Università degli Studi di Palermo (in Convenzione
con l'Università degli Studi di Messina)

**CLINICAL MEDICINE AND SCIENCE OF BEHAVIOR**

Department of Internal Medicine and Medical Specialties (DIMIS) –
University of PALERMO
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# ASYMMETRY OF SELECTIVE ATTENTION IN HEALTHY SUBJECTS AND PATIENTS WITH CERVICAL FOCAL DYSTONIA

**MED/48 - M_PSI/02**

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XXIX cycle - Academic Year 2013-2014

# Declaration

*I, Gaetana Chillemi, declare that this thesis titled, "Asymmetry of selective attention in healthy subjects and patients with cervical focal dystonia", and the work presented in it are my own. I confirm that:*

- *This work was done mainly while in candidature for a research degree at this University.*
- *The experiments were planned and conducted by myself.*
- *In the experiments with patients, I received the help from Prof. Angelo Quartarone, Prof. Raffaella Ricci and Dr. Francesca Morgante in the patient's recruitment and assessment.*
- *Analysis and interpretation of the data was conducted by myself with the help of Dr Alessandro Calamuneri.*
- *Where I have consulted the published work of others, this is always clearly attributed.*
- *Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.*
- *I have acknowledged all main sources of help.*

Signed: Gaetana Chillemi

Date: 09.02.2017

*To Juliette and Luigi*

## Abstract

The environment continuously provides a wealth of information through our senses. This poses a major challenge to our brains to effectively process the relevant pieces of information over space and time, involving attentional processes. Attention selects, modulates and sustains focus on information most relevant for behaviour going beyond our limited capacity to process competing options. Voluntary allocation of attention to features, objects, or regions in space is controlled by top-down mechanisms. On the other hand, salient stimuli can automatically attract attention, even though the subject does not have intentions to attend to these stimuli. A key question is how attention is shaped by the presence of objects, in particular with respect to object exposure time.

In healthy subjects, it is well known that the spatial features of objects influence attention processes. It has been shown that visuospatial attention is asymmetrically distributed with a systematic bias towards the left visual field. In contrast, there seems to be a rightward bias for audiospatial attention, yet this notion is controversial. In patients with idiopathic focal dystonia, processing of spatial and temporal information has been shown to be impaired, but it remains unclear how much impaired sensory processing is linked to abnormal biases in spatial attention.

This thesis explored the role of selective attention in healthy subjects and dystonic patients employing novel paradigms which require shifts of spatial and temporal processing in response to visual and auditory cues.

The results obtained in healthy subjects showed a rightward bias for auditory attention. Together with the evidence of a leftward bias for visuospatial attention, the results support the idea of modality-specific auditory and visual attentional systems. Furthermore, the experiments provided evidence that

temporal attention may be spatially driven, again, expressing a leftward bias for the visual modality and a rightward bias for the auditory modality.

In contrast to healthy individuals, patients with idiopathic cervical dystonia and prominent torticollis displayed a consistent leftward bias for visual stimuli. This was also the case in patients in whom dystonia was worse on the right side of the body. This abnormal leftward attentional bias in dystonic patients with torticollis indicates an aberrant hemispheric lateralization of the visuospatial attentional system in idiopathic cervical dystonia. Finally, attentional processes were influenced by the "phenotype" of idiopathic cervical dystonia. We found a double dissociation in the performance between patients presenting with laterocollis or torticollis. The laterocollis sub-group showed a significant alteration of auditory processing, whereas temporal processing was impaired in the torticollis sub-group.

In conclusion, this work suggests that differences in deployment of auditory attention are related to individual differences in visuospatial attentional processing. Moreover, it is especially important to design rehabilitation treatment for individuals who have sustained damage to portions of the parietal-basal ganglia-cerebellum network and may be suffering from various attentional disorders.

## Acknowledgments

*I would like to thank Professor Angelo Quartarone, Professor Hartwig R. Siebner and Professor Raffaella Ricci for the guiding along these years, the inspiration and support of this work. I would give my special thanks to Dr Alessandro Calamuneri and Caterina Formica for their collaboration and patience. Finally, I would like to thank the patients and their family for their generosity to participate this work. Last, but not least, I would like to thank my family for the understanding and love during the past few years.*

**Referee** (Title, Name): Prof. HARTWIG SIEBNER

## Evaluation Report for the PhD Thesis

SELECTIVE ATTENTION ASYMMETRIES ON HEALTHY SUBJECTS AND DYSTONIC PATIENTS

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Copenhagen 02-12-2016

(place and date)

(signature of referee)

***Further Remarks***

Very innovative behavioral study with potential clinical impact.

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## *Evaluation Summary*

| very good | good | satisfactory | sufficient |
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Wuerzburg, 2.12.2016
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## *Further Remarks*

This is a well-conducted thesis combining several studies evaluating selective attention in healthy subjects and dystonic patients. In particular, Gaetana Chillemi explored the role of selective attention with different paradigms requiring shifts of spatial and temporal processing in response to visual and auditory cues. The main result was an alteration of spatial processing in patients with laterocollis, while impairment of temporal processing was described in subjects with torticollis, thus further supporting the hypothesis of dysfunctional fronto-parietal-cerebellum attentional network in dystonic patients. These findings are of great value in further understanding the pathophysiological mechanisms of dystonia and to develop individualised treatment options.

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## List of Abbreviations

Stimulus Onset Asynchrony (SOA)

Inter Stimulus Interval (ISI)

Mental number line (MNL)

Cervical idiopathic Dystonia (CD)

Short intracortical inhibition (SICI)

Myoclonus-dystonia (DYT11)

Ionotropic receptor for γ-aminobutyric acid (GABA_A)

Silent period (SP)

Intracortical inhibition (LICI)

Metabotropic transmembrane receptors for gamma-aminobutyric acid (GABA-B)

Surround inhibition (SI)

Focal hand Dystonia (FHD)

Functional magnetic resonance imaging (fMRI)

Positron Emission Tomography (PET)

Eye blink classical conditioning (EBCC)

Intracortical facilitation (ICF)

Motor evoked potential (MEP)

Voxel based morphometry (VBM)

Transcranial magnetic stimulation (TMS)

Visuospatial task (VST)

Visuo-audio spatial task (VAST)

Accuracy (ACC)

Reaction time (RT)

Repeated-measures ANOVA (rm-ANOVA)

Greenhouse-Geisser degrees of freedom (df)

Visuo temporal (VTT)

Audio Temporal task (ATT)

References exposure time (RET)

Targets exposure time (TET)

Rightward errors (+)

Leftward errors (-)

Linear mixed models (LMM)

Akaike Information Criteria (AIC)

Torticollis (TC),

Laterocollis (LC),

Controls (C)

Visual analog scale (VAS)

Left hand(LH)

Right hand(RH)

Posterior parietal cortex (PPC)

Standard Error of the Mean (SEM).

