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# **EFFECTS OF VISUAL AND TACTILE TRAINING ON MOTOR BEHAVIOUR**

A thesis  
presented to the School of Psychology at the University of Kent  
in partial fulfilment of the requirements for the degree of  
Doctor of Philosophy

by

Antonio Zafarana



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## Abstract

Human sensory abilities are crucial for interaction with the environment. It is known that the way we perceive the world through our senses can be improved following training. Sensory training and motor behaviour have been widely investigated, however, the direct effect of an improved sensory ability on motor behaviour is not clearly understood. In the visual domain, it has been shown that visual perception is affected by the space in which the stimuli are presented, with a better performance when stimuli are near (peripersonal space) compared to far (extrapersonal space) from our body. In the tactile domain, it has been shown that tactile training is an effective procedure to improve spatial acuity, however, there is contrasting evidence regarding whether such improvement is affecting motor behaviour. The role of visual and tactile training and their effects in space and on motor behaviour are investigated through two lines of research. The *first line* of research investigated the effectiveness of visual training when stimuli are presented near compared to far from the body. Surprisingly, we found that, differently from what happens in visual perception, visual training is more effective in the far compared to the near space. We suggest that such an effect is possibly due to greater deployment of attention in the far space, which could make the learning more impactful and generalisable across spaces. The *second line* of research explored the effect of passive tactile training (Repetitive Somatosensory Stimulation) applied to a finger, on hand motor behaviour and corticospinal excitability. Results revealed that passive tactile training affects the performance in a tactile task and in turn, modulates motor behaviour. Overall, this research provides new insights regarding the efficacy of visual perceptual learning in space (peripersonal vs extrapersonal) and the potential role of tactile passive training in altering motor behaviour.

**Keywords:** visual learning, tactile learning, peripersonal space, extrapersonal space, motor behaviour, corticospinal excitability, tactile acuity, Transcranial Magnetic Stimulation

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## **Covid-19 statement**

The PhD journey that resulted in the current thesis began in October 2019. The Covid-19 epidemic burst out less than six months after the project started, resulting in significant repercussions for the project. The original plan of my PhD project was to focus only on the impact of tactile training on motor functioning, however, as I am sure everybody remembers, “touching” or even being close to someone suddenly became out of question.

Therefore, all my planned empirical studies, which were supposed to be carried out in person in a laboratory setting (behavioural and neurostimulation experiments) were stopped. On top of that, the uncertainty of when, and if, everything would go back to normal with free laboratory access, had a huge impact on my schedule and project management. To mitigate the impact of COVID-19 new rules, once it was clear that the situation was not going to improve soon, I decided to start working on visual training. Thus, I focused not just on one sensory domain (tactile), but two (tactile and visual). I, therefore, set up and performed an online study and then, when the laboratories re-opened, I immediately started to run more empirical laboratory-based experiments. I was able to complete all the experiments described in this thesis, however, due to the disruption of COVID-19, the recruitment of participants drastically changed compared to the rate I had before the pandemic. This statement was included to provide a complete view of the “out of ordinary” effort that is behind the work presented in the present thesis.

## List of acronyms

|       |                                         |
|-------|-----------------------------------------|
| AAT   | Arm Ability Training                    |
| ADB   | Abductor Digiti Minimi                  |
| APB   | Abductor Pollicis Brevis                |
| ARAT  | Action Research Arm Test                |
| CS    | Conditioning Stimulus                   |
| CSE   | Corticospinal Excitability              |
| DTI   | Diffusion Tension Imaging               |
| EEG   | Electroencephalography                  |
| EMG   | Electromyography                        |
| EPS   | Extrapersonal Space                     |
| FDE   | Fiducial Registration Error             |
| FDI   | First Dorsal Interosseous               |
| fMRI  | functional Magnetic Resonance Imaging   |
| GOT   | Grating Orientation Task                |
| HASTe | Haptic Active Sensation Test            |
| ICF   | Intracortical Facilitation              |
| ICMS  | Intracortical Microstimulation          |
| ISI   | Inter-stimulus Interval                 |
| LAI   | Long Afferent Inhibition                |
| LGN   | Lateral Geniculate nucleus              |
| LICI  | Long-interval Intra-cortical Inhibition |
| LQ    | Laterality Quotient                     |
| LTP   | Long-Term Potentiation                  |

|      |                                            |
|------|--------------------------------------------|
| MEG  | Magnetoencephalography                     |
| NMDA | N-methyl-D-Aspartate                       |
| PPS  | Peripersonal space                         |
| RMT  | Resting Motor Threshold                    |
| RMAT | Roeder Manipulative Aptitude Test          |
| RSS  | Repetitive Somatosensory Stimulation       |
| RT   | Reaction Time                              |
| S1   | Primary Somatosensory cortex               |
| S2   | Secondary Somatosensory cortex             |
| SAI  | Short Afferent Inhibition                  |
| SEF  | Somatosensory Evoked Field                 |
| SEP  | Somatosensory Evoked Potential             |
| SICF | Short-interval Intra-cortical Facilitation |
| SICI | Short-interval Intra-cortical Inhibition   |
| TMS  | Transcranial Magnetic Stimulation          |
| TS   | Test Stimulus                              |
| V1   | Primary Visual Cortex                      |
| V2   | Secondary Visual Cortex                    |
| VR   | Virtual Reality                            |

## Chapter 1 : General introduction

From the moment we are born, we begin learning. Learning is a process that allows us to grow, change, and adapt to new situations, to become better in many domains. This process can take various forms and can be observed and studied from the neurophysiology of the single cells changing their number of receptors in the membranes, to the social aspects of a group of people moving in perfect synchrony. Learning is often the result of training (Draganski et al., 2004; Green & Bavelier, 2008; Herholz & Zatorre, 2012; May, 2011; Rosenzweig & Bennett, 1996; Sampaio-Baptista et al., 2019). For instance, a musician spending hundreds of hours training to play an instrument, a pilot learning to fly a plane, or simply a baby starting to walk.

Training typically involves a significant amount of time and effort, and it consists of several attempts and errors before something can be learnt. Other times, we train for a certain ability without even realising it, such as learning to distinguish between two faces or two objects (Bova et al., 2007; Chung & Thomson, 1995; Mondloch et al., 2003; Nelson, 2001; Nishimura et al., 2009; Pereira & Smith, 2009). Perceptual learning can encompass all five senses, thus leading to better performances in a task involving sight, smell, touch, hearing or taste (Green et al., 2018; Seitz, 2017). These are a few examples suggesting that our perceptual abilities can be trained and thus improved until we achieve good skills in various domains.

Several studies (Fahle et al., 1995; Fiorentini & Berardi, 1980; Song et al., 2005) have repeatedly shown that visual training can improve trainees' performance for a specific characteristic of the stimuli (e.g., orientation) and that this improvement can be observed also when stimuli are presented in different locations in the external space (Bakhtiari et al., 2020; Sireteanu & Rettenbach, 2000). Space is indeed an important factor that affects perception and learning. Recent studies have shown the presence of an advantage for processing visual stimuli that are close to the body compared to those that are far from it (Ahsan et al., 2021; Blini et al., 2018). Specifically, in tasks such as size,

orientation, or object discrimination, studies (Ahsan et al., 2021; Blini et al., 2018) have shown that participants are faster and more accurate when stimuli are near their body rather than far from it. Furthermore, this advantage is also present in tasks involving the process of complex visual stimuli such as faces (Ahsan et al., 2021; Dureux et al., 2021). However, whether visual training has different effects when it takes place within a space in which all our movements occur (peripersonal space, PPS) or outside of it (extrapersonal space, EPS), is still unknown. Namely, is visual learning following the same rule as visual perception, or is it different when it occurs near compared to far from the observer? This is the question that led to the visual training experiments that are the subject of investigation in the *first line* of research of my PhD work.

The *second line* of research will focus on the tactile domain, and in particular, on the role of tactile learning in shaping motor behaviour. Our ability to regulate our movements is largely dependent on the somatosensory system, which constantly feeds the motor system with information about the location of our body parts and the condition of the skin surface (Conner et al., 2021; Glazebrook et al., 2020; Scott, 2016). It has been shown that precise motor coordination can be very challenging when an action is performed without or with poor tactile input (Augurelle et al., 2003; Gentilucci et al., 1997; Johansson & Westling, 1987). Furthermore, retained somatosensation, sensorimotor tract integrity, and somatosensory cortex activity, have been considered strong indicators of motor function recovery in some neurological conditions (e.g., strokes) (Carey, 2017; Ingemanson et al., 2019; Meyer et al., 2014). Therefore, modulating (e.g., enhancing) the somatosensory component of the sensorimotor system through tactile training, can be an effective way to support motor recovery.

One of the techniques that have been shown to be successful in promoting tactile learning and inducing cortical plasticity in the somatosensory cortices, is Repetitive Somatosensory Stimulation (RSS), which is a completely passive tactile training (Godde et al., 1996, 2000; Pleger et al., 2003). Thus, since there are close connections between the somatosensory and motor cortices (Catani et al.,

2012) (see Chapter 5 for further detail), it is conceivable that RSS also affects motor performance. In this respect, in literature there are a few neuropsychological studies (Kattenstroth et al., 2012, 2018; Smith et al., 2009) that investigated these effects, however, results are inconsistent across them. This is the question that motivated the tactile training experiments of the *second line* of research of my PhD thesis.

In this introductory chapter, I will first define the concept of visual training and the literature relating to it, while also presenting the rationale behind the three empirical visual training studies, which consist of Chapters 2, 3 and 4, respectively. Then, I will move on to introduce the concept of tactile training, describing the motivation behind the two empirical tactile training studies. In Chapter 5, I will present a review paper that provides evidence of the anatomical and physiological connections between the somatosensory and motor systems. Moreover, Chapters 6 and 7 contain two empirical studies investigating the relationship between tactile training and motor behaviour. Finally, Chapter 8 is a general discussion of my findings in relation to the previous literature and the future perspectives that my results open on these topics.

## **1.1 Visual training**

Several studies have investigated many aspects of visual perception that can benefit from training. For instance, stimulus orientation (Schoups et al., 1995; Vogels & Orban, 1985), texture discrimination (Karni & Sagi, 1991), spatial phase (Fiorentini & Berardi, 1980) and several more.

The ability to learn, discriminate and recognise objects, faces, and animals are crucial abilities for successful interaction with the environment and our survival. The processes of visual identification, discrimination, and recognition become even more complex when the object/stimulus is amongst others, as it usually happens in our environments. How many times have we looked for something that we could not find? Everywhere we look, our current field of view contains an enormous amount of information and being able to find a specific stimulus, within our visual field, is the result of a process called visual search. However, in order to find what we are currently seeking,

we need to overcome our biological and computational limitations, such as having visual stimuli fall in a small region of space, where we have a high spatial resolution. Attention is the mechanism that allows us to select and prioritise certain information over others (Carrasco, 2011).

Visual search performance has several everyday life important implications. For instance, in a situation in which a certain item (e.g., a bag) has to be searched to find potentially dangerous items as during security checks at the airport (Clark et al., 2012). Thus, improving the visual search ability might be beneficial for practical applications outside the laboratory (Clark et al., 2012). It has been shown that visual training can lead to enhanced performance in visual search tasks (Sigman & Gilbert, 2000). For instance, Sigman and Gilbert (2000) trained participants to find a triangle in a particular orientation (target), which could appear randomly in one of 24 locations, among other triangles in different orientations (distractors). They found that the learning effects, and better performance, were specific for the trained-oriented object and did not generalise to the untrained ones or different spatial locations. However, other studies on perceptual learning indicated that performance improvements in visual search tasks can also generalise to untrained spaces (Sireteanu & Rettenbach, 1995, 2000).

In addition to azimuth and elevation, space can also be an important factor during a visual search in distance. There are three primary spaces in which inputs can be coded based on distance: personal space (body surface), peripersonal space (PPS) and extrapersonal space (EPS). The PPS is a multimodal processing area that surrounds our body and is where we interact directly with the immediate surroundings (di Pellegrino & Làdavas, 2015; Serino, 2019). The division of space in PPS and EPS was initially shown by research on neglect patients who exhibited a selective impairment in the space near or far from them (Paterson & Zangwill, 1944). Later, a series of neurophysiological studies in monkeys showed the presence of bimodal neurons that respond to both visual and tactile stimuli (Duhamel et al., 1998; Graziano & Gross, 1993; Leinonen, 1980; Rizzolatti et al., 1981a, 1981b). Specifically, these neurons are activated by touch on the body surface as well as by vision near specific body parts (hand, face and trunk) (Graziano & Gross, 1993; Rizzolatti et al., 1981b,

1981a), but not from visual stimuli that occur far from the body. A similar dissociation in the representation of space (PPS, EPS) is also present in humans, as shown by neuroimaging (Brozzoli et al., 2011, 2012; Makin et al., 2007) and neuropsychological (di Pellegrino et al., 1997; Farnè et al., 2000, 2005; Làdavas, Di Pellegrino, et al., 1998; Làdavas, Zeloni, et al., 1998) studies.

Previc (1990) originally proposed the hypothesis that visual processing can differ depending on the spatial location of the stimuli, and more subsequent research has confirmed that visual processing can be better in a certain region of space compared to others (Asanowicz et al., 2013; Blini et al., 2018; Hafed & Chen, 2016; Nasr & Tootell, 2020). Recent studies have shown that both accuracies and reaction times are better for tasks involving stimulus's features discrimination (size, orientation, shape) when stimuli are presented in the near (PPS) compared to the far (EPS) space (Ahsan et al., 2021; Blini et al., 2018). Moreover, even tasks using high-level visual stimuli, such as faces, found enhanced performance in the peripersonal space rather than the extrapersonal space (Ahsan et al., 2021). Based on these findings, it appears that stimuli that are near our body have an increased salience (Spaccasassi et al., 2019) and are processed differently – i.e. better compared to those far from the observer (Blini et al., 2021). However, it is still unknown whether this advantage is observed in the context of visual perceptual learning. To answer this question, I have carried out a series of studies in which I tested whether visual perceptual learning has different effects when the training occurs in our peripersonal/action space or a space far from our body.

Thus, each of the empirical visual training studies described in this PhD thesis (Chapters 2, 3 and 4), will investigate aspects of the visual domain of perceptual learning and how this interacts with the space in which movements occur (PPS). Starting with examining whether visual training has a different effect based on whether is carried out in the space within which we can act or in the space outside our body reach (Chapter 2). Next, I investigated the role of the hemispace (right or left) in which the stimuli occur, to evaluate whether this influences the magnitude of the visual learning (Chapter 3). Lastly, the third study (Chapter 4) explored the potential mechanisms underlying the

specific effects found in the previous two studies, namely a prominent role of the far space in visual learning.

## **1.2 Tactile training**

Touch is one of the senses inextricably linked to the motor system. If we think about it, most of our movements require us to touch something, such as grabbing a cup of tea, using a tool, etc. It has been shown that grasping and manipulating an object requires an intense interaction of the tactile and motor systems (Johansson & Flanagan, 2009; Moscatelli et al., 2019). This is clearly shown by studies which demonstrated that blocking tactile inputs, either by peripheral anaesthesia or deafferentation, significantly changed motor function, particularly disrupting precise motor coordination (Johansson & Westling, 1987; Miall et al., 2019; Monzée et al., 2003; Witney et al., 2004).

The perception of touch may be lost or considerably diminished in some pathological conditions such as stroke (Carey et al., 1997; Ennis et al., 2016; Gierthmühlen et al., 2012; Tinazzi et al., 2009), but also in the healthy elderly population (Wickremaratchi & Llewelyn, 2006). Hence, it is important to endeavour to regenerate the functionality of the tactile aspect of the sensorimotor system (Gentilucci et al., 1997; Johansson & Westling, 1984; Moscatelli et al., 2019) possibly through tactile training.

Compared to the amount of research on visual training, the one on tactile training appears scarce. Despite this, back in 1890, William James had already written about the impact of experience and learning on tactile discrimination in the section titled “The improvement of discrimination by practice” of his seminal book “The Principle of Psychology I” (1890) (James, 1890). Since then, researchers have conducted several studies to investigate the effect of tactile training on tactile perception (Franz & Kilduff, 1934; Harris et al., 2001; Mukherjee, 1933; Sathian & Zangaladze, 1997).

There are two main types of tactile training. One is the “active” training, which requires

attention and effort in order to achieve an effect that can be seen in improved performance in several tasks such as frequency, interval, and grating discrimination (Debowska et al., 2016; Harris et al., 2001; Kaas et al., 2013; Nagarajan et al., 1998; Sathian & Zangaladze, 1997; Spengler et al., 1997). The other type is the “passive” training, which contrary to the active one, does not rely on attention and is completely effortless. Recently, it has been shown that passive training methods (differently from the commonly used active-training approaches), such as RSS, can be effective in inducing learning.

One of the first studies showing an RSS application was conducted by Godde, Spengler & Dinse (1996), who demonstrated, in rats and humans, that repetitive tactile stimulation of distinct receptive fields, for several hours, located in the paws and fingers tips, leads to cortical reorganisation and enlarged representations of the stimulated skin areas (Godde et al., 1996). The RSS-induced effects have also been shown at the cortical level in humans using electroencephalography (EEG) (Pleger et al., 2001) and magnetoencephalography (MEG) (Godde et al., 2003) techniques. These studies showed a lateral dipole shift (indicating an enlargement of the stimulated body part’s representation) and an increase in strength (higher number of neurons responding) for the right index finger stimulation (trained body part). Moreover, after RSS training on the right index finger, functional magnetic resonance (fMRI) studies have revealed an enlargement of the right index finger representation and an enhancement of the blood oxygenation-level dependent (BOLD) signal amplitudes in the contralateral S1 and S2 cortices (Hodzic, 2004; Pleger et al., 2003). This evidence indicates that the RSS affects the somatosensory cortex plasticity.

It has been demonstrated that the somatosensory and motor networks are anatomically and neurophysiologically connected (Catani et al., 2012; Eickhoff et al., 2006; Fling et al., 2013; see also Chapter 5 of this thesis). Thus, given the effects of RSS on the somatosensory cortex and the strong connection between the somatosensory and motor systems, it is reasonable to think that RSS can also affect motor performance. Yet, whether the RSS-induced improvement affects motor behaviour is

much debated.

Answering this question might be very informative for clinicians, as some individuals with motor and/or sensory impairments may benefit from an RSS intervention as an easy and affordable way to aid their recovery. The purpose of the *second line* of research was to investigate the processes that support RSS and determine if the behavioural enhancement shown in tactile performance, induced by RSS can, to some extent, be transferred to the motor cortex and thus affect motor behaviour. The ultimate goal of this second line of my research (Chapters 6, 7) is to leverage this understanding to provide additional theoretical knowledge that can be potentially used to develop novel somatosensory-motor rehabilitation approaches for those patients who suffered from neurological sensory-motor impairments.

To answer this question, Chapter 5 reports a literature review on the anatomical and physiological relationships between the somatosensory and motor systems. Moreover, two empirical studies in which I applied RSS training at the fingers are described in Chapters 6 and 7. The first empirical study (Chapter 6), focuses on examining the effects of RSS on tactile performance in both right and left index fingers and thumbs evaluated using a two-point discrimination task (2PDT). Moreover, I examined the motor performance of both hands by using the Grooved Pegboard test, which allows for the measurement of fine motor dexterity. The second empirical study (Chapter 7) is an in-depth investigation of the RSS effect on motor behaviour, by measuring the changes in the motor corticospinal excitability by applying transcranial magnetic stimulation (TMS) on the left M1, and subsequently recording participants' behavioural performance in a grooved pegboard task.

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## Chapter 2 : Visual perceptual learning is effective in the far but not in the near space

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## **Abstract**

Visual shape discrimination is faster for objects close to the body, in the peripersonal space (PPS), compared to objects far from the body. Visual processing enhancement in PPS occurs also when perceived depth is based on 2D pictorial cues. This advantage has been observed from relatively low-level (detection, size, orientation) to high-level visual features (face processing) (Ahsan et al., 2021; Dureux et al., 2021). While multisensory association also displays proximal advantages (Zanini et al., 2021), whether PPS influences visual perceptual learning remains unclear. Here, we investigated whether perceptual learning effects vary according to the distance of visual stimuli (near or far) from the observer, illusorily induced by leveraging the Ponzo illusion. Participants performed a visual search task in which they reported whether a specific target object orientation (e.g., triangle pointing downward) was present among distractors. Performance was assessed before and after practising the visual search task (30 minutes/day for 5 days) at either the close (near group) or far distance (far group). Results showed that participants that performed the training in the near space did not improve. By contrast, participants that performed the training in the far space showed an improvement in the visual search task in both the far and near spaces. We suggest that such improvement in the far training is due to greater deployment of attention in the far space, which could make the learning more effective and generalise across spaces.

## 2.1 Introduction

It is now well-established that sensory experience can change perceptual processes (Maniglia & Seitz, 2018; Seitz & Watanabe, 2005). This phenomenon is called perceptual learning and it has been studied extensively by looking at several stimulus features, such as orientation (Schiltz et al., 1999), motion (Matthews & Welch, 1997), contrast (Sowden et al., 2002), texture (Karni & Sagi, 1991), and many others (Seitz, 2017). Visual studies have consistently demonstrated that performance can improve considerably after a certain amount of training (Fine & Jacobs, 2002; Watanabe & Sasaki, 2015). In a seminal study, Sigman and Gilbert (2000) tested participants on a visual search task in which they had to report whether a triangle with a specific orientation (0, 90, 180, 270 degrees) was present or not amongst 23 distractor triangles with different orientations arranged in a square. Then, they trained participants for a specific triangle orientation for 4-6 days. When participants were tested again on all the triangle orientations, their performance showed that visual perceptual learning occurred, specific to the orientation of the triangle. Namely, when the training was performed based on a particular stimulus orientation (e.g., triangle oriented upward), the performance improvement was specific to that orientation (e.g., triangle oriented upward). Furthermore, the learning effect was also restrained to the spatial location of the visual field in which the training was performed; thus, improvement was observed only at the specific eccentricity in which the training was performed and not at other eccentricities.

Space can be an important factor not only in azimuth and elevation but also in distance. There are different spaces in which stimuli can be coded: personal space (body surface), peripersonal space (PPS) and extrapersonal space (EPS). The PPS is a multisensory processing region surrounding our body and in which we interact with the close environment (Brozzoli et al., 2014; Bufacchi & Iannetti, 2018; Serino, 2019). The division of space in PPS and EPS was first suggested by studies in neglect patients who showed a selective impairment in the near and far spaces (Paterson & Zangwill, 1944). Putative neural underpinnings of PPS and EPS dissociation have been found in monkeys which have

revealed the existence of bimodal neurons in several brain areas which are active when either visual or somatosensory inputs are present (Rizzolatti et al., 1981). However, these neurons fire more strongly when stimuli are close compared to far from the body (Graziano & Gross, 1993; Matelli et al., 1986; Rizzolatti et al., 1981). Similar neural structures were suggested to exist also in humans from both neuroimaging (Bernasconi et al., 2018; Brozzoli et al., 2011; Makin et al., 2007) and behavioural studies (di Pellegrino et al., 1997; Farnè & Làdavas, 2000; Halligan & Marshall, 1991; Serino et al., 2015).

Recently, Blini and colleagues (2018), used a 2-D Ponzo Illusion and 3-D VR settings to investigate human visual discriminative abilities in PPS and EPS spaces. They carried out a series of experiments in which they manipulated the retinal size (constant or naturally scaled) and the setting (Ponzo illusion or VR). They found that discrimination of objects located in peripersonal space is better than extrapersonal space in terms of speed of response, with no speed/accuracy trade-off. Importantly, the results were similar across 3D and 2D settings (virtual reality and Ponzo Illusion). Similarly, Ahsan and colleagues (2021) (see also Dureux et al., 2021), explored whether perceived depth modulates performance on different visual tasks involving either low-level (size and orientation discrimination) or higher-level (face identification) visual properties using the Ponzo Illusion. They showed that both precisions and reaction times were better when stimuli were presented in the near (PPS) compared to the far (EPS) space. These studies converge in showing that there is a general advantage for processing stimuli that are near compared to far from the body. In addition, multisensory associative learning processes also display proximal advantages (Zanini et al., 2021). Yet, whether this PPS processing advantage applies to visual perceptual learning remains unsettled.

In this study, we investigated whether visual perceptual learning is affected by the location of the stimuli in space (near and far from the observer). Participants carried out a visual search task, both in the near space (PPS) and far space (EPS), whereby they had to report the presence of a target, which was a triangle with a specific orientation (either 0, 90, 180 or 270 degrees), randomly appearing

amongst distractors bearing other orientations (modified after Sigman and Gilbert 2000). Performance was assessed both before and after a training session in which participants were trained by repeated blocks of the visual search task, either in PPS or EPS, looking only for one specific orientation. Based on the previous studies showing a PPS advantage for visual processing (Ahsan et al., 2021; Blini et al., 2018; Zanini et al., 2021), we predicted to observe a larger improvement in performance for participants who trained in the near compared to the far space, but only for the trained orientation (Sigman & Gilbert, 2000). Moreover, owing to the previously documented degree of topological specificity of the improvement (Sigman & Gilbert, 2000), we additionally predicted the benefit following the near-space training to be specific for the PPS.

## **2.2 Materials and methods**

### **Participants**

Thirty-six participants (mean age = 28.17, range = 21 – 57; 23 females) took part in the study. We conducted a priori power analysis in G\*Power version 3.1.9.7 (Faul et al., 2009) using the data from (Sigman & Gilbert, 2000; N=4) to estimate the minimum sample size to compare the performance for trained orientation before and after training. The effect size in Sigman & Gilbert's study was 12.12, thus by setting an alpha criterion to 0.05 and power to 0.99, the resulting sample size for a two-tailed paired t-test was 3. Since they trained participants until they reached a certain performance level for the trained orientation, we calculated the effect size from the difference between trained and untrained orientations after training. For the same reason and because the number of trials in our study was substantially smaller (reduced to 1/4<sup>th</sup>) and we had two different groups as well, we decided to use a bigger sample size (N=18 for each group). All participants had normal or corrected-to-normal vision. The study was approved by the ethics committee of the School of Psychology, University of Kent and was carried out according to the principles of the 1964 Declaration of Helsinki as updated by (World Medical Association, 2013).

## Apparatus and stimuli

The visual search task was built in PsychoPy 3 (Peirce et al., 2019) and it was delivered online on Pavlovia (*Pavlovia*). Participants were instructed to perform a series of online visual search tasks using their personal computers or laptops at home. The choice to perform the task online was primarily dictated by the covid-19 outbreak at the time of the testing. Given that each participant used their screens with different dimensions and resolutions, the size of the visual stimuli was scaled based on the dimension of the participant's display so that stimulus size remained constant across participants. To do so, participants had to resize a credit card appearing on their screen using the arrows on their keyboards. They used their credit card (which has a standard size) and positioned it on their screen superimposing it to the image. As mentioned, this process ensured a constant dimension of visual stimuli presented across the different participants' screens. Visual stimuli consisted of 24 triangles arranged into a 5 x 5 matrix with a fixation dot in the middle (Figure 2.1). Each triangle had black outlines and a white fill. The sides of every triangle were 7 millimetres (mm) in length and 6.1 mm in height and they were located at 14 mm distance from their respective centres of mass. Therefore, the square matrix subtended 70 x 70 mm. Triangles were presented on top of a white background image depicting a room (see Figure 2.1) which created a 2D depth perspective (Ponzo illusion) thus producing two illusory spaces, i.e. – one near and another far from the observer. The near space was located in the lower half of the screen (Figure 2.1A), whereas the far space was located in the upper half of the screen (Figure 2.1B). Virtual Reality (VR) and Ponzo illusion are typically used to create a visual setting in which the space can be divided into two sections, one considered near (peripersonal) and the other regarded as far (extrapersonal). The 'Ponzo illusion' (Ponzo, 1910) is an optical effect that leads the brain to misperceive the actual size of an object when it is presented in a perspective scenario (Gregory, 1963; Leibowitz et al., 1969; Prinzmetal et al., 2001). As a result, stimuli that have the same characteristics in terms of size are perceived and processed as different when placed in a perspective setting (distant stimuli are perceived as larger

than near stimuli even if they have the same physical and retinal size). The brain uses depth cues to estimate the distance between the stimuli and the size of stimuli is rescaled based on how far they seem to be by following Euclid's Law (Sperandio & Chouinard, 2015). Thus, this method allows the creation of a PPS and an EPS while maintaining the same physical visual angle for both spaces. Participants responded to the target presence by pressing P (target present) or A (target absent) on a keyboard (standard QWERTY keyboard).

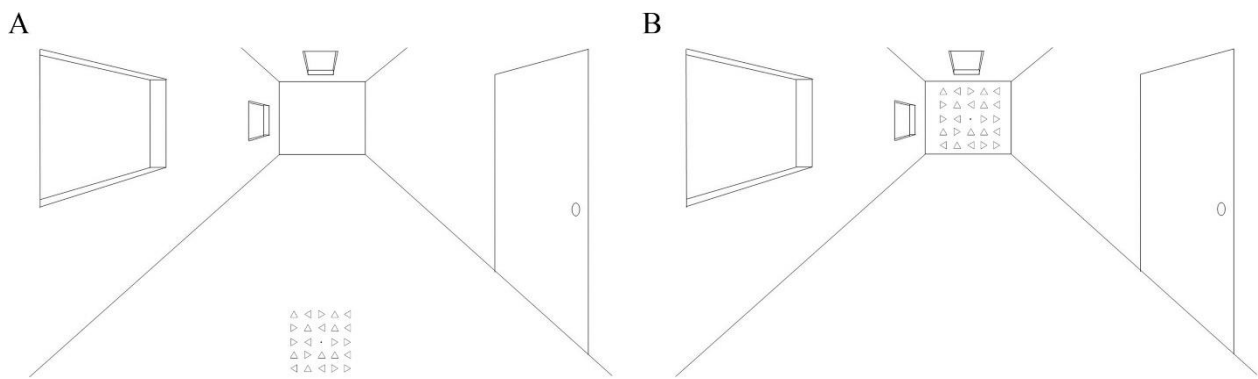


**Figure 2.1 Visual setting (vertical Ponzo illusion) example.** Depiction of the stimuli presentation in the near (A) and far (B) conditions. The stimuli were presented within a background scenario of a room.

## 2.3 Design

There were 4 experimental conditions (see Figure 2.2). Eighteen participants performed training in the near space and other eighteen in the far space. Moreover, the training was performed only for one of the four triangle orientations, the specific orientation varied across participants.

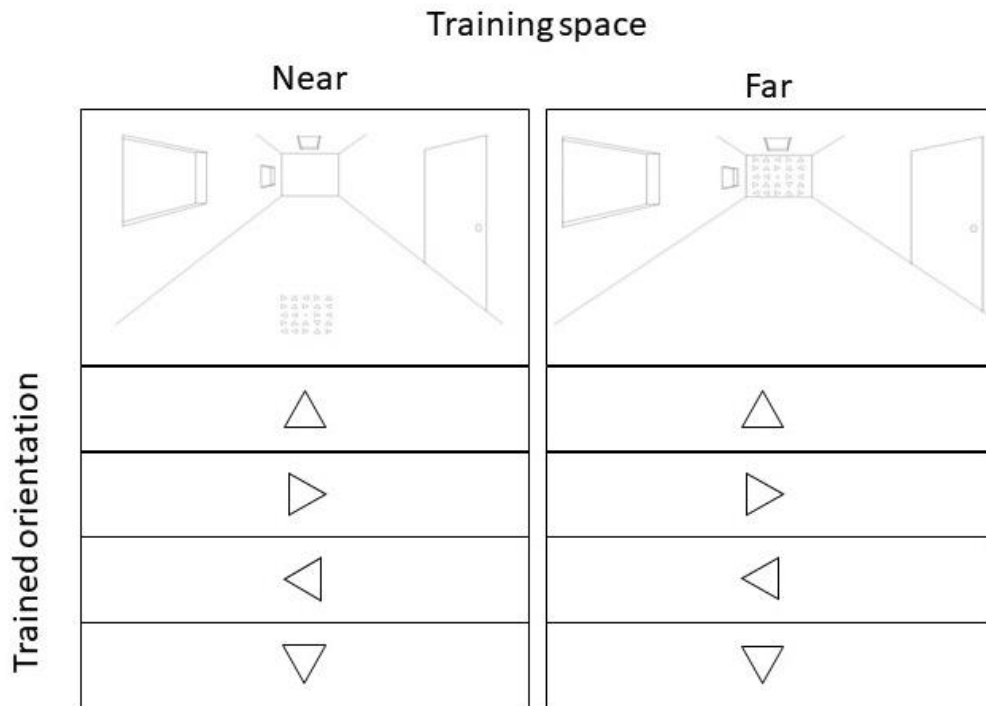


**Figure 2.2. Training space and orientation conditions.** All possible experimental conditions. Participants were trained on one specific orientation (i.e., triangle pointing up, right, left, or down) either in the near or far space.

The experiment consisted of two testing phases and a training period between the two phases (see Figure 2.3). There were three within-participants factors: ORIENTATION (Trained, Untrained), TIME (Before, After), and SPACE (Near, Far) and one between-participants factor: TRAINING (in the near space, in the far space). The trained orientation was counterbalanced across participants.

