asked to sign a consent form for your voluntary participation. During testing and intervention protocol, you will simply be asked to either relax or engage with the observation of an action, while we apply TMS to your scalp, to activate the motor areas of your brain. You will also wear surface electrodes on your hand, to monitor muscle activity. During the intervention, you will be asked to observe a video of a hand squeezing a ball, and at the same time imagining yourself performing the same movement.

As sitting for an extended duration may be uncomfortable, you will be able to let us know when you wish to move around without affecting the progress of the session. It is very important to us that you do not experience any discomfort, and also that you are happy to continue. If not just let us know and we will stop immediately.

What are the possible disadvantages and risks of taking part?

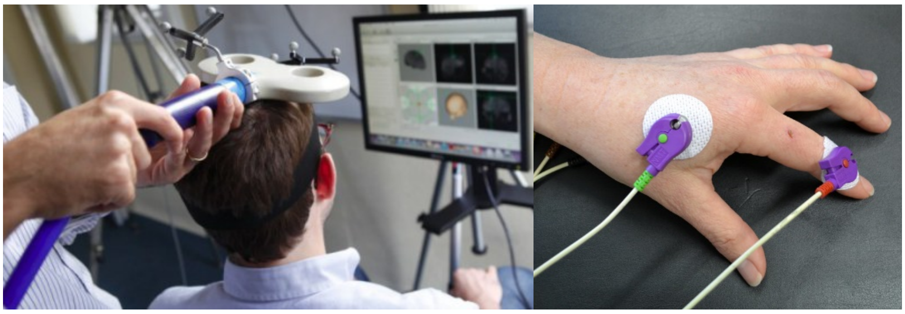


Figure 18 - On the left, a representation of the TMS technique. On the right, the electrode placement for sEMG

TMS and sEMG (figure 2) are both safe techniques and without any known long-term risk. They have been used in research and clinical settings for over 25 years. We are required to use a health screening procedure before written consent, to screen for known contraindications for TMS, in compliance with safe conduct of TMS-based research. Although TMS is painless and a non-invasive procedure, the activation of muscles during TMS may cause some brief and minor discomfort – but you should not feel any pain at all. If at any time you experience any irritation, pain or become uncomfortable or anxious, then please let us know; we will discontinue the session. Some additional side effects have been reported following TMS, such as fainting during participation, or transient hearing changes due to the clicking sound of the electromagnet. However, the incidence of both of these is extremely rare in healthy participants for this type of TMS-based study. Should you feel anxious or unwell at any time during the session, please let us know and we will stop. Some mild skin irritation can also occasionally arise from the electrode adhesive when fixed to the skin during sEMG; however, this is also very rare. Mild headaches may sometimes occur following TMS as a result of either the stimulation, or from its positioning over the scalp for an extended period of time. We will follow up one or two days after your participation in this study, to ask you about any adverse symptoms that you may have experienced.

Will my taking part in this study be kept confidential?

Any information about you obtained in the study will be confidential, and the data will be anonymized. All paper files and experimental data will be encrypted and kept in safe, restricted computer files and locked cabinets. No details about you, as a participant, will be shared with anyone, and you will not be identified in any way. Only group summary information will be provided in any related publications of the findings, including at relevant academic conferences. The data from this study will be retained in compliance with university regulations by the researchers for a maximum of five years, and the data will be kept on encrypted/password protected devices. Confidentiality may be broken during instances of legal or ethical investigations.

What are the possible benefits of taking part?

There are no direct benefits of taking part in this study. That said, you may learn more about this type of research in participating, and about your ability to imagine performing movements!

What if something goes wrong?

During the course of the session you will be monitored for possible side-effects and should you have any concerns or worries or become anxious for whatever reason we will discontinue the procedure. However, if you are harmed due to someone's negligence, then you may have grounds for legal action (please see 'What are the indemnity arrangements?' below).

What will happen to the results of the research study?

Results from the study will contribute to a doctoral thesis. The findings may inform other future studies, and also be published in scientific journals. If you wish to receive a report summary of the study, then please let us know and we will provide this by email.

Who is organizing and funding the research?

This research has been organized by Mr. Fabio Castro, Dr. Daniel Bishop and Dr. Alex Nowicky, and funded by Centre for Cognitive Neuroscience, Brunel University London

What are the indemnity arrangements?

Brunel University London holds insurance policies, which apply to this study. If you can demonstrate that you experienced harm as a result of your participation in this study, you may be able to claim compensation. Please contact Professor Peter Hobson, Chair of the University Research Ethics Committee (Peter.hobson@brunel.ac.uk) if you would like further information about insurance arrangements which apply to this study.

Who has reviewed the study?

This study has been reviewed and approved by the College of Health and Life Sciences Research Ethics Committee, at Brunel University London.

Passage on the University's commitment to the UK Concordat on Research Integrity

Brunel University London is committed to compliance with the Universities UK Research Integrity Concordat. You are entitled to expect the highest level of integrity from our researchers during the course of their research.