Primary motor cortex (M1)

## Outline of this thesis

This thesis is organized as follows:

**Chapter 1** – Introduction, divided into 2 parts. The first one outlines the neuropsychology and neurophysiology of selective attention system. The second part presents a review of the neurophysiology of Idiopathic Cervical Dystonia.

**Chapter 2** – Methods and Materials – describe the materials, the experimental design, and data analysis for each experiment.

**Chapters 3-4** – Results chapters – describe the experimental work: the aims, the results and the discussion of each study. Specific goals of each study were the following:

- To deepen the role of attentional bias on cross modal interplay between visual and auditory stimuli when both are manipulated spatially and temporally (Chapter 3).
- To explore of spatial and temporal cognitive processing in different pattern-types of Dystonia (Chapter 4).

**Chapter 5** – Conclusion, divided into 3 parts. The first and second part treat the neurophysiology of selective attention in healthy subjects and Dystonia. The last part explore the possible role of multisensory integration in rehabilitation of cognitive impairment.

# Chapter 1

# Introduction

*"Perception shapes priorities, priorities shape people"- Ben Thompson*

We use learned regularities to help and interpret the complexities of the world and make life easier and simpler. People perceive stimuli within the world, select the relevant ones only and move to them; but these processes could go wrong and what could be the consequences?

Attention is the key to that. It allows us to selectively process the vast amount of information with which we are confronted, prioritizing some aspects of information while ignoring others. The existence of different selective attention mechanisms is well documented in neurological diseases as well as healthy subjects.

Dystonia is a movement disorder characterised abnormal postures of the affected body part. Despite this overt motor phenotype, there is evidence of sensory abnormality, suggesting the presence of a primary deficit in sensory processing. The underlying mechanism of this disease may therefore include the manner in which stimuli are perceived and processed according attentional biases.

This chapter introduces the concept of selective attention. Secondly, the techniques as well as a methods used on selective attention are presented. Furthermore, it is discussed Cervical Dystonia, concentrating particularly on the deficits in sensory processing. At the end of the chapter, it is presented the aim of this thesis, which is to investigate the selective attentional processes in healthy subjects and Dystonia.

## 1.1 Taxonomy of attention

Contrary to common belief, attention does not refer to a single process, but is an umbrella term referring to several processes (Treisman, 1980). It selects,

modulates, and sustains focus on information most relevant for behaviour going beyond our limited capacity to process competing options.

I would like to propose an attention taxonomy based on the types of control that it operates over the targets of attention in order to clarify the terms that I am going to use in this work.

We can distinguish three different aspects of attention: alerting, orienting, and executive control (Petersen and Posner, 2012). Alerting is defined as maintaining a state of high sensitivity to incoming stimuli (Marrocco and Davidson, 1998). Orienting is the selection of information from sensory input (Corbetta et al., 2000; Posner, 1980). Lastly, executive control is defined as involving the mechanisms for resolving conflict among possible responses (Botvinick et al., 2001; Bush et al. 2000). In order to the second aspect, orienting or selective attention, another distinction can be done between top-down cognitive and bottom-up perceptual mechanisms of attention. Top-down attention refers to the voluntary allocation of attention to certain features, objects, or regions in space (Beauchamp et al., 1997; Bressler et al, 2008; Giesbrecht, et al., 2003). On the other hand, salient stimuli can automatically attract attention, even though the subject had no intentions to attend to these stimuli (Schreij et al., 2008). This was also the case in whom attention is refered to the selection and modulation of sensory information, as it initially comes into the mind, generally in a modality-specific representation and often with episodic tags for spatial locations (spatial attention) and points in time (temporal attention). Two anatomically and functionally attention systems are distinct in the human brain (Corbetta and Shulman 2002) with respect to top-down and bottom-up mechanisms of attention. A dorsal frontoparietal system is proposed to mediate the top-down guided voluntary allocation of attention to locations or features, whereas a

ventral frontoparietal system is assumed to be involved in detecting unattended or unexpected stimuli and triggering shifts of attention.

### 1.2Attention as selective process

The typical environment provides much more sensory stimulation than can be processed effectively in space and time. Futhermore, several lines of evidence support the existence of distinct cerebral pathways in the visual as well as in the auditory systems. For both systems, the role of selective attention is fundamental. Selective attention optimizes the use of the sensory systems limited resources by enhancing the relevant representations, while diminishing the irrelevant representations (Carrasco, 2011), with respect to object locations (spatial attention) as well as to stimulus identification (object-based attention). Moreover, attention over space and time enhances our ability to select and recognize objects and anticipate expected events (Mackay, 2007). Although numerous studies have investigated spatial attention, relatively fewer studies have explored the allocation of attention over time. Moreover, most research on attention has focused on visual processing, but environmental space is monitored by multiple sensory modalities. By reason, there is a burgeoning interest in developing a comprehensive understanding of multisensory attention, including auditory processing.

There are two main types of selective attention:

- spatial attention, in which attention is deployed to relevant locations with or without accompanying eye movements (Posner, 1980);
- object-based attention in which attention is influenced or guided by object structure independently of its location (Shomstein and Behrmann , 2008).

### 1.2.1 Mechanism of covert spatial attention

Spatial attention mechanisms evolved to guide and control eye movements (Rayner 2009), so attention and eye movements are tightly interlinked (Deubel and Schneider 1996, Hoffman and Subramaniam 1995, Kowler et al. 1995). Spatial orienting and saccadic control employ overlapping neural systems (Corbetta et al. 1998). However, eye movements and attention are dissociable (Hunt and Kingstone 2003, Juan et al. 2004). That is, spatial attention can be overt, linked with the guidance of eye movements, or covert, in that a location can be attended without being foveated.

Humans being are able to select and acquire visual information preferentially within a locus of peripheral vision without shifting gaze (Posner, 1980; Kinchla, 1992; Egeth, 1997). This ability, known as covert spatial attention, often is compared metaphorically with a mental spotlight that illuminates a selected area or object for enhanced processing.

A growing body of evidence has demonstrated that there are two types of covert visual attention systems that select information and facilitate its processing: endogenous and exogenous (Carrasco, 2011). The former corresponds to our ability to voluntary monitor information at a given location. The latter, corresponds to an automatic orienting response to a location where sudden stimulation occurs. These terms refer to the temporal nature of each type of attention: at least 300 ms are necessary to deploy endogenous attention (Liu et al., 2007), while from 100 to 200 ms are necessary for deployment of exogenous attention (Szpiro and Carrasco, 2015).