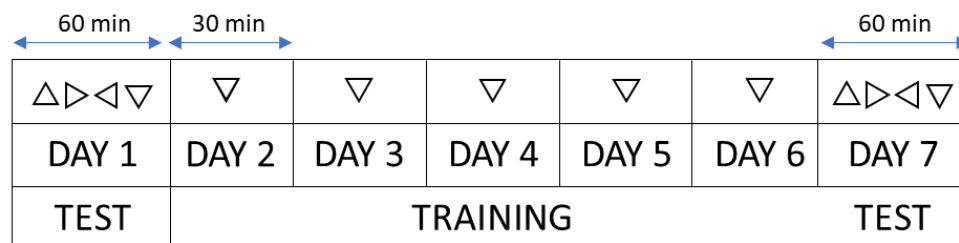


**Figure 2.3 Online visual study timeline.** Timeline of the experiment, including a first-day testing phase (Before training) lasting 60 minutes in which the four different triangle orientations were tested as targets. A five-day training lasting 30 minutes (min) in which only one orientation was used as a target. Note that the training orientation was varying across participants. Finally, the last day after-training testing phase in which all four orientations were tested as targets.

## 2.4 Procedure

Participants were contacted by email and received instructions on how to carry out the different tasks. The experiment lasted seven days. Participants received one link for each day and used the links to access Pavlovia which let them perform the tasks for the respective day. Participants received detailed instructions on how to carry out the tasks in a bullet list for each day. The experiment began with a testing phase, based on the sequence order (A: near-far, B: far-near), in which participants started the visual search task on the near or far space and then completed the task on the other space. The near and far blocks were performed separately, and the order was counterbalanced across participants. In this pre-training testing phase, participants were presented with a target, which was a triangle pointing either up, down, left, or right, at the beginning of each block (4 in total, one for each orientation). Each block consisted of 150 trials, 20% of which were null (the target being absent). The target was presented 5 times in each of the 24 possible locations in the 5 x 5 matrix. There were a total of 1200 trials, 600 in the near space and 600 in the far space.

Each trial had a total duration of 3000ms and started with the presentation of the visual stimuli for 300ms (Figure 2.4). Then, participants had 2700ms to give their responses before the start of the next trial. The subsequent stimulus was presented even if the participant did not report any response. The background image (i.e., room) was displayed on the screen throughout the whole block. Participants indicated whether the target was present (by pressing P) or absent (by pressing A). The training consisted of the same visual search task performed during the testing phases and lasted 30 minutes each day. The only difference was that each participant was trained by repeating blocks in a specific target orientation (i.e., up, down, left or right) and only in a specific space (near or far). Instead, in the testing phases, participants had to complete blocks for all four orientations and in both spaces. Moreover, the training phase consisted of a total of 3000 trials (600 each day). At the end of the experiment, participants received either credits or money as compensation for their time regardless of their performance.

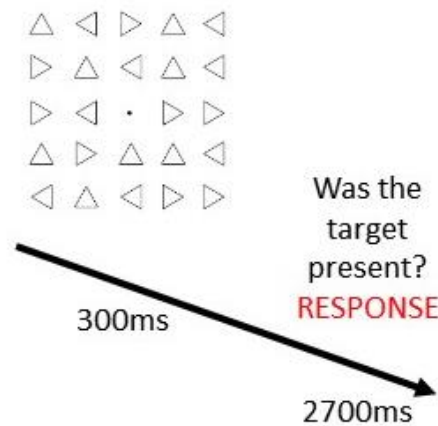


**Figure 2.4 Visual search display example.** At the beginning of each block, participants saw a target (e.g., a triangle pointing down) at the centre of the screen until they pressed the arrow on the keyboard pointing in the same direction to confirm they understood the orientation. In each trial, 24 triangles appeared for 300ms. Immediately after participants had to report whether the target was present or absent. The triangles seen above here were presented in the near or far space.

## 2.5 Analyses

To assess participants' performance, their responses were divided into the proportion of hits (target present - response present) and false alarms (target absent - response present). If the participant did not press any key, the response was categorised as absent. These proportions were then used to compute the d-prime ( $d'$ ) and the criterion values (Swets et al., 1961).  $d'$  was calculated using the formula:  $d' = z(H) - z(FA)$  whereas for the criterion we used the following formula:  $c = -(z(H) + z(FA))/2$ . False alarms and hits proportions were adjusted to 0.01 when their values were 0 and to 0.99 when their values were 1.

Linear mixed-effects models were used to examine performance as measured by the d-prime (Baayen et al., 2008). The fact that mixed-effects models are based on single-trial data rather than averaged data, does not assume independence among observations, and take into consideration the covariance structure of the data, including random effects, are all significant advantages (i.e., individual variability). A model with random effects was created. When a linear mixed model contains the most intricate random structure that does not restrict model convergence, the

generalisation is at its best (Matuschek et al., 2017). Following the sequential introduction of random factors, likelihood tests were used to determine how well the models fit (i.e., this was done by comparing the residuals of each model and then selecting the one with significantly lower deviance as assessed by a chi-square test). All models had a random intercept for the participant. We started by evaluating the impact of random slopes for orientation (trained, untrained), time (before, after) and space (near, far). These were all within-participants factors. Once we found the best random slope for the model, we started to test the fixed effects. Thus, orientation, time, space, training, and their interactions were evaluated. To determine if the improvements in model fit were statistically significant, we used likelihood ratio tests as stated above (for a similar approach see also Blini et al., 2018). The raw data and the whole analysis pipeline for the linear mixed model which was carried out with the open software R (RStudio Team, 2020) are available on osf (see link below). Such analyses have been performed on the performance in the before (i.e., day 1) and after (i.e., day 7) testing phases. All post hoc tests are corrected for multiple comparisons using Holm-Bonferroni.

## 2.6 Results

### **d-prime**

Our null models contained random slopes for time when the d prime was evaluated. The model fit significantly improved when the model, including a main effect of time, was tested against the null model,  $\chi^2(1, N=36) = 11.39, p < .001$ , Cohen's  $d = 0.43$ , 95% CI = [0.25, 0.60]. Thus, participants' performance improved when comparing the before ( $M \pm SE = 0.61 \pm 0.08$ ) to the after-training testing phase ( $M \pm SE = 0.85 \pm 0.09$ ),  $\beta = 0.25$ ,  $SE = 0.07$ , 95% CI = [0.10, 0.38]. These results were confirmed by a two-tailed paired sample t-test,  $t(35) = -3.61, p = .001$ . We also found a significant two-way interaction Training x Time which improved the model fit  $\chi^2(1, N=36) = 4.72, p = .03$ , Cohen's  $d = 0.73$ , 95% CI = [0.46, 1.00]. Participants who carried out the training in the far space had a higher d-prime after ( $M \pm SE = 0.93 \pm 0.12$ ) compared to before ( $M \pm SE = 0.55 \pm 0.11$ ) the

training  $\beta = 0.28$ ,  $SE = 0.13$ , 95%  $CI = [0.03, 0.51]$ . Post hoc test confirmed that there was an improvement from before to after training in the far space,  $t(34) = -4.23$ ,  $p = .001$ . Finally, the orientation x time x training interaction was tested against the model including their main effects and the model fit was significantly better  $\chi^2(1, N=36) = 13.28$ ,  $p = .01$ , Cohen's  $d = 0.88$ , 95%  $CI = [0.45, 1.32]$ . There was a significant improvement for the participants that did the training in the far space for the trained orientation before ( $M \pm SE = 0.48 \pm 0.12$ ) compared to after ( $M \pm SE = 0.98 \pm 0.13$ ) the training  $\beta = -0.40$ ,  $SE = 0.16$ , 95%  $CI = [-0.70, -0.08]$  in both spaces. Post hoc test confirms the results  $t(63) = 4.72$ ,  $p < .001$ . Therefore, when doing the training in the far space participants improved their performance for the trained orientation both in the near and far space (see Figure 2.5).

### **Criterion**

Our null models contained random slopes for time when the criterion was analysed. We found a main effect of Orientation, thus the model fit significantly improved compared to the null model,  $\chi^2(1, N=36) = 4.90$ ,  $p = .03$ , Cohen's  $d = 0.16$ , 95%  $CI = [0.009, 0.30]$ . Participants were more conservative when tested for the trained ( $M \pm SE = 1.18 \pm 0.07$ ) compared to untrained ( $M \pm SE = 1.09 \pm 0.07$ ) orientations,  $\beta = -0.09$ ,  $SE = 0.04$ , 95%  $CI = [-0.17, -0.005]$ . The orientation x training interaction was tested against the model including only their main effects and fit improved significantly  $\chi^2(1, N=36) = 8.25$ ,  $p = .004$ , Cohen's  $d = 0.35$ , 95%  $CI = [0.13, 0.56]$ . Participants who did the training in the near space were more conservative when tested for the trained orientation ( $M \pm SE = 1.16 \pm 0.11$ ) compared to untrained ( $M \pm SE = 0.96 \pm 0.11$ ),  $\beta = 0.23$ ,  $SE = 0.08$ , 95%  $CI = [0.08, 0.38]$ .

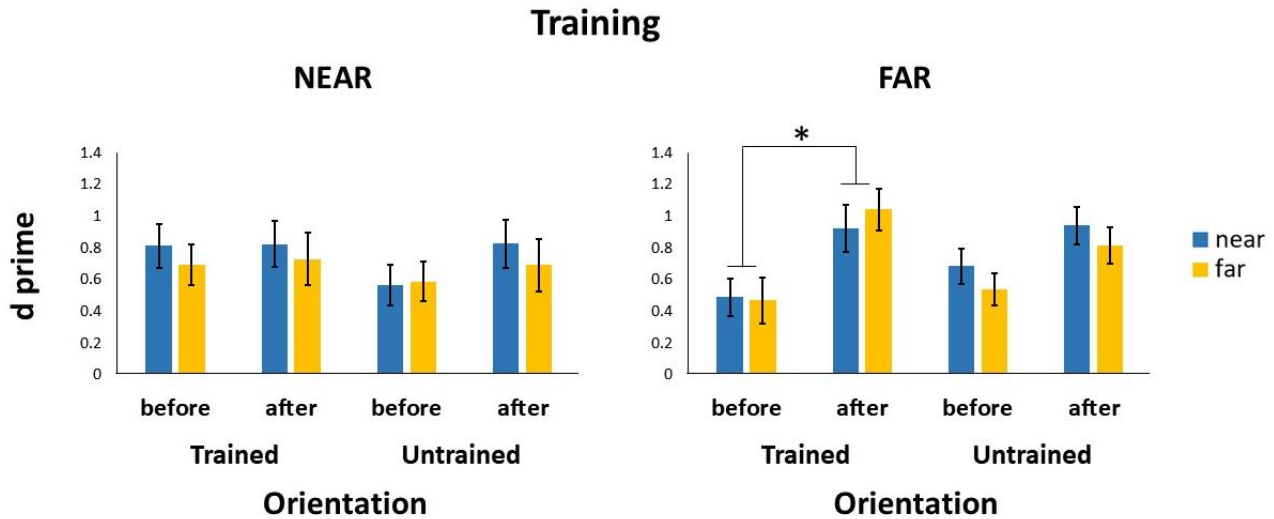


**Figure 2.5 Visual training d-prime results.** Bar charts illustrate d-prime values for the participants who trained in the near space (left panel) and those who trained in the far space (right panel). The data inside each chart are divided into Orientation (trained and untrained) and Space (near in blue and far in yellow). Error bars represent the standard error of the mean ( $\pm$ SEM). \* $p < .05$ .

The orientation  $\times$  time  $\times$  training interaction was tested against the model including their main effects and the model fit was significantly better  $\chi^2(1, N=36) = 13.54, p = .009$ , Cohen's  $d = 0.48$ , 95% CI = [0.14, 0.83]. Participants who carried out the training in the near space were more conservative when tested before the training for the trained ( $M \pm SE = 1.24 \pm 0.12$ ) compared to the untrained ( $M \pm SE = 0.95 \pm 0.12$ ) orientations,  $\beta = -0.20$ ,  $SE = 0.16$ , 95% CI = [-0.48, 0.10]. We also found a training  $\times$  orientation  $\times$  space interaction, thus the model fit significantly improved compared against the null model,  $\chi^2(1, N=36) = 12.25, p = .02$ . However, the model included only a significant time  $\times$  training interaction,  $\beta = 0.3$ ,  $SE = 0.19$ , 95% CI = [0.007, 0.78]. Participants who underwent the training near were more conservative when carrying out the task in the near space for the trained ( $M \pm SE = 1.19 \pm 0.11$ ) compared to untrained ( $M \pm SE = 0.92 \pm 0.11$ ) orientations, Cohen's  $d = 0.47$ , 95% CI = [0.17, 0.77].

## 2.7 Discussion

In the present study, we examined whether visual perceptual learning affects performance differently depending on the space in which the training is performed, namely the *peripersonal* or *extrapersonal* space, illusorily induced by leveraging the Ponzo illusion. Contrary to our predictions, based on large evidence pointing at perceptual processing advantages in the near space, we found that visual perceptual learning was effective only when participants carried out the training in the *extrapersonal* space. Moreover, when the training occurred in the *extrapersonal* space, the performance improved in both the *peripersonal* (near) and *extrapersonal* (far) spaces, showing a spatial generalisation of the learning that is at odd with the largely documented specificity of perceptual learning effects, typically limited to the trained orientation, spatial location and eccentricity (Crist et al., 1997; Karni & Sagi, 1991; Schoups et al., 1995; Shiu & Pashler, 1992). Such a spatial generalisation, however, emerged only for the distance component of the task as, in keeping with previous works (Sigman & Gilbert, 2000), participants were significantly more accurate in the visual search task for the specifically trained orientation in the far space.

Typically, visual learning changes in performance are exclusive to the specific trained feature of the stimulus, and sometimes the improvement is even restricted to the trained eye and visual field, without generalisation effects (Crist et al., 1997; Fiorentini & Berardi, 1980; Karni & Sagi, 1991; Schoups et al., 1995; Shiu & Pashler, 1992). However, recent studies have revealed that there are certain situations in which transfer of learning can occur (Doshier & Lu, 2017; Fahle, 2005; Sagi, 2011). Furthermore, the learning effect should not be considered completely specific, since performance on the visual search task improved substantially for the trained orientation, though a similar not significant trend was visible for the untrained orientations. Importantly, since visual search performance at baseline (i.e., before training) was not significantly different whether carried out in the near or far space, the effect we newly report here cannot be ascribed to a general difference in performance in the two spaces. Overall, these results are at odds with previous work on visual

perception where an advantage for the processing of stimuli in the near compared to the far space has been recently documented (Ahsan et al., 2021, 2022; Blini et al., 2018; Dureux et al., 2021). In the following, we consider several factors that can potentially determine the unexpected far-space advantage in perceptual learning.

One possibility is that our results are due to attention being deployed differentially in space during visual training. In keeping with this possibility, Abrams et al., (2008) investigated whether hand proximity alters visual processing. In their study, they used visual search, inhibition of return, and attentional blink tasks with two spatial conditions, one in which the participants' hands were near the visual stimuli and one in which they were far from the stimuli. Similarly, to the present study, the results for the visual search task showed that participants were faster when stimuli were far from the hands. In the inhibition of return task, participants saw a peripheral cue followed by a target in the same or different locations. When the delay between the cue and the target was short, they observed a facilitation that was interpreted as an attentional engagement at the cued location (thus shorter RT), whereas at long delays there was a slower response that they interpreted as an inhibition due to attentional disengagement and the return of attention to the cued location (longer RT). They found lower inhibition of return only when stimuli were presented near the hands, whereby participants' attentional disengagement from the cued location was delayed/disrupted. In their last task, participants had to detect two targets amongst a series of stimuli presented rapidly. When the time between the two targets was around a few hundred milliseconds, the identification of the second target was impaired (attentional blink). The results demonstrated higher difficulty in attentional disengagement from the first target when hands were near compared to far from the stimuli. Based on these findings, in our study participants might have had more difficulties in moving their attention rapidly and between objects (triangles) in the near space. Even though no difference between spaces was evident at baseline, attentional processes might have implied a larger extent during the perceptual

training in the extrapersonal space, where participants could more easily disengage and reorient attention.

Additionally, the Ponzo illusion is an optical illusion that, due to the perspective cues, leads to perceiving stimuli that appear further in space as larger compared to stimuli in the near space even though they have the same physical size and identical retinal projection (Gillam, 1973; Gregory, 1963; Leibowitz et al., 1969; Prinzmetal et al., 2001). Thus, participants were likely to perceive stimuli in the far space as relatively larger and this might have facilitated visual learning in the far space. However, stimuli in the near space should still have been perceived as similar in size compared to those originally used by Sigman & Gilbert (2000). In this respect, here we should have observed performance improvement similar to their work, though this was not the case. This suggests that when perceptual learning is engaged across space in depth, far(ther) distances may benefit from the most, if not all the training-induced improvement. Thus, the mere presence of the two spaces (near and far), namely depth perspective, may not be directly comparable with the situation in which only one space is present as in Sigman & Gilbert's (2000) study.

Another, non-mutually exclusive possibility is that the greater effectiveness of visual learning in the far compared to the near space could be originating from an evolutionary mechanism. Previc (1990) theorized an ecological perspective of the functional segregation of the near and far visual processing, which appears to have a bias towards the lower and upper visual fields respectively. The critical link between near space (peripersonal space) and visuomotor skills, as well as the far space (extrapersonal space) and visual searching abilities, can be traced back to the change to an erected position (Allman, 1977; Bishop, 1962; Goldman-Rakic, 1987; Hewes, 1961; Hill, 1972; Hunt, 1994; Polyak, 1957; Richmond et al., 2001; Snodderly, 1979). Recent studies (Nasr & Tootell, 2018, 2020), have shown that in the brain areas involved in visual depth perception (V2, V3A), neurons representing the lower visual field respond more strongly to near compared to far stimuli, whereas neurons that represent the upper visual field have the opposite pattern. These results are compatible

with the idea of different stimulus processing by the visual system for the lower-near and upper-far visual fields based on ecological (see above) and statistical frequencies of natural environments (Yang & Purves, 2003). Moreover, Nasr and colleagues (2018; 2020) also found that in V3A there are “near-preferring” clusters of neurons that had a bias toward low spatial frequency (global) visual perception compared to far-preferring ones. Both vision and hearing appear to be related to the statistics of the environment. Specifically, sounds at higher frequencies tend to be at an elevated point (head-centred), thus there is a frequency-elevation mapping, and the outer ear anatomical conformation seems to maximise this mapping (Parise et al., 2014). Visual stimuli in natural scenes tend to be further when they are in the upper visual field and closer when they are in the lower visual field (Ooi et al., 2001; Yang & Purves, 2003). In sum, although in our experiment the predisposition to visual search in far space and upper visual field could not be observed before the training, it might have become relevant during the training/learning phase.

Although it is out of the scope of this study to discern the relative contribution of the factors considered above, they seemingly point to a common feature we could term as a ‘predisposition’ to visual perceptual learning for stimuli that are visually far (or illusorily perceived as such). Moreover, we would like to note the possibility that visual perceptual learning for near stimuli may require longer training compared to far stimuli, as suggested by the fact that performing the training in near space did not improve the visual search of the trained orientation. Importantly, none of the previous research investigating the difference in peripersonal and extrapersonal space examined the effects of training. Thus, the present findings pave the way for new research avenues toward the relationships between perceptual learning and perceived distance.

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## Chapter 3 : Mind the depth: visual perceptual learning is better in the far space

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### Credit author statement

**Antonio Zafarana:** Conceptualisation, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Visualisation; **Laura Hunt:** Investigation, review; **Carmen Lenatti:** Investigation; **Munashe Makwiramiti:** Investigation; **Alessandro Farnè:** Conceptualisation, Methodology, Validation, Formal analysis, Writing, review & editing; **Luigi Tamè:** Conceptualisation, Methodology, Validation, Formal analysis, Resources, Writing, review & editing, Funding acquisition.

## Abstract

Visual objects in the peripersonal space (PPS), that is the space closely surrounding our body, are perceived faster than farther ones, appearing in the extrapersonal space (EPS). This shows preferential processing for visual stimuli near our bodies. Such an advantage should favour visual perceptual learning occurring near, as compared to far from observers. However, we recently provided opposite evidence from an online testing protocol, showing larger perceptual learning in the far space. To settle this apparent contradiction, here, we ran two laboratory-based experiments investigating whether visual training in PPS and EPS has different effects on learning performance in a visual search task. We used the horizontal Ponzo Illusion to create a lateralized depth perspective, while participants completed a visual search task in which they reported whether a specific target object orientation (e.g., a triangle pointing upward) was present or absent amongst distractors. This task was completed before and after a training phase. Participants were trained by repeating the visual search task for a given orientation in either the (illusory) near or far space for one hour. To control for laterality, in Experiment 1 the near space was in the left hemispace, whereas in Experiment 2 it was in the right hemispace. Results showed that, in both experiments, participants were more accurate after training in the far space, whereas training in the near space led to either improvement in the far space (Exp. 1), or no change (Exp. 2). The left or right side to which distances were associated also modulated participants performance, showing a larger visual perceptual learning when stimuli were presented in the left compared to the right hemispace. Therefore, despite the well-established visual processing advantage in PPS, visual perceptual learning seems to be more effective in the far space. Moreover, the left hemispace appears to induce a greater advantage for learning as it affects near training. We propose that depth is a fundamental dimension of human learning as, to some extent, it is the hemispace in which the stimuli appear.

### 3.1 Introduction

Humans, and many other species too, have a remarkable ability to learn from visual experience. Protracted training on specific elements of the visual scene improves our perceptual abilities through a process called perceptual learning (Gilbert et al., 2009; Sagi, 2011; Seitz & Dinse, 2007). Perceptual learning occurs in several if not all sensory domains: vision, touch, smell, hearing and taste (Green et al., 2018). Research in vision has investigated visual perceptual learning using a variety of tasks (for a review see Doshier & Lu, 2017; Lu et al., 2011). While the mechanisms driving visual learning remain debated (Ahissar & Hochstein, 2004; Bejjanki et al., 2011; Maniglia & Seitz, 2018), previous work has highlighted the high degree of specificity of such learning processes. Changes in performance are usually exclusive to the specific trained stimulus, or even the trained eye or visual field, without generalisation effects (Crist et al., 1997). Sigman & Gilbert (2000), for example, trained participants for several days in detecting a triangle with a specific orientation (target) embedded in an array of triangles with different orientations (distractors). They found that performance improved for the trained orientation and not the untrained ones and that the learning effects did not transfer to spatial locations close to the target one (Sigman & Gilbert, 2000). Thus, performance benefits are thought to be associated with a top-down cortical modulation from higher-level visual areas on the activity of early retinotopic areas (Sigman et al., 2005).

However, space is a very important dimension when processing stimuli in the external environment as their occurrence in the different parts of the hemispace (up, down, right, left) may determine different processes (Asanowicz et al., 2013; Berlucchi et al., 1974; Losier & Klein, 2004). Another important spatial factor is depth, that is the distance at which stimuli occur with respect to the observer's body, as well-established dissociations exist in terms of processing when stimuli are in the *peripersonal* rather than *extrapersonal* space (Brozzoli et al., 2011; Rizzolatti et al., 1981; Serino, 2019). The former represents the area that is close to our body while the latter represents the space that extends farther. Neurophysiological studies in monkeys revealed the existence of

populations of neurons that specifically respond to both tactile and visual stimuli only when these are presented near the body (Andersen et al., 1985; Graziano & Gross, 1993; Gross & Graziano, 1995). Similarly, neuropsychological symptoms in humans, like visuo-tactile extinction, are known to increase at a shorter distance from patients' body surface (di Pellegrino et al., 1997; Làdavas, Di Pellegrino, et al., 1998; Làdavas, Zeloni, et al., 1998). Several studies have thus investigated visual perception in the peripersonal space and converged in showing perceptual facilitation for stimuli close to the observers (Abrams et al., 2008; Ahsan et al., 2021; Blini et al., 2018, 2021; Dureux et al., 2021; Reed et al., 2006, 2010). Not only simple detection (Blini et al., 2018), but also visual discrimination is faster when stimuli are presented near compared to far from the body (Blini et al., 2018). Participants are also more accurate in visual discrimination tasks according to (Ahsan et al., 2021) findings. Further research has shown that participants are more accurate as well as faster for high-level visual tasks, specifically face perception/discrimination when faces appear in the peripersonal compared to the extrapersonal space (Ahsan et al., 2021; Dureux et al., 2021). Moreover, attention resources during visual search tasks are biased towards the peripersonal space, as indicated by increased difficulty (higher reaction time) in disengaging attention from stimuli when they are near rather than far from the body (Abrams et al., 2008).

Considering this large body of evidence favouring privileged visual processing in the peripersonal space, one would expect that visual perceptual learning should also benefit from this closeness advantage. Yet, the only available study, conducted online during the covid-19 outbreak, reported opposite evidence; namely, visual perceptual learning may actually be more efficient in the extrapersonal space (Zafarana, Farnè, Tamè, under review, Chapter 2). In that study, participants who trained in a visual search task in the extrapersonal space became more accurate, whereas those who trained in the peripersonal space showed no significant changes in performance. However, in that study, we used a vertical version of the Ponzo Illusion to create the depth perspective. This makes the upper part of the screen associated with the far space and the lower part with the near space, which

according to Previc functional specialisation theory (Previc, 1990), are linked to higher visuomotor processing in the near/lower space and better visual search/recognition in the far/upper space. Therefore, to control for these confounding effects, in the present study, we focused on the horizontal dimension of space in which stimuli can be presented, thus left and right sides. Moreover, as that was an online experiment (Chapter 2), we could not monitor participants' distance from the screen, display settings (e.g., luminosity, contrast etc.), or their gaze.

In the present study, we systematically examined whether visual perceptual learning has different effects in the peripersonal and extrapersonal space. We used a modified version of the horizontal Ponzo Illusion (see Figure 3.1) to create a depth perspective that would make one side as being either near or far from the observer (similar to Ahsan et al 2021). We tested participants on a visual search task in which they had to report whether a target object (i.e., triangle) in a specific orientation amongst 23 distractors was present or absent, both before and after a training phase. Critically, in both the testing and training phases, the visual display could illusorily appear either in the peripersonal or extrapersonal space. Two groups of participants were trained either in the near or far space for one of four possible orientations (triangle pointing up, down, right, left). To control for any laterality effects, the illusorily near and far conditions were associated with the left and right side of the display (Experiment 1) or the reverse (Experiment 2). In addition, we used an eye-tracker to monitor participants' gaze during the training and testing phases (see Figure 3.2) to ensure participants were looking at the expected side of space.

If PPS visual advantage applies also to visual perceptual learning, we should expect an increment in performance for the trained orientation in the near and not in the far space. Alternatively, and in keeping with the recent results, if the visual advantage for visual perceptual learning applies to the EPS, we should expect an improvement in performance after the training in the far but not near space and that this learning effect would be specific (only for the trained orientation).

## 3.2 Experiment 1

First, we investigated the effects of visual training on a visual search task in two groups of participants, one trained in the *peripersonal* space (near the body) and the other trained in the *extrapersonal* space (far from the body). The near space was presented in the participants' left hemispace, whereas the far space was presented in the participants' right hemispace. We measured participants' performance in a visual search task before and after the training in both spaces. Note that differently from our previous study (Chapter 2), the depth perspective here is created on the left and right hemifield rather than on the top and bottom part of the hemifield. Additionally, differently from our previous study here the training lasted only one hour and occurred on the same day rather than distributed over 5 days.

### 3.2.1 Materials and methods

#### Participants

Forty-four participants (mean age = 23, range = 18 – 48; 35 females) took part in the experiment. Based on data from a previous study we conducted online (Chapter 2), a priori power analysis was performed using G\*Power version 3.1.9.7 (Faul et al., 2009) to estimate the sample size to compare the performance for the trained orientation before and after training. The effect size in that study was Cohen's  $d=0.88$ , which is considered large according to Cohen's (1988) criteria. If the significance criterion is  $\alpha = 0.05$  and power = 0.99, the minimum sample size required for this effect size is  $N = 26$  (total) for a two-tailed paired sample t-test. Hence, the resulting sample size of  $N = 20$  per group is enough to test the research hypotheses. We slightly increased the number of participants to compensate for the reduced number of trials during this training ( $t = 1200$ ) compared to the previous study ( $t = 3000$ ). All participants had normal or corrected-to-normal vision. The study was approved by the local ethics review committee at the School of Psychology, University of Kent and was carried out according to the principles of the 1964 Declaration of Helsinki as updated by (World Medical

Association, 2013). Thirty-eight participants were right-handed (mean = 95, range: 89–100) and four were left-handed (mean = -91, range: -100 – -82). Handedness was determined using the Edinburgh Handedness Inventory with the laterality quotient (LQ) (Oldfield, 1971).

### 3.2.2 Apparatus and stimuli

The visual search task was built in PsychoPy 3 (Peirce et al., 2019) and it was presented on a Dell U2312HM Monitor with a refreshing rate of 60 Hz and 1920 x 1080 pixels display resolution. Participants carried out the task in a laboratory room and were sitting at 89 cm from the screen, measured from their eyes. They also regulated the height of the seat to find a comfortable position to place their head on the chin rest (see Figure 3.2).

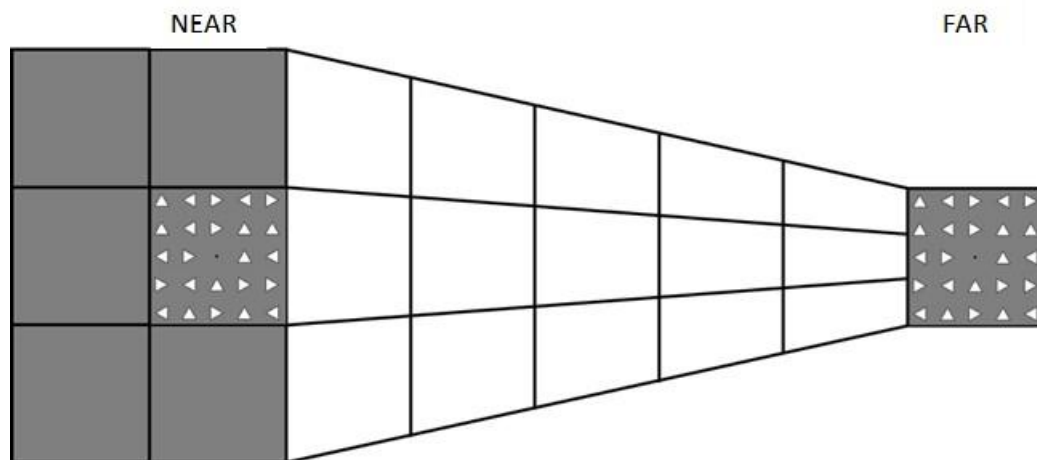


**Figure 3.1 Visual setting (horizontal Ponzo illusion) example (Exp 1).** Depiction of the depth perspective that has been used to create the spaces for the stimuli presentation for the near (left) and far (right) conditions. In the near condition, the task was carried out on the square on the left side of the visual field. Thus, stimuli (triangles) appeared on the left side while the matrix of triangles on the right side was always present without flashing. In the far condition, it was the other way around, stimuli were fixed on the left side of the screen and the visual detection task was performed on the right.

Visual stimuli consisted of a 5 x 5 matrix of 24 triangles with a fixation black dot positioned in the middle of the matrix. Each triangle had black outlines and a white fill. The sides of every triangle were  $0^{\circ} 27'$  in length and there was a  $0^{\circ} 54'$  distance from their centres, therefore, the matrix

subtended  $4.5^\circ \times 4.5^\circ$ . Stimuli were presented on top of a white and grey background image (see Figure 3.1) which created a 2D depth perspective (Ponzo illusion) producing two illusory spaces (near and far from the observer). The background image used, created a horizontal depth perspective resulting in near space on the left half of the screen and the far space on the right half. Participants' task was to report whether the target was present or absent by pressing "P" or "A" respectively on a keyboard (standard QWERTY keyboard) using their hands.



**Figure 3.2 Visual training experimental setup.** Experimental setting including computer, eye tracker and headrest.

### Eye-tracker

Participants' gaze was monitored and recorded using the Tobii x120 Eyetracker with a sampling rate of 60 Hz, continuously recording the gaze of both eyes throughout the experiment. Participants' head was stabilized thanks to a chin/headrest in front of which the eye tracker was positioned, just below the screen (Figure 3.2). This was used to confirm that participants were gazing at the designated point of space, either near or far based depending on the condition. Before commencing the experiment,

the eye tracker was calibrated. Five circles, appearing randomly on the screen's four corners and in the centre, were used as the calibration points.

### 3.2.3 Design

This was a mixed-subject experimental design with 3 within-subject factors and one between-subject factor (see Figure 3.3). Participants trained in the near or far space and only on one specific orientation (up or down).

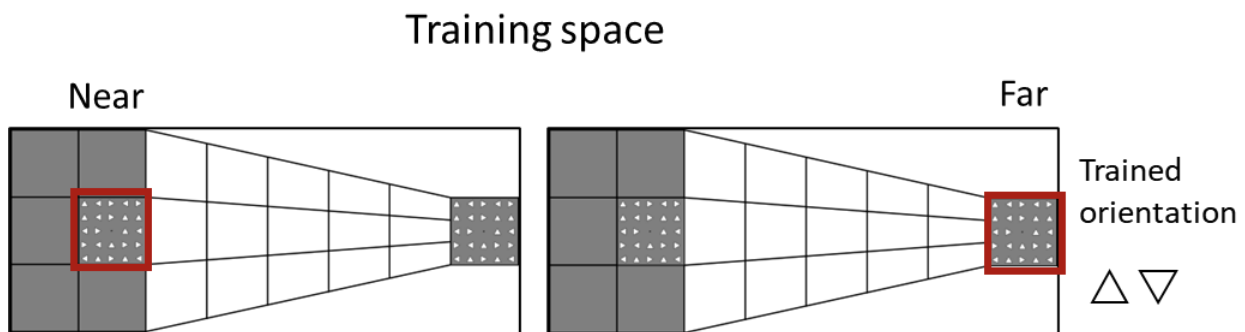


**Figure 3.3 Near and far training spaces (Exp 2).** All possible experimental conditions. Participants were trained on one specific orientation (i.e., triangle pointing up or down) in the near (left) or far (right) space. The near and far spaces are highlighted by a red square in the depiction, however, this was not present in the experiment.