CONTACTS FOR FURTHER INFORMATION ABOUT THE STUDY

Fabio Castro (Main Researcher),

Tel.: +44(0) 7490328732;

Email: fabio.castro@brunel.ac.uk

Dr. Daniel Bishop (First Supervisor),

Tel.: +44(0)1895267513;

Email: daniel.bishop@brunel.ac.uk

Dr. Alexander Nowicky (Second Supervisor),

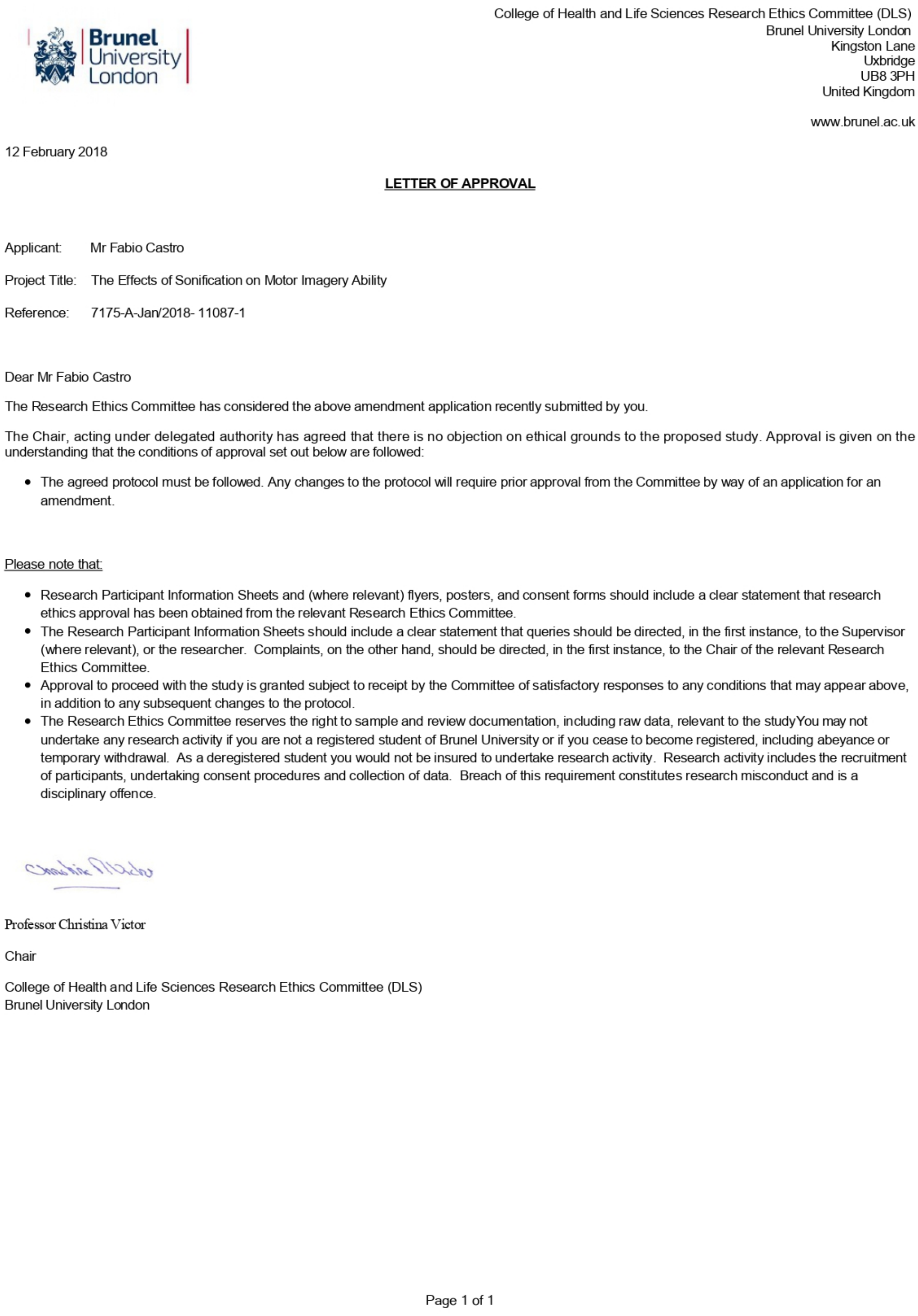
Tel.: +44(0)1895268813;

Email: alexander.nowicky@brunel.ac.uk

CONTACT FOR COMPLAINTS AND QUESTIONS ON THE WAY THE RESEARCH WAS CONDUICTED

Professor Christina Victor, Chair College of Health and Life Sciences Research Ethics Committee. Email: christina.victor@brunel.ac.uk

APPENDIX H – RESEARCH ETHICS COMMITTEE APPROVAL FOR STUDY 3



College of Health and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

www.brunel.ac.uk

12 February 2018

LETTER OF APPROVAL

Applicant: Mr Fabio Castro

Project Title: The Effects of Sonification on Motor Imagery Ability

Reference: 7175-A-Jan/2018- 11087-1

Dear Mr Fabio Castro

The Research Ethics Committee has considered the above amendment application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the studyYou may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Christina Victor

Chair

College of Health and Life Sciences Research Ethics Committee (DLS)
Brunel University London

APPENDIX I – PARTICIPANT INFORMATION SHEET FOR STUDY 3

College of Health and Life Sciences

Department of Life Sciences

PARTICIPANT INFORMATION SHEET

The Effects of Sonification on Motor Imagery Ability.