A specific procedure assessing covert attention is the Posner (1980) cueing paradigm, in which observers are asked to report as quickly as possible the presence of a peripherally presented target, which can be preceded by a central or peripheral cue (see figure 1). This paradigm allows to compare the

subject's performance in conditions where attention is deliberately directed to either a given location (attended condition), away from that location (unattended condition) or distributed across the display (neutral or control condition).

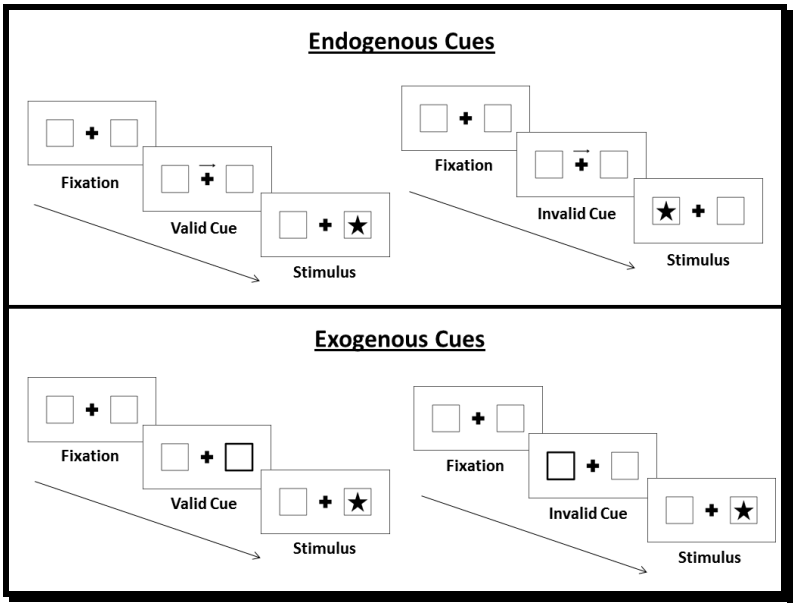



**Figure 1**: Posner's paradigm (Posner, 1980).

We used a similar paradigm to investigate endogenous attention. Moreover, we created an acoustic variant of the task, since we also wanted to study the mechanisms involved in audio-spatial attention (Chillemi, Calamuneri et al., accepted).

### 1.2.2 Mechanism of object-based attention

It well is known the priority of object's spatial features on visual attention processes, but there is a burgeoning interest in understanding on how attention can be shaped by the exposure times of objects (object-based attention). Just as there are limitations on the quantity of information that can be processed simultaneously in space, there are limitations on the speed with which objects can be processed in temporal sequence (Roque, 2015).

Shomstein and Behrmann (2008) found that longer exposure times of stimuli allowed more time for perceptual grouping and figure-ground segmentation leading to the best object representation. Moreover, they observed that effects of this representation diminished with longer delay occurring between onsets of reference and target stimuli (Stimulus Onset Asynchrony, SOA). These results suggest that object-based effects can be explained in terms of strength of object representations (established as by longer exposure durations as well as by pictorial cues) and probabilistic contingencies in the visual environment (with respect to temporal distance between two stimuli).

We want to explore the contribution of the exposure time on object-based effects by means of a new paradigm that required participants to estimate the duration of target stimuli with respect to a reference stimulus. Keeping constant the Inter-Stimulus Interval (ISI), i.e. the time between the offset of the reference stimulus and the onset of the following target stimulus, we have manipulated the target duration only. In addition, we used stimuli with different colours to obtain high level of strength of object representation.

Since we want to study the mechanisms involved in visual as well as auditory attention, we have built two parallel versions (i.e. visual and auditory) of temporal task.

### 1.2.3 Multisensory integration

We live in a multisensory world in which we are continually deluged with stimulus input through multiple sensory pathways. For effective cognitive functioning, we must continually select and appropriately integrate together those inputs that are the most relevant to our behavioural goals from moment to moment.

Recent findings suggest that multisensory integration can occur across various stages of stimulus processing that are linked to, and can be modulated by, attentional system.

The evidence in favour of the existence of bidirectional influences between attention and multisensory integration is considerable. Under certain circumstances the co-occurrence of stimuli in different modalities can lead pre-attentively and automatically to multisensory integration in a bottom-up fashion, which then makes the resulting event more likely to capture attention and thus, capitalize available processing resources (Van der Burg et al., 2008). In other situations, however, top-down directed attention can influence integration processes for selected stimulus combinations in the environment (Talsma et al., 2005; Van Ee R et al., 2009).

Another way that attention can interactively influence the processing of stimulus inputs in different sensory modalities that occur at the same time has been termed cross-modal spreading of attention, which has been found to occur even when the visual and auditory stimuli arise from different spatial locations (spatial attention) (Busse et al., 2005). Very interesting, it was found auditory stimulus can elicit a different brain response when paired in time with a visual stimulus spatially attended (versus unattended): a visuospatial attention system determines which stimulus in the visual modality is to be selectively processed (top-down system); then, attention spreads across modalities to encompass the auditory component (bottom-up system). Such a result is thus consistent with a spread of attention across modalities and space, occurring via a systems-level cascade of top-down and bottom-up influences. It is also known that the properties of the cues play a key role in the spatial attention (Theeuwes, 2000). Two main classes of visual cues are distinguished in this contest: endogenous and exogenous cues. An endogenous cue is typically a central, symbolic cue (e.g., an

arrowhead); it is supposed to influence attention by voluntary system in a top-down manner. Besides this voluntary control of attention, there is a simpler, automated form of attentional modulation. If a cue suddenly appears in the periphery, it automatically attracts visuospatial attention (exogenous cues). This is a form of bottom-up control of attention. Many studies have investigated the link between auditory cues and visual targets with respect to the endogenous and exogenous properties of the cues (Spence at al., 2007). Only few works have been conducted on the cross modal interplay between endogenous visual cues and audio targets (Blurton et al., 2015). In addition, although sound sources can be localized exclusively on the basis of auditory cues, localization accuracy improves if the cue is also visible to the subject (King, 2009). Facilitation of sound localization by visual information has been mainly observed in animals studies (Schroeder and Foxe 2002; Bizley et al, 2007), but scant evidence exists on humans (Sosa et al., 2010).