The experiment consisted of two testing phases and a training phase between them (see Figure 3.4). There were three within-participants factors: Orientation (Trained, Untrained), Time (Before, After), and Space (Near, Far). There was also a between-participants factor: Training (Near, Far). The trained orientation was counterbalanced across participants.

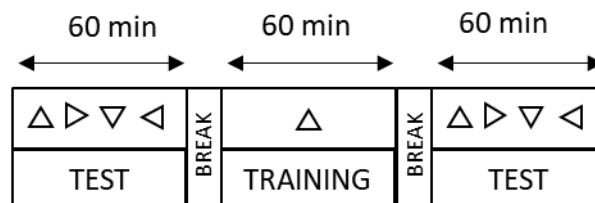


**Figure 3.4 Visual training experimental timeline** Timeline of the experiment including a testing phase lasting 60 minutes in which the four different triangle orientations were tested as a target in separate blocks; a training phase lasting 60 minutes in which only one orientation was used as a target. Finally, the last hour post-training testing phase in which all four orientations were tested as the target.

### 3.2.4 Procedure

Participants gave written consent before starting the experiment in accordance with the procedure and protocols of the University of Kent. The experiment started with a testing phase and participants began the visual search task either in the near or far space according to the sequence order (i.e., A: near-far, B: far-near) and then they performed the same task in the opposite space. In each test phase (before and after training), participants were presented with a target, a triangle pointing up, down, left, or right, at the start of each block (four in total, one for each orientation). Each block consisted of 150 trials, 20% of which were null, that is the target was not present, but it was present in the remaining 80% of the trials. The target was presented five times at each of the 24 possible locations of the 5 x 5 matrix. A total of 2,400 trials, 1,200 at near space, and 1,200 at far space were performed equally split before and after the training. Each trial had a total duration of 3000ms and began with the presentation of a 300ms visual stimuli (matrix of triangles flashing). Participants were then given 2700ms to answer before the next trial began. The stimuli of the following trial were presented even if the response was not given. The background image (Ponzo illusion) was statically displayed on the screen throughout the whole block (Figure 3.3). Participants indicated whether the target was present (by pressing “P”) or absent (by pressing “A”). Each of the three phases lasted about 1h as the total duration depended on the participants since they were allowed to take a break in any of the 16 available pauses (every 3 minutes 45 seconds). Participants underwent a practice phase during which they learned how to perform the task. Once ready, they started the actual experiment. The visual task used was the same for all three phases (before-testing, training, and after-testing) except for the following aspects. In the training phase, participants were trained by repeating blocks in a specific target orientation (up or down) and only in one of the two spaces. This resulted in 2 possible conditions for each training group: orientation up and orientation down for the respective trained space (near, far). The order of the blocks near and far in both testing phases was counterbalanced.

Finally, at the end of the experiment, participants received either credits or monetary compensation for their time, regardless of their performance.

### 3.2.5 Analyses

We used the proportion of hits (target present and response “P”) and false alarms (target absent and response “P”) to calculate both the d-prime ( $d'$ ) and the criterion (Swets et al., 1961). If no key was pressed, the response was classified as absent. When the false alarm rate or the hit rate was 0, their values were adjusted to 0.01; when the false alarm or hit rates were 1, their values were adjusted to 0.99. The d prime was calculated using the formula:  $d' = z(H) - z(FA)$  while for the criterion we used the following:  $c = -(z(H) + z(FA))/2$ . The  $d'$  and criterion values obtained were entered as dependent variables in linear mixed-effects models. We decided to use linear mixed-effects models because they have been proven to be useful methods that take into account random effects such as inter-participant variability, allow generalisation across participants and factors, and do not have the several variance-covariance limitations/assumptions of the repeated measures analysis of variance (rmANOVA). We followed a data-driven approach to create the model with the most complex random structure by adding each variable (orientation, time, space, training) step by step as a random effect and then testing the significance of each and keeping those that improved the model fit. The model fit, which indicates how well the model explains the data, was assessed by likelihood tests on the  $\chi^2$  values. We then evaluated the role of fixed effects (orientation, time, space, training) and their interactions. In the case of variables' interaction effects, their impact was compared against a model including their main effects. These analyses were performed only on the data in the before- and after-testing phases and not on the training phase. Raw data and analysis scripts are available on osf ([https://osf.io/g23tb/?view\\_only=80a01dc618d4452bb936ea62820cddbdb](https://osf.io/g23tb/?view_only=80a01dc618d4452bb936ea62820cddbdb)).

## Eye tracker

We started by selecting the left gaze x and right gaze x coordinates as well as the left and right gaze y coordinates for all the trials when the stimuli were presented, and the eyes were open (could be detected). Then, we calculated the mean for both x and y coordinates and we used a Kernel Distribution Estimation Plot to present them thus, creating a colour map (see Figure 3.6 below).

## 3.2.6 Results

### d-prime

Our null model, thus the model with the best random structure, had orientation and time as random effects. The model with the orientation and time interaction was significantly better than the one with their main effects,  $\chi^2(1, N=44) = 5.31, p = .021$ , Cohen's  $d = 0.29$ , 95% CI = [0.1, 0.47]. We found that participants' performance after the training was significantly higher for the trained ( $M \pm SE = 0.71 \pm 0.08$ ) compared to untrained ( $M \pm SE = 0.55 \pm 0.08$ ) orientation,  $\beta = -0.15$ ,  $SE = 0.07$ , 95% CI = [-0.27, -0.02]. These results were confirmed by a post hoc test corrected for 6 multiple comparisons (Bonferroni-Holm corrected),  $t(43) = 2.97, p = .023, d = 0.29$ . The time x space interaction was tested against the null model including their main effects and the model fit was significantly better,  $\chi^2(1, N=44) = 4.76, p = .03$ , Cohen's  $d = 0.2$ , 95% CI = [0.1, 0.47],  $\beta = 0.14$ ,  $SE = 0.06$ , 95% CI = [-0.01, 0.27]. However, post hoc tests corrected for multiple comparisons (Bonferroni-Holm corrected) did not show any significant differences between the levels of the variables (all  $p > 0.36$ ). We also found that the orientation x time x space interaction significantly improved the model fit,  $\chi^2(1, N=44) = 14.05, p = .007$ . Nevertheless, the model's summary showed only a significant time x space interaction,  $\beta = 0.25$ ,  $SE = 0.09$ , 95% CI = [0.09, 0.45]. After training (both near and far), participants were significantly better for the trained ( $M \pm SE = 0.78 \pm 0.08$ ) compared to the untrained ( $M \pm SE = 0.55 \pm 0.08$ ) orientation, but only when the task was carried out in the far space, Cohen's  $d = 0.42$ , 95% CI = [0.15, 0.69]. We also conducted a post hoc test corrected

for 28 multiple comparisons (Bonferroni-Holm corrected) to further confirm the results,  $t(43) = 3.83$ ,  $p = .02$ ,  $d = 0.42$ . The performance on the near space after training (both near and far), was not significantly different between the trained ( $M \pm SE = 0.64 \pm 0.08$ ) and untrained ( $M \pm SE = 0.56 \pm 0.08$ ) orientations,  $t(43) = 1.20$ ,  $p = 1.00$ ,  $d = 0.15$ .

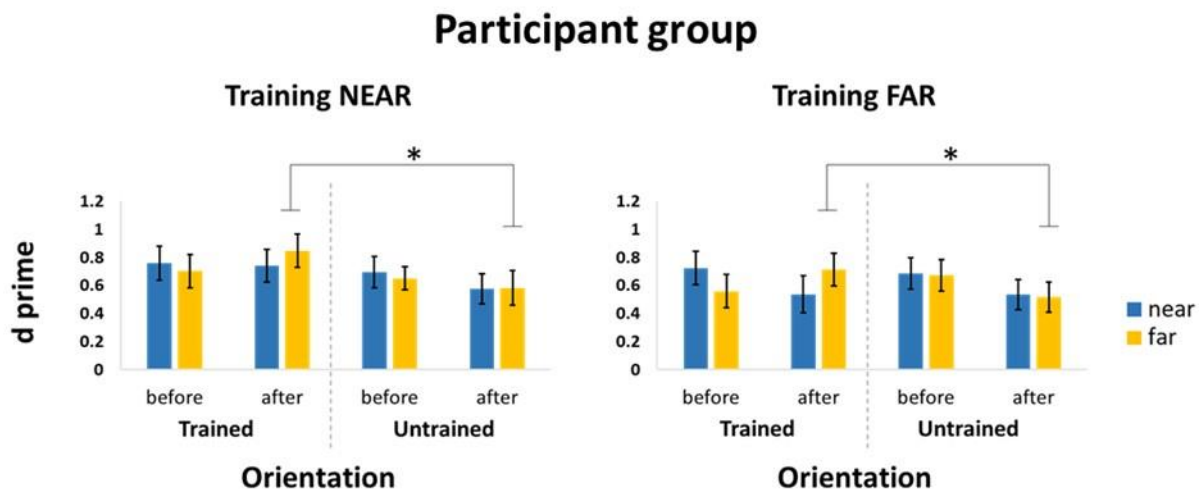


**Figure 3.5 Visual training d-prime results (Exp 1).** Bar charts show the d-prime values for the participants who trained in the near space (left panel) and those who trained in the far space (right panel). The data presented in the chart are divided into Orientation (trained and untrained) and Space (near in blue and far in yellow). Error bars represent the standard error of the mean ( $\pm SEM$ ).  $*p < .05$ .

## Criterion

Our null model, which included the best random structure, had time as a random effect. The analyses showed a main effect of orientation, therefore the model fit with time as the fixed effect was significantly better than the null model,  $\chi^2(1, N=44) = 4.43$ ,  $p = .035$ , Cohen's  $d = 0.12$ , 95% CI = [0.1, 0.22]. Participants were more conservative when carrying out the visual search task for the trained ( $M \pm SE = 1.18 \pm 0.08$ ) compared to untrained ( $M \pm SE = 1.11 \pm 0.08$ ) orientations,  $\beta = -0.07$ ,  $SE = 0.03$ , 95% CI = [-0.14, -0.004].

## Eye tracker

As shown in Figure 3.6, results from the eye tracker monitoring confirmed that participants were focusing on the quadrant they were instructed to look at through the experimental conditions. This assured that they were effectively performing the test in the near or far spaces accordingly to the instructions.

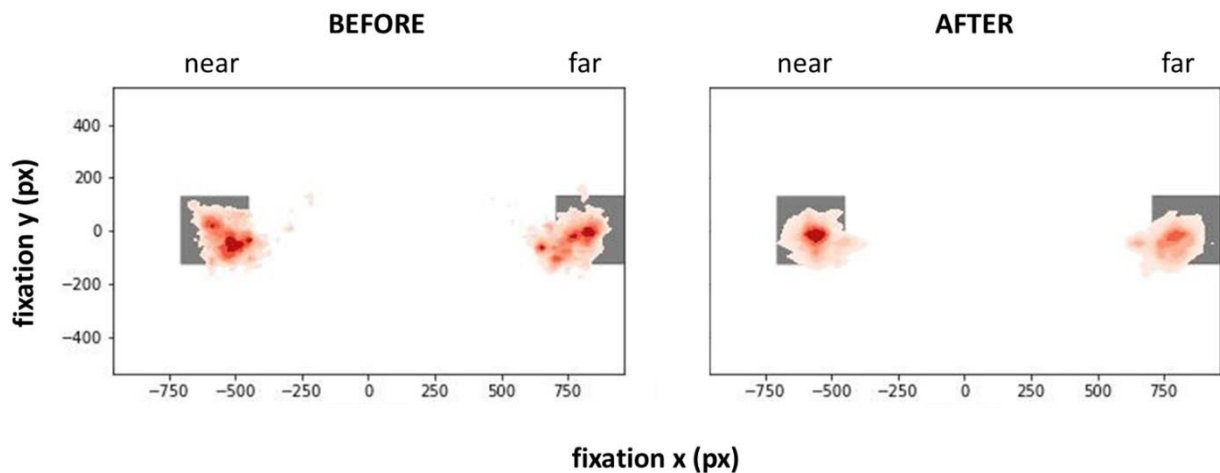


**Figure 3.6 Eye-tracking data visualisation (Exp 1).** Graph showing the average of the gaze data of all participants before and after the training, regardless of the space in which the task was carried out.

### 3.2.7 Discussion

In Experiment 1, we found that participants performed better when tested in the far space in the trained orientations, regardless of whether they trained in the near or far space. This shows that the training in the far space led to improvements that were localised and specific to the trained space and orientation, whereas the training in the near space improved performance specific for the trained orientation, but this effect was only visible when tested in the far space. The difference between trained and untrained orientations is most likely driven by an increased sensitivity for the trained orientation and a decrease in performance for the untrained orientation. This effect is similar to what we found in a previous study (Chapter 2), in which the training improved only in the far space. Here though, both the near and far-trained groups showed improvement in the far space. One possible

reason for this discrepancy may relate to the position where we created the illusory depth perspective. In our previous work this position was either top or bottom, whereas, in this study, the positions were left and right. Indeed, the left hemispace in which the illusory near space was created in the present study may have played a special role in the learning process (Jewell & McCourt, 2000). Many studies have shown that healthy participants have a leftward bias, also called pseudoneglect (Bowers & Heilman, 1980), in several tasks (Charles et al., 2007; Nicholls et al., 1999). For instance, when participants have to determine the centre of a line they tend to bisect the line towards the left compared to the actual centre, which indicates that they perceive the left side of the line as longer (Jewell & McCourt, 2000). This bias has been attributed to the prevalence of visuospatial attention directed towards the left hemispace (Mattingley et al., 2004; Nicholls & Roberts, 2002). Based on these findings, it could be that the left hemispace assignment we made for the near and far space could have influenced the participant's performance. To control for this possibility and replicate the far space advantage in visual perceptual learning, we ran another experiment.

### **3.3 Experiment 2**

As mentioned, an aspect that could have led to Experiment 1's results is the hemispace (left and right) in which the near and far conditions were respectively displayed. To test this possibility, in Experiment 2 we reversed the near and far conditions with respect to the hemispace in which the stimuli were presented (i.e., near to the right and far to the left hemispace). Thus, a group of participants trained in the right hemispace (near) and the other group in the left hemispace (far).

#### **3.3.1 Materials and methods**

##### **Participants**

Forty participants (mean age = 24, range = 19 – 49; 29 females) took part in the experiment. Based on the data from Experiment 1 (N=42), we carried out an a priori analysis using G\*Power version

3.1.9.7 (Faul et al., 2007) to estimate the necessary sample size for the comparison between trained and untrained orientation after the training in the far space. The effect size in the two experiments was 0.42, which corresponds to a medium effect, based on Cohen's (1988) criteria. When the significance criterion is  $\alpha = 0.05$  and power = 0.80, the estimated sample size is  $N = 47$  (thus 23/4 participants per group) for a two-tailed paired sample t-test. However, due to the high difficulty of the recruitment processes during the covid pandemic, we were able to reach 20 participants in each group, slightly below the expected number. All participants had normal or corrected-to-normal vision. The study was approved by the local ethics review committee at the School of Psychology, University of Kent and was carried out according to the principles of the 1964 Declaration of Helsinki as updated by (World Medical Association, 2013).

### Visual search task

The stimuli used in this experiment were identical to the ones used in Experiment 1, except for the location of the illusory space. Instead of having the near space on the left half of the screen and the far space on the right half, it was the other way around. Therefore, the new background image created a depth perspective that resulted in the near space on the right hemisphere and far space on the left hemisphere (Figure 3.7).

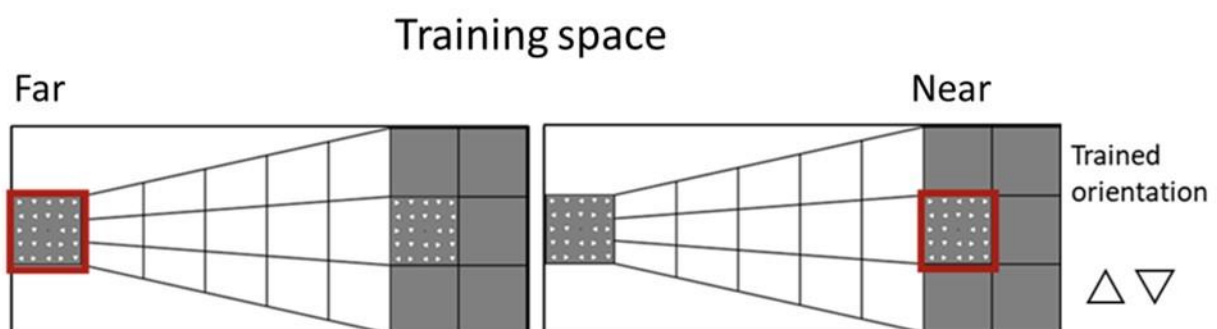


**Figure 3.7 Near and far training spaces (Exp 2).** The portrayal of the stimuli presentation for the far (left) and near (right) spatial conditions. The participants received training on a single orientation (a triangle pointing up or down) in either the near or far space. In the illustration, a red square designates the near (right) and far (left) spaces; in the experiment, this square was absent.

### 3.3.2 Procedures and analyses

The procedures for this experiment were identical to the one used in Experiment 1 with the following exceptions. Participants carried out the training in the near space on the right half of the screen and training in the far space on the left half of the screen. The analyses carried out were identical to Experiment 1. All post hoc tests were Bonferroni-Holm corrected for multiple comparisons.

### 3.3.3 Results

#### d-prime

Our null model, the model that has the best random structure, included time as a random effect. The model with the orientation and training interaction had a significantly better fit than the one consisting of their main effects,  $\chi^2 (1, N=40) = 4.55, p = .03, \beta = -0.16, SE = 0.07, 95\% CI = [-0.29, -0.01]$ . However, post hoc Bonferroni-Holm corrected multiple comparisons and showed that there was no significant difference between the levels of the two variables. We also found that the model fit is significantly higher when the orientation x time x training interaction is included compared to the model with their main effects,  $\chi^2 (1, N=40) = 10.65, p = .03$ . Despite this, the model summary showed no significant effect nor interaction.

Finally, the orientation x time x space x training interaction was tested against the model including only their main effects and the former model fit was significantly better,  $\chi^2 (1, N=40) = 25.13, p = .009$ . However, the model summary indicated only a significant time x space x training interaction,  $\beta = 0.62, SE = 0.20, 95\% CI = [0.25, 0.98]$ . Participants who trained in the far space had a significantly better performance for the trained ( $M \pm SE = 0.87 \pm 0.11$ ) compared to the untrained ( $M \pm SE = 0.55 \pm 0.12$ ) orientation after the training and when the task was done in the far space. We conducted 2 post hoc paired t-tests based on our hypotheses (Chatham, 1999; Kwon, 1996; Ruxton & Beauchamp, 2008), which confirmed the d-prime was higher for trained rather than the untrained

orientation for the group that trained in the far space  $t(19) = 3.03, p = .014$ , Cohen's  $d = 0.63$ , 95% CI = [0.17, 1.10]. On the other hand, participants who trained in the near space did not show a significant difference between the trained ( $M \pm SE = 0.50 \pm 0.11$ ) and untrained ( $M \pm SE = 0.61 \pm 0.11$ ) orientations in the far space after the training,  $t(19) = -1.08, p = 0.59, d = -0.22$ , 95% CI = [-0.51, 0.6]. Finally, an exploratory analysis based on the observed results revealed that there was also a significant improvement in participants' performance when they did the training in the far space for the trained orientation from before ( $M \pm SE = 0.52 \pm 0.10$ ) to after ( $M \pm SE = 0.87 \pm 0.11$ ) the training, but only when the task was carried out in the far space,  $t(19) = 2.54, p = .02$ , Cohen's  $d = 0.57$ .

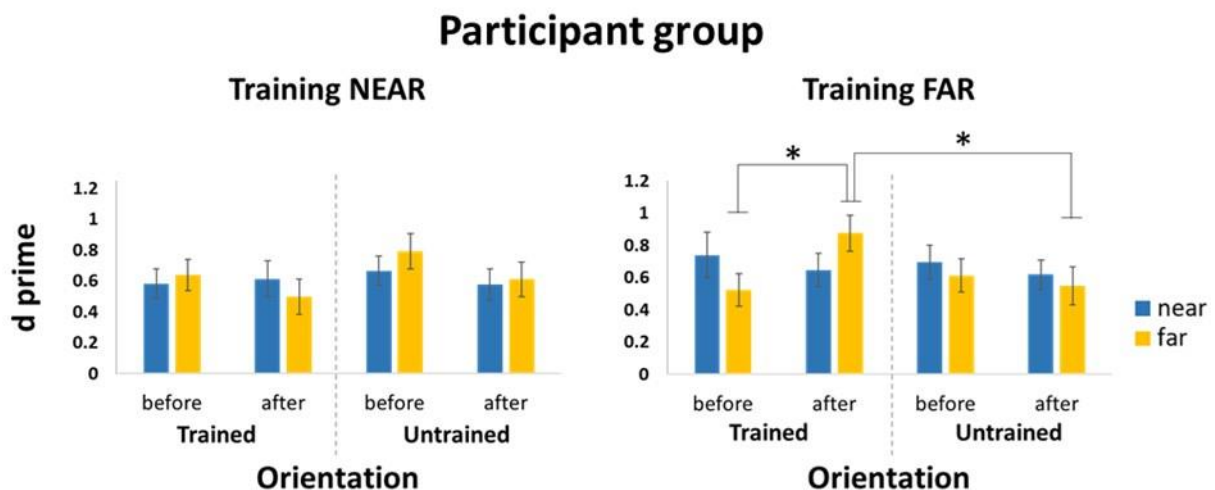


**Figure 3.8 Visual training d-prime results (Exp 2).** Bar charts show the d-prime values for the participants who trained in the near space (left panel) and those who trained in the far space (right panel). The data presented in the chart are divided into Orientation (trained and untrained) and Space (near in blue and far in yellow). Error bars represent the standard error of the mean ( $\pm SEM$ ). \* $p < .05$ .

## Criterion

The analyses revealed that the model with the best random structure had only time as a random effect, thus we used it as our null model. We tested the models including the fixed effects for orientation, time, space and training and their interactions but we found no significant model ( $p > .05$ ).

## Eye-tracking

As shown in Figure 3.9, similar to Experiment 1, participants were focusing on the quadrant they were instructed to look at throughout the experimental conditions. This assured that they were effectively performing the test in the near or far spaces accordingly to the instructions. However, in this Experiment, it can be noted that for the after-test in the right hemispace, there was a greater variability with reduced focus on the quadrant.

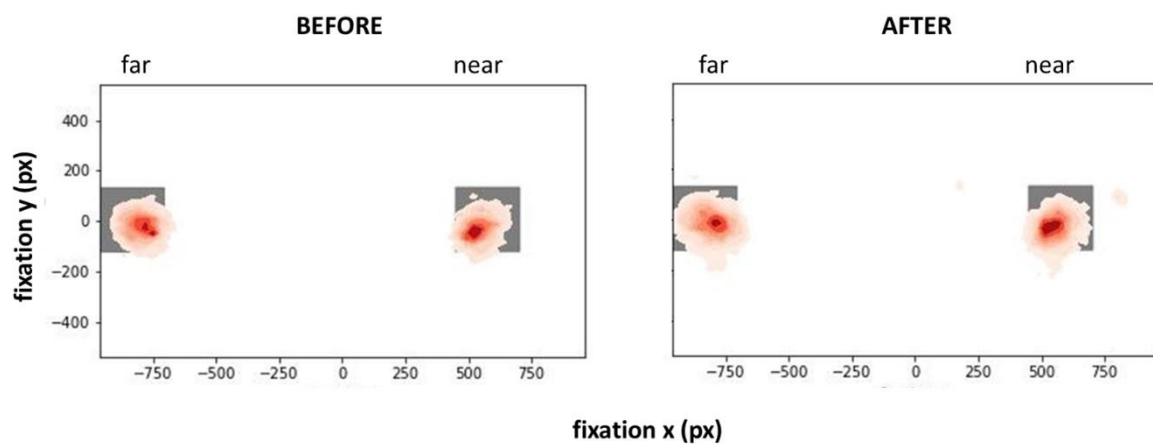


**Figure 3.9 Eye-tracking data visualisation (Exp 2).** Graph showing the average of the gaze data of all participants before and after the training, regardless of the space in which the visual search task was carried out.

### 3.3.4 Discussion

Experiment 2 showed, as in Experiment 1, that the participants who trained in the far space had a significant improvement in their performance (higher  $d'$ -prime) for the trained orientation, but only when tested in the far space. On the other hand, the group who trained in the near space did not show any significant change after training. Therefore, while the results indicate a robust effect of visual perceptual learning in the far space, differently from Experiment 1, here the training resulted to be space specific. These findings may imply that the hemispace in which the training is performed plays a role in the effectiveness and generalizability of the training.

### 3.4 General discussion

In this study, we investigated if visual perceptual training has different effects based on whether the stimuli are presented near or far from the body (*peripersonal* and *extrapersonal* space). In Experiment 1, participants had the near space in the left visual hemifield and in Experiment 2 they had it in the right visual hemifield. In both experiments, one group of participants were trained by repeating a visual search task of a triangle in a specific orientation in the near space, whereas the other group of participants were trained in the far space. When the near space was on the left side of the screen, we found that both the participants who trained in near and far spaces after the training had a significantly better performance (for the trained orientation) when tested in the far space (Experiment 1). When the near space was on the right side of the screen and the visual search task was carried out in the far space only the group of participants who trained in the far space showed better performance (for the trained orientation) after the training in the far space (Experiment 2).

These findings bring support to those reported in the online study using a similar paradigm (Chapter 2). In addition to replicating initial evidence of a far advantage, this study provides robust additional evidence of such an advantage by offering further internal replication of such far learning advantages (or similar). Hemispace might affect the magnitude of the far space advantage, however, it is the depth dimension that leads to the visual perceptual learning effects.

Overall, the results of the present study show that visual training always produces an improvement in the far space when participants performed the visual training in the far space and sometimes also when they did the training in the near space. The key factor that seems to drive the greater effectiveness of the training in Experiment 1 (near and far training group improvement in the far space) seems to derive from the hemispace in which the training is performed. Indeed, the left hemispace seems to be more effective in this learning process.

As described above, in Experiment 1, training in near space induced a learning effect although not in the trained space but only in the far space; whereas Experiment 2 showed that training in near

space led to no significant changes. Thus, the fact that in Experiment 1, the near space was on the left side of the screen whereas, in Experiment 2, it was on the right side, might have been important for the learning effects. It appears then, that doing training on the left hemispace is more effective when it contains the near space. These results are in accordance with the literature suggesting an attentional bias towards the left hemispace (Jewell & McCourt, 2000; Mattingley et al., 2004; Toba et al., 2011).

Neuropsychological dissociations in neglect patients (Bowen et al., 1999; Esposito et al., 2021; Mesulam, 1981; Stone et al., 1992; Weintraub & Mesulam, 1987), as well as the findings of neuroimaging studies (Cavézian et al., 2012; Çiçek et al., 2009; Fink et al., 2000; Foxe et al., 2003; Longo et al., 2015), have demonstrated that the left hemispace is specialised for visuospatial attention. However, it is unclear whether our results in the two hemispaces can be explained by this left hemispace advantage, as in our task, participants were directing their gaze towards the instructed hemispace. So, stimuli presentation was not tachistoscopic.

In summary, we found that training in the far space leads to significant improvements in performance on a visual search task in the trained location that is specific to the trained orientation. On the other hand, training in the near space results in a better performance but only in the far space or no change at all, based on whether it is carried out on the left or right hemispace, respectively. Therefore, our results suggest that visual training is more effective when performed in the far space or the left hemispace. Such advantage can derive from a combination of two mechanisms: a ‘predisposition’ to visual perceptual learning for stimuli that are visually far from the observer (Chapter 2) and a greater visuospatial ability to locate and process visual stimuli that fall within the left compared to the right visual hemispace.

### **Data availability**

All data have been made publicly available via OSF and can be accessed at ([https://osf.io/g23tb/?view\\_only=80a01dc618d4452bb936ea62820cddb](https://osf.io/g23tb/?view_only=80a01dc618d4452bb936ea62820cddb)). The design and analysis plan for the experiment were not preregistered.

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## **Chapter 4 : Magnocellular and parvocellular pathways recruitment in visual perception near and far from the body**

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## Abstract

Visual information is processed differently based on whether the stimuli are presented near (*peripersonal space*, PPS) or far (*extrapersonal space*, EPS) from the body. A series of previous studies from our laboratory (Chapters 2 and 3) have focused on investigating whether this spatial difference can still be observed when we learn to look for specific visual target stimuli among distractors. We found that there is a greater improvement due to visual learning in the far compared to the near space. However, it is unclear which mechanisms subserve such an effect. Previous studies suggested that the magnocellular and parvocellular pathways may selectively process visual stimuli when they are presented in the PPS or the EPS. However, there is not much evidence supporting such a notion and, to what extent this is the case remains unclear. In this study, we examined the involvement of the magnocellular and parvocellular pathways in a visual search task, when performed near compared to far from the observer. We used the Ponzo Illusion to evoke the illusory perspective of depth to distinguish between the two spaces. In the visual search task, participants had to report whether a target (i.e., a triangle) with a specific orientation was present or not among a matrix of distractors (i.e., triangles in other orientations). In one condition, we used the grey and white colours of the stimuli and background to preferentially activate the magnocellular pathway. Whereas, in another condition, we used isoluminant green and red colours to selectively recruit the parvocellular pathway. Contrary to our expectations, participants' accuracy was higher for the magnocellular pathway, regardless of the space (PPS or EPS) in which the task was performed. We interpreted these results as evidence that changing only the chromatism of the stimuli is not enough to selectively activate one of the two pathways. Future studies should investigate whether other specific features (e.g., task difficulty, spatial frequency), possibly combined with chromatism (i.e., chromatic or achromatic), can selectively activate the magnocellular or parvocellular pathways and ultimately unveil their role in spatial perception (and perhaps learning) of stimuli near and far from the observer.

## 4.1 Introduction

When we look for a specific object in the environment, we have to select certain visual stimuli of interest among distractors. Such a process is typically known as visual search (Hoffman, 1979; Koopman, 1956a, 1956b, 1957; Neisser, 1964). Before being able to find and recognise an object, incoming visual inputs have to be processed. However, visual information is processed differently and by different cells, depending on the nature of the signal. Looking at colourful stimuli, for instance, activate specific cells (i.e. cones) compared to non-colourful ones (i.e. rods) (Jacobs, 1993; Solomon & Lennie, 2007). Over the past decade, several studies have suggested new theories regarding the two main visual pathways (magnocellular and parvocellular) that are essential for visual processing. Specifically, it has been proposed that these pathways have preferential processing for certain stimuli characteristics such as colour, motion, and contrast. Nevertheless, both of these pathways originate in the retina where they receive inputs from different cells (see Edwards et al., 2021 for a review).

Ganglion cells in the retina receive inputs from bipolar cells which in turn receive signals from photoreceptors. Ganglion cells can be divided into midget and parasol cells depending on their morphology (Leventhal et al., 1981). Midget cells have small dendrites, respond well to colour, have a high spatial resolution (thus can identify small details), and makeup most (70%) of the projecting cells to the dorsal later geniculate nucleus (LGN) of the thalamus. Parasol cells have larger dendritic fields, are “colour-blind”, have a high temporal resolution, very short response latency, and correspond to the 10% of the total projections to the LGN (Dacey & Petersen, 1992). Parasol cells project to the lower two layers of the LGN consisting of magnocellular cells, whereas the upper four layers (parvocellular cells) receive projections from midget cells (Edwards et al., 2021). The magnocellular pathway projects to layers 4Ca and 4B of the primary visual cortex (V1) which then projects to both the secondary visual cortex (V2) and area V5/MT. The parvocellular pathway ends primarily in layers 4Cb in V1 that then projects to V4 in the temporal cortex. The pathway where the

information travels from V1 to the parietal cortex is called the dorsal stream, whereas the pathway from V1 to the inferotemporal cortex, is known as the ventral stream (Mishkin & Ungerleider, 1982).

Several studies have examined these two pathways and their specificity in the processing of certain types of visual information. In 1982, Ungerleider and Mishkin hypothesised, based on the results of numerous previous experiments (see Ungerleider & Mishkin, 1982 for a review), that the dorsal stream is specialised in spatial perception, thus in identifying the location of a stimulus in space (WHERE), whereas they suggested that the ventral stream is specialised for object perception, namely defining the identity and characteristics of an object (WHAT). Goodale and Milner (1992), proposed a model in which they suggested that both streams receive and process information regarding the characteristics of the stimuli and their locations but the visual inputs are just processed differently (Goodale & Milner, 1992). The dorsal stream uses visual information about size, shapes, and target location to allow the implementation of an action plan, thus becoming essential for online control of movements. On the other hand, the ventral stream uses visual inputs to identify targets which allows us to decide on the suitable path of action (Milner & Goodale, 1998).