We would like to invite you to take part in our research study on the effects of sonification on motor imagery ability. Before you decide whether to participate, it is important that you understand why the research is being conducted and what it will involve, so please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The main purpose of this project is to explore the effect of sound on motor imagery ability, under different conditions. A second aim of this project is to explore the neural correlates of sonification, and its relationship with the sensorimotor areas of the brain.

Why have I been invited to participate?

You have been asked to participate in this study because you are 18 years old or older, you are right-handed and you do not have any known neurological condition. Moreover, your vision is normal or corrected to normal, and you do not have any known auditory disability.

Do I have to take part?

Participation is voluntary, and it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. Participation in the study entitles you to receive compensation of £10 in Amazon vouchers, that you will receive at the end of the tests.

What will happen to me if I take part?

If you decide to take part in our study, you will attend the Psychomotor Laboratory, Heinz Wolff Building, Brunel University London, on two separate, but consecutive days. A schematic representation of the study schedule is depicted in Table 1 on the next page.

Prior to the first visit, you will complete two questionnaires, to determine your handedness and your self-assessed motor imagery ability. On Day 1 you will take part in the pre-Training measurement, in which we will assess your baseline ability to imagine movements. In this session, we will use non-invasive techniques i.e. electroencephalography (EEG) during an active motor imagery tasks, as well as during a perceptive, sound recognition task. In addition, you will engage in a mental chronometry task, to assess your baseline motor imagery temporal accuracy.

After this set of measurements, you will undertake the first of two training sessions. According to the group you will be randomly assigned, you will watch videos comprising repetitions of movements, with or without sound accompaniment, and then you will imagine the same movement. You will do this for the whole training period (you will have pauses in betweentrials). You will repeat this session on Days 2. Also on Day 2, you will complete a post-training assessment, comprising the same sets of measurements collected on Day1.

Table 1 - Measurements Schedule.

Day 1	**Day 2**
Pre-Training Measurements (120 minutes)	Training Session (20 minutes)
Training Session (20 minutes)	Post-Training Measurements (120 minutes)

What are the possible disadvantages and risks of taking part?

The present study does not represent a hazard to your health and safety. The measurements will include non-invasive techniques only, which may only cause light discomfort. During the study, however, you may experience ‘mental tiredness’, due to the extensive use of motor imagery.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to negligence, you may have grounds for a legal action at your own cost.

Will my taking part in this study be kept confidential?

All information collected about you during the research will be kept strictly confidential. Any information about you that leaves the university will have your name and address removed so that you are unidentifiable.

What will happen to the results of the research study?

The data and the results of the analysis of the data collected during the measurements will be used for writing a Doctor of Philosophy dissertation. In addition, the results may be presented in conferences and published in international journals. The results will be presented in an anonymous way, with no personal details provided that might indicate the identity of the participant. You can request to know your results once the measurements are completed.

Who has reviewed the study?

This study has been reviewed by the College Research Ethics Committee.

Passage on the University's commitment to the UK Concordat on Research Integrity

Brunel University is committed to compliance with the Universities UK Research Integrity Concordat. You are entitled to expect the highest level of integrity from our researchers during the course of their research.

CONTACTS FOR FURTHER INFORMATION ABOUT THE STUDY

Fabio Castro (Main Researcher),

Tel.: +44(0)7453659069;

Email: fabio.castro@brunel.ac.uk

Dr. Daniel Bishop (First Supervisor),

Tel.: +44(0)1895267513;

Email: daniel.bishop@brunel.ac.uk

Dr. Alexander Nowicky (Second Supervisor),

Tel.: +44(0)1895268813;

Email: alexander.nowicky@brunel.ac.uk

CONTACT FOR COMPLAINTS AND QUESTIONS ON THE WAY THE RESEARCH WAS CONDUICTED

rofessor Christina Victor, Chair College of Health and Life Sciences Research Ethics Committee christina.victor@brunel.ac.uk

APPENDIX J – SONIFICATION REPORT FORM

College of Health and Life Sciences

Department of Life Sciences

Brunel University London

VERBAL REPORT ON SONIFICATION

ID: ____________________ Date: ____________

1. Please, could you tell me your thoughts on the sound accompaniment that you heard during the training?

2. How did you find the sound, in terms of its pleasantness?

0 1 2 3 4 5 6 7 8 9 10

Highly unpleasant — Highly pleasant

3. To what extent did the sound help you to imagine performing the movement as you practised it?

0 1 2 3 4 5 6 7 8 9 10

Not at all — Completely

If yes, then in what ways?

4. To what extent, during the 'motor imagery task', did you imagine the sound in synchrony with the imagined movement?

Not at all

Completely

If yes, then in what ways?

5. To what extent, do you think that the sound improved your ability to imagine the movement?

Not at all

Completely

If yes, then in what ways?