### 1.2.4 Attentional Bias

In healthy individuals, visuospatial attention is asymmetrically distributed, resulting in a modest but systematic leftwards bias: such a bias can be consistently observed when healthy participants perform different types of visuospatial tasks, such as line bisection (Leone and McCourt, 2010), luminance (Nicholls and Roberts, 2002), stimulus size (Charles et al., 2007), and numerosity estimation (Nicholls et al., 1999), and face processing (Levy and Heller, 1981). In all these tasks a left hemispace advantage of visuospatial processing can be observed. Such constellation of left sided asymmetries of spatial attention is called pseudoneglect (Jewell and McCourt, 2000). Based on the abovementioned evidence, it has been hypothesized that localization of left-sided stimuli might be more accurate and/or faster than localization of right-sided stimuli (Sosa et al., 2009).

Whereas visuospatial attention is biased toward the left hemispace, some evidence suggests that audiospatial attention may possess a rightward spatial bias (Sosa et al., 2010).

Other interesting findings supposed that the temporal representation of numbers is arranged along a mental line, called the mental number line (MNL) (Umiltà et al., 2009, Oliveri et al., 2008). In people who read from left to right, the MNL is spatially oriented from left to right, with small magnitude numbers represented on the left-hand side of the line and numbers of larger magnitude represented on the right-hand side (Dehaene et al., 2003). On one hand, the findings involved that it is easier and quicker to select the larger of two numbers when they are numerically distant than when they are closer (for example, 8 and 3 are compared faster than 8 and 6), referred to as the distance effect (Moyer and Landauer 1967). On the other hand, the findings supported the idea that attention is asymmetrically distributed, resulting in a modest but systematic leftwards bias (Leone and McCourt, 2010; Nicholls, 2002; Charles, 2007) in favour of small magnitude (then shorter interval). In analogy to left-biased asymmetries, one might speculate that temporal attention may express with a decreasing gradient from fast to slow intervals.

### 1.2.5 Scientific aim

This thesis was designed to study in depth selective attention mechanisms that underly covert spatial attention as in the visual as well as in the auditory modality. An additional aim was to investigate object-based attention over time again using visual and auditory stimuli. If selective attention is a supramodal process, it can be predicted that healthy individuals express a similar leftward bias in visual as well as auditory spatial tasks. Alternatively,

if selective attention is modality specific then the biases in visual and auditory spatial judgments might show a dissociation.

### 1.3 Dystonia

Dystonia is characterised by sustained contraction of reciprocal muscles with pattering, overflow and mirror movements. It is sometimes accompanied by tremor and can be triggered by specific tasks (Burke and Fahn, 1988). The prevalence of dystonia ranges from 15 to 30 per 10,000 people (Nutt, 2000), with some estimates suggesting it is increased to 732 per 100,000 people aged over 50 (Müller, 2002). Dystonia can be classified by the age of onset, distribution of affected body parts and causes (Albanese *et al.*, 2011). A descriptive classification categorises it as primary torsion dystonia, Dystonia-plus syndromes, primary paroxysmal dyskinesia and dystonia, hereditary neurodegenerative dystonia, and secondary dystonia (Fahn, 2011). Primary dystonia is most common (Albanese, 2011), which includes cervical dystonia, blepharospasm, child-onset generalised dystonia, oromandibular dystonia, laryngeal dystonia and writer's cramp.

In particular, we will focus our attention on cervical idiopathic Dystonia (CD), which is characterized by patterned involuntary contractions (Albenese, 2013) involving the muscles of the neck and it can lead to the head and neck twisting (Torticollis) or being pulled forwards (Antecollis), backwards (Retrocollis), or sideways (Laterocollis); often these abnormal movements are unilateral (to the right side or left) and involve the contralateral cerebral area.

Cervical Dystonia has long been considered as a basal ganglia disease and primarily a motor disorder. However, increasing evidence supports the involvement of sensory processing and the cerebellum in Dystonia. Below, we will explore the neurophysiology of cervical idiopathic Dystonia in the

motor system. We will also investigate the roles of sensory abnormalities and the cerebellum in the neuropathology of primary torsion Dystonia.

### 1.3.1 General neurophysiology of cervical idiopathic Dystonia

Cervical Dystonia is characterised by excessive co-contraction of the agonist and antagonist muscles, resulting in unwanted body spasms. Initially, it was thought that the basal ganglia were the primary site of pathogenesis. The major pathophysiological abnormalities proposed are loss of inhibition within the motor system (Hallett, 2011) and an excessive response to experimental protocols that produce plastic changes within the motor system (Quartarone and Pisani, 2011). Recently published neurophysiological studies have further elucidated the underlying mechanism.

The excess movement of cervical Dystonia is mainly explained by loss of inhibition (Hallett, 2011). This has been demonstrated at cortical, brainstem and spinal cord levels. Loss of reciprocal inhibition in generalised Dystonia and in the affected hand of focal hand Dystonia (Nakashima et al., 1989; Tisch et al., 2006) demonstrated inhibitory abnormalities at a spinal cord level, and decreased inhibition of blink reflex recovery in generalised Dystonia (Tisch et al., 2006) and Blepharospasm (Berardelli et al., 1985) support the involvement of the brainstem. Co-contraction of antagonist muscles may be partially related to abnormal reciprocal inhibition.

At a cortical level, short intracortical inhibition (SICI) investigated by transcranial magnetic stimulation revealed a loss of intra-cortical inhibition in patients with focal hand Dystonia (Ridding et al., 1995). A loss of inhibition can also be found in myoclonus-dystonia (DYT11), gene carriers who lack symptoms (Edwards et al., 2003). Bilateral hemisphere impairment in those with unilateral symptoms and abnormalities in non-manifesting carriers suggest that a loss of inhibition is a fundamental problem which may

not be sufficient in its own right to cause Dystonia. In addition, the link between ionotropic receptor for γ-aminobutyric acid (GABA-A) and SICI (Di Lazzaro et al., 2000) indicates that there is a relationship between inhibitory neurons and Dystonia. Silent period (SP) and long intracortical inhibition (LICI) are impaired in focal Dystonia (Espay et al., 2006; Kimberley et.al., 2009), mainly in the affected body part (Chen et al., 1997; Espay et al., 2006). These two tests represent metabotropic transmembrane receptors for gamma-aminobutyric acid (GABA-B) involvement and are different from SICI. Surround inhibition (SI) was also found to be impaired in several studies (Stinear and Byblow, 2004; Beck et al., 2008). It reflects the ability to suppress the activation of irrelevant muscles during movement. The impairment of SI in focal hand Dystonia (FHD) may explain the overflow phenomenon in the clinical manifestation of Dystonia. Excessive plastic changes have been noted within the cortical and brainstem levels (Quartarone et al., 2003; Quartarone et al., 2008; Quartarone and Pisani, 2011).