Empirical evidence supporting this specialisation of processing, “perception” for the ventral stream and “action” for the dorsal, can be found in lesion studies both in monkeys (Pohl, 1973; Ungerleider & Mishkin, 1982) and humans (Goodale et al., 1991; Goodale & Milner, 1992). For instance, monkeys with lesions in the inferotemporal cortex show an impairment in visual discrimination tasks, however, their performance is not affected in visually guided behaviours. Conversely, monkeys with lesions in the posterior parietal cortex have a significant deficit in visually guided movements but no impairment in visual discrimination tasks (Ungerleider & Mishkin, 1982). With regards to humans, a similar dissociation has been found in patients with visual form agnosia (inferotemporal lesion), which is characterized by the inability to identify visually presented objects based on their size, shape or orientation nor match or discriminate between two of them. It was shown that these people had no issues in visuomotor behaviours which required rotating the hand or

performing a precision grasp (Ganel & Goodale, 2019; Milner & Goodale, 2008). By contrast, patients with optic ataxia (posterior parietal lesion), which consists of severe impairment in reaching for visual targets, orienting and shaping the hand for grasping and online visuomotor control (Andersen et al., 2014) do not have difficulties in carrying out visual perceptual tasks involving objects' sizes, shapes or orientations (Goodale, 2014; Perenin & Vighetto, 1988).

Thus, it appears that the ventral stream is essential for visual perceptual processing whereas the dorsal stream is crucial for performing visually guided actions. Although, recent studies have challenged this strict dichotomy suggesting that the dorsal stream might send global object shape structural information to the ventral stream, which instead shows greater sensitivity to objects' local features (Ayzenberg & Behrmann, 2022). The association “ventral stream-perception” and “dorsal-stream-action” finds further support in studies that showed that visual information is processed differently based on their location in space, namely when it occurs in the peripersonal (close to our body) or extrapersonal (far from our body) space. Evidence of the different processing of visual information in these two spaces has been found in several studies in monkeys (see Cléry et al., 2015 for a review). For instance, the surgical unilateral removal of the postarcuate area (area 6) and the frontal eye fields (area 8) resulted in a double dissociation; monkeys had a severe impairment in attending to and grasping objects (food) in the contralateral peripersonal space after area 6 ablation, and a stronger visual neglect in the extrapersonal space compared to peripersonal space after area 8 removal (Rizzolatti et al., 1983). A similar dissociation in spatial processing was also found in studies in humans (di Pellegrino & Làdavas, 2015; Farnè et al., 2000, 2005; Serino, 2019). For instance, Halligan and Marshall (1991), found that a patient with right hemisphere damage had severe visuospatial neglect in the peripersonal space, but no impairment in the extrapersonal space (Halligan & Marshall, 1991). These findings were later corroborated by other neuroimaging (Brozzoli et al., 2011; Quinlan & Culham, 2007; Weiss et al., 2000, 2003) and neurostimulation studies in humans (Bjoertomt et al., 2002; Lane et al., 2013).

On the dissociation between peripersonal and extrapersonal space, Blini et al. (2018) demonstrated that visual shape discrimination was faster when the objects were presented in the peripersonal rather than in the extrapersonal space. A peripersonal space advantage, specifically higher accuracy, was also found when participants had to carry out tasks involving size, orientation discrimination, and face recognition (Ahsan et al., 2021). Overall, the works described suggest a general advantage of processing different features of visual stimuli in the peripersonal compared to the extrapersonal space.

By contrast, other studies have shown instead that there is an advantage in the extrapersonal space compared to the peripersonal space when examining visual learning rather than visual perception. In a series of studies in our laboratory, we trained participants to detect a visual stimulus (triangle) in a specific shape orientation either in the peripersonal or extrapersonal space (Chapters 2 and 3). Using a visual search task, we tested them before and after a visual training phase in both spaces, to examine whether the learning effects were different based on the locus of the training. We found that visual perceptual learning was effective in the far space, but not always in the near space (depending on the hemispace in which the stimuli were presented). Such results are somehow surprising in relation to previous literature suggesting a possible spatial dissociation in the visual stimuli processing between learning and perception. We hypothesised that this difference could be possibly due to a different recruitment of the parvocellular/ventral pathways in the visual learning task, as such pathways seem to preferentially respond for one rather than the other space. However, it is unclear what is the relative contribution of these pathways to the processing of visual stimuli in the peripersonal and extrapersonal spaces.

Here, we examined the contribution of the magnocellular and parvocellular pathways to the performance in a visual search task in the near and far spaces. We specifically designed a task that selectively recruits the magnocellular or the parvocellular pathways. As suggested by previous studies on the topic (Abrams & Weidler, 2014; Lane et al., 2013; Li et al., 2011; Valdés-Conroy et al., 2014),

we expected to see a double dissociation, with better performance in the magnocellular condition when the visual task is performed in the peripersonal space compared to the parvocellular. Whereas, we predict better performance in the extrapersonal space when the task is performed in the parvocellular condition compared to the magnocellular one.

## **4.2 Materials and methods**

### **Participants**

Thirty-five participants (mean age = 23.26, range = 18-32; 20 females) took part in the experiment. Previous similar studies analysed the reaction times, thus effect sizes for the accuracy were not available. For this reason, we decided to use a sample size that was close to those in similar experiments, Blini et al., (2018) N=32 and Goodhew & Clarke (2016) N=35. 5 participants were excluded from the analyses because of negative d-prime values, they were most likely not able to perform the task. All participants had normal or corrected-to-normal vision. The study was approved by the local ethics review committee at the School of Psychology, University of Kent and was carried out according to the principles of the 1964 Declaration of Helsinki as updated by (World Medical Association, 2013). 28 participants were right-handed (mean =  $91 \pm 3$ , range: 57–100) and two were left-handed (mean =  $-76.97 \pm 1.97$ , range: -75-78.95). Handedness was determined using the Edinburgh Handedness Inventory with the laterality quotient (LQ) (Oldfield, 1971).

### **4.3 Apparatus and stimuli**

The visual search task was built in PsychoPy 3 (Peirce et al., 2019) and it was presented on a ZOWIE XL LCD Monitor with a refreshing rate of 240 Hz and a display resolution of 1920 x 1080 pixels. Participants carried out the task in a laboratory and were seated at 66 centimetres (cm) from the screen. They were allowed to adjust the height of the seat to find a comfortable position to place their head on a chin rest (see Figure 4.1).

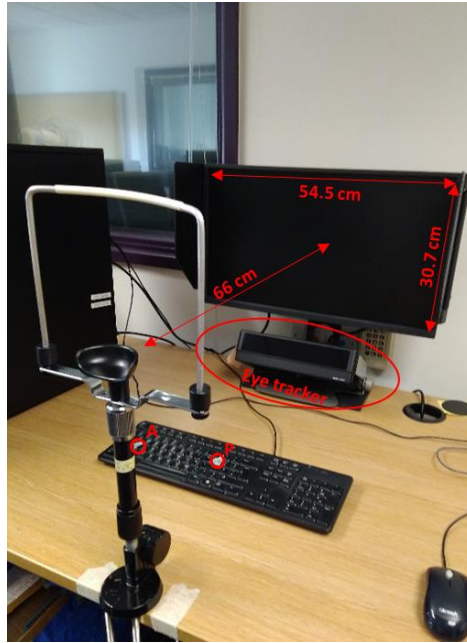


**Figure 4.1 Magnocellular and Parvocellular experimental setup.** Experimental setting including computer, eye tracker and headrest.

The visual stimuli were made up of 24 triangles in a 5 x 5 matrix with a fixation dot in the middle. In the magnocellular condition, triangles had grey fill and white outlines (Figure 4.2A). In the parvocellular condition, triangles had an isoluminant red outline and green fill (Figure 4.2B). Every triangle was  $0^{\circ} 27'$  in length and there was a  $0^{\circ} 54'$  distance from their centres. As a result, the matrix was  $4.5^{\circ}$  by  $4.5^{\circ}$ . The Ponzo illusion was used to create a depth perspective (see Figure 4.2) resulting in the two illusory regions (near and far from the observer) in which the stimuli were presented. Due to the horizontal depth perspective produced by the background image, the near space was located on the left half of the screen and the far space was located on the right. The target's presence was reported by the participants. Participants reported whether the target was present or absent by pressing "P" or "A", respectively, on a keyboard (standard QWERTY keyboard). Both hands were used to respond. Performance was assessed by accuracy.

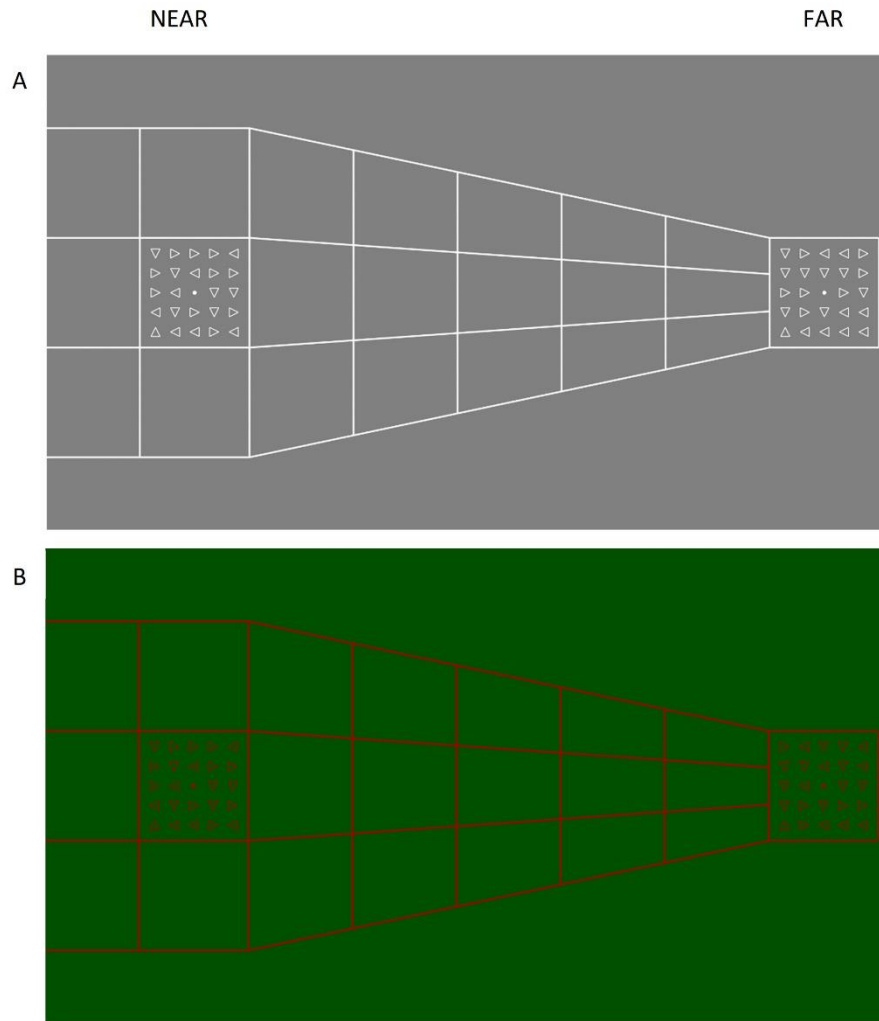


**Figure 4.2 Magnocellular and Parvocellular conditions example.** Depiction of the stimuli' presentation in the near (left) and far (right) space in which the triangles appeared for both the magnocellular (A) and parvocellular (B) conditions. For the magnocellular condition, the background was achromatic, whereas, for the parvocellular condition, the background was chromatic. In the near condition, the task was carried out on the square on the left. Thus, triangles appeared on the left side while the matrix of triangles on the right side stayed fixed without changing. In the far condition, it was the other way around, stimuli were fixed on the left hemisphere and appeared on the right hemisphere. The colours used in the actual task could have had different luminosity due to the pre-task (see procedure below).

## Eye-tracker

Participants' gaze was monitored and recorded throughout the experiment using the Tobii x120 Eyetracker with a sampling rate of 60 Hz. Throughout the experiment, the eye-tracker was constantly capturing the gaze of both eyes. In order to maintain the head in a steady and uniform position across all participants, a chin/headrest was used. The eye tracker was placed just below the screen on the table in front of the participants (Figure 4.1).

By using an eye tracker, we were able to check that participants were looking at the specified location of space, near or far depending on the condition. The calibration of the eye tracker was performed before commencing the experiment. Calibration consisted of five circles presented randomly in the four corners and the middle of the screen, which participants had to follow with their gaze in order to pass the procedure.

### Heterochromatic flicker photometry

This method is one of the several ones that can be used in order to selectively activate the magnocellular or parvocellular pathway (Edwards et al., 2021). Similar to previous studies (Cheng et al., 2004; Ibarbia-Garate & Paz-alonso, 2022; Kveraga et al., 2007), achromatic stimuli were used to selectively recruit the magnocellular pathway, whereas chromatic and isoluminant stimuli were used to preferentially excite the parvocellular pathway.

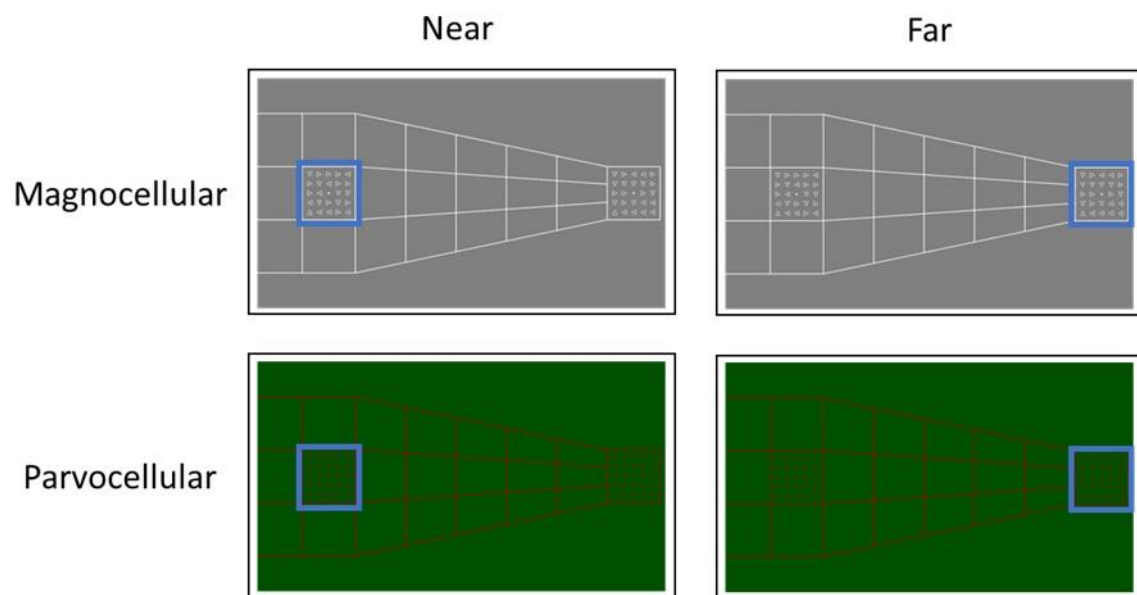


**Figure 4.3 Magnocellular and Parvocellular conditions in both spaces.** All possible experimental conditions. Participants were tested on one specific orientation (i.e., triangle pointing up) in the near and far spaces both in the magnocellular and parvocellular conditions. The near and far spaces are highlighted by blue squares in the image, however, these were not present in the experiment. Note that the colours of stimuli and background in the parvocellular condition might have had different luminosities than those displayed here.

The pair of isoluminant green and red colours were determined by each participant, before commencing the experiment following the eye tracker calibration. They had to select from two rows of red and green circles, alternating at different frequencies, the one that was flickering the least.

#### **4.4 Design**

As shown in Figure 4.3, we used a within-participant experimental design with two factors, Pathway (Magnocellular, Parvocellular) and Space (Near, Far). The order of the conditions was counterbalanced to control for potential confounding effects. Participants carried out the visual search task in the near and far spaces, both for the magnocellular and parvocellular conditions.

#### **4.5 Procedures**

Participants gave written informed consent before starting the experiment in accordance with the procedure and protocols of the University of Kent. Participants were seated in front of the screen, and they were allowed to adjust the height of the chair to find a comfortable position to place their head on the chin rest. Before commencing, they were instructed to perform a calibration task to attune the eye tracker. The experiment started with the heterochromatic flicker photometry (pre-task) in which participants chose between several alternating green and red colours, the ones that they perceived as flickering the least, thus isoluminant (Cheng et al., 2004; Cushing et al., 2019; Edwards et al., 2021; Kveraga et al., 2007). The red and green colours determined in this task were then used in the parvocellular condition for both the background image and stimuli. Once that was done, they started the main visual search task. Participants began the visual search task either in the near or far space and with the magnocellular or parvocellular condition, according to a pre-defined counterbalanced order (e.g., magno near - magno far, parvo far - parvo near). Each block consisted of 150 trials, 20% of which were null. Therefore, the target (triangle pointing up) found amongst the distractors (triangles with the other three orientations) was not present, but it was present in the remaining 80%

of the trials. The target was randomly presented five times at each of 24 possible positions in a 5 x 5 matrix. Participants completed a total of 600 trials, 300 in the near space and 300 in the far space. In each space, 150 trials were for the magnocellular condition (grey and white), and 150 for the parvocellular condition (green and red). Each trial consisted of the display of the 5x5 matrix of triangles for 600 milliseconds (ms). Then, the matrix disappeared, and participants had 1300ms to respond before the next trial started. Throughout the entire block, the background image (Ponzo Illusion) was visible on the screen. Each block lasted 7.5 minutes, however, the total duration (30 minutes) depended on the participants, since they were allowed to take breaks at variable intervals. The visual task used was the same for all four conditions (magno near, magno far, parvo near, parvo far). Finally, at the end of the experiment, participants received either credits or money as compensation for their time and they were debriefed.

## 4.6 Analyses

Responses from participants were broken down into hits (target present - response present) and false alarms (target absent - response present) to evaluate their performance. The responses were categorised as absent if the participant failed to press any keys. The values for the d-prime ( $d'$ ) and the criterion (Swets et al., 1961) were then calculated using these proportions. While we used the calculation  $c = -(z(H) + z(FA))/2$  to determine the criterion,  $d'$  was derived using the formula  $d' = z(H) - z(FA)$ . When these values were 0 or 1, the proportions of false alarms and hits were adjusted to 0.01 and 0.99, respectively.

The d-prime performance metric was used to analyse performance using linear mixed-effects models (Baayen et al., 2008). Mixed-effects models include several important benefits, including the use of single-trial data rather than averaged data, the absence of the assumption of observational independence, and consideration of the covariance structure of the data, including random effects (i.e., individual variability). The random effects were included in a model. The generalisation is at its

finest when a linear mixed model comprises the most complex random structure that does not hinder model convergence (Matuschek et al., 2017). Probability tests were performed to measure how well the models fit after the sequential addition of random components (i.e., this was done by comparing the residuals of each model and then selecting the one with significantly lower deviance as assessed by a chi-square test). For interindividual variability, we included a random intercept in each model.

We began by analysing the effects of the random pathway (magno, parvo) and space (near, far) slopes on the model. Both variables were within-participant. We began testing the fixed effects after determining the ideal random slope for the model. Thus, the interactions between the pathways and the spaces, as well as their respective main effects were assessed. As mentioned above, we utilised likelihood ratio tests to examine if the gains in model fit were statistically significant (for a similar approach see also Blini et al., 2018). The raw data and whole analytic process for the linear mixed model, which was performed with the free programme R (RStudio Team, 2020), are available on osf ([https://osf.io/xz82h/?view\\_only=2ee5cf02b7164a5ab687d742151f35f5](https://osf.io/xz82h/?view_only=2ee5cf02b7164a5ab687d742151f35f5)).

## 4.7 Results

Our null model, which represented the model with the best random structure had only “participant” as a random effect.

### **d-prime**

The model fit significantly improved when the model including a main effect of Pathway was tested against our null model,  $\chi^2(1, N=30) = 8.21, p = .004$ , Cohen’s  $d = 0.31$ , 95% CI = [0.08, 0.53]. Thus, participants’ performance was significantly higher in the magnocellular ( $M \pm SE = 1.53 \pm 0.10$ ) compared to the parvocellular ( $M \pm SE = 1.35 \pm 0.10$ ) condition,  $\beta = -0.18$ ,  $SE = 0.06$ , 95% CI = [-0.31, -0.07]. This result was further confirmed by a two-tailed paired sample t-test,  $t(89) = 2.92, p = .005$ . Models including a main effect of space,  $\chi^2(1, N=30) = 2.56, p = .11$ , and the interaction

between Pathway and Space,  $\chi^2(1, N=28) = 1.33$ ,  $p = .25$ , were not significantly different from the null model and the model including Pathway and Space as main effects, respectively. Overall, as shown in Figure 4.4 analyses showed that participants were performing better in the achromatic compared to the chromatic condition.

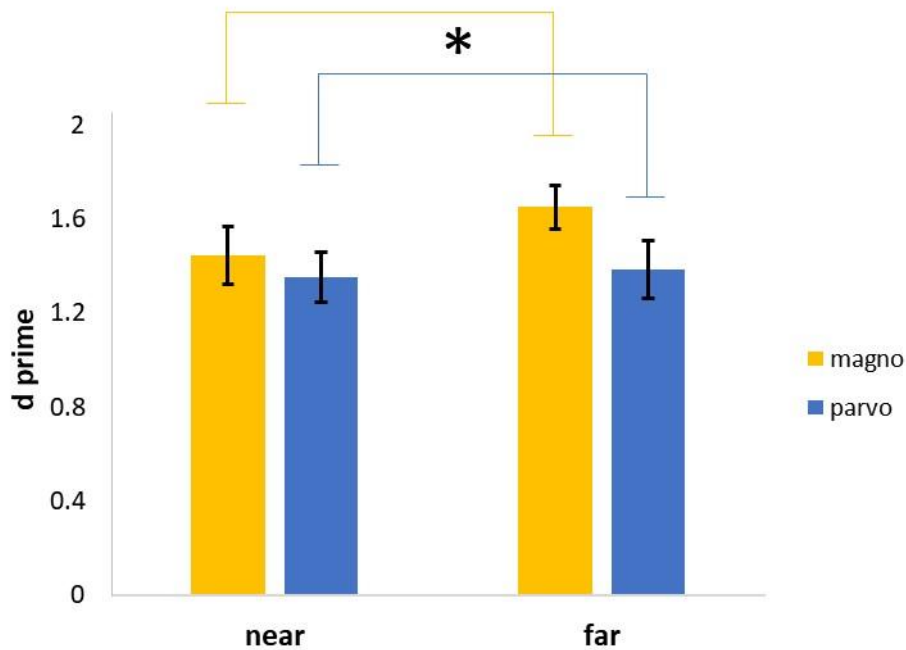


**Figure 4.4 Magnocellular and Parvocellular d-prime results.** Bar charts illustrating d-prime values for the near space on the left hemispace and far space on the right hemispace. The data are categorised as magnocellular (yellow columns) and parvocellular (blue columns). Error bars represent the standard error of the mean ( $\pm$ SEM).  $*p < .05$ .

## Criterion

Our null models only contained random effects for “participant” when the criterion was analysed. Model fit did not improve when Pathway,  $\chi^2(1, N=30) = 1.05$ ,  $p = .31$ , or Space,  $\chi^2(1, N=30) = 0.004$ ,  $p = .98$  were included. However, the model consisting of the Pathway and Space interaction was significantly different from the one including their main effects,  $\chi^2(1, N=30) = 5.05$ ,  $p = .03$ ,  $\beta = -0.19$ ,  $SE = 0.09$ ,  $95\% \text{ CI} = [-0.35, -0.02]$ . Despite this, post hoc paired t-tests Bonferroni-Holm

corrected for 6 multiple comparisons showed that there was no significant difference between the levels of the two factors.

## 4.8 Discussion

In this study, we examined the different contributions of the magnocellular and parvocellular pathways, when participants perform a visual search task in the near (peripersonal) and far (extrapersonal) space. The design of this experiment is similar to the one we used in a series of previous studies (Chapter 2; Chapter 3) on the influence of space on visual perceptual learning. Here, we used stimuli that are supposed to preferentially activate magnocellular or parvocellular neurons to disentangle their roles in visual search tasks when performed near and far from the body. Contrary to our expectations, we found that participants were more accurate when the magnocellular pathway was recruited, both in the peripersonal and extrapersonal spaces. However, we did not reveal any significant preference for one pathway or the other in relation to the position of the stimuli in space (peripersonal or extrapersonal). We will now discuss the possible reasons that led to these results as well as potential future studies that can help to clarify this notion.

One of the important aspects to consider is the difficulty of the task. Performing simple tasks (i.e., detection) leads to higher magnocellular activation whereas complex tasks (i.e., identification, discrimination) result in increased parvocellular activation (Li et al., 2011). The task used in the current study was a visual search task with low levels of efficiency (Wolfe, 2010, 2020), thus, it can be classified as a difficult task. Therefore, we should have expected greater recruitment and thus superior performance of the parvocellular pathway, instead, we found better accuracy in the magnocellular condition.

Another crucial factor to consider is the role of attention. Goodhew & Clarke (2016) demonstrated that the activation of the magnocellular pathway in the near space and the parvocellular pathway in the far space is determined by the attentional demands of the task. Specifically, in high

attentional demanding tasks (e.g., a large number of distractors in a visual search), the parvocellular pathway becomes more prominent regardless of the space in which the stimuli are presented (Goodhew & Clarke, 2016). This element might explain the fact that there was no difference between the two spaces, although the pathway resulting in higher accuracies is the opposite (magnocellular). Such overall improvement for the condition that was supposed to activate the magnocellular pathway (i.e., achromatic) may be simply because some participants reported the chromatic condition to be more tiring.

Furthermore, even the size of the focus of attention has different effects on the two visual pathways. According to previous findings, attending a narrow size region of space enhances parvocellular neurons activity and spatial acuity as a result, whereas it does not affect magnocellular neurons (Goodhew et al., 2017). These results are in contrast with those observed in the present study since our visual search task was supposed to require a small focus of attention (i.e., finding a specific shape among very similar ones). Thus, suggesting that our results were affected by other factors.

Another element that influences the recruitment of the magnocellular or parvocellular pathway is the spatial frequency of the stimuli. Indeed, the magnocellular pathway has higher contrast sensitivity for low spatial frequency stimuli whereas the parvocellular pathway has it for high spatial frequency ones (Abrams & Weidler, 2014). Thus, it might be that the performance in our visual search tasks depended more on low spatial frequencies since we found higher accuracies on the magnocellular pathway condition.

On the bases of what we have discussed regarding our results in relation to previous studies, it may be that our conditions were not able to activate exclusively one pathway or the other and that we ended up recruiting mostly the magnocellular pathway.

Future studies should focus on trying to adapt other features of the stimuli such as luminance contrast and spatial frequencies, and isoluminance, to improve the possible differential activation of the two pathways. Moreover, another aspect that would be interesting to manipulate is the attentional

demands of the task, making the visual search task easier by decreasing the number of distractors or modifying (extending or shortening) the duration of the stimuli presentation. We are currently running two studies in which we manipulate the attentional demands, by having longer and shorter presentation times compared to the present one, so that we can examine its effects on the visual search task.

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## Chapter 5 : Somatosensory impact on motor cortex: how touch shapes motor behaviour

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**Antonio Zafarana:** Conceptualisation, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Visualisation; Dollyanne Muret: Conceptualisation, Methodology, Validation, Formal analysis, Writing, review & editing; Alessandro Farnè: Conceptualisation, Methodology, Validation, Formal analysis, Writing, review & editing; Luigi Tamè: Conceptualisation, Methodology, Validation, Formal analysis, Resources, Writing, review & editing, Funding acquisition.

## **Abstract**

The ability to manipulate objects is a critical skill for humans. A such complex function is carried out primarily by the motor system. However, such a process would not be possible without the continuous information provided by the somatosensory system, regarding body parts' position and the status of the skin. The somatosensory feedback is particularly important when a movement must be adjusted while performing an action. Effective interactions between the somatosensory and motor systems are indeed paramount for performing fine motor behaviour, as made dramatically clear by brain damage. Somatosensory deficits following lesions of the nervous system have received little attention compared to motor control. Yet, patients suffering from somatosensory deficits usually show reduced recovery of motor functions, preserved somatosensation being a good predictor of motor recovery. Despite the importance of touch in shaping motor behaviour, the functional relationships between the somatosensory and motor systems remain unclear. To fill this gap and examine the potential role of somatosensory information in modulating motor behaviour, here we focus on studies that investigated the crosstalk between the somatosensory and motor systems and, in particular on the role of touch in shaping motor behaviour. We will start by describing, across different species, the anatomical and neurophysiological connections between these systems and the nature of these communications (i.e., excitatory, and inhibitory). We will then present evidence from neuropathological studies and the severe consequences of somatosensory signals' disruption on motor performance. Finally, we will report on a series of studies showing how passive tactile training can induce plasticity in the somatosensory cortices and in turn the benefits that this might have on motor behaviour.

## 5.1 Introduction

The ability to manipulate objects plays a crucial role in humans' daily life as it is a fundamental part of our interaction with the environment. To fulfil this role, our motor control depends heavily on the somatosensory system, which continuously provides information to the motor system about the position of our body parts, and the status of their skin surfaces (Gentilucci et al., 1997; Scott, 2016). Somatosensory and motor systems are indeed extensively inter-connected anatomically at both cortical (Catani et al., 2012) and spinal levels (Balaskas et al., 2020; Baldissera et al., 1981), somatosensory feedback allowing for effective and fast adjustment of movements execution (Moscatelli et al., 2019; Preston & Ehrsson, 2016). This is evident in several everyday life situations, whereby precise calculation and balance of forces determined by the interactions between the sensory inputs and motor outputs are used to accurately grasp a mug full of coffee and bring it to the mouth without spilling it out (Johansson & Westling, 1984).

Implementation of action cannot be executed as intended if the two networks are not communicating effectively (Scott, 2016). This has been proven by a series of experiments on monkeys whose afferent sensory signals from muscles or skin were interrupted at different levels of the spinal cord. In a pioneering study, Mott & Sherrington, 1895 showed that as a result of hand and foot deafferentation, monkeys were not able to perform fine movements (i.e., grasping), whereas deafferentation of the whole forelimb except for the hand and foot made monkeys unable to execute relatively less complex movements (i.e., walking) (Mott & Sherrington, 1895). From these behavioural observations, the authors concluded that: “afferent impulses, both from the skin and from the muscles, especially the former, as related to the palm and sole, are necessary for carrying out highest-level movements” (Mott & Sherrington, 1895, p. 614). Since then, substantial evidence of interactions between the somatosensory and motor systems has been gathered from a wide range of studies using different approaches and models. Several studies on animals (Aronoff et al., 2010; Kinnischtzke et al., 2016; Krubitzer & Kaas, 1990; Mao et al., 2011) and humans (Berlot et al., 2019;

Catani et al., 2012; Eickhoff et al., 2010), have disclosed the underlying neuro-anatomical and neuro-physiological connections between sensory and motor brain regions.

This review has a twofold aim. First, we wish to make clear the importance of the entwined relationship between the somatosensory and motor systems for human behaviour by analysing some of its key aspects in depth. To this aim, we will unfold the anatomical and neurophysiological pathways connecting the sensory and motor systems by critically reporting paradigmatic studies in animals and neuroimaging works in humans. At the functional level, we will also report and discuss data on the inhibitory and excitatory nature of these connections. In humans, both excitatory and inhibitory pathways between somatosensory and motor cortices have indeed been revealed, for example by works combining cutaneous afferent stimulation and Transcranial Magnetic Stimulation (TMS) (Bikmullina et al., 2009; Chen et al., 2015; Kukaswadia et al., 2005; Pilurzi et al., 2013; Sailer et al., 2002; Tokimura et al., 2000). The functional exploration of these sensorimotor connections will then be complemented by insightful cases from neuropathological studies, focusing on patients with stroke (Borich et al., 2015; Frías et al., 2018; Ingemanson et al., 2019; Schaechter et al., 2012; Sullivan & Hedman, 2008; Wu et al., 2006) and focal dystonia (Avanzino, Tinazzi, Ionta, & Fiorio, 2015; Melgari et al., 2013) as paradigmatic examples of the loss of efficient sensorimotor communication. Not last, we will examine the effects of somatosensory deprivation and the disruption of afferent inputs coming from the skin on motor performance. A good illustration is provided by the work of Augurelle and colleagues (2003), in which local anaesthesia in the index finger and thumb to interrupt cutaneous afferents produced impairments in motor performance involving object manipulation.