Several studies demonstrate shifts in motor cortex excitability of dystonic patients, in particular, a reduction of inhibition, an excessive motor evoked potential facilitation and a shorter cortical silent periods and an increase of corticospinal motor output (Allam, 2007). In particular, a repetitive transcranial magnetic stimulation (TMS) study by De Vries (2012) supported the evidence of an overactivation in bilateral prefrontal and posterior parietal areas along with a reduced activation in the anterior parietal area during movement execution and imagery finger-tapping tasks. It has also been presented a case of FHD's patients with biased spatial attention (Ricci, 2014). These observations supported the idea that parietal cortex has an important role of multimodal sensory integration in CD patients.

### 1.3.2 The relationship between Dystonia and the cerebellum

Although Cervical Dystonia has long been considered to be related to dysfunction in the basal ganglia, an increasing amount of evidence implicates a relationship between Dystonia and the cerebellum. Data from anatomy, animal models, clinical data and electrophysiological studies all provide supporting evidence.

The basal ganglia have traditionally been regarded as a pivotal area in the generation of Dystonia. The observation that lesions within the basal ganglia cause Dystonia supports this concept (Bhatia and Marsden, 1994). By Schulze-Bonhage and Ferbert (1995) was observed a patient with an extended tumour involving the right basal ganglia and frontoparietal white matter with a large surround oedema. In the case reported, tumour growth was linked to a laterocollis pattern with inclination of the head to the right side only when basal ganglia began to be involved. With tumour extension into the internal capsule and white matter surrounding the basal ganglia, Dystonia improved and paresis developed. This clinical finding have led to the hypothesis that Dystonia may arise when striatal lesions leave the pyramidal tract relatively intact. The therapeutic effects of deep brain stimulation of the basal ganglia in primary generalised Dystonia strengthen this notion (Vidailhet, 2005). The hypothesis of a lack of inhibitory function in the basal ganglia towards the cerebral cortex plays an important role in the generation of involuntary movement (Mink, 1996).

However, a later Positron Emission Tomography (PET) study in DYT1 mutation manifesting carriers shows that increased metabolism, not only in the basal ganglia and motor cortex but also in the cerebellum, points out the possible role of the cerebellum in Dystonia (Niethammer et al., 2011). In the cerebellum, anatomically, there are direct di-synaptic connections between the dentate nucleus and the striatum (Hoshi, 2005), as well as another

disynaptic projection from the subthalamic nucleus to the cerebellar cortex, as demonstrated in the brain of monkeys (Bostan et al, 2010). These connections demonstrate the direct route between the cerebellum and basal ganglia that can influence each other. In animal studies, the removal of the cerebellum could eradicate the dystonic symptoms in mice caused by calcium channel point mutation (Neychev et al., 2008) and prevent the development of Dystonia in genetic dystonic rats (LeDoux et al., 1993; Devanagondi et al., 2007). Moreover, Dystonia can also be caused by microinjection of kainic acid into the cerebellar vermis of mice (Pizoli et al., 2002). The studies of the cerebellum in dystonic patients have been guided by these anatomical findings and animal models.

Clinically, torticollis pattern is a common symptom of posterior fossa tumour (Extremera, 2008). In a review of 143 cases of posterior fossa tumour, 23% of cases developed torticollis patterns, with surgical removal of the cerebello-pontine angle tumour improving cervical dystonia symptoms in two case reports (Krauss, 1997). In addition, cerebellar stroke can produce blepharospasm and oramandibular Dystonia (Rumbach, 1995; O'Rourke, 2006; Waln and LeDoux, 2010). In neurophysiological studies, dystonia patients did not show any effects of reduced MEP, decreased SICI or increased intracortical facilitation (ICF) when combined with cerebellar stimulation, three effects seen in normal subjects (Brighina, 2009). Another important piece of evidence comes from eye blink classical conditioning (EBCC) which is abnormal in adult onset focal Dystonia (Teo et al., 2009). The mechanism of EBCC depends on cerebellar circuitry related to Purkinje cells and the interpositus nucleus (Yeo and Hesslow, 1998). In neuroimaging studies, the increased activity of the ipisilateral cerebellum was shown in Positron Emission Tomography (PET) (Odergren, 1998), fMRI (Preibisch, 2001) and a voxel based morphometry (VBM) study also showing increased

white matter density in the cerebellar flocculus (Draganski, 2003). To sum up, the cerebellum is part of a distributed network involved in the regulation of cortical oscillatory activity in Idiopathic Cervical Dystonia.

### 1.3.3 The relationship between Dystonia and sensory abnormalities

Sensory symptoms were reported many years ago in patients with Dystonia (Marsden et al., 1976; Tolosa, 1981), but they did not attract too much attention and have been regarded as sequelae of the abnormal posture.

Despite the 'motor' definition of Dystonia, there is increasing evidence that non-motor features, mainly in the sensory domain, are also present (Fabbrini et al., 2008; Kuyper et al., 2011). Nevertheless, there is increasing evidence from clinical symptoms to neurophysiology and behavioral experiments that supports the role of sensory abnormalities in Dystonia.

Initially, Ghika (Ghika et al, 1993) reported 11 consecutive oromandibular Dystonia patients having sensory abnormalities before Dystonia onset, speculating that it could be the earliest manifestation of an evolving process in cranial, and perhaps other, focal Dystonia. 70% of cervical Dystonia patients report a sensory trick phenomenon (Stamelou et al., 2012), and focal hand Dystonia can be induced by applying vibration to the affected arm (Kaji et al., 1995), As a result, sensory impairment has been deduced as playing a role in Dystonia.

Additional neurophysiologic evidence also supports that sensory impairment is a component of Dystonia. The N30 component was attenuated during movement in normal subjects, but was unchanged in patients with task specific Dystonia (Murase et al., 2000). Patients with Dystonia have enlarged with overlapping sensory receptive fields found during EEG and MEG studies (Bara-Jimenez, 1998; Elbert, 1998), with a higher spatial discrimination threshold (Bara- Jimenez, 2000), temporal discrimination

threshold (Aglioti et al., 2003; Fiorio et al., 2008; Kagi et al, 2013; Tinazzi et al., 2013) and impaired hand mental rotation ability (Fiorio et al., 2003).

All these abnormalities are due to a dysfunction in sensory processing with a loss of lateral inhibition either in space or in time (Tinazzi et al., 2000; Serrien et al., 2000). In fact, a series of studies have found that mild abnormalities in the primary sensory system are present in patients with Dystonia both in spatial (Meunier et al, 2001; Klintenberg et al., 2002; Burke and Fahn., 1988) and temporal (Tinazzi et al., 2002, Fiorio et al., 2008) domains.