Besides constituting the core of our first aim, these sections will be propaedeutic to achieve the second aim of this review. This consists in providing both empirical and theoretical grounds for developing novel somatosensory-to-motor rehabilitation strategies, for people suffering from brain injury and other neurological conditions. To this aim, the last section will examine the impact of

short- and long-term tactile learning on the motor system. Most active training procedures typically imply attention-demanding and effortful tasks to be performed intensively for a prolonged period of time. Although these techniques may be effective, they are time-consuming and demanding for people, especially for certain populations such as elderly or stroke patients (Albert & Kesselring, 2014; Hunter & Crome, 2002; Teasell et al., 2006). Thus, here we will focus on passive learning paradigms and particularly on repetitive somatosensory stimulation (RSS), which applied at the tip of one or multiple fingers has been proven to be effective in modulating tactile performance. Likely relying on the interactions that will be detailed in the first sections of this review, the importance of the beneficial effects produced by RSS training over motor performance will be discussed (Kalisch et al., 2007, 2010; Kattenstroth et al., 2018; Kojima et al., 2018; Ladda et al., 2014; Onishi et al., 2013; Smith et al., 2009). Altogether, this review will provide a much-awaited state of the art of the key functional aspects of sensorimotor crosstalk and their neural underpinnings and will hopefully pave the way to the development of much-needed innovative, sensory-to-motor therapeutic approaches for clinical populations.

## **5.2 Anatomical and neurophysiological interactions between the somatosensory and motor cortices**

The somatosensory and motor systems are anatomically heavily interconnected both within and across hemispheres, as documented in several species. Here, we will proceed following a phylogenetical order, reporting first results from species that are evolutionarily distant from humans. While the phylogenetic “tree” includes different lineages based on comparative studies of neocortex organisation (Krubitzer & Seelke, 2012), we will direct our attention to macaques given that these are popular animal models to study the neural basis of human dexterity as prehension is similar in macaques and humans (for a review see Yan, Sobinov, & Bensmaia, 2021). This section is not meant to exhaustively delineate all pathways and connections between somatosensory signals and motor

output. Instead, we will concentrate mainly on the early cortical brain regions (i.e., primary somatosensory (S1) and motor (M1) cortices) even though a few studies will include other regions (e.g., the secondary somatosensory cortex (S2) and spinal cord) (see Gharbawie, Stepniewska, Qi, & Kaas, 2011).

Evidence of dense connections between the sensory and motor systems was provided by a study that examined the long-range connections of the mouse's primary somatosensory barrel cortex, which is the cortical region receiving signals from the whiskers through the thalamus (Aronoff et al., 2010). Other studies showed that S1 (postcentral gyrus) axons project to M1 and vice versa with reciprocal connections between these two brain areas (Kinnischtzke et al., 2016; Mao et al., 2011; Petreanu et al., 2009; Rocco-Donovan et al., 2011). This information reveals the intricate anatomical circuits that may be used by M1 (projecting to S1 and then receiving input back) to perform “sensory-guided adjustments” in motor behaviour (see also Figure 5.1A). However, S1 has been recently proposed to modulate motor behaviour even directly. A recent study (Karadimas et al., 2020) showed that S1 pyramidal neurons' activity, which preceded movement onset, was highly correlated with the locomotor speed in mice. Moreover, S1 photostimulation produced an increase in the spinal neuron network generating locomotor activity, with no interference from other cortical, subcortical areas (pharmacologically blocked and M1 was even removed) or sensory feedback. Activation of the S1 pyramidal neurons that project to the cervical spinal cord also resulted in higher speed overall whereas inactivating this pathway led to impaired locomotion (Karadimas et al., 2020). In a similar vein, Chang and colleagues (2022) showed that silencing the inputs that S1 receives from S2 significantly disrupt the hind paw movements during locomotion in mice (Chang et al., 2022). These findings show that S1 in mice has a direct pathway to transmit motor signals independent from M1 or other areas typically involved in motor activity.

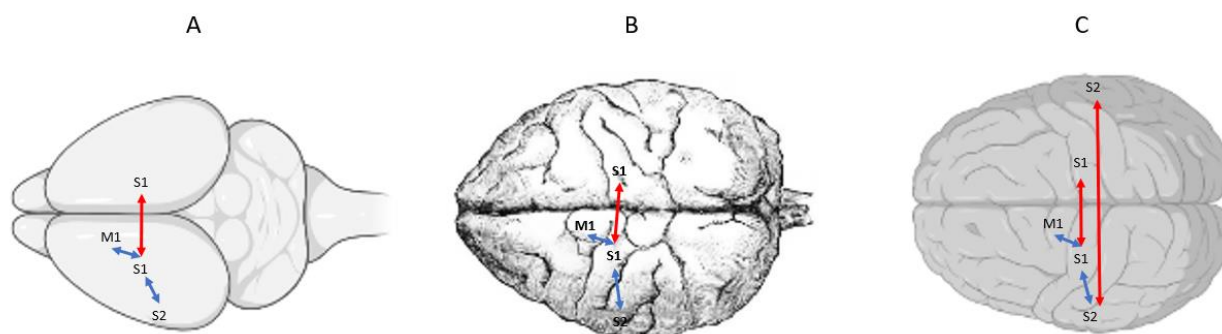


**Figure 5.1 Somatosensory and motor cortices anatomical connections.** Schematic representation of the connections between S1, M1 and S2 in the mice (A), macaques (B) and human cortices (C). The brain sizes reported in this image are not to scale and are presented for illustrative purposes only. Blue arrows correspond to the intra-hemispheric connections whereas red arrows to the interhemispheric ones.

Anatomical connections between somatosensory and motor cortices have also been explored in species closer to humans in terms of neocortical organisation, such as monkeys. Tract tracing studies unveiled an intricate pattern of intra- and inter-hemispheric connections between S1 and M1 (Burton et al., 1995; Gharbawie et al., 2011; Jones et al., 1978; Krubitzer et al., 1986; Krubitzer & Kaas, 1990; Künzle, 1978; Morecraft et al., 2015; Pons & Kaas, 1986; Stepniewska et al., 1993) and their respective projections to S2 (Krubitzer & Kaas, 1990; Künzle, 1978). S1 is indirectly connected to M1 in the contralateral hemisphere also via the transcallosal connections between the two S1 and via S2 which is highly connected to S1 and M1 (Krubitzer & Kaas, 1990). Furthermore, S2 has reciprocal ipsilateral connections with S1 and M1 as well as with the contralateral S2 (Krubitzer & Kaas, 1990) (Figure 5.1B). At the functional level, intracortical microstimulation (ICMS) of S1 has been found to evoke movements in primates (Baldwin et al., 2018) and to affect recorded muscle activity (Widener and Cheney 1997), often of inhibitory nature. Reciprocally, recordings of M1 neural activity in awake monkeys demonstrated that a group of neurons was responding to afferent tactile stimuli on the fingers or hand when there were no movements (Lemon, 1981). The authors also showed that some M1 neurons might receive cutaneous inputs directly from the thalamus without

relying on S1, as demonstrated by the short latency of the response (around 10 ms). This shows that cutaneous afferent inputs directly affect the motor cortex activity (see also Rosén & Asanuma, 1972).

Several human studies have corroborated these findings (intra-hemispheric S1-M1 connections) in animals. For instance, Catani and colleagues (2012) investigated the structural intrahemispheric connections of the pre- and post-central gyri using diffusion tensor imaging (DTI) in conjunction with a post-mortem examination. This method revealed many groups of u-shaped tracts connecting S1 and M1 homuncular representations, such for instance the paracentral lobule tract connecting S1 and M1 “foot” representations and the superior, ventral and transverse tracts connecting S1 and M1 at the level of the hand area (Catani et al., 2012).

Eickhoff et al., 2010 analysed the intra-hemispheric anatomical and functional connectivity of S2 using both probabilistic tractography on diffusion tensor imaging (DTI) data and meta-analytic connectivity modelling on a functional database. They found the presence of tracts linking S2 and S1 and slightly weaker (less dense) connections between S2 and M1. The functional analysis revealed that the structural connectivity between S1 and S2 is stronger than the functional one, whereas the opposite trend was found between S2 and the premotor cortex. Finally, the structural and functional connectivity between M1 and S2 were approximately equal in strength.

Regarding the inter-hemispheric structural connectivity, which is thought to support inter-hemispheric inhibition/excitation processing (Ni et al., 2009), the examination of the transcallosal tracts connecting homologous S1 and M1 regions using DTI (Fling et al., 2013) revealed moderate S1 inter-hemispheric connection, and dense fibre tracts connecting M1 regions (Figure 5.1C). Taken together, the works described in this section provide compelling and converging evidence that the somatosensory and motor systems have strong interconnections with one another both at the intra- and inter-hemispheric levels.

### 5.3 Functional role of sensorimotor interactions

In this section, we will consider the properties of the above-recalled connections and the kinds of interaction through which sensory and motor systems exchange information. We will examine the excitatory and inhibitory nature of these connections, the features that modulate them and how they interact with each other. Ultimately, we will summarise a series of empirical evidence suggesting the functional role that these dense interconnections serve.

It has been shown that if electrocutaneous stimulation of peripheral nerves close to a target muscle precedes a TMS pulse over M1, the resulting motor-evoked potential (MEP) from the targeted muscle may be inhibited or facilitated (Lazzaro et al., 2005; Tokimura et al., 2000; Udupa et al., 2009). For these reasons, TMS is considered an ideal tool to assess sensorimotor function (Reis et al., 2008; Staines & Bolton, 2013; Turco et al., 2018). The following section reports on studies whereby TMS has been applied over the hand area in M1 and MEPs were recorded from the first dorsal interosseus (FDI) unless specified otherwise. The emergence of such excitatory and inhibitory effects is modulated by factors such as stimulation onset, type of afferent nerves (mixed or cutaneous), somatotopic distribution (homotopic or heterotopic stimulation), stimulation intensities (both peripheral and TMS) and specific neurotransmitters involved (GABA, ACh) (Turco et al., 2018). Each of these factors, which provides evidence of the mechanisms underlying the interactions between S1 and M1, will be discussed in detail in this section. The importance of stimulation onset has been demonstrated by Delwaide & Oliver (1990), who showed that peripheral stimulation reduced MEP amplitude evoked by single-pulse TMS applied on the contralateral M1 when the interstimulus interval (ISI) between the sensory afferent stimulus and TMS is short (about 20ms) or long (about 200ms). The former is called short-latency afferent inhibition (SAI), and the latter is long-latency afferent inhibition (LAI) (Chen, Corwell, & Hallett, 1999). Using electroencephalography (EEG), Tokimura and Colleagues (200) found that the afferent input inhibits motor corticospinal excitability as early as 5ms from the arrival of the input in the cortex, suggesting that this effect occurs at the

cortical level through a rather direct pathway connecting the sensory and motor systems (Tokimura et al., 2000).

The type of afferent nerves involved in SAI has been explored by Bayle and colleagues (2016) using either median nerve or cutaneous digital nerve stimulation to examine the relationship between the type of afferent sensory fibres (mixed or purely sensory), somatosensory evoked potentials (SEP) and SAI. They found that SAI is positively correlated both with the recruitment of sensory afferent fibres and somatosensory excitability, as measured by variations in SEPs amplitude (Bailey et al., 2016). This suggests that the magnitude of M1 inhibition (i.e., SAI) depends on both the sensory afferent volley (i.e., fibres recruited) and S1 excitation (i.e., SEPs).

The third factor/parameter affecting SAI is the somatotopic distribution. The stimulation is considered homotopic if the afferent stimulation is applied near the targeted muscle of the TMS (e.g., MEP recorded from FDI and afferent stimulation of index finger or thumb) and heterotopic if it is far from the targeted muscle (e.g., MEP recorded from FDI and afferent stimulation on the little finger). To analyse how somatotopic distribution affects sensorimotor integration, Classen and colleagues (2000) applied electrical stimulation on the right thumb or little finger of one hand while delivering a TMS pulse over M1. They measured the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscle responses at different inter-stimulus intervals between the afferent stimulus and TMS (Classen et al., 2000). Results showed that *homotopic* conditioning stimulation caused inhibition at short ISI (20ms) and excitation at long ISI (100s), whereas *heterotopic* stimulation caused inhibition at both ISIs although the inhibition was weaker for the short interval (Classen et al., 2000). These results suggest that this interaction is mediated both by the state of the muscle (relaxed or contracted) and that cutaneous and motor signals are integrated into a somatotopically organised fashion, though, the timing between the afferent stimuli can alter such organisation (Tamè et al., 2015). A neuroimaging (functional magnetic resonance imaging, fMRI) study in humans, using a repetition suppression paradigm (Tamè et al., 2012), showed a finger-specific response in S1 following the

contralateral tactile stimulation of the fingers (index and middle fingers). Intriguingly, authors found also a deactivation pattern in M1 that was mirror symmetric to the finger-specific response in S1. Following up on this study, Tamè and colleagues combined a similar adaptation paradigm with an SAI protocol in which they applied TMS over M1 to investigate how spatial and temporal aspects of tactile inputs may affect motor outputs/excitability (Tamè et al., 2015). They found that electrocutaneous stimulation of the same finger lessened the amount of MEP inhibition compared to different fingers, specifically at short ISIs. On the other hand, at long ISI, MEPs were significantly more inhibited, regardless of the stimulated fingers. These results suggest that time is a crucial factor in determining how spatial information is transferred from S1 to M1. The topographic separation of the fingers found at short ISI might be explained by its relevance as feedback during movements (e.g., grasping). (Johansson & Flanagan, 2009).

A fourth factor influencing the excitatory and inhibitory sensorimotor interaction is stimulation intensity. Increasing TMS intensity has been shown to modulate the afferent inhibition effect (Ni et al., 2011). This is probably because a higher TMS intensity stimulates a greater number of neurons thus the inhibition induced by somatosensory afferent inputs struggles to exert the same effect over a larger population activity. At the same time, the intensity of the median nerve stimulation has also been demonstrated to significantly regulate the afferent inhibition strength (Ni et al., 2011; Turco et al., 2017). These and related findings were observed thanks to the implementation of protocols such as short-interval intra-cortical inhibition (SICI) and long-interval intra-cortical inhibition (LICI), which used TMS to assess inhibition in the human motor cortex. In these paradigms, a subthreshold TMS pulse, called conditioning stimulus (CS), is applied shortly (1-5ms) or later (50-200ms) before a supra-threshold TMS pulse called test stimulus (TS), both delivered to M1. Conversely, if the ISI between the CS and the TS is within 8-15ms, intra-cortical facilitation (ICF) is observed (Kujirai et al., 1993 Ziemann, Rothwell, & Ridding, 1996). Moreover, short-latency

intracortical facilitation (SICF) is elicited when the CS and TS are peri- or supra-threshold and applied with an ISI of 1-3ms (Tokimura et al., 1996).

The neuromodulation processes involved in SAI have been suggested to be related to GABA activity, which appears to modulate cortical excitability through the inhibition of cholinergic transmission (Metherate & Ashe, 1995). Some results support the idea that inhibition involving GABA modulates the task-related activity of motor neurons (Matsumura et al., 1992). Based on this information, Di Lazzaro and colleagues (2000) tested whether inhibitory and excitatory circuits between the somatosensory and motor systems are GABA-dependent or not. The authors found that scopolamine, which is an anticholinergic agent, significantly reduced the resting motor threshold, as well as the effects of the SAI produced by median nerve stimulation. However, the administration of scopolamine did not seem to affect either SICI or SICF, suggesting that these mechanisms rely on different neuromodulators (Di Lazzaro, Profice, et al., 2000). Since then, several studies corroborated these results suggesting that SAI is likely to rely on a cholinergic pathway that is modulated by GABA (Müller-Dahlhaus et al., 2008; Turco et al., 2018). Altogether, these studies provide important information that can help delineate the neuronal pathway that is used to integrate somatosensory and motor signals by knowing the receptors that affect their patterns of excitation and inhibition (SAI, SICI, LICI). Finally, the inhibitory and excitatory interactions between sensory and motor stimuli deeply influence each other, as demonstrated by several studies (Alle et al., 2009; Kukaswadia et al., 2005; Sailer et al., 2002; Udupa et al., 2009). These results suggest that somatosensory inputs have an impact on motor processing although it is not clear whether these afferent inputs influence directly M1 (thalamocortical) or is occurring through S1 (corticocortical) (Turco et al., 2018 for a review).

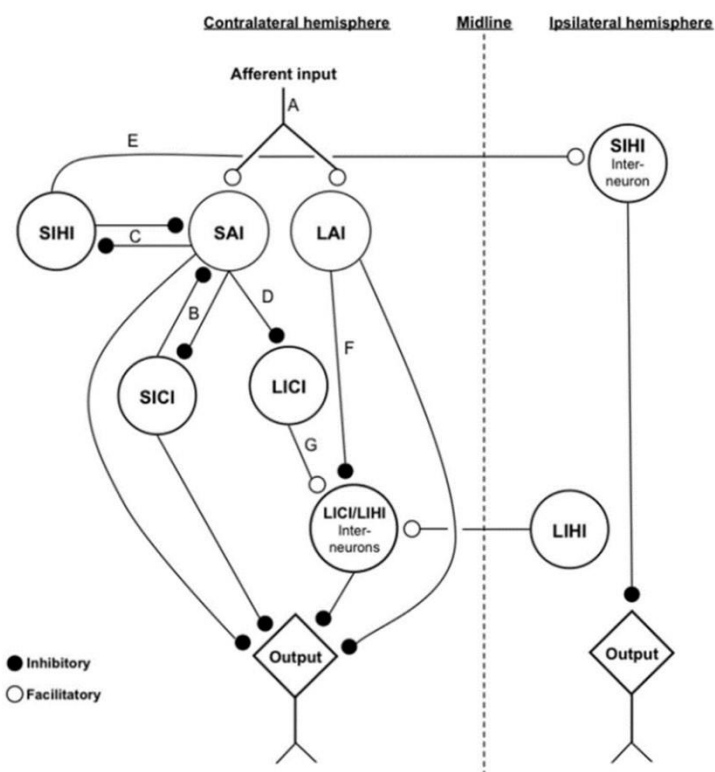


**Figure 5.2 Working model of somatosensory inputs and motor outputs interactions [Taken from Turco et al., 2018].** Working Model of the interactions between the somatosensory inputs and motor outputs analysed by using the TMS. The dotted line defines the midline between the left and right hemispheres. In this example, afferent inputs arrive at the contralateral hemisphere (i.e., right hand → left hemisphere) activating SAI or LAI (based on ISI) which then inhibit the motor output while interacting with other motor processes (i.e., SICI, LICI).

In conclusion, somatosensory afferent inputs significantly reduce motor outputs when delivered at specific timings (SAI, LAI). Moreover, the impact of M1 inhibition can be somatotopically or not somatotopically distributed depending on S1 excitability and the features (i.e., timing, location and intensity of the afferent stimuli) of the sensory afferent signals. Furthermore, thanks to the intracortical inhibitions in M1 and their interactions with the afferent inhibitions (SAI, LAI) we were able to comprehend that these processes underlie, at least in part, different structures/pathways. Finally, the studies we described demonstrate that the mechanisms underlying facilitation and inhibition interactions between S1 and M1 are based on cholinergic and GABAergic neurons' activity.

## 5.4 Neuropathological evidence of sensorimotor interactions

Since S1 and M1 are highly interconnected and influence each other, it is expected that neurological conditions or brain lesions affecting either system would alter sensorimotor performances. In this section, we will discuss how brain lesions can affect the interaction between the somatosensory and motor system. Leveraging very selective experimental lesions in M1 of mice, Fukui and colleagues (2020) showed that S1 processing was impaired during the acute phase of the infarct (corresponding to less than 30 days after stroke in humans), thus suggesting a direct link between somatosensory and motor cortices. A paradigmatic example of disrupted somatosensory and motor interaction is provided by stroke patients, in which 50% to 80% display some kind of somatosensory dysfunction in the post-stroke period (Chia et al., 2019; Kessner et al., 2019) and especially in the tactile domain (66% of 102 patients had impaired or absent tactile sensation) (Tyson et al., 2008).

The sensory dysfunction experienced by people after a stroke has been reported to be one of the important prognostic factors for the recovery of their motor functions (Carey, 2017; Kessner et al., 2016; Reding & Potes, 1988). This is supported by the fact that early somatosensory evoked potentials (SEPs) in stroke patients can be predictive of motor recovery (Kusoffsky et al., 1982). Somatosensory evoked fields (SEFs) recorded using MEG from S2 contralateral to the affected hand of patients who suffered from an ischemic stroke that damaged either the parietal lobe (sparing S1 and S2) and insula, or subcortical areas, were correlated with the results of two motor tests (Pegboard Test and Action Research Arm Test: ARAT) measuring hand motor function (such as grip, grasp) 1-7 days, 3-4 weeks and 3 months after stroke (Forss et al., 2012). Despite its limitations in terms of damaged regions (relatively large) and sample size (relatively small), the results from this study support the notion that S2 may be involved in modulating the somatosensory afferent input to M1 used to accomplish a successful sensorimotor integration process.

Similar results were found using fMRI. Schaechter and colleagues (2012) assessed the motor function of the affected arm in patients at 3-4 weeks (T1), 3 months (T2) and 1 year (T3) after the

stroke, using the Fugl-Meyer Stroke Scale. The BOLD signal was recorded in the sensorimotor cortex following tactile stimulation of the intact and affected hand. It was observed that the change in the ipsilesional sensorimotor cortex was positively correlated with the motor recovery observed between T1 and T2 (Schaechter et al., 2012). These findings suggest that the relationship between the somatosensory and motor networks is also critical for effective motor recovery.

The importance of changes in the sensorimotor system after stroke (chronic stroke with variable lesion volume and location) has been further explored using DTI (Borstad et al., 2016). Authors found that the microstructural integrity of thalamus-S1, thalamus-M1, and S1-S1 tracts was significantly reduced and this was also positively correlated with the affected hand performance in a haptic perception task (HASTe), with 90% of the variance of the HASTe scores explained by these tracts' integrity (Borstad et al., 2016). These findings may be driven by somatosensory recovery alone since the task used measures haptic performance. Despite this limitation, it has to be kept in mind that, as mentioned earlier, somatosensory deficits are significant predictors of motor recovery (see Carey, 2017 for a review).

Somatosensory network integrity has been demonstrated to be an important factor in the treatment of motor function recovery (Ingemanson et al., 2019). Ingemanson and colleagues (2019) asked participants with chronic stroke to undergo a 3-week sensorimotor training consisting of 1 hour-long finger movements task using the index, middle or both fingers for grasping and flexing (playing a virtual guitar). They found that the differences in treatment gain (hand function) between the patients were best explained by the proprioception measured at baseline. Moreover, the overall damage to the somatosensory system (S1, S2 and thalamocortical spinal tract) and the connectivity between ipsilesional M1 and S2 were the only two significant predictors of the treatment-induced hand function gain (Figure 5.3).

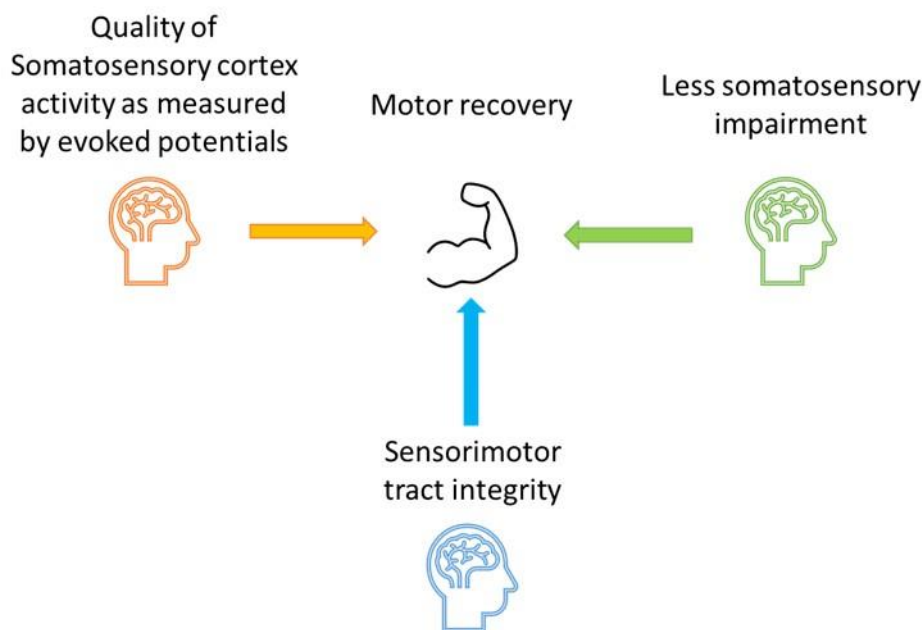


**Figure 5.3 Factors that predict better motor recovery.** There is a relationship between the quality of early somatosensory cortex activity as measured by evoked potentials, preservation of somatosensory functions and integrity of the sensorimotor tracts, and the extent of motor recovery.

TMS has also been used to temporarily interfere with the activity of a cortical area thus creating a “virtual lesion” in healthy people by delivering either single or repetitive pulses following specific protocols. One of these protocols is the repetitive TMS (rTMS) which consists of trains of TMS pulses interleaved with a pause that can be delivered at different frequencies and intensities. By applying either a sham or a 1Hz rTMS over the S1 in healthy individuals during implicit motor learning, Vidoni and colleagues (2010) were able to show that interfering with S1 processing significantly altered motor performance. This suggests that S1 is necessary for the formation of an accurate motor plan/internal model of movement sequence (Vidoni et al., 2010). Further investigation on motor learning by Kumar et al. (2019) revealed that delivering continuous theta burst TMS (cTBS, 3 pulses at 50 Hz every 200ms for 40s) on S1 immediately after an implicit motor learning task almost eliminated retention, but did not alter retention when applied after 24h, once learning was already

consolidated. Moreover, cTBS on M1 following learning had little effect on retention thus indicating that S1 plays a crucial role in implicit motor learning consolidation.

Abnormalities in somatosensory and motor integration have also been suggested to play a role in other disorders such as focal dystonia which is characterized by involuntary movements either at rest or during action execution (Fahn et al., 1998). Focal hand and cervical dystonia are two common forms of dystonia and several studies have explored the mechanisms and networks underlying them (Albanese et al., 2013; Avanzino et al., 2015). Tactile spatial acuity is reduced in patients with focal hand dystonia as measured by the two most common spatial discrimination tasks: the two-point discrimination task (2PDT), in which two probes separated by different distances are applied to the skin of the participant who has to tell whether they have been touched by 1 or 2 probes; and the grating orientation task (GOT), in which the orientation of gratings of varying width has to be discriminated (Molloy et al., 2003; Sanger et al., 2001). Tasks requiring somatosensory and motor integration such as reaching a specific object with the upper limb without vision suggested that patients with focal hand dystonia have an impaired integration of proprioceptive information with motor activity (Inzelberg et al., 1995). However, the important role of the somatosensory system in focal dystonia has been further demonstrated by several studies examining multiple factors such as sensorimotor integration, proprioceptive information and temporal/spatial somatosensory discrimination (see Conte et al., 2019; Desrochers et al., 2019; Konczak & Abbruzzese, 2013 for review).

The evidence provided by the neuropsychological studies we reported, highlights the critical role played by the somatosensory system and the sensorimotor integration for motor functions. Therefore, structural and functional brain changes and inhibitory and excitatory relationships between somatosensory and motor areas are essential aspects to consider when examining any motor outcomes. Moreover, this evidence provides indications that the somatosensory system plays a critical role in the recovery of motor functions.

As reviewed above, S1 plays an important role at the central level in sensorimotor performance, but how important are the peripheral tactile inputs arising from the skin *per se*? We now examine how disrupting somatosensory signals at the periphery can affect motor performance.

Many studies showed that removing tactile inputs, via peripheral anaesthesia or deafferentation, significantly altered motor performance, especially fine motor coordination (Augurelle et al., 2003; Gentilucci et al., 1997; Johansson & Westling, 1984; Monzée et al., 2003; Moscatelli et al., 2019). Johansson and Westling (1984) tested the impact of tactile afferent signals in precise motor tasks involving grasping and lifting objects with different types of surfaces using only the index finger and thumb. The two fingertips were anesthetised so that only motor and proprioceptive signals remained available. Results showed that the proper adaptation to the frictional condition of the objects was absent, leaving the grip force and load force unbalanced. Specifically, objects made of silk (the most slippery material used) slipped and the grip force became needlessly too much (Johansson & Westling, 1984).

In a similar study, Gentilucci and colleagues (1997) asked participants to use their index fingers and thumbs (pinch position) to reach, grasp and then lift cylindric objects having the tips of these fingers anaesthetized or not (control). Results showed that when the fingertips were anesthetised participants' grasping performance was impaired, and objects slipped in 30% of the trials vs 0% in the control condition, in keeping with what Johansson and Westling (1984) found.

Proprioception has been shown to be critical for the plasticity of the body representation for action (Body Schema). Cardinali et al. (2016), by testing a patient with right upper limb deafferentation, showed that there were several alterations in the kinematic profile of her proprioceptively deafferented arm when reaching objects (baseline session before tool use). Another recent study by Miall and collaborators (Miall et al., 2019), analysed the difference between three rare cases of deafferented people (normal motor pathway but no sensation of touch in the arms or hands) and healthy individuals when grasping and lifting objects using all the fingers. Results showed

that although deafferented participants developed compensatory strategies, there were still significant differences between their kinematics and those of the control group, suggesting a bigger reliance on vision and more fingers to avoid object slipping impairments in everyday manual abilities. Similar results were already found by another study (Rossi et al., 1998) in which MEPs evoked by TMS over the left motor hand area were analysed from both right FDI and ADM muscles before and after the anaesthetic block of the right median (sensory and motor) and radial (only sensory) nerves at the level of the wrist. They found that MEPs latency difference during active contraction vs. relaxation was decreased in FDI but not in ADM. Authors interpreted these results as proof of the impact of tonic tactile inputs coming from the skin surrounding the contracted muscle on the corticospinal excitability of that specific muscle (since their absence also decreased MEPs amplitudes from the FDI).

Peripheral somatosensory inputs have also been demonstrated to be important factors for motor learning (see Matur & Oge, 2017 for a review). For instance, Bernardi et al. (2015) found that participants could learn a motor task (reaching an object) through passive movement training associated with visual feedback to the same extent as the active movements. Passive movements have the same kinematics as active movements but without the motor output thus these results can be seen as led mainly by somatosensory information (proprioception) (Bernardi et al., 2015). This evidence is supported by Ohashi et al. 2019, who found that an increment of S1 excitability (SEPs) at the early stages of motor training correlates with behavioural improvements in motor performance while an increase of M1 excitability (MEPs) was only present at the later stages of learning (Ohashi et al., 2019). In summary, the evidence presented in the latter section demonstrates that tactile input arising from the periphery is also essential for motor ability.

## **5.5 Effects of tactile training on motor performance**

A particularly interesting phenomenon that we believe deserves attention in the context of the role of the somatosensory system on motor function is the effect of tactile learning. In the previous chapters,

we have presented evidence of the somatosensory and motor systems connections and their excitatory and inhibitory interactions. Moreover, neuroimaging, neuropathological and behavioural studies discussed so far showed that the somatosensory network can affect motor behaviour thanks to S1-M1 intra- and inter-hemispheric connectivity through inhibition, excitation, and haptic information. Based on this knowledge, tactile learning becomes important to this review because it can effectively alter the somatosensory cortex and this may have, in turn, a significant impact on motor function. Several methods have been used to induce somatosensory changes, for instance, Vahdat et al. (2014) revealed that somatosensory perceptual training in neurotypical individuals leads to changes in the functional connectivity between S1 and M1, which were positively correlated with motor performance change.

The effects of somatosensory training have also been investigated in patients with focal hand dystonia (Zeuner et al., 2002) since this disease seems to result from impairments in both somatosensory and motor functions. The training consisted of Braille reading for 1 h/day for 5 days the 1 week and then 30 min/day for 7 weeks. Motor functioning was measured by both the Fahn dystonia scale, which indicates the arm dystonia disability, and a standard paragraph writing. After training, patients had increased spatial tactile acuity (almost comparable to healthy controls) and improved motor performance. Rosenkranz and colleagues (2008) used another technique based on muscle vibration, to stimulate the proprioceptive system in patients with hand dystonia. This training was able to increase the corticospinal excitability (reduced SICI) of all muscles (Rosenkranz et al., 2008). Promising results were also found when using electrical nerve stimulation for two weeks on the forearm flexor muscle, which produced improvements in dystonic symptoms 3 weeks after the training (Tinazzi et al., 2006).

Recently a new passive tactile learning method, called repetitive somatosensory stimulation (RSS), that targets the mechanoreceptors but not the afferent nerves as done by the electrical

stimulation, has been developed. Moreover, this paradigm offers the advantage of providing total control over the time and spatiotemporal distribution of the stimulation.

When applied at the tip of one or multiple fingers for 20 minutes to 3 hours, at various frequencies depending on the protocol duration (Godde et al., 2000; Lesemann et al., 2015), RSS induces transient cortical plasticity in S1 and S2 (Dinse et al., 2003b; Godde et al., 2003; Pleger et al., 2001, 2003) together with tactile acuity improvement at the stimulated skin area (Dinse et al., 2003a; Godde et al., 2000). Whereas the exact mechanisms underlying the effects of RSS remain undetermined, RSS was designed to mimic the stimulation used to induce synaptic plasticity via long-term potentiation (LTP) following the Hebbian postulates that synchronous neural activity (e.g., simultaneous coactivation of different receptive fields) is a requirement for driving plastic changes (Hebb, 1949). This assumption has been supported by evidence that both cortical and perceptual changes induced by RSS depend on NMDA-receptors (Dinse, Ragert, Pleger, Schwenkreis, & Tegenthoff, 2003b) and are inversely modulated by GABAergic activity (Dinse et al., 2003a). Indeed, administering a GABA receptor agonist or an N-methyl-D-aspartate (NMDA) receptor blocker before RSS abolishes both the cortical and behavioural effects of RSS. The Hebbian mechanisms subserving RSS have been further supported by evidence that RSS effects are also mediated by cholinergic mechanisms known to modulate learning and NMDA-dependent synaptic plasticity, including LTP (Bliem et al., 2008). This was demonstrated by the administration of a cholinergic antagonist before RSS which resulted in an absence of tactile acuity improvements and even acuity impairments in some participants (Bliem et al., 2008). These findings support the idea that RSS is a protocol that drives both cortical and behavioural changes using Hebbian synaptic plasticity mechanisms.