In Dystonia, previous psychophysiological studies have investigated only temporal and spatial characteristics, as explanation of a dysfunction in sensory processing with a loss of lateral inhibition either in space or in time (Tinazzi et al., 2000; Tinazzi et al., 2002; Tinazzi et al., 2009), whereas the definition of such processing are controlled at higher cognitive level has not been sufficiently addressed. In addition thesestudies have mostly focused on somatosensory stimuli finding out that somatosensory maps are alterated and produce blurred/altered representations of a person's body in focal dystonia (Frasson et al., 2001; Serrien et al., 2000; Carbon et al., 2003; Fiorio et al., 2003) with only a few studies investigating processing of visual stimuli, and no studies exploring processing of auditory stimuli, with only a few studies investigating processing of visual stimuli (Putzki et al., 2006; Irvine et al., 2011; King 2009), and no studies exploring processing of auditory stimuli.

### 1.3.4 Conclusion

Idiopathic cervical dystonia can be viewed as a circuit disorder, involving the basal ganglia-thalamo-cortical as well as cerebello-thalamo-cortical pathways (Lehéricy, 2013, Quartarone and Hallet, 2013). The incorrect motor drive from the brain may cause various motor patterns of cervical Dystonia, the most common of which are the laterocollis and the torticollis; more rarely, we have dystonic tremor.

In this thesis, I examined whether in patients with cervical dystonia the processing of spatial and temporal perception is impaired at high cognitive level using recognition tasks that require attention to span both in the visual and auditory domains. Moreover, we further hypothesized that different movement pattern type of cervical Dystonia (Laterocollis, Torticollis, dystonia with prominent tremor) may induce different cognitive deficit within dystonic population.

### 1.4 Aims of the thesis

This thesis has three main aims.

The first aim of this thesis is to investigate selective attention processes in space and time in the visual as well as auditory domain.

The second aim is to inspect how this spatial and temporal information is distributed on attentional control system.

The final aim is to explore spatial and temporal "cognitive" processing in idiopathic cervical dystonia and its possible contributions to the underlying sensory dysfunctions.

In accordance with the above aims, Chapter 2 will explore the procedures used to study spatial and based-object attention on selection of visual as well as auditory stimuli; Chapter 3 will employ those on healthy subjects in order to confirm the role the selective attention as explanation of a supramodal control system. Chapter 4 will explore the spatial and temporal processing in Dystonia patients and their relationship with different dystonic pattern. Chapter 5 will argue the attentional asymmetries role based on the knowledge ascertained from the previous chapters.

# Chapter 2

# Methods and Materials

## 2.1 FIRST STUDY "Endogenous orienting of visual attention in auditory space"

The first aim of this work was to study the mechanisms underlying covert spatial attention in the visual and auditory modalities and the influence of visual cues on deployment of audiospatial attention. To this end, we used paradigms similar to the one introduced by Posner (1980) to investigate top-down endogenous (i.e. goal-driven) attention (Chillemi, et al., 2016 b.). The second aim of the study was to investigate how the presence of a bias in the deployment of visuospatial attention, as measured on a different visuospatial task, might correlate with spatial processing in both visual and auditory domains. To this end, participants performed a line bisection task, which constitutes one of the most commonly used tests for the evaluation of visuospatial attention in both healthy and neurologically impaired individuals (Ricci et al., 2000, 2012; 2014; Ricci and Chatterjee, 2001; Savazzi et al., 2007; Chieffi et al., 2014). We hypothesized that if spatial attention is supramodal, then localization of visual and auditory left-sided targets should be more accurate and/or faster than localization of right-sided ones, supporting a right hemispheric dominance for visual and auditory processing. Alternatively, if spatial attention is modality specific, then the directional bias of visual and auditory spatial judgments might be potentially dissociable. In this case, we might also predict enhancement of sounds localization by visual cues. Finally, if individual differences in deployment of visuospatial attention affect deployment of audiospatial attention, we should expect a weaker rightward audiospatial attentional bias in individuals with more pronounced pseudoneglect.

### 2.1.1 Participants

Thirty-eight participants (21 females, mean age 55.60 years, age range 38-71 years) gave informed consent to participate to this study, which was approved by the local ethical committee.

The participants' hand dominance was assessed using the Short form of the Edinburgh Handedness Inventory test (Veale, 2014). Furthermore, eye dominance was determined using a variant of the Hole-in-the-Card test (Durand and Gould, 1910). All the participants were right-handers, 27 wereright-eye dominant and 11 were left-eye dominant.

### 2.1.2 Procedure

*Line bisection task*

The Line Bisection Task was adopted in order to measure visuospatial attentional bias. This is one of the most commonly employed tasks to assess pseudoneglect in healthy subjects (Schenkenberg, 1980). At each trial, the participant was presented with a horizontal line on a sheet of paper (A4 format, see Figure 3.a). The subject was then asked to mark the center of the line with a pen. Each participant performed 20 trials, using the left hand on half of the trials and the right hand on other half. The hand order was counterbalanced across subjects.

*Spatial tasks*

After the line bisection task, participants were asked to perform two spatial recognition tasks requiring the spatial localization and recognition of visual and auditory stimuli. Before each run, subjects underwent a training session to become familiar with task instructions. For each task, trials were fed at a constant inter-trial interval of 3500 ms; task order was counterbalanced across subjects:

Visuospatial task (VST) (Figure 2.a). The visual cue (exposure time= 500 ms) consisted of an arrow that could point rightward, leftward, downward or upward. Control trials consisted in an uninformative cross placed at the center of the screen. After 200 ms, a target stimulus (a 190x190 pixels wide white square, exposure time = 500 ms) appeared in one of four possible locations: to the left, to the right, above or below the center of the monitor. The subject was required to identify target location by pressing the corresponding arrows (left, right, up or down arrow) present on the keyboard, using the first finger of the right hand, as fast as possible. Based on the relationship between cue and target, three conditions could be identified: congruent (the cue pointed towards the target), incongruent (the target pointed in the opposite direction relative to the position of the cue), or neutral (the target was preceded by a cross at the centre of the monitor). This resulted in twelve possible conditions: congruent-up, congruent-down, congruent-right, congruent-left, incongruent-up, incongruent-down, incongruent-right, incongruent-left, neutral-up, neutral-down, neutral-right and neutral-left. During the task, each condition was shown six times in a randomized order, resulting in 145 trials divided in four sessions.

Visuo-audio Spatial task (VAST) (Figure 2.b): A visual cue (exposure time= 500 ms) consisted either in an arrow pointing to the right or to the left, or a cross at the centre of the monitor (control condition). Target sound consisted in a beep (WAV, 44kHz, 16bit, duration 2000 ms) produced by either the right or left speaker (lateral locations) or simultaneously by both speakers (central location). Participants were asked to press a key as soon as possible when they localized the sound position using the arrows present on the keyboard as described above.

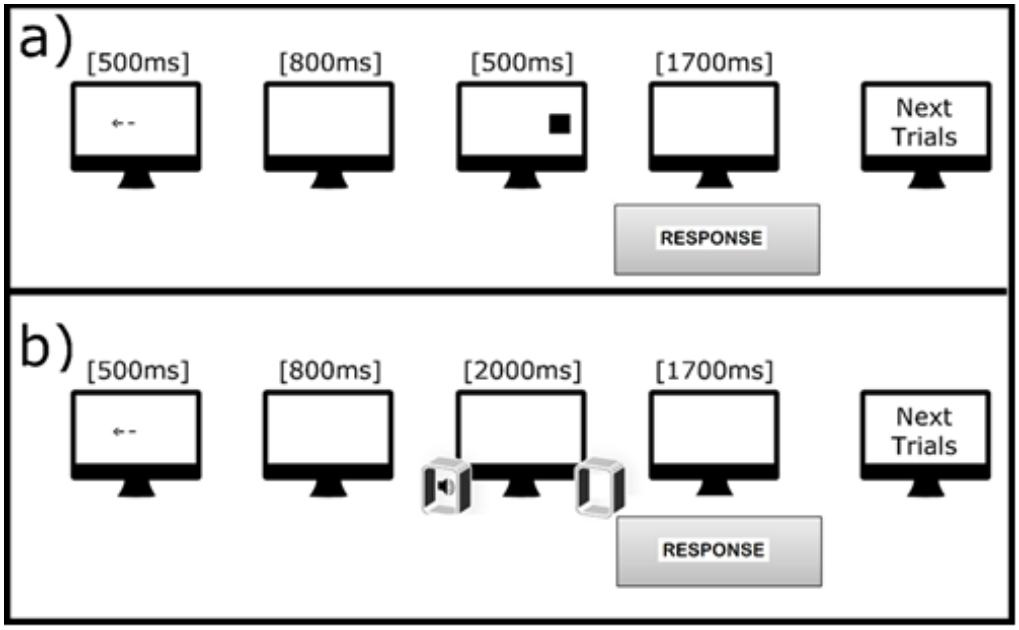



**Figure 2**: Cartoon showing trials used in the Visuospatial (VST) and visuo-audio spatial (VAST) tasks. a) Example of an incongruent trial in VST. b) Example of a congruent trial in VAST.

By combining congruency and position factors, we had a total of nine possible combinations: congruent-left, incongruent-left, congruent-right, congruent-central, incongruent-right, incongruent-left, incongruent-central, uninformative-right, uninformative-left and uninformative-central. In total 72 trials were administered, divided in 2 blocks.

### 2.1.3 Statistical Analyses

From VST and VAST participants' accuracy (ACC) and reaction time (RT) were extracted and averaged for each condition. Analyses were conducted using repeated-measures ANOVA (rm-ANOVA): for VST, *congruency* (three levels: congruent, incongruent, uninformative) and *position* (four levels: right, left, upward, downward) were used as within-subjects factors. For VAST, *congruency* (three levels: congruent, incongruent, uninformative) and *position* (three levels: right, left, central) were used as within-subjects factors. From the line bisection study, we further measured the distance (in millimetres) between subjects' sign depicted on the shit of paper and the

actual paper center; positive values were given to signs placed on the right side of paper center. rm-ANOVA was conducted using *repetition* (ten levels), *hand* (two levels: right, left) as within-subjects factors.

For all analyses, age, gender and eye dominance were included as covariates in the model. Greenhouse-Geisser degrees of freedom (df) correction was used to account for potential assumptions violation in the model. When necessary, Bonferroni correction was applied on post-hoc tests to obtain a global significance threshold of 0.05.

The Spearman's correlation coefficient was used to explore possible relationships between scores obtained on the line bisection task and accuracy rates and reaction times on the VST and VAST. Although line bisection task was performed with both hands, we took under consideration only performances related to right hand, since all subjects gave task responses with their right hands. Scores from all repetitions were averaged together to obtain a single measure for each subject (*AVG_RIGHT*). Data were corrected for multiple comparisons by using Bonferroni correction to reach a global significance threshold of 0.05.

## 2.2 SECOND STUDY: "Spatially- driven temporal appraisals"

The literature showed that the numerical representation is arranged along a mental line, called mental number line (MNL) (Umiltà et al., 2009; Oliveri et al., 2008). In people who read from left to right, the MNL is spatially oriented from left to right, with smallest magnitude numbers represented on the left-hand side of the line (Dehaene et al., 2003). This theory is linked with the idea that attention is asymmetrically distributed with a systematic leftward bias (Nicholls and Roberts, 2002; Charles et al., 2007); this effect is called pseudoneglet when applied to spatial attention (Leone and McCourt, 2010).

The aim of this study is to understand how attention bias can influence object temporal representation. To this end, we developed a novel paradigm by asking the participants to estimate the duration of target stimuli with respect to reference ones. By keeping constant the Inter-Stimulus Interval (ISI) and OSA, (Sambetha et al., 2004), we explicitly manipulated the target duration only. Since we were interested in studying the mechanisms involved in both visual as well as in the auditory selective attention, we have built two parallel versions of this task.

We hypothesized that object-based attention is modality specific, and that biases in visual and auditory spatial appraisals are expected are potentially dissociable.

### 2.2.1Participants

The sample involved is the same in the previous study.

### 2.2.2Procedure

Again, we have used the *Line bisection task* used in the first study, in order to have an independent measure of each individual visuospatial attentional bias (Schenkenberg et al., 1980).

*Temporal tasks*

Subjects were required to evaluate whether the duration (i.e. exposure time, ET) of a target stimulus, visual or auditory, was different from that of a reference stimulus.