RSS has been reported to modulate the somatosensory system using several neuroimaging techniques (e.g., fMRI, MEG, EEG) and behavioural tests such as 2PDT and GOT (e.g., Godde, Ehrhardt, & Braun, 2003; Godde et al., 2000; Hodzic, 2004; Kalisch et al., 2007; Muret et al., 2016; B. Pleger et al., 2001). In a recent study, experimenters applied RSS to the index, middle and ring

fingers at 20 Hz for 40 min while recording participants' EEG. They found that the stimulation produced a 20 Hz steady-state response in S1 without signs of habituation (Brickwedde et al., 2020). Several fMRI studies showed an increased representation of the stimulated finger(s) in S1 and S2 after RSS (Hodzic, 2004; Pleger et al., 2003, 2016). Furthermore, several studies reported significant improvements (between 13% and 29%) in participants' tactile spatial ability at the stimulated finger (see Parianen Lesemann et al., 2015 for a review) that were in some cases positively correlated with cortical changes in the contralateral S1 (Dinse et al., 2003b; Godde et al., 2003; Höffken et al., 2007; Pleger et al., 2003). Most interestingly, RSS has been reported to improve tactile perception not only at the stimulated sites but also in physically distant, unstimulated body parts. The extent of RSS-induced perceptual changes across body parts that, though physically remote, are cortically close to the stimulated site, has been investigated by Muret and colleagues (2014). In this study, the authors applied RSS on participants' right index finger and measured tactile spatial acuity, using the 2PDT, on the right and left index fingers, upper lips and cheeks. Results revealed improved spatial discrimination on the stimulated right index finger but also both sides of the upper lips and the cheek ipsilateral to the stimulated finger (Muret et al., 2014). These findings suggest that RSS-induced plasticity might modulate a broader brain network (or S2) than initially thought, without necessarily being dependent on, or limited by, cortical closeness (Muret & Dinse, 2018).

Other studies have explored possible RSS effects on sensorimotor performance. For instance, Kalisch et al., (2008) applied RSS on all fingers of the right hand in neurologically typical elderly, whose somatosensory and motor abilities were impaired compared to young adults. Results showed improved fine haptic performance in a task in which participants had to place a cubic object in one out of five designated boxes after haptic exploration with no vision. As well as decreased time to complete the pegboard task (both versions with short and standard pins) after RSS. A similar study on elderly participants was carried out, though RSS delivery on all fingers of the right hand was protracted for 2 days a week for 4 weeks (Kalisch et al., 2010). Haptic performance (measured with

the same task as above) significantly improved after RSS and the gain was maintained for up to 2 weeks after the end of the stimulation. The fine motor performance of participants measured by the pegboard task also improved, with faster performance still being observed after 1 week. However, the tactile domain showed the longest improvements, participants' performance in the 2PDT for d1, d2, and d3 returned to baseline level after 1 week whereas d4 required 2 weeks and d5 kept decreasing on the last test session. Converging evidence comes from an experiment that applied RSS on young adults' fingers of the non-dominant hand before a comprehensive motor training called arm ability training (AAT) repeated 60 min a day for 10 days (Ladda et al., 2014). Measures of motor performance of participants' trained and untrained hands were assessed before and after AAT using the AAT tasks (divided into visually-guided and sensory-guided movements), the pegboard test and the Roeder Manipulative Aptitude Test (RMAT, which measures speed and dexterity of arm, hand and finger movements). The results showed that overall, the trained (left) hand had a 34% improvement in all AAT tasks compared to the 24% of the right hand. Before the training, the left-hand performance was worse than the right one for sensory-guided movements, however, after the training, the left-hand performance became as good as the right one (Ladda et al., 2014). Similar results were found in a study (Lotze et al., 2017) in which participants were divided into two groups, one receiving repetitive electrical stimulation followed by one hour of AAT for two weeks whereas the other one did only one hour of AAT for two weeks. The repetitive electrical stimulation was applied on all fingertips of the non-dominant hand and the AAT only involved that arm. Results showed that the stimulation significantly increased participants' performance gain in all AAT tasks (see also figure 5.4). These results suggest that RSS might be used together with other sensorimotor training to further enhance performance in healthy individuals.

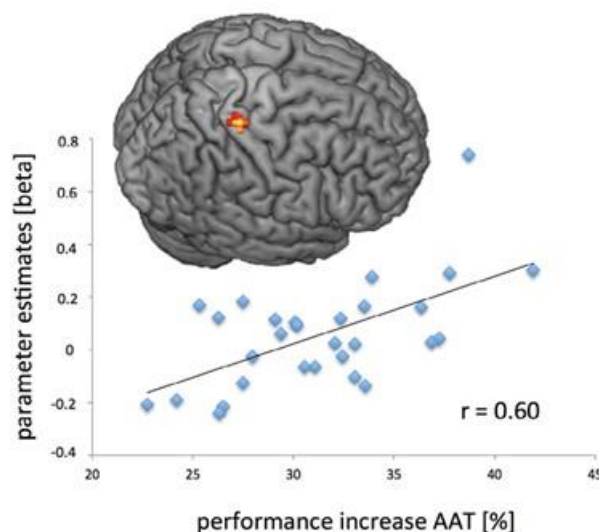


**Figure 5.4 Tactile and motor changes correlation [Taken from Lotze et al., 2017].** Illustration of the linear regression analysis between the fMRI activation in the contralateral S1 after the RSS stimulation and the percentage of motor performance improvement measured by the Arm Ability Training (AAT).

RSS might be beneficial for sensorimotor recovery in stroke patients (Smith et al., 2009). To address this question, in a study conducted by Smith and colleagues (2009), RSS was applied on all fingers of the contralesional affected hand for 90 minutes a day, 4 days a week, for 6 weeks. A battery of tests was performed throughout the training and after it, to assess changes in tactile acuity (GOT), haptic object recognition (objects made of LEGO bricks), fine motor performance (pegboard test), absolute tactile threshold, motor tapping task and other motor functions (Woelf motor function test). Although results should be taken with caution, due to the small sample size, patients with right-hemisphere brain lesions (N=2) had some improvement on average for all the tasks across time, whereas patients with left-hemisphere brain lesions (N=2) had little improvement after the intervention and one of them even had a relapse. In a single-blind sham-controlled study on 46 subacute strokes (Kattenstroth et al., 2018), patients received either RSS or a sham RSS on all fingers of the affected hand for 45 minutes per day, 5 days a week for 2 weeks along with their standard stroke rehabilitation therapy. Patients performed a series of tests before and after the training to evaluate their tactile acuity (GOT), fine motor performance (pegboard test), grip strength (Jamar hand

dynamometer), functional hand sensorimotor abilities (Jebsen-Taylor Hand Function Test), and proprioception performance (Bochum Joint Position Sense Assessment). Total performance index on 4 domains (sensory, motor, proprioception and everyday abilities) based on all the tests administered showed that patients who received RSS had a greater improvement in the sensory domain compared to those who received sham RSS. In the motor domain, the gain was 27% for the RSS group and 17% for the sham group. However, no significant differences were observed regarding proprioception and everyday tasks (picking up small objects, using a teaspoon for feeding) between the two groups. These results suggest that repetitive passive stimulation (i.e., RSS) can, to some extent, restore somatosensory perception and sensorimotor performance in stroke patients.

Altogether, these studies show that repetitive mechanical and electrical stimulations at the periphery have a great impact on the somatosensory system, both at cortical and behavioural levels and to some extent on the motor system although these effects are to be explored more in-depth by future studies. A major advantage of tactile passive stimulation is that it does not require attention or active participation, although it is very effective in driving plasticity changes. Therefore, it can be particularly suitable in cases in which patients have restricted mobility and/or are not capable of performing active training.

## **5.6 Conclusion and future perspectives**

In this chapter, we reviewed the literature delineating the somatosensory impact on the motor system. We have described the S1 and M1 reciprocal connections and even S1 activity directly affecting motor performance and M1. Moreover, we have highlighted a consistent pattern of both intra- and interhemispheric connections between S1, M1 and S2 across multiple species (mice, monkeys and humans) from several studies that used a wide range of techniques. The analyses of the sensorimotor interactions revealed that somatosensory afferent stimuli can significantly modulate motor excitability if they are delivered at a specific time. Furthermore, S1 excitability has been proven to

affect motor output. Finally, these processes have been shown to be related to neurotransmitter activity GABA and ACh providing important clues to understanding the neural pathways subserving these somatosensory and motor interactions. From the neuropathological cases reported, we have also observed the importance the somatosensory system plays in sensorimotor integration. In the studies we discussed, the somatosensory activity and network integrity in patients with brain lesion or neurological disorder was revealed to be an important element for their motor performance recovery.

The significance of sensorimotor integration for accurate movement execution has been repeatedly confirmed by studies exploring different aspects of somatosensory information such as touch or proprioception. Combining the knowledge regarding the relationship between the somatosensory and motor systems with synaptic plasticity, tactile stimulation studies have tried to induce cortical and behavioural changes. From the evidence presented, RSS has shown that passive tactile training can significantly modulate the somatosensory system both at the cortical and perceptual levels. Although the effect of repetitive passive mechanical stimulation on motor activity remains to be explored in full, we believe that it is a very promising field of study for opening novel therapeutics interventions and thus it deserves certainly further investigation. Since it has been shown that RSS-induced effects that can be modulated by the alteration of cholinergic and GABA activities, as it has been demonstrated for SAI, we could speculate that the neural pathway that is activated by the RSS inputs might be similar to the one involved in SAI.

RSS should be further evaluated to establish whether it can become a useful technique in the context of sensorimotor recovery in elderlies or stroke patients since touch has been proven to be essential for fine manual dexterity. In the future, the effects of RSS on both motor corticospinal excitability and motor performance (measured by a purely motor task instead of sensorimotor ones) should be further explored to unfold the mechanisms of the somatosensory and motor systems communication.

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## Chapter 6 : Effects of perceptual improvement induced by repetitive somatosensory stimulation on motor performance

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## **Abstract**

Somatosensory signals are essential to motor system control and tactile impairments can result in a significant reduction in the quality of motor abilities. Patients suffering from somatosensory deficits usually show reduced recovery of motor functions, preserved somatosensation being a good predictor of motor recovery. Despite the importance of their functional relationship, the somatosensory and motor systems interactions are still unclear. Repetitive somatosensory stimulation (RSS) applied on a finger is known to improve performance in a two-point discrimination task (2PDT), supposedly thanks to its effect of increasing the cortical representation of the stimulated body part in the somatosensory cortices. Yet, whether the RSS-induced improvement in touch perception affects the activity of the motor cortex remains unknown. Answering this question is important because this technique could be used as an effortless (passive training) method to help the recovery of patients with motor and/or sensory impairment. Here, we assessed the effects of RSS on motor behaviour. Tactile performance and motor skills were evaluated before and after 3 hours of RSS training by using a 2PDT (tactile assessment) and a pegboard (motor assessment) task. The training consisted of an RSS or sham stimulation for separate groups of participants. Results showed that, after training, tactile performance improved for the trained finger (right index) only after the RSS. Results on motor performance showed that execution times were faster for the right hand (RSS target hand) in the group trained with sham RSS. We suggest that RSS can influence the participants' motor performance possibly through an inhibitory somatosensory to motor process.

## 6.1 Introduction

Touch allows us not only to perceive stimuli coming from the external world but also to perform actions appropriately. This is evident in various everyday life situations, where the balance of forces required to accomplish simple tasks such as grasping an object (e.g., a cup of coffee) is based on the interaction between sensory inputs and motor outputs (Johansson & Westling, 1984). Temporary or long-lasting loss of tactile feedback severely hampers the ability to execute an action correctly, especially fine motor coordination (Augurelle et al., 2003; Gentilucci et al., 1997). In some pathological conditions, the sense of touch can be lost or significantly reduce due to some brain damage (Carey et al., 1997; Moseley et al., 2008; Tinazzi et al., 2009). Sensory loss and impairment are common features found in several diseases such as stroke (Smith et al., 2009) and complex regional pain syndrome (David et al., 2015). Trying to restore the functionality of the tactile component of the sensorimotor mechanism is therefore a pressing challenge (Gentilucci et al., 1997; Johansson & Westling, 1984; Moscatelli et al., 2019).

One of the key challenges in rehabilitation is that most patients are unable (or struggle) to perform active training due to ageing or health conditions, making passive training the golden target of rehabilitative protocols. A promising method that proved to be effective in inducing tactile learning (Kalisch et al., 2010; Kattenstroth et al., 2012, 2018; Smith et al., 2009) and thereby improving patients' sensorimotor abilities, is a completely passive training-independent approach called repetitive somatosensory stimulation (RSS). RSS has been successfully tested in young healthy participants and was found to induce cortical changes and improved tactile spatial acuity when applied to the fingertips (Godde et al., 1996, 2000; Pleger et al., 2001, 2003). In a typical RSS protocol, participants receive repetitive mechanical tactile stimulation on a body part (usually the tip of one or multiple fingers) for about 3 hours, while pursuing other everyday life activities such as reading or watching a video. Such tactile stimulation has the effect of co-activating simultaneously a large number of tactile receptive fields (Godde et al., 2000; Pleger et al., 2003). As a result, tactile

spatial discrimination acuity is significantly improved by about 20% as measured by the two-point discrimination thresholds (2PDT) task on the trained fingers (Kalisch et al., 2007) as well as on remote cortical regions (based on the homunculus representation in S1) such for instance the upper lips (about 10%, Muret et al., 2016; Muret & Dinse, 2018). Moreover, it has been found that the training increases the somatosensory cortical representation of the stimulated fingers both in the contralateral primary (S1) and secondary (S2) somatosensory cortices (Dinse et al., 2003b; Godde et al., 2003; Hodzic, 2004; Pleger et al., 2001, 2003).

While the impact of RSS on somatosensory cortices has been investigated (though sparsely), little is known about its impact on the motor system (Erro et al., 2018; Freyer et al., 2012; Heba et al., 2017; Kattenstroth et al., 2012). Many studies have demonstrated that the somatosensory and motor systems are directly connected (Catani et al., 2012; Tamè et al., 2012) and work together (see Chapter 5 for a review) allowing for the execution of appropriate movements (Ackerley & Kavounoudias, 2015; Augurelle et al., 2003; Johansson & Westling, 1984; Ohashi et al., 2019; Ostry & Gribble, 2016), particularly when hands are used for manual dexterity (Rossi et al., 1998). Furthermore, S1 has been proven to be necessary for motor learning since its temporary disruption before motor training significantly reduced motor skill learning (Vidoni et al., 2010). Overall, the strong anatomical and functional connections between the sensory and motor cortices recalled here suggest that RSS may have an impact on motor performance as well; however, most of the previous studies have been done on neurological patients and it is unclear how and to what extent RSS is affecting motor behaviour in healthy individuals.

This study aimed to investigate whether the RSS protocol affects motor performance. Half of our participants received RSS on the right index fingertip, whereas the other half received sham stimulation as a control. Participants' behavioural performance was assessed before and after the training (RSS or sham) using a 2PDT task (Höffken et al., 2007; Pleger et al., 2016; Ragert et al., 2003) to assess tactile performance on the right and left index fingers and thumbs, and the grooved

pegboard task to assess the motor dexterity performance of the two hands. We decided to measure the performance of these fingers because they are the ones used in the pegboard task. We expected to see improved performance for the 2PDT task but only in the RSS-stimulated finger (i.e., right index finger) and not in the left index finger and thumbs. We also predicted a change in performance in the pegboard task (i.e., either faster or slower execution times) with the right hand after RSS compared to the left hand. At the same time, we expected to observe no significant changes after the sham stimulation both on the 2PDT and pegboard tasks.

## 6.2 Materials and methods

### Participants

Forty-two participants (mean age = 21.38, range = 19 – 33; 34 females) took part in the study and were randomly assigned to the two groups. We performed a priori power analysis in G\*Power version 3.1.9.7 (Faul et al., 2009) using the data from a few studies (Pleger et al., 2003; N=18; Godde et al., 1996, N=35) so that we could estimate an appropriate sample size to compare the 2PDT threshold for the right index finger before and after the RSS. The effect sizes from these two studies were 1.31 and 1.08 respectively, consequently, the sample size for a two-tailed paired t-test was calculated to be 10, and 14 per group respectively, by setting alpha criteria to 0.05 and power to 0.99. Since the slight differences in performance in the 2PDT baseline sessions, we decided on a higher number of participants in each group. All participants had normal or corrected-to-normal vision. Handedness was determined using the Edinburgh Handedness Inventory with the laterality quotient (LQ). 38 participants were right-handed (mean =  $93.65 \pm 1.67$ , range: 57.9–100) and 4 were left-handed (mean =  $-87.9 \pm 4.69$ , range: -100 – -80). The study was approved by the local ethics committee at the School of Psychology, University of Kent and was carried out according to the principles of the 1964 Declaration of Helsinki as updated by (World Medical Association, 2013).

### 6.3 Procedure

Participants gave written consent before starting the experiment in accordance with the procedure and protocols of the University of Kent. Participants were randomly assigned to the RSS or sham group. Participants performed the 2PDT and pegboard tasks before and after the training (RSS or Sham) on the right index finger, based on their assigned group. In the pegboard task, participants were seated in front of the pegboard, and they were asked to insert all pegs (25) one by one as fast as possible. In the event of a participant dropping a peg, the instruction was to pick it up and insert it, before taking another peg from the pile.

Participants had to perform two sessions of the 2PDT, positioning either the right or left arm (based on the tested finger) on the device while leaving the other in the same position. The experimenter used the 2PDT device to present, in pseudorandomized order, each of the probes 8 times. Thus, each session had 64 trials which assessed the spatial acuity of the participant's left and right index fingers and thumbs. They were instructed to remain as still as possible throughout the experiment and to report whether they felt 1 or 2 tips after each probe presentation. The vision of the device was prevented.

In the training phase, participants were left free to conduct an activity that did not require movement (e.g., listening to music or watching movies). The experimenter then set the RSS/sham on the participant's right index finger and instructed them to avoid unnecessary movements throughout the training stimulation phase (3 hours).

Finally, at the end of the experiment, participants were debriefed and then received either credits or monetary compensation for their time regardless of their performance.

## 6.4 Apparatus and stimuli

### Two-point discrimination task

As shown in Figure 6.1, the 2PDT device consisted of seven pairs of needles/probes (diameter, 200 $\mu$ m) with separation distances of 0.7, 1.0, 1.3, 1.6, 1.9, 2.2, and 2.5 mm. In addition, zero distance was tested with a single needle/probe. The needles/probes were mounted on a rotatable disk that allowed the experimenter to switch rapidly between distances. The spring-mounted apparatus allowed also control for the force applied. There was a total of 64 trials, with each probe being presented, in a pseudorandomized order, 8 times per finger. There were 4 breaks (one every 16 trials) of 1 minute to avoid habituation that might appear in the region of the tested skin.

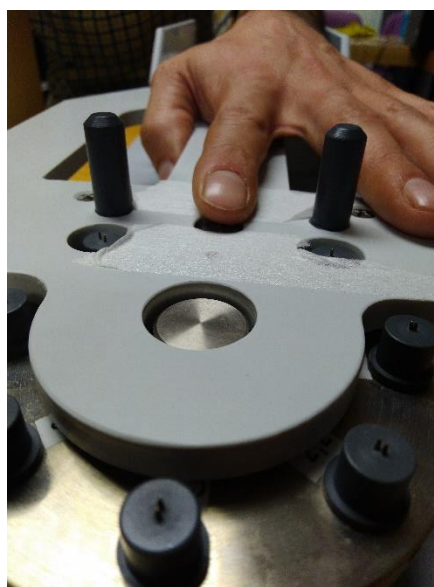


**Figure 6.1 Two-point discrimination device image.** Two-point discrimination device as seen from the experimenter's viewpoint. The 8 distances were on a rotatable disk; thus, the light grey part was lifted allowing the experimenter to switch the distance, and then the probe was presented to the participants by pressing the light grey section down right above the central hole, dovetailing perfectly.

This task was delivered on the distal phalanges of participants' index fingers and thumbs (see Figure 6.4). Participants were blindfolded, and they were instructed to judge whether one or two points were presented by saying "one" or "two". The response was manually recorded by the experimenter. Before the actual test, a familiarisation phase allowed for the optimal positioning of

the finger on the device and participants were presented with the two extreme probes (0mm and 2.5mm) until they were able to correctly distinguish them three times (Muret et al., 2014). The presentation of the different probes was always kept parallel to the longitudinal axis of the finger. No feedback was provided to participants about their accuracy.

### **Pegboard**

The device used was the Grooved Pegboard (Jamar) with 25 pegs (Figure 6.2). Participants picked one peg from the heap using only the index and thumb fingers of either the left or right hand, which were tested in separate sessions. Then, they inserted the peg starting on the top left corner if they were using the right hand and the top right if they were using the left hand. The task consisted of filling all the rows as fast as possible while following the correct order and without skipping any holes. If a peg was dropped, participants had to pick it up before picking the next one from the pile.

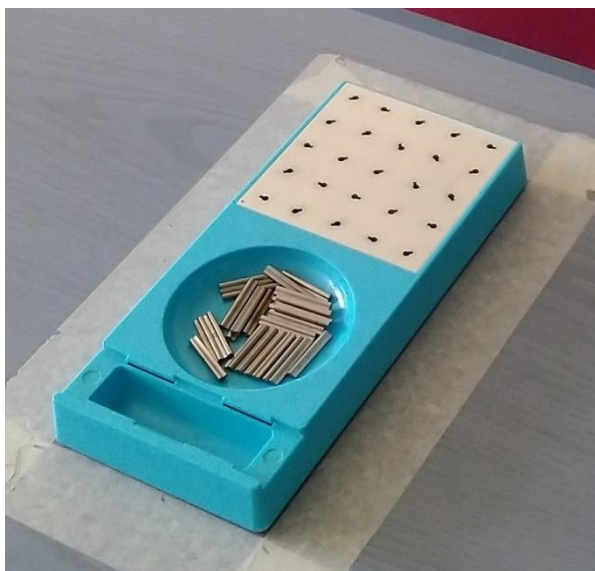


**Figure 6.2 Grooved pegboard task image.** Grooved pegboard from the experimenter's point with the pegs already placed in the designated area from which participants have to pick them up.

## Stimulation Protocols

### Repetitive Somatosensory Stimulation (RSS)

The RSS protocol was the same as the one that has been successfully used in several previous studies (Dinse et al., 2003a, 2006; Godde et al., 2003; Muret et al., 2014, 2016; Pleger et al., 2001, 2003). To simultaneously coactivate several receptive fields representing the skin area of the right index fingertip (D2), a small solenoid (diameter: 8 mm) was taped to the volar surface of the right D2 fingertip, delivering the tactile stimuli (Figure 6.3). The RSS sequence consisted of brief supra-threshold tactile stimuli (single pulse duration: 10ms) with inter-stimulus intervals following a Poisson distribution and ranging between 0.1 s and 3 s to prevent habituation. The average stimulation frequency was 1 Hz, and the total duration of the intervention was 3 hours. Pulses were recorded and then played using a portable MP3 player. Participants were instructed to reduce the use of their fingers to the minimum while they were watching a movie or a video during the intervention.

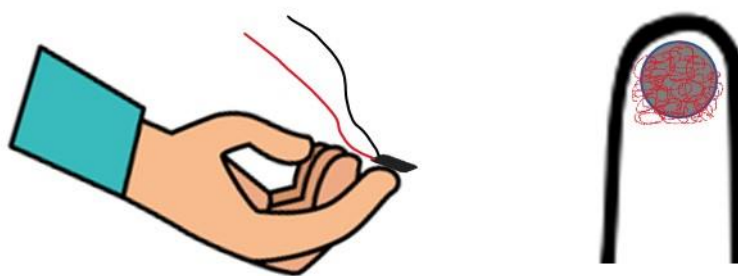


**Figure 6.3 Repetitive somatosensory stimulation image.** Schematic Illustration of the RSS speaker on the right index finger (left panel) and the area stimulated by the RSS (grey circle) with the coactivation of the numerous receptive fields (cartooned as red outlines) in the tip of the right index finger (right panel).

### Sham Stimulation

The sham stimulation was in every aspect similar to the real RSS, except for the duration and distribution of tactile stimuli. While RSS consisted of stimuli delivered continuously for the 3 hours, the sham consisted of stimuli delivered only during six blocks of 2.5 minutes spread over the 3 hours

of the protocol, with no stimulation between them. Therefore, the total duration of effective stimulation was only 15 minutes over the 3 hours.

## 6.5 Design

The experiment was randomized, single-blind, counterbalanced and sham-controlled. Thus, participants were randomly assigned to the experimental or the control group. The order of the conditions was changed so that all possible sequences were performed the same number of times (AB-AB, AB-BA, BA-AB, BA-BA) to avoid any potential confound effects deriving from sequence and order of presentation. The control group was important to account for the placebo effect, in which participants receiving a sham stimulation still reported having a post-training effect as if it was real training.

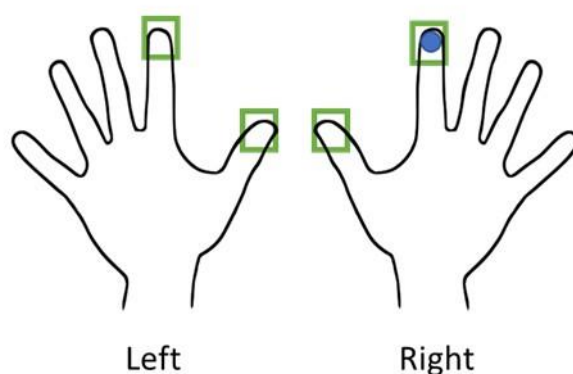


**Figure 6.4 RSS stimulation and testing sites.** Image showing the RSS stimulated finger (blue circle, right index finger) and the fingers tested using the 2PDT task (green squares, right D1, D2 and left D1, D2).

Measuring the placebo effect in the control group allows us to estimate what portion of the reports from the experimental group was due to an effect that is the result of the RSS stimulation and what portion is likely due to the placebo effect. The parameters for the sham RSS allowed us to reduce the

possible bias that could have been found if the stimulation was perceptually different or simply switched off.

Thus, this study was a mixed design with one between-participants factor: group (RSS, sham) and two within-participants factors: time (before, after) and finger (right D2, left D2, right D1, left D1), with behavioural performance (2PDT and pegboard) as dependent variables.

## 6.6 Analyses

### 2PDT

Binary logistic regression was used to fit a psychometric function and the mean of the responses “two” as a function of the distance between the probes for each participant, finger and session. The participant’s tactile threshold for each finger and session (before and after training) was then obtained from the fitted data to allow the comparison of the performance before and after training. The threshold was the distance at which the participant responded “two” 50% of the time. The data was entered into 2 three-way mixed ANOVA (one for index fingers and one for thumbs) with the factors: Group (RSS, sham), Session (before, after) and Side (left, right). Changes in the tactile threshold ( $\Delta$ ) between the two sessions (before-, after- training) were also calculated using the following formula:  $[(\text{threshold post} - \text{threshold pre}) / \text{threshold pre}] * 100$ , for a similar approach see (Muret et al., 2014). Due to technical difficulties, seven out of 42 participants did not have a second baseline session thus, the first session was used instead. Moreover, two participants' data for the thumbs were excluded from the analyses because of aberrant values (i.e., for one both baseline sessions had negative threshold values and the other had a threshold of about 30 SD from the mean). All the post hoc analyses have been Bonferroni-Holm corrected for multiple comparisons.

## **Pegboard**

The execution times (RTs), measured in seconds (e.g., 90 seconds), for right and left hands both before and after training were entered into a three-way mixed ANOVA with two within factors: Hand (right, left), Session (before, after) and one between participants factor: Group (RSS, sham). One participant performed the task in over 6 minutes (more than 5 SD) thus, was excluded from the subsequent analyses.

## **2PDT and Pegboard correlation**

A Pearson correlation analysis was performed between the 2PDT thresholds for both index fingers and thumbs and the execution times for both hands to investigate whether these values before and after training were correlated. We also examined whether there was a correlation between the changes in the 2PDT threshold (in percentage) and RTs in the Pegboard task. Correlation analyses were carried out with the open software R (RStudio Team, 2020).

## **6.7 Results**

### **2PDT**

The three-way repeated measures ANOVA for the index fingers showed a significant main effect of side ( $F(1,40) = 8.15, p = .007, \eta_p^2 = 0.17$ ), revealing a significantly higher acuity threshold for the left index finger relative to the right index finger. Thus, participants were better overall at the 2PDT task with their right index finger compared to the left index finger. Moreover, there was a significant two-way interaction between session and side,  $F(1,40) = 5.35, p = .026, \eta_p^2 = 0.12$ . Post-hoc tests corrected for multiple comparisons revealed that after the training the threshold for the right index finger ( $M \pm SE = 1.43 \pm 0.05$ ) was significantly lower compared to the left index finger ( $M \pm SE = 1.59 \pm 0.05$ ), ( $t_{(39)} = -3.67, p = .003, d = -0.56$ ). Therefore, after either training, participants' performance in the 2PDT task was better with the right index finger rather than the left index.

Critically, we found a significant three-way interaction between session, side and group,  $F(1,40) = 10.68$ ,  $p = .002$ ,  $\eta^2 = 0.21$ . Post-hoc tests corrected for multiple comparisons revealed a significant threshold decrease for the right index finger after RSS,  $t(39) = 3.85$ ,  $p = .007$ ,  $d = 0.85$ , which was not the case for the sham group ( $t(39) = -1.26$ ,  $p = 1.00$ ,  $d = -0.28$ ; see Figure 6.5). Furthermore, a significant difference between the thresholds of the right and left index fingers was found only after RSS ( $t(39) = -4.72$ ,  $p < .001$ ,  $d = -1.02$ ; see Figure 6.5). These results indicate that after receiving RSS, participants became significantly better at the 2PDT task with the stimulated finger (right index) but not the homologous finger of the other hand. This is compatible with the pattern of results found in previous studies (Lesemann et al., 2015) and validates our approach and the efficiency of the RSS training.

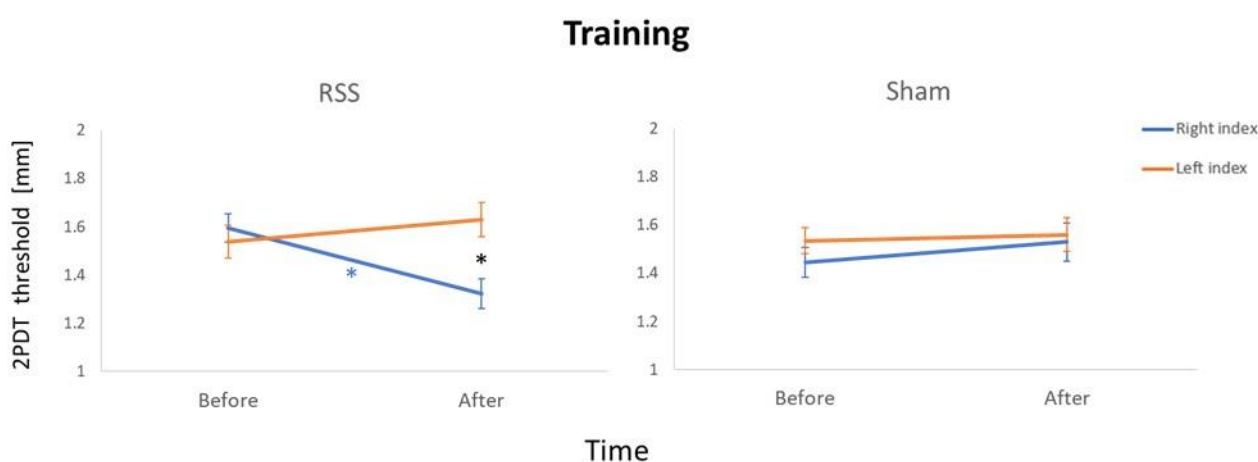


**Figure 6.5 Tactile perception results after tactile training.** Graph showing the average 2PDT thresholds (in millimetres) before and after RSS (left panel) and Sham (right panel) stimulations. Blue and orange lines represent thresholds for the right and left index fingers respectively. Error bars represent the standard error of the mean ( $\pm$ SEM). \*  $p < .05$

Relative threshold changes ( $\Delta$ ) indicated that participants who underwent the RSS training, had a performance gain of about  $16\% \pm 4$  on average for the right index finger whereas their performance slightly decreased by  $8\% \pm 5$  on average for the left index finger. On the other hand, participants who did the Sham intervention showed a minor reduction in performance by  $8\% \pm 5$  and

3%  $\pm$  5 for the right and left index fingers, respectively. The three-way repeated measures ANOVA for the thumbs showed no significant main effects nor interactions, (all  $p$  values  $> .14$ ).

## Pegboard

The three-way repeated measures ANOVA revealed a significant main effect of session,  $F(1,39) = 23.72$ ,  $p < .001$ ,  $\eta_p^2 = 0.38$ . As expected, participants became faster after the training ( $M \pm SE = 104.93 \pm 3.28$ ) compared to before ( $M \pm SE = 95.88 \pm 3.28$ ). We also found a significant hand  $\times$  group interaction,  $F(1,39) = 5.85$ ,  $p = .02$ ,  $\eta_p^2 = 0.13$ . Post-hoc tests corrected for multiple comparisons revealed that execution times in the RSS group were significantly lower for the right hand ( $M \pm SE = 96.57 \pm 4.52$ ) compared to the left hand ( $M \pm SE = 106.45 \pm 4.52$ ) hand,  $t(39) = -3.37$ ,  $p = .011$ ,  $d = -0.44$ . Furthermore, we found a significant interaction between session, hand and group,  $F(1,39) = 6.38$ ,  $p = .016$ ,  $\eta_p^2 = 0.15$ . It also showed that the execution times before RSS were significantly lower for the right ( $M \pm SE = 100.1 \pm 4.21$ ) compared to the left ( $M \pm SE = 113.1 \pm 5.73$ ) hand,  $t(39) = -3.43$ ,  $p = .025$ ,  $d = -0.57$ .

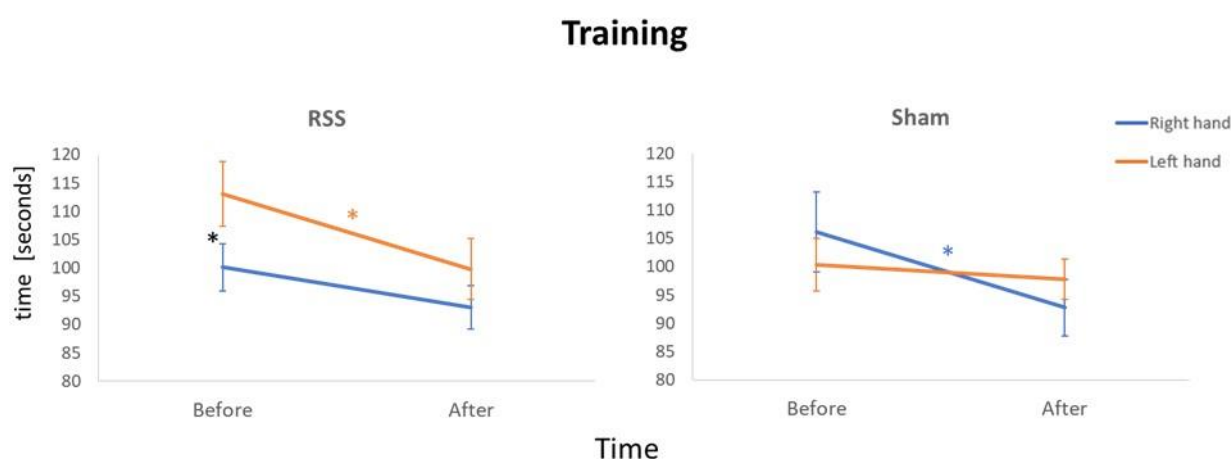


**Figure 6.6 Motor performance results after tactile training.** Graphs illustrating the execution times (expressed in seconds) for the pegboard task before and after the training. The data are divided based on the intervention, RSS (left panel) or Sham (right panel). The blue lines indicate the right-hand finger motor performance, while the orange lines represent the left-hand finger motor performance. Error bars represent the standard error of the mean ( $\pm$ SEM). \*  $p < .05$

Moreover, the participants' group that underwent the sham stimulation had a significant decrease in execution time for the right hand from ( $M \pm SE = 106.1 \pm 7.06$ ) to ( $M \pm SE = 92.8 \pm 4.94$ ;  $t(39) = 3.71$ ,  $p = .01$ ,  $d = 0.59$ ). The analysis also revealed that participants who did the RSS intervention became significantly faster in performing the motor task with the left hand ( $M \pm SE = 113.1 \pm 5.73$ ) compared to before the training ( $M \pm SE = 99.8 \pm 5.36$ ;  $t(39) = 3.79$ ,  $p = .008$ ,  $d = 0.59$ ).

To explore possible relations between performance in the 2PDT task and performance in the pegboard task, we ran correlation tests between the changes in performance due to training in both tasks. There were no significant correlations between the performance in the 2PDT and the pegboard tasks.

## 6.8 Discussion

In this study, we investigated whether a passive tactile protocol (i.e., RSS) known to improve performance on a tactile task (2PDT) has any effects on a motor task (i.e., pegboard). We tested two separate groups of participants, one that received RSS and one that received a sham stimulation to control for potential placebo effects similar to what has been done in previous studies (e.g., Macchione, 2018; Muret et al., 2014). We found that participants who underwent the RSS intervention had a significantly lower 2PDT threshold, which represents a better performance in the tactile task, only on the stimulated body part (i.e., right index finger). By contrast, the other tested fingers did not show any changes. As predicted, in accordance with previous studies (Godde et al., 1996, 2000; Kalisch et al., 2008), participants who underwent the sham intervention did not show any significant changes both when tested on the stimulated and unstimulated fingers. This replicates previous findings using the same paradigm and validates our approach (Lesemann et al., 2015). After the training, the motor performance of participants in the RSS group significantly improved, namely, they were faster at completing the pegboard task using their left unstimulated hand, whereas it remained unchanged when using the right hand. By contrast, participants that underwent the sham

intervention showed the opposite pattern, with shorter execution times with the right hand and no significant changes with the left hand. These results show that motor performance is selectively affected by RSS training. Note that in previous studies, differently from our work, authors applied RSS training on the whole hand or multiple fingers rather than a single finger. Such an approach might have induced this discrepancy in the body part affected by the motor performance. However, the pattern of results is more complex than what we expected. We will discuss these results below in relation to the current literature on somatosensory and motor interactions.

The pattern of changes observed after RSS are in agreement with the findings of previous studies that showed a reduction in the 2PDT threshold of the stimulated finger (right index) and no changes to the left index finger (Bliem et al., 2008; Godde et al., 2000; Höffken et al., 2007; Pleger et al., 2001, 2003). This improvement in the 2PDT has been also considered a confirmation of the RSS effects, although there are several factors influencing the resulting measures (see Dinse & Tegenthoff, 2018). With regard to the thumbs, we did not observe any change in the 2PDT threshold and so far only one study has measured the 2PDT thumbs threshold before and after RSS, which reported an increase in performance for the left thumb (opposite to the RSS targeted right index finger) but no improvement for the right thumb (Macchione, 2018).

Regarding the impact of RSS on motor performances, we found that performance on the grooved pegboard task improved with the left hand but not with the right. Instead, participants became faster on the grooved pegboard with the right hand after the sham. Therefore, it is plausible to assume that the RSS is having an inhibitory effect on the motor system, particularly on the stimulated hand.

Many studies have shown that the somatosensory and motor systems are heavily interconnected (see Chapter 5). Our hypotheses were based on the assumption that the induced changes of RSS in the somatosensory cortices (Dinse et al., 2003b; Muret et al., 2016; Pleger et al., 2003) are affecting the motor cortices and in turn the motor response. Such interactions can sometimes be inhibitory (Bailey et al., 2016; Tokimura et al., 2000) and sometimes excitatory (Chen,

2004; Iriki et al., 1989; Jacobs et al., 2014; Terao et al., 1999). Examples of inhibitory effects are provided by the short (SAI) and long afferent inhibition (LAI) studies, in which the motor-evoked potentials (MEP), elicited by the transcranial magnetic stimulation (TMS), are reduced/suppressed when a tactile afferent stimulus is delivered in specific time ranges (about 20-25 or 200-1000ms) before the TMS pulse (Tamè et al., 2015; Toepp et al., 2021; Turco et al., 2018).

We suggest that in our study the RSS had an inhibitory effect on the right-hand motor excitability and at the same time released the left hand from the interhemispheric inhibition that normally regulates the interaction between the two hands in unimanual movements (Cincotta & Ziemann, 2008; Ferbert et al., 1992; Grefkes et al., 2008; Vercauteren et al., 2008). Indeed, after the training, an improvement in the somatosensory response (lower 2PDT) for the stimulated finger in the RSS group induced an inhibitory effect of the motor system (no improvement in the motor task) specifically for the right hand, as participants improved their performance for the left hand. Moreover, participants of the sham RSS group showed such improvement for the right hand. Such an inhibitory effect is compatible with a previous study showing a direct cortico-cortical inhibitory effect of S1 over M1 (Tamè et al., 2015). Moreover, decreased motor cortex excitability has been also shown in the context of the rubber hand illusion, as a result of synchronous stimulation of the hand (della Gatta et al., 2016).

Few previous studies used a pegboard task after an RSS protocol in healthy (Kowalewski et al., 2012) and stroke patients (Kattenstroth et al., 2012, 2018; Smith et al., 2009). Kowalewski and colleagues (2012) found that participants were faster at completing a pegboard task with small pegs (considered difficult) with their right hand after RSS was applied on the right index finger and thumb. The difference in their results compared to our study can be traced back to the fact that both fingers used in their pegboard version received RSS, the absence of a sham group and their simpler pegboard version compared to the grooved one used in our study. If we take into account lateral inhibition processes between fingers (Severens et al., 2010) in our study, the RSS applied on the right index

finger might have increased its somatosensory excitability which in turn led to stronger lateral inhibition on the right thumb (probably not detected by 2PDT) while the sham stimulation would not have done so. Thus, participants who received a sham stimulation did not have any tactile perception changes in the right thumb and could improve their performance on the pegboard task with the right hand. The lack of improvement with the left hand might be due to participants being right-handed and the great difficulty of the task. On the other hand, after RSS, the interhemispheric inhibition (Carson, 2020) between homologous index fingers might have led to a decreased tactile perception in the left index finger which in turn enhanced the left thumb's, due to a lateral inhibition mechanism. However, we found no significant changes in the left 2PDT thresholds therefore there is still not enough evidence to support this interpretation.

The pattern of possible between-fingers transfer of the RSS effects might also be inferred from the results observed in tactile mislocalisations experiments, which indicate that index finger stimulation results in a higher mislocalisation of tactile stimuli to the middle finger and slightly the ring and below guessing chances on the thumb and little finger. On the other hand, tactile stimulation of the thumb leads to higher changes in the mislocalisation profile on the index, middle and ring fingers but not the little finger (Schweizer et al., 2001). Thus, it can be assumed that the RSS applied on the right index finger would have its highest influence on the middle and ring neighbouring fingers (between fingers) rather than the thumb. Previous RSS studies showed that transfer of RSS effects can spread to non-adjacent body parts, given that RSS delivered on the right index finger can transfer to the lips (Muret et al., 2014, 2016). Furthermore, RSS applied on the forearm led to a localised improvement in the 2PDT task on that specific body part, but does not transfer to other body areas, suggesting that RSS transfer is not always topographic and to some extent may be influenced by the body part functional role (Muret & Dinse, 2018).

In conclusion, we replicated the 2PDT results of previous studies using the RSS protocol and extend them by showing that the tactile improvements induced by the RSS influence motor

performance as measured by the grooved pegboard task. This effect appears to be inhibitory, however, further investigation is required to understand the actual pattern of interaction between the RSS and the motor performance given that the tactile and motor tasks did not correlate.

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## **Chapter 7 : Effects of repetitive somatosensory stimulation on motor behaviour and corticospinal excitability**

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## **Abstract**

Somatosensory and motor cortices are anatomically and functionally connected, and it has been shown that they significantly affect one another. We also know that performing precise movements require the interaction between somatosensory and motor signals. Repetitive somatosensory stimulation (RSS) is a passive tactile training that increases the cortical representation of the stimulated area (usually the right index finger) in the primary somatosensory cortex (S1) as well as other functionally connected cortical areas. In a previous study (Chapter 6), we found that RSS had an impact on motor performance as measured by the pegboard task, however, it is not clear whether this change is due to a change in the primary motor cortex (M1) excitability. Thus, in this study, we assessed participants' motor corticospinal excitability by recording motor evoked potentials (MEPs), elicited by the transcranial magnetic stimulation (TMS), from the right first dorsal interosseous. We also tested participants' tactile performance as measured by a two-point discrimination task (2PDT), while the motor performance was assessed with the grooved pegboard task. The measures were taken before and after a training phase of RSS or sham. We found no significant differences in the right index finger 2PDT thresholds both after the RSS and sham. Moreover, there were no significant changes in the pegboard task performance between the training and between the right and left hands. Finally, we only found a significant main effect of intensity for the MEPs. These results indicate that by increasing the TMS pulse intensity the MEPs amplitudes rose, regardless of the time or training session (RSS vs sham). We suggest that RSS might have an impact on motor corticospinal excitability, however, this could not be determined in this study most likely due to the considerable role played by interindividual variability and the small sample size.

## 7.1 Introduction

Every movement we perform is the result of intercommunication between the somatosensory and motor signals (Ackerley & Kavounoudias, 2015; Moscatelli et al., 2019; Scott, 2016). The importance of this interaction has also been observed in several neurological conditions, such as stroke and focal dystonia (Abbruzzese & Berardelli, 2003; Avanzino et al., 2015; Borich et al., 2015; Ingemanson et al., 2019; Perruchoud et al., 2014). For instance, it has been shown that somatosensory evoked potentials found in these patients at subacute phases of stroke are correlated with the extent of motor recovery (Kusoffsky et al., 1982). Furthermore, motor performance is impaired when there is a permanent disruption of somatosensory inputs (Miall et al., 2019; Richardson et al., 2016) or even a temporary loss (Augurelle et al., 2003; Gentilucci et al., 1997).

These studies show that without somatosensory inputs, fine movements such as grasping, become more challenging consisting of slower actions, reduced dynamic control of force, larger grip aperture, and other kinematic alterations. Given the close anatomical and physiological interdependence between these two systems (see Chapter 5), several studies have examined the potential role that can be played by the somatosensory system in motor rehabilitation (Chen et al., 2018; Sharififar et al., 2018; Yang et al., 2019) as sometimes the former is preserved.

One of the several approaches that have been demonstrated to promote somatosensory cortex plasticity is repetitive somatosensory stimulation (RSS; Godde et al., 2003; Heba et al., 2016; Pleger et al., 2003). RSS is a passive tactile training protocol that induces simultaneous coactivation of a large number of receptive fields in the stimulated body part, leading to cortical plasticity in the somatosensory cortices (Dinse et al., 2003b; Godde et al., 1996, 2000; Pleger et al., 2001). In a typical RSS procedure, after 3 hours of stimulation applied to a body part (usually the right index finger), is typically observed an enhancement in tactile spatial abilities as well as an increase in the cortical representation of the stimulated body part in the somatosensory cortices (S1 and S2) (Hodzic, 2004; Muret et al., 2016; Pilz et al., 2004; Pleger et al., 2003). The behavioural improvements seen after

RSS are not restricted to the body part stimulated, but rather generalise to other body parts (Macchione, 2018; Muret et al., 2014). For instance, it has been shown that by applying RSS on the right index finger, the performance on the two-point discrimination task (2PDT) improve also for both upper lips (Macchione, 2018; Muret et al., 2014, 2016; Muret & Dinse, 2018), namely regions that are cortically close even if physically distant. Moreover, the cortical representation of the lips, but not the forearm, is affected by RSS applied on the right index finger (Muret et al., 2016), which shows that RSS-induced plasticity effects do not transfer only based on cortical proximity, but other mechanisms that are still under investigation. Given the findings presented so far regarding the role of the somatosensory system in motor performance and the interaction between S1 and primary motor cortex (M1), it can be assumed that stimulation that changes S1 activity (i.e., RSS) might affect M1 and in turn the motor behaviour.

In a previous study (Chapter 6), we tested the changes in tactile (2PDT) and motor (grooved pegboard) performance in two groups of participants who received either the RSS training or sham training. We found a performance improvement in the 2PDT task only in the right index finger (i.e., trained finger) after the RSS training but not after the sham training. Performance on the pegboard task, which was used to evaluate participants' motor abilities, showed that they were significantly faster with the left hand, but not the right one after RSS, and faster with the right hand but not the left one after sham stimulation. These findings were interpreted as evidence that the changes induced by RSS in the right index cortical representation in S1 were having an inhibitory effect on M1. However, in such a study we used only behavioural testing to estimate the somatosensory and motor changes, though, it remains unknown whether the motor cortex activity can be altered by an RSS intervention.

The present study aimed to investigate whether the RSS protocol affects corticospinal excitability (CSE) and motor performance using a combination of transcranial magnetic stimulation (TMS) approach and behavioural measures. CSE was assessed by measuring the Motor Evoked Potential (MEP) from the First Dorsal Interosseous (FDI) following a single pulse TMS over the

contralateral M1, with respect to the RSS-trained finger (right index finger), before and after an RSS training and sham training in different sessions for the same participants. Specifically, CSE was assessed pre- and post-RSS/Sham training by creating an I/O stimulus-response (or tuning) curve in which different intensities of TMS were applied in a randomized order. M1 stimulation was performed with the support of an open-source Neuronavigation system (InVesalius, Souza et al., 2018), which ensured a precise localisation and monitoring of the position of the TMS coil over the scalp across trials and sessions. Participants' behavioural performance was assessed through a 2PDT (Höffken et al., 2007; Pleger et al., 2016; Ragert et al., 2003) and a pegboard (Kalisch et al., 2008, 2010) task. If the RSS affects the CSE and motor performance, in addition to the improvement in the tactile acuity at the trained finger (i.e., 2PDT task), we expect to see a difference in the characteristics of the MEPs response after RSS in the contralateral M1 compared to after the sham training.

## **7.2 Materials and methods**

### **Participants**

Fifteen participants (mean age = 26.8, range = 21–42; 9 females) took part in the experiment. Since an effect size could not be determined, because of the absence of similar TMS studies, we decide to have a sample size that was the average of previous RSS studies measuring neural changes (N=14, 16, 14, 15) (Höffken et al., 2007; Pleger et al., 2001, 2003; Rocchi et al., 2017). The study was approved by the local ethics review committee at the School of Psychology, University of Kent and was carried out according to the principles of the 1964 Declaration of Helsinki as updated by (World Medical Association, 2013). All participants were right-handed (mean =  $88.09 \pm 4.37$ , range: 42.86 – 100). Handedness was determined using the Edinburgh Handedness Inventory with the laterality quotient (LQ) (Oldfield, 1971). Participants received either credits or money as compensation for their participation.

## 7.3 Apparatus and stimuli

### Two-point discrimination task

As shown in Figure 7.1, the tactile 2PDT apparatus included seven pairs of needles or probes with a diameter of 200  $\mu$ m and spacing intervals of (0.7, 1.0, 1.3, 1.6, 1.9, 2.2, and 2.5 mm). Moreover, a single probe was used to evaluate the zero distance. A rotating disc on which the needles or probes were attached allowed for quick switching between distances. The equipment made it possible to adjust the amount of force used. Each probe was shown eight times in a pseudorandomized order during the course of the 64 trials. Additionally, there were four 1-minute pauses (one after every 16 trials) to prevent habituation on the area of the skin tested. The participant's right index finger's distal phalange was tested with this task. Having no sight of the device, the participants had to state "one" or "two" to indicate if one or two probes were being applied. The researcher recorded the participants' answers to each presentation.



**Figure 7.1 Two-point discrimination device image.** The image shows the two-point discrimination device as viewed from the researcher's perspective. In order to let the participants feel each distance, the 7 different pairs of probes and the single probe are mounted on a rotational disc. Thus, the experimenter can rapidly change between the probe being presented and the next one, by simply lifting the upper part (in light grey), which then fits perfectly for the probe presentation when it is pressed down.

Before the test, participants underwent a familiarisation process to determine the ideal placement of the tip of the tested finger on the instrument. They were then put through three trials of the test until they could correctly identify the two easiest probes (0 mm and 2.5 mm, representing 1 and 2 respectively) (Muret et al., 2014). The various probes were always presented with their longitudinal axes parallel to the finger. Throughout the experiment, no feedback was given on their performance.

### **Pegboard**

To assess behaviourally the motor performance, we used the 25-peg Grooved Pegboard (Jamar) (Figure 7.2). Only the index and thumb fingers of the left and right hands, depending on the session, were used to grab one peg from the pile. Participants had to commence by placing the peg in the hole on the top left corner of the device if they were using their right hand and the top right corner if they were using their left hand. The task was to rapidly fill up every row while maintaining accuracy and not skipping any holes. Participants could not choose a new peg from the pile when a peg was dropped, rather they had to pick up the dropped one first and then continue.

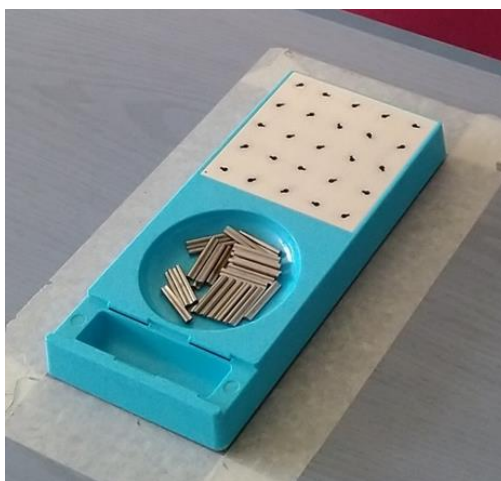


**Figure 7.2 Grooved pegboard task image.** The picture displays the grooved pegboard used in the experiment, from the examiner's perspective. The pegs are placed in the designated area from which the participants have to take them.

## TMS & Physiological measures

The TMS stimulation consisted of a single pulse delivered on the left M1 representing the right index finger. MEPs were recorded by an electromyogram (EMG) obtained through Ag-AgCl surface disc electrodes (Ambu Neuroline 710), positioned over the FDI of the finger. FDI is considered a reliable source for the read-out of motor processes (Bikmullina et al., 2009). TMS was performed using a PowerMAG (Mag & More) magnetic stimulator connected to an eight-shaped coil. The position and orientation of the coil were continuously recorded employing a Neuronavigational software (inVesalius) (Souza et al., 2018) and kept constant throughout the two sessions before and after the training (Table 1). The Fiducial Registration Error (FRE), which is the root square mean of the distance between the image fiducials used before and after registration, was maintained under 3mm (recommended precision for navigation) although due to technical difficulties, this was not always feasible. For each participant, the resting motor threshold (RMT) was determined as the minimum stimulation intensity that generated MEPs of 50 $\mu$ V or higher on 5 out of 10 trials with the hand at rest. TMS was applied both before and after training, however, participants received TMS before or after the grooved pegboard task based on the sequence counterbalancing.

| Training | Time   | x             | y             | z           |
|----------|--------|---------------|---------------|-------------|
| RSS      | before | - 29.8 (0.44) | - 13.6 (0.27) | 51 (0.43)   |
|          | after  | - 30.8 (0.09) | - 13.4 (0.13) | 51 (0.41)   |
| Sham     | before | - 28.9 (0.73) | - 14.6 (0.17) | 48,1 (0.44) |
|          | after  | - 29.5 (0.53) | - 14.6 (0.17) | 48.2 (0.43) |

**Table 7-1 Neurostimulation coordinates (InVesalius).** The table illustrates the participant's mean for the coordinates (MNI) of the stimulated site throughout the different sessions. Due to the differences between the standard template and the actual participant's head, the coordinates might not correspond to the standard MNI of the left M1.

The TMS intensity used was similar or the same (pre vs post RSS  $p = .32$  and sham,  $p = .42$ , see results for more details) for most of the participants in the before and after training sessions, however, there was a single participant in which it changed significantly. Moreover, due to technical

issues, the sampling rate frequency for the EMG signal was different across participants and sometimes sessions. The two sampling rate frequencies used were 1000 and 5000 Hz. Note that due to the window we were examining, this should not have affected our results.

## **Stimulation Protocols**

### **Repetitive Somatosensory Stimulation (RSS)**

We used an RSS protocol that has been previously successfully applied by other researchers that performed similar investigations (Dinse et al., 2003a, 2006; Godde et al., 2003; Muret et al., 2014, 2016; Pleger et al., 2001, 2003; see also Chapter 6). A compact solenoid with a diameter of 8mm was fixed to the palmar surface of the right D2 distal phalanx and used to administer tactile stimuli, which coactivated the several receptive fields in that region. To avoid habituation, the RSS sequence uses short supra-threshold tactile stimuli (single pulse duration: 10ms) separated by inter-stimulus intervals between 0.1s and 3s following a Poisson distribution. The entire coactivation time was 3 hours, with an average stimulation frequency of 1 Hz. An MP3 player, which had been used to record the pulses beforehand, was then used to play them. Participants were told to watch movies or series as well as continue with their usual activities without using their fingers more than what was strictly necessary.

### **Sham stimulation**

Except for the length and frequency of the tactile stimuli, the sham training was identical to the actual RSS in all respects. In the RSS, the transmission of the tactile stimuli occurred over a period of three hours and was only separated by arbitrary inter-stimulus intervals; in this stimulation, the stimuli occurred over a period of three hours, but only within six blocks of 2.5 minutes, with no inter-stimulus intervals. Therefore, throughout the course of the three hours, the final amount of significant stimulation had been 15 minutes.

## 7.4 Design

The study was a within-participants design with 2 within-subjects factors: time (before/after training), and training (RSS, sham). The behavioural performances (2PDT and Pegboard) and motor responses (i.e., MEPs) were the dependent variables. The experiment was double-blind, counterbalanced and sham-controlled. In one session participants received the RSS, whereas, in the other session, they underwent a sham stimulation. The order of the two sessions (RSS, sham) was counterbalanced so that half of the participants had the RSS training in the first session and the other half had the sham training. Each participant carried out the second session at least 3 days after completing the first one to control for potential carry-over effects. Regarding the tasks, the order of the pegboard and the TMS testing was counterbalanced (Figure 7.3) to prevent any possible confounding effects resulting from presentation order and sequence. All the possible sequences (AB-AB, AB-BA, BA-AB, BA-BA) were repeated the same number of times. The sham training was crucial to account for the placebo effect and has the two stimulations as similar as possible. So that even after getting a sham training, participants might still believe and experience post-training effects as if they had received the genuine RSS training. By analysing the placebo effect in the sham session, it was also possible to assess how much of the reports from RSS sessions were generated by an effect that was a result of the RSS stimulation and how much it was potentially caused by a placebo effect.



**Figure 7.3 Experimental design and timeline of the TMS study.** The image illustrates the experimental design with the outline of the day of the experiment with the different durations (approximately) of the tasks. Based on the session, the training consisted of RSS or sham training. Motor Evoked Potential (MEP), and input/output curve (I/O) are also shown as part of the design.

Moreover, as a double-blind study, neither the participants nor the researchers performing the testing knew which participants received the RSS training and which received the sham training when the behavioural testing was performed. The training was conducted by a third party who did not take part in the other steps of the experimental testing, so their beliefs about the intervention did not influence the outcome. Moreover, by using the specific setting (described above) on the sham RSS, we were able to lessen any confounding variables that could have been present in the participants' responses had the stimulation been merely turned off.

## 7.5 Procedure

Participants came to the laboratory for the first of the two sessions and based on the sequence order, they were then either prepared for the TMS testing phase or asked to carry out the Pegboard task at first. For the TMS phase, 3 electrodes were placed on the participants' right FDI, then the neuronavigational system was set up. After that, participants left M1 was localised according to a standard procedure used in a previous study that estimated such coordinates on a scalp template (Holmes & Tamè, 2019). Therefore, we used as a TMS stimulation starting point a location that corresponded to approximately 5 cm lateral and 0.5 mm anterior from the participant's vertex. TMS biphasic pulses were applied over the left M1 with the hand at rest to elicit MEPs that were recorded from the right FDI. This procedure was used to find the participants' RMT. Once the optimal site to target the right FDI was found, in order to develop the I/O curve, 10 pulses were applied for each of the 6 TMS intensities (from 90% to 140% of the RMT in steps of 10%). The order of the TMS intensities was randomly applied and counterbalanced.

The grooved pegboard task required participants to insert all the pins into the rows as quickly as they could with either the right or left hand, in accordance with the sequence order while sitting in front of the pegboard. Once they had completed the task with one hand, they carried out the same task with the other hand. Participants were instructed to complete two sessions of the 2PDT after the

TMS and pegboard phases, posing the right arm on the device while leaving the other in a relaxed position. Each probe was delivered eight times using the 2PDT device in a pseudorandomized order. Thus, there were 64 trials in total in each block that evaluated the participant's right index finger's spatial acuity. After each probe application, participants were asked if they felt 1 or 2 tips. The vision of the device was prevented throughout the experiment. To obtain a reliable measurement, the experimenter tested the right finger twice during the course of two 2PDT blocks. The data from these phases represented the participants' baseline measures.

Following that, depending on the session, participants received either the RSS or the sham training. The experimenter told the participants that they were allowed to engage in an activity that did not demand mobility throughout the 3 hours of stimulation (e.g., listening to music, or watching a video on the laptop). Thus, the participant's right index finger was taped to an mp3 player with the RSS/sham training set on it. They repeated the exact testing process as before the training (i.e., TMS, pegboard and 2PDT) after the stimulation was over. In the TMS testing, the experimenter used the M1-FDI coordinates that had been found before the training to stimulate the same brain area and location on the scalp. Finally, participants were debriefed and instructed to come back for the second session no less than 3 days later, so that they could undergo the same tests, but receive the opposite training (RSS or sham depending on the first session).

## 7.6 Analyses

### 2PDT and Pegboard tasks

The mean of the answer "two" was fitted using binary logistic regression as a function of the distance between the probes for each participant and time. After that, we assessed the 2PDT thresholds before and after RSS and sham training by extracting the participant threshold for the right index finger each time from the fitted data. The distance to which the participant replied "two" and "one" in equal proportion represented the threshold. Index finger data was included in a two-way repeated measures

ANOVAs with the following factors: session (RSS, sham) and time (before, after), The formula:  $[(\text{threshold post-training} - \text{threshold pre-training})/\text{threshold pre-training}] * 100$  was used to evaluate the percentage of change from the baseline thresholds after training.

Right, and left hands' response times, measured in seconds (e.g., 100), were entered into a three-way repeated measures ANOVA with the following factors: training (RSS, sham), time (before, after) and hand (right, left).

### **2PDT and Pegboard correlations**

To determine if these values were linked before and after each training, we entered the changes in the 2PDT threshold (%) for the right index finger and the response times for both hands into a Pearson correlation analysis. Thus, the association between the shifts in the 2PDT threshold (%) and those in the pegboard task was investigated.

### **TMS**

All the EMG data were filtered using a pass band and notch filters (0.015–500 Hz, notch: 50 Hz). The peak-to-peak MEP amplitudes (mA) between 15 and 50ms after the TMS pulse were computed using a custom-written MATLAB script. After that, the mean MEP amplitudes for each intensity were normalised to the RMT, since the intensity was not always constant, using the following formula (D'Amour & Harris, 2014; Tamè et al., 2014):

$$10 * \log_{10}\left(\frac{MEP_x}{MEP_{RMT}}\right), \text{ where } x \text{ stands for the intensity computed}$$

The mean MEP amplitudes were then analysed by a three-way repeated measures ANOVA with factors training (RSS, sham), time (before, after), and intensity (90, 100, 110, 120, 130). Bonferroni-holm correction for multiple comparisons was applied on all the post hoc paired t-tests.

We also computed the MEP's changes between the before and after training sessions for each stimulation intensity using the formula:

$$(\text{MEP}_{\text{after}} - \text{MEP}_{\text{before}}) / \text{MEP}_{\text{before}}$$

The results were entered into a 2-ways repeated measures ANOVA with factors training (RSS, sham) and intensity (90, 100, 110, 120, 130) to examine the respective training-induced changes with respect to baseline values. Moreover, we carried out 2 two-way repeated measures ANOVA with factors training (RSS, sham) and time (before, after) to analyse the changes in the RMT amplitudes. Finally, the MEP onsets were analysed by a three-way repeated measures ANOVA with factors training (RSS, sham), time (before, after), and intensity (90, 100, 110, 120, 130). Due to technical issues in data recording, one participant was excluded from the analyses.

## 7.7 Results

### 2PDT and Pegboard

For the 2PDT task, thresholds for the right index finger were submitted to the two-way repeated measures ANOVA, which showed that there was no significant main effect nor interactions, (All  $ps > .41$ ). For the pegboard task, we carried out a two-way repeated measures ANOVA for the hands' performance times and we found a significant main effect of hand,  $F(1,14) = 5.69$ ,  $p = .032$ ,  $\eta^2 = 0.29$ . Therefore, participants were faster overall at completing the pegboard task with their right ( $M \pm SE = 1.20 \pm 0.05$ ) compared to their left ( $M \pm SE = 1.31 \pm 0.06$ ) hand. However, we did not find any other significant main effects or interactions (All  $ps > .37$ ).

## 2PDT and Pegboard correlation

Pearson's correlation analysis between the changes in performance showed that there were no significant relationships between the execution times in the Pegboard task and the 2PDT thresholds (All  $ps > .05$ ).

## TMS

### *Amplitudes*

The MEPs amplitude was entered into a three-way repeated measures ANOVA with factors training (RSS, sham), time (before, after), and intensity (90, 100, 110, 120, 130); and we found a significant main effect of TMS intensity (Figure 7.4). However, probably due to the high number of observations in each participant's intensity factor, Mauchly's test of sphericity was violated, therefore, we applied a Greenhouse-Geisser correction,  $F(1,13) = 38.40$ ,  $p < .001$ ,  $\eta^2 = 0.76$ . As it is reasonable to expect, MEP's amplitudes became higher as the intensity of the TMS pulse increased, 90 ( $M \pm SE = -4.09 \pm 1.33$ ), 100 ( $M \pm SE = 1.28 \pm 1.33$ ), 110 ( $M \pm SE = 4.83 \pm 1.33$ ), 120 ( $M \pm SE = 7.83 \pm 1.33$ ), 130 ( $M \pm SE = 10.88 \pm 1.33$ ). Post-hoc results indicated that MEP amplitudes at 90% were significantly lower than those at 100%  $t(13) = -4.04$ ,  $p < .001$ ,  $d = -0.72$ , 110%  $t(13) = -6.72$ ,  $p < .001$ ,  $d = -1.20$ , 120%  $t(13) = -8.97$ ,  $p < .001$ ,  $d = -1.60$  and 130%  $t(13) = -11.22$ ,  $p < .001$ ,  $d = -2.01$ . Those at 100% were also significantly lower than the amplitudes at 110%,  $t(13) = -2.68$ ,  $p = .030$ ,  $d = -0.48$ , 120%,  $t(13) = -4.93$ ,  $p < .001$ ,  $d = -0.88$  and 130%,  $t(13) = -7.23$ ,  $p < .001$ ,  $d = -1.29$ . Finally, the amplitudes at 110% were significantly smaller than the ones at 130%,  $t(13) = -4.55$ ,  $p < .001$ ,  $d = -0.81$ . There were no differences between the MEP amplitudes when TMS was used to stimulate at 120% and 130% of the RMT.

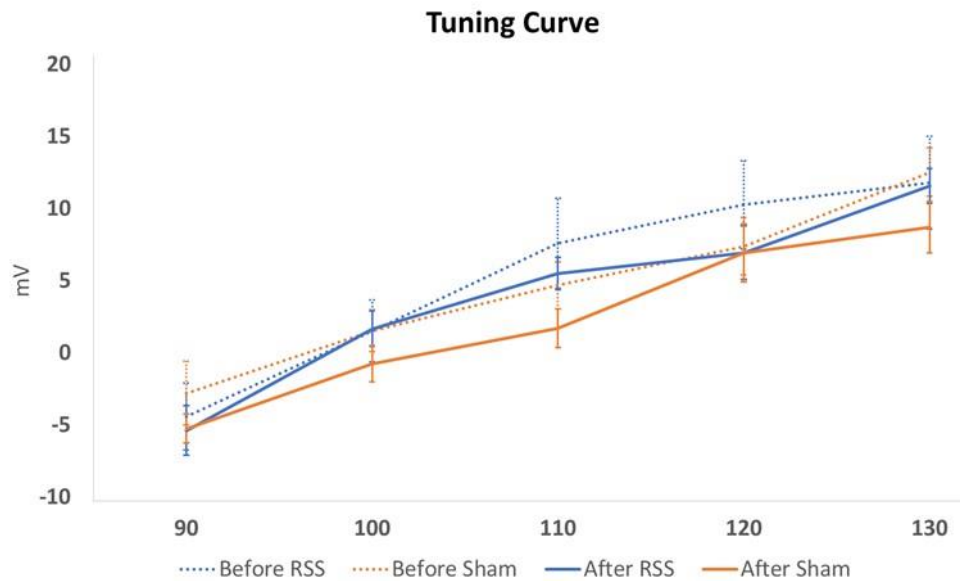


**Figure 7.4 Tuning curve (I/O) after tactile training.** The graphs show the I/O tuning curve of the MEP amplitudes before (dotted lines) and after (solid lines) each training (bottom).

We also analysed the RMT amplitudes using a two-way repeated measure ANOVA with factors training (RSS, sham) and time (before, after), which showed that there were no significant differences between the training or times (All  $ps > .13$ ). As shown in Figure 7.5, there was no significant difference between the RMT of any of the conditions tested, (All  $ps > .35$ ).

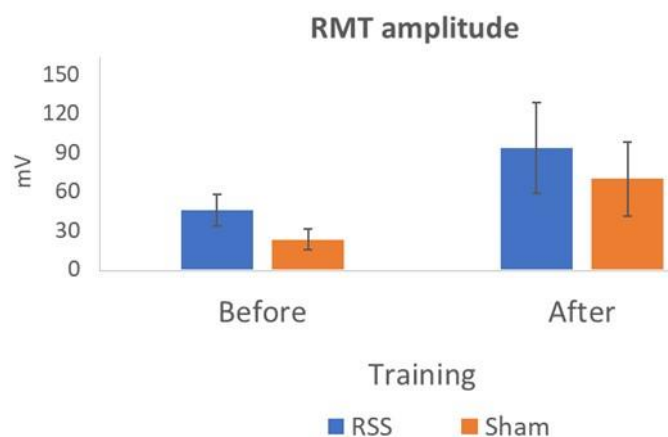


**Figure 7.5 Resting motor threshold amplitudes after tactile training.** The bar chart illustrates the RMT amplitudes before and after each training.

Finally, as shown in Figure 7.6, the ANOVA analysing the change of MEP amplitudes from baseline for each training showed that there were no significant main effects nor interactions (All  $ps > .37$ ).

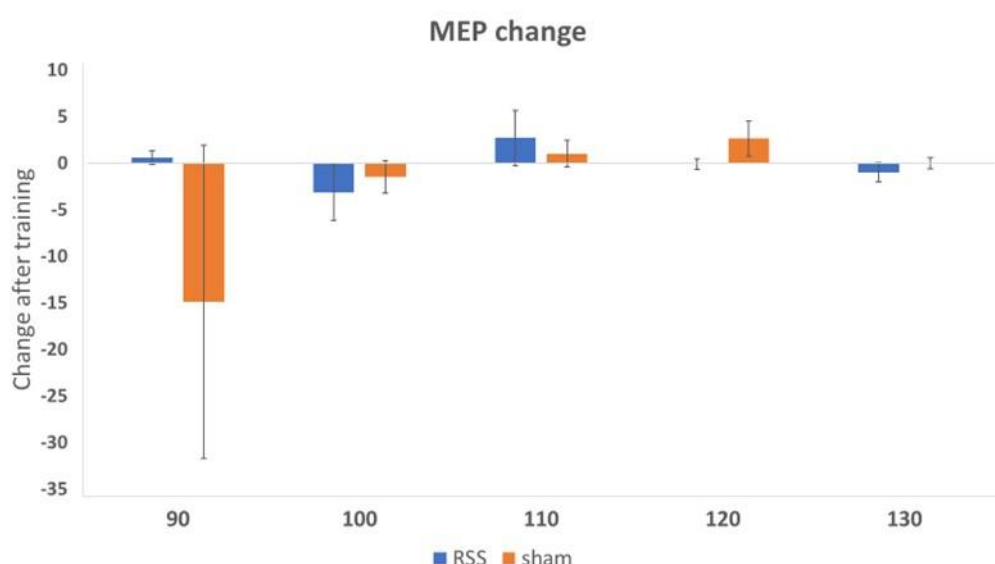


**Figure 7.6 Motor evoked potential changes after tactile training.** The bar chart shows the mean difference in MEP amplitudes after each training for all the stimulation intensities.

### Onset

The MEP onsets for all the intensities were included in a three-way repeated measures ANOVA with factors training (RSS, sham), time (before, after), intensity (90, 100, 110, 120, 130), which revealed that there were no significant main effects nor interactions (All  $ps > .11$ ). Furthermore, the MEP onsets for the RMT showed no significant differences (All  $ps > .47$ ).

## 7.8 Discussion

In this study, we investigated whether the RSS influences motor corticospinal excitability in addition to the known tactile improvements. However, contrary to our expectations, we did not find any significant change in the tactile discrimination (2PDT) and motor (pegboard) tasks performance when

comparing them before and after the RSS training. The tactile improvements have been usually considered an indicator of the cortical plasticity changes in the somatosensory cortex induced by RSS (Godde et al., 2003; Hodzic, 2004; Höffken et al., 2007; Pleger et al., 2001, 2003). Therefore, it is expected that if the RSS did not lead to any variation in the somatosensory cortex, consequently there would not be any alteration in the motor system activity. In a previous study (Chapter 6) we found that RSS affects both tactile and motor performance. We will try now to identify the potential reasons for the discrepant results between these two studies.

In our previous work (Chapter 6), forty participants were tested and divided into two groups, so that 20 participants received the RSS training and the other 20 received sham training. Both tactile (2PDT) and motor (Grooved pegboard) performance were measured before and after the training to assess the changes between the two sessions and training. Instead, in the current study we tested 15 participants (14 in the analyses), who received both the RSS and sham training in different sessions at least 3 days apart and were tested in tactile (2PDT) and motor (Grooved pegboard, TMS) domains before and after each training. Therefore, we used a within-participant design to test both RSS and sham training on the same participants, a procedure that was never done before in the RSS literature. We introduced this variation with the aim of increasing the power of our design and improving the recruitment process. In the previous studies, a larger sample size might have compensated for the high interindividual variability, whereas this issue became evident in the current study as we used a smaller sample. Thus, the lack of a significant effect both for the tactile and motor tasks in this study might be explained by the interplay of some of these and other factors.

One possibility can be the high variability in participants' performance combined with a small sample size. Indeed, some participants' results were compatible with what has been reported in previous studies in the RSS literature, i.e., a decrease in the 2PDT right index threshold after RSS but not after the sham, whereas others had the opposite effect. In this regard, it has been shown that learning and plasticity can be affected by several factors, such as GABA concentration in the

somatosensory cortex. High levels of GABA before RSS, correspond to high learning gains in the 2PDT performance for the right index (Heba et al., 2016). Moreover, the resting state alpha rhythm in the postcentral parietal cortex (contralateral to the RSS application site) before the training predicts the learning effect as measured by the 2PDT (Freyer et al., 2013). Additionally, interindividual variability can derive from different grey matter thicknesses (Conde et al., 2012) and brain-derived neurotrophic factor gene (BDNF) polymorphism (Cheeran et al., 2008). Based on all these elements, although unlikely, we might have recruited participants who had an overall lower propensity for plasticity (Yang et al., 2020), which combined with the small sample size further affected the results.

The current study was longer and more demanding than the previous one we performed on a different sample (chapter 6), therefore, factors such as fatigue, concentration, and willingness to cooperate might have had an impact on the results. Thus, it must be taken into account that, as suggested by Dinse and Tegenthoff (2018), issues in an RSS study might be deriving not only from the biological/genetic features of participants, as described above but also from these temporary characteristics (Dinse & Tegenthoff, 2018).

Based on this interpretation, their impact would have been restricted to psychophysical testing, since one of the best advantages of RSS stimulation is that is not affected by attention (Dinse & Tegenthoff, 2018; Godde et al., 1996, 2000; Pleger et al., 2001). Following this view, the RSS might have had an effect, but this was not detected by the behavioural tasks which require high levels of attention and concentration. On the other hand, there is not enough evidence to suggest this view and that the RSS leads to no changes in MEP characteristics (amplitude, onset).

Therefore, the question regarding the impact of RSS on motor corticospinal excitability remains open. Our study provides important information that needs to be considered in future works investigating this question. Despite the issues found in the current study, the within-participant, double-blind, and sham-controlled design we adopted, seems a solid method to examine the potential RSS effects on motor corticospinal excitability. Future studies might consider increasing the sample

size, obtaining stable 2PDT thresholds for both index fingers and thumbs on the days before the training session to reduce session duration, and possibly having a baseline measure of GABA concentration in S1 (e.g., paired-pulse stimulation or Magnetic Resonance Spectroscopy).

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## **Chapter 8 : General discussion**

### **8.1 Main results**

The goal of my thesis was twofold: investigate the role of stimuli proximity from the body on visual training and the role of tactile training in motor behaviour. Therefore, two main lines of research were established. The first line of research focused on examining whether carrying out visual training in a space in which we can directly and physically interact with the objects (PPS) around us leads to different results compared to when the training is performed in a space in which we cannot directly act on objects (EPS). This question was investigated in the studies described in Chapter 2 and extended to the role of the hemispace (left vs right) in Chapter 3. Since we found an improvement in the visual training for stimuli in the far space compared to the ones in the near space, the study reported in Chapter 4 was developed to determine the different visual pathways that potentially led to this dissociation. The second line of research focused on investigating the effect of a specific tactile passive training (RSS) on motor behaviour. Chapter 5 consisted of a review paper in which we delineated the rationale behind the hypothesis that tactile training might have an impact on the motor system and motor behaviour by describing the dense anatomical and physiological connections between these two systems. In Chapter 6, this question was empirically addressed in a behavioural study, evaluating participants' tactile and motor performance before and after RSS training. Chapter 7, further explores the influence of tactile training on the motor system and behaviour using TMS to estimate the effect of tactile training on corticospinal excitability.

Results of the study in Chapter 2, showed that visual training in the space near the body and within our reach does not have a significant effect on performance (d-prime) in a visual search task, whereas if the training is carried out in a space far from the body, it is effective in improving participants' performance. Moreover, this effect generalised to the untrained space (peripersonal space). The results of studies 2 and 3 (Chapter 3), demonstrated that visual training can be highly specific and confirmed that enhancement in performance always occurs in a space far from the body.

Furthermore, these studies proved that the effects were not due to several confounding variables, such as the functional specialisation of the upper and lower visual hemifields, distance from the screen, display settings (e.g., luminosity, contrast etc.), and gaze. In addition, they suggest that the visual hemispace (right or left) in which the training takes place, has a selective impact on the effectiveness of the training carried out in the near space. Study 4 (Chapter 4) results, although unexpected, were not able to disentangle the role of the parvocellular and magnocellular pathways in the visual perception of stimuli near and far from the body. Note that this last study was not involving any visual training, rather it was focusing only on visual perception.

Regarding the tactile training, study 5 (Chapter 6) revealed that repetitive somatosensory stimulation significantly improves performance on the two-point discrimination task only for the trained right index finger (i.e., trained finger), as this was not the case for the left index finger and both thumbs (i.e., untrained fingers). Furthermore, this study showed that RSS affects not only the somatosensory system, but also, to some extent, the motor system, given that participants were faster in the grooved pegboard task with the left hand in the group receiving the RSS training. Finally, in study 6 (Chapter 7) we did not replicate the effect of RSS on tactile or motor performance, namely, there were no improvements in participants' tactile and motor abilities following the RSS or sham training. Moreover, seemingly the corticospinal excitability was not affected by the training. We suggest that the lack of an effect of training in this later study can be most likely reconducted to substantial methodological differences between the two studies. The main findings of the visual and tactile training will be separately described in further detail in the following sections.

### **8.1.1 Visual training**

The main result of the *first part* of the work presented in this thesis on visual learning is that learning to find an object is more effective if visual training occurs on stimuli that are far rather than near the body. In Chapter 2, we revealed that visual perceptual learning was only successful when individuals

carried out the training in the extrapersonal space, contrary to our predictions, which were based on a substantial amount of research pointing to perceptual processing benefits in the region near the body (Ahsan et al., 2021; Blini et al., 2018; Dureux et al., 2021). Furthermore, when training took place in the extrapersonal space, performance increased in both the peripersonal (near) and extrapersonal (far) regions (see figure 8.1), demonstrating a spatial generalisation of the learning. This result differs compared to some previous reports that suggest specificity of the perceptual learning effects, as typically confined to the trained stimulus' feature (e.g., orientation, spatial position, or eccentricity) (Crist et al., 1997; Karni & Sagi, 1991; Schoups et al., 1995). However, participants were considerably more accurate in the visual search task only for the particularly trained orientation in the far space, thus this spatial generalisation only appeared for the distance component and not for orientation.

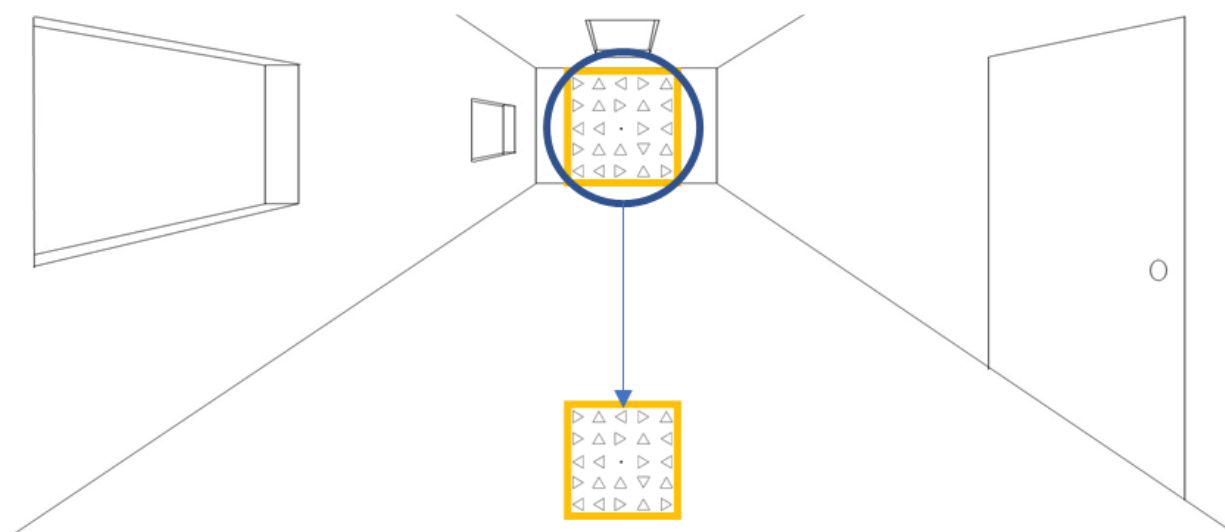


**Figure 8.1 Summary of the findings from Chapter 2.** This is the picture that appeared on the screen during a typical trial for the study in Chapter 2. When the training was carried out in the far space (blue circle), there was an improvement in the performance in both spaces (yellow squares). Note that the blue and yellow highlights are presented for illustrative purposes only.

In Chapter 3, we used a horizontal Ponzo illusion, rather than a vertical one, to create a depth

perspective. Importantly, the created illusorily spaces (near and far) were paired with the left and right sides of the display in the first study, and the opposite in the second study, to account for potential laterality effects.

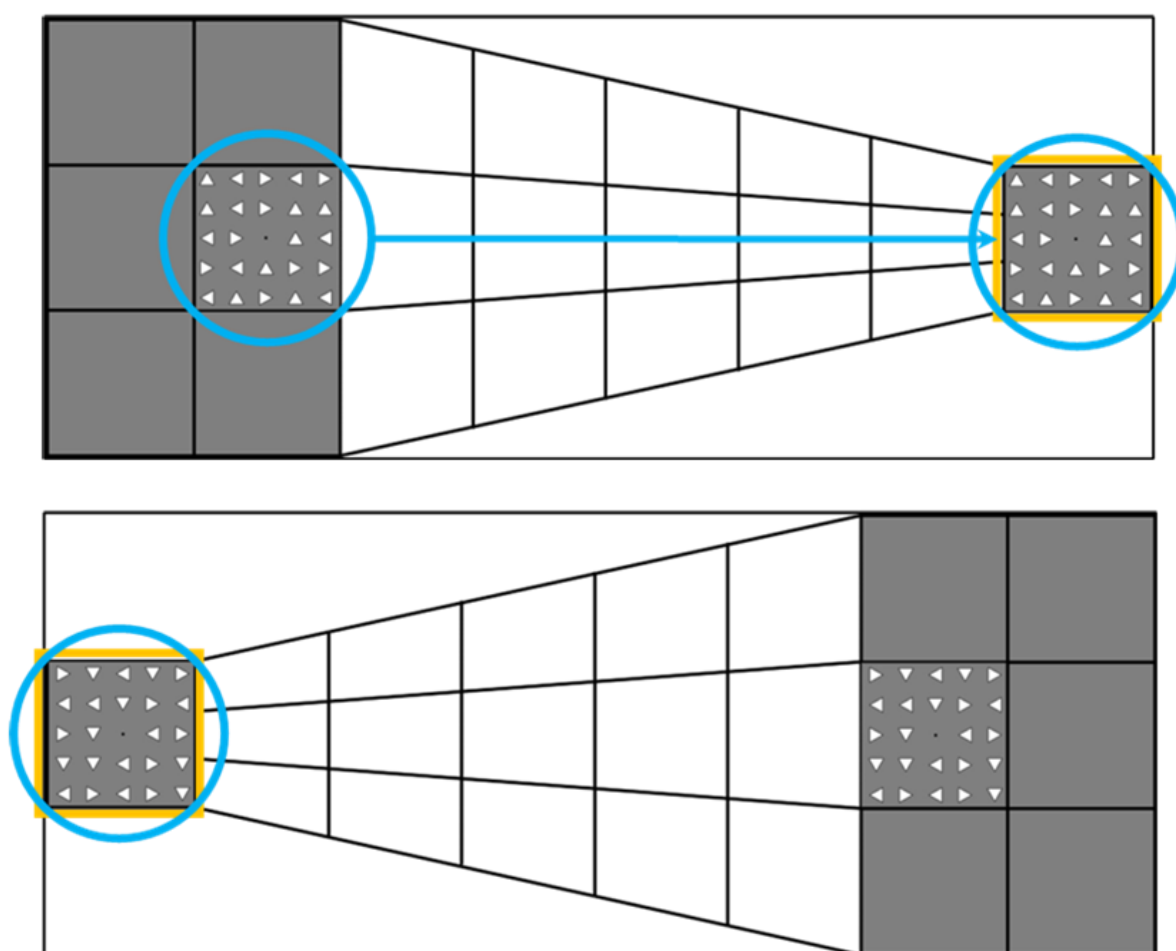


**Figure 8.2 Summary of all the findings for the visual training.** These are the pictures that were presented in a typical trial in Study 1 (*top*) and Study 2 (*bottom*) in Chapter 3. In experiment 1, when the training was carried out either in the near or far space (blue circles) there was an improvement only in the performance in the far space (yellow square). In experiment 2, when the training was carried out in the far space (blue circle) performance significantly improved only in the far space (yellow square). Note that the blue and yellow highlights are presented for illustrative purposes only.

These studies demonstrated that when the near space was on the left side of the screen (Figure 8.2, *top*), participants' accuracy significantly increased (for the trained orientation) in the far space regardless of whether they trained in the near or far space. When the near space was on the right side of the screen (Figure 8.2, *bottom*), participants who trained in the space far from the body, reported a

considerably enhanced sensitivity ( $d'$ ) for the trained orientation and not for the other orientations in the far space.

On the basis of these results, it appears that our visual search abilities might have the predisposition to learn with stimuli that are in a space far from our body. These learning effects might be due to differences in attentional processes in space, which have been demonstrated in some previous studies (Couyoumdjian et al., 2003; Gawryszewski et al., 1987; Losier & Klein, 2004; Reed et al., 2006). A possibility is that stimuli within our reach, near our body, have automatic attentional priority and it is more difficult to disengage attention from them (Abrams et al., 2008), as they may have a prominent role in performing an action (Brockmole et al., 2013; Reed et al., 2010) or they can represent a threat (Franconeri & Simons, 2003; Graziano & Cooke, 2006; Spaccasassi et al., 2019). In agreement with these findings, when stimuli are near our bodies not only they are detected faster than when they are far from it (Reed et al., 2006), but they can also be discriminated more rapidly (Blini et al., 2018) and with higher accuracy (Ahsan et al., 2021). This near-the-body space advantage of visual stimuli identification and/or discrimination seems to apply to several visual features, such as size, shape, and orientation (Ahsan et al., 2021; Blini et al., 2018; Dureux et al., 2021).

Intriguingly, the studies in Chapter 3 (Figure 8.2) demonstrated that participants always experience performance gain in the far space; however, when training is performed in the left hemispace, even training in near space results in far space improvements (Figure 8.2, *top*). So, it seems that, when taking place in the left hemispace, the visual training is overall more beneficial. These findings are consistent with the body of research claiming that there is a general advantage to processing stimuli that occur in the left hemispace (Bowers & Heilman, 1980; Charles et al., 2007; Jewell & McCourt, 2000; Mattingley et al., 2004; Toba et al., 2011). Therefore, training on the left visual hemispace might be enhanced due to the superior visuospatial attention processing of the right hemisphere. This speculation regarding visual hemispace differences in visual learning and their neural underpinnings will require further investigation as our studies (Chapters 2, 3) were only

behavioural.

Visual perception, differently from visual learning, in the space near and far from the body has been suggested to be guided by different neural pathways. Particularly, the magnocellular and parvocellular pathways, which project primarily to the dorsal and ventral streams, respectively. In simple terms, the magnocellular neurons have a high temporal resolution (thanks to the high conductivity speed), poor spatial resolution, and high sensitivity to contrast and motion, whereas the parvocellular have the opposite pattern (Livingstone & Hubel, 1988; Ungerleider & Mishkin, 1982). Several studies have shown greater activation of the magnocellular pathway when visual stimuli are presented near our body (Makin et al., 2012; Weiss et al., 2000, 2003). At the same time, increased recruitment of the parvocellular pathways has been demonstrated for visual stimuli appearing in the extrapersonal space (Li et al., 2011).

In Chapter 4, we investigated the involvement of these two pathways in a visual search task, by creating two conditions in which one of the two pathways was selectively recruited. Results showed that performance was better in the magnocellular pathway condition, regardless of the space in which the task was performed. This result is not what we expected, namely, a double dissociation showing the magnocellular condition being better (higher accuracy) in the space near the body, whereas the parvocellular is better in the space far from the body. These findings might have been considerably affected by different factors that modulate the magnocellular and parvocellular pathways, such as task difficulty, attentional demands, and stimuli characteristics (i.e., spatial frequency, colour, and luminance) (Abrams & Weidler, 2014; Goodhew et al., 2017; Goodhew & Clarke, 2016; Li et al., 2011). The most likely explanation of the overall improvement for the achromatic condition, which was intended to engage the magnocellular pathway, may simply be attributable to the fact that the chromatic condition was more tiring as some individuals mentioned this aspect in the debriefing.

Overall, these series of studies (Chapters 2, 3, and 4) were the first to show that visual training

is effective when it is conducted in a space far from the body, whereas when visual training is performed in a space near the body, it might induce perceptual improvements if it is carried out in the left hemispace, but the better sensitivity is still observed only in the far space (Figure 8.2 *top*). This specific visual perceptual learning advantage in the far space was found in one online (Chapter 2) study and two lab-based studies (Chapter 3), thus, it appears to be very solid. Finally, we interpreted these results as evidence that the peripersonal space might induce opposite performances in visual learning (reduced) and perception (enhanced), although the reasons for this difference are still unknown.

### 8.1.2 Tactile training

The results of the *second part* of the work presented in this thesis on tactile learning are different between the behavioural (Chapter 6) and neurostimulation (Chapter 7) studies. In the *behavioural study*, results showed that participants who received RSS training reported a considerable decrease in the 2PDT threshold, which indicates improved tactile acuity on the trained body part (i.e., right index finger) (Figure 8.3). Furthermore, the RSS effect was local, as it did not transfer either to the right thumb or the opposite hand (left D1 and D2). As expected, participants who underwent sham training did not show any significant improvements when evaluated on the trained and untrained fingers, in accordance with previous studies (Godde et al., 2000; Kalisch et al., 2008). Interestingly, we observed that the RSS-induced effects on the somatosensory system influenced the performance of a motor dexterity task (grooved pegboard task). Particularly, participants who received the RSS training became significantly faster at completing the grooved pegboard task with their left hand, whereas the participants who underwent the sham training improved with their right hand (Figure 8.3).

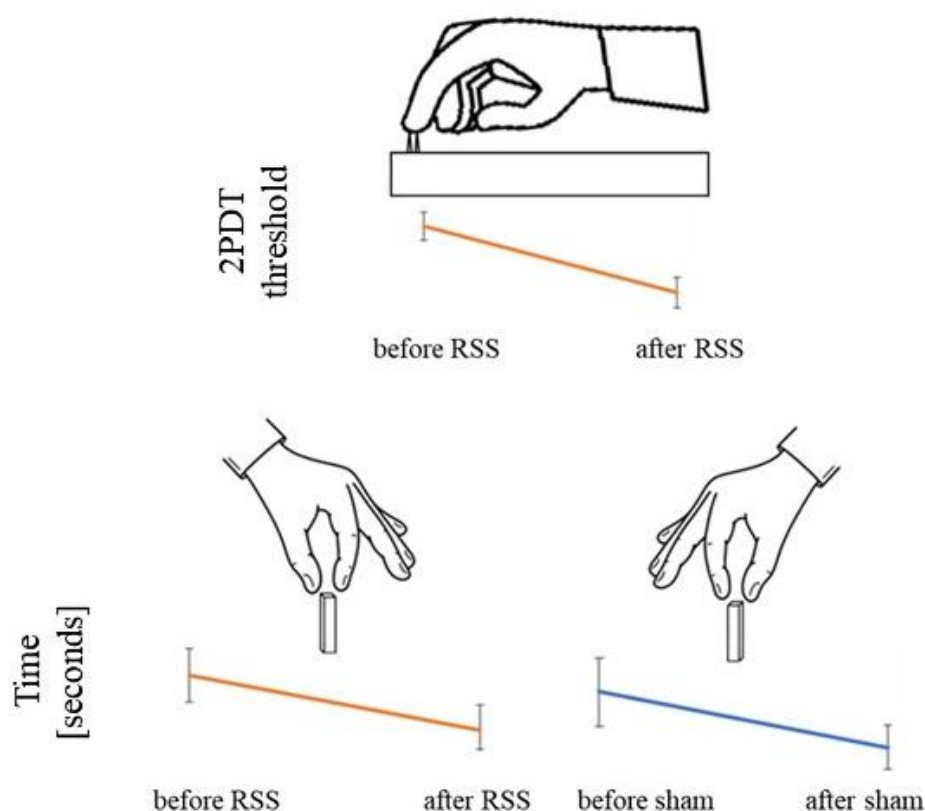


**Figure 8.3 Summary of all the main findings for the tactile training.** The first image (*top*) indicates the decrease in the 2PDT threshold after RSS for the right index. The two images (*bottom*) represent the lower execution time in the grooved pegboard task with the left hand after RSS (left), and with the right hand after sham (right).

Based on all this information, we might speculate potential scenarios to explain the processes behind the observed results in motor behaviour. Our rationale was founded on the assumption that the generated RSS changes in the somatosensory cortices should impact the motor cortices and therefore the motor response. It has been shown that these interactions can generally work in an excitatory or inhibitory manner (Chen et al., 1999; Jacobs et al., 2014; Tokimura et al., 2000). In the case of RSS, the results observed in Chapter 6 suggest an inhibitory effect on the motor system. Indeed, RSS training led to lower 2PDT thresholds in the right index finger (stimulated body part), which in accordance with previous studies, is associated with higher activity in the somatosensory cortices (Höffken et al., 2007; Pleger et al., 2001, 2003). Therefore, it can be speculated that the higher somatosensory excitability inhibited the right-hand motor excitability (ipsilateral), while concurrently releasing the left hand from the interhemispheric inhibition that ordinarily controls the

coordination of the two hands during unimanual movements (Grefkes et al., 2008; Tinazzi & Zanette, 1998; Vercauteren et al., 2008).

Another aspect to take into account is lateral inhibition (Biermann et al., 1998). Lateral inhibition is a result of neurons activating in response to a specific location, which causes less neuronal activity in nearby regions. If this process is applied to Chapter 6 findings, then higher right index finger activation should have led to a lower right thumb sensitivity which might have resulted in slower reaction times in the grooved pegboard task with the right hand.

This pattern, therefore, would explain the presence of improvement with the left hand and not with the right hand in the grooved pegboard task after the RSS training and the faster performance with the right hand (dominant one) observed in the sham group after training.

In the *neurostimulation study* (Chapter 7), participants did not show any difference in performance after the RSS or sham training. This was true for both the tactile and motor tasks. Similar results were found also when we compared the corticospinal excitability, as there were no differences in the MEPs amplitude between the pre and post-RSS and sham training. The main explanation for the discrepancy between the results in the studies described in Chapters 6 and 7, is probably a difference in the methodological protocol. However, the lack of 2PDT changes in the trained finger after RSS shows that the high interparticipant variability, sample size and fatigue might have played a substantial role in this study. In light of this, the question of whether RSS influences motor corticospinal excitability remains unanswered. Nonetheless, this study offers novel information on the key role played by the methodological approach used in revealing the RSS training effect on the somatosensory and motor systems.

## 8.2 Conclusions and Perspectives

The results of this thesis provide new considerable information regarding perceptual learning in the visual and tactile domains.

By showing that visual perceptual learning is better in the far space, I have paved the way for a new branch of research investigating the distance component in perceptual learning. Furthermore, the visual training effects are greatly reduced (or impaired) in the peripersonal space, which is intrinsically related to action. This suggests either an overall advantage for learning to find objects when they are far from us or perhaps that these objects have to be relevant for motor behaviour (e.g., evoking affordance, graspability, interaction) for the learning to occur near us. Therefore, these findings open new questions regarding visual training and its relationship with space and motor behaviour, which will need to be further explored by future studies.

The findings illustrating that RSS can affect motor behaviour show that this protocol can also be used to modulate motor performance rather than being restricted to the somatosensory system. Furthermore, since the changes in the motor behaviour appear to be inhibitory for the ipsilateral hand, this method might be used to correct cases of maladaptive plasticity or bring balance to inhibitory-excitatory sensorimotor interactions.

In conclusion, there are still plenty of aspects to be discovered about visual and tactile training and its respective relationships with the motor domain. Using the outcomes of this thesis, several factors have been added, which will potentially lead to more investigations and discoveries.

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