1) Visuo-Temporal task (VTT) (Figure 2. a.): In this task, the reference stimulus was a green square (size 190x190 pixels) that could appear at the center of the screen for either 1400 ms (reference's short exposure time, FAST RET) or 2000 ms (reference's long exposure time, SLOW RET). 1500 ms later (ISI duration) the target stimulus (a red square,

190x190 pixels) appeared in the same position. For the FAST condition, target exposure times (TET) were: 800 ms (shorter-shorter), 1100 ms (shorter), 1400 ms (equal), 1700 ms (longer) and 2000 ms (longer-longer. For the SLOW condition, following TETs were employed: 1400 ms (shorter-shorter), 1700 ms (shorter), 2000 ms (equal), 2300 ms (longer), 2600 ms (longer-longer).At each trial, subject had to decide whether the duration of the target stimulus was equal, shorter, or longer, than the duration of the reference stimulus. They were asked to respond as fast as possible - after target presentation - by using arrow keys on a standard computer keyboard (right arrow for longer, left arrow for shorter, down arrow for equal). Therefore ten possible conditions were created: fast-shorter-shorter, fast-shorter, fast-equal, fast-longer, fast-longer-longer and slow-shorter-shorter, slow-shorter, slow-equal and slow-longer, slow-longer-longer. A total of 72 trials equally distributed across conditions were fed, divided in 2 blocks.

2) Audio-Temporal task (ATT) (Figure 2. b.): The reference stimulus, a beep tone (WAV, 44kHz, 16bit), was presented for either 1000 ms (FAST RET) or 1700 ms (SLOW RET) by two speakers, arranged in line with the computer screen, one to the right and the other to the left of it. 1500 ms later (ISI duration), the target stimulus was presented. For the FAST condition, target exposure times (TET) were: 500 ms (shorter-shorter), 750 ms (shorter), 1000 ms (equal), 1250 ms (longer) and 1500 ms (longer-longer. For the SLOW condition, following TETs were employed: 1200 ms (shorter-shorter), 1450 ms (shorter), 1700 ms (equal), 1950 ms (longer), 2200 ms (longer-longer).

At this stage, it is important to remark that subjects were unaware of the subdivisions we used to distinguish either between shorter-shorter and shorter TETS, or between longer or longer-longer TETs. The four tasks were implemented by using the Psychopy software (Peirce et al., 2007), release 1.81 on Windows 7 OS. Stimuli were presented with a Dell workstation with 21-inch Dell monitor (resolution 1680x1050pixels) and two speakers that were equidistant from the computer monitor. Participants were comfortably sitting in front of the monitor at a distance of 70 cm. They were instructed to maintain their gaze on the central box, where a fixation central point was present for the duration of the entire trial.

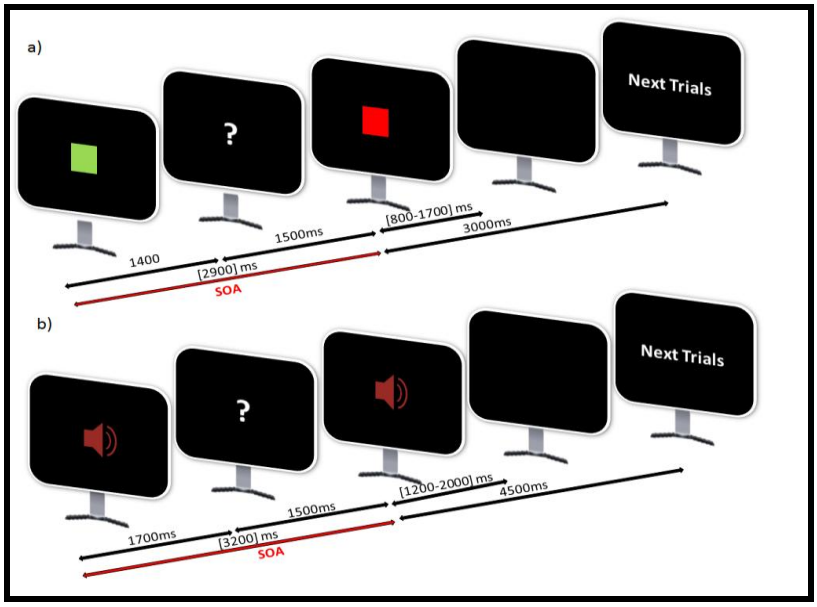



**Figure 3**: Cartoon showing trials used in the visual temporal (VTT) and auditory temporal (ATT) tasks. **a)** Example of a fast Reference-exposure time (RET) trial in VTT. **b)** Example of a slow Reference-exposure time (RET) trial in ATT.

In all the tasks, the dependent measures were: the accuracy, as the number of correct responses, with values ranging from 0 to 1, where a value of 1 indicated that all answers for a given condition were correct; reaction time as the interval between the stimulus presentation and the participant's response, measured in milliseconds.

### 2.2.3 Statistical Analyses

From VTT and ATT participants' accuracy (ACC) and reaction time (RT) were extracted and averaged for each condition. Analyses were conducted using repeated-measures ANOVA (rm-ANOVA): for both VTT and ATT, Reference-exposure time, RET (two levels: fast and slow) and Target-exposure time, TET (five levels: shorter-shorter, shorter, equal, longer, longer-longer) were used as within-subjects factors. In the line bisection study, we further measured the distance (in millimetres) between subjects' sign depicted on the sheet of paper and the actual paper center; positive values were given to signs placed on the right side of paper center. rm-ANOVA was conducted using REPETITION (ten levels) and HAND (two levels: right, left) as within-subjects factors.

For all analyses, age, gender and eye dominance were included as covariates in the model. Greenhouse-Geisser degrees of freedom (df) correction was used to account for potential assumptions violation in the model. When necessary, Bonferroni correction was applied on post-hoc tests to obtain a global significance threshold of 0.05.

Spearman's correlation coefficient was used to explore the possible linear relationships between scores obtained on the line bisection task and both the accuracy rates and reaction times gathered from VTT and ATT tasks. Despite line bisection task was performed with both hands, we took under consideration performances obtained only with the left hand. This choice was motivated by the fact that pseudoneglect is known to exist only in the left hand. Scores from different trials were averaged together (AVG_LEFT). Data were corrected for multiple comparisons by using Bonferroni correction to reach a global significance threshold of 0.05.

## *2.3* THIRD STUDY *"Biased visuospatial attention in cervical Dystonia"*

There is increasing evidence of non-motor, sensory features, mainly involving the spatial domain in cervical dystonia (CD). With the current study we wanted to further investigate whether non-motor symptoms in patients with CD might also involve higher levels visuospatial processes. In particular, we aimed to assess the presence of a putative directional bias in the deployment of visuospatial attention and its possible relationship with two different types of the disease, i.e. Laterocollis and Torticollis. Specifically, we asked whether Laterocollis and/or Torticollis patients, who show different patterns of lateralized cervical dystonia, might also manifest differences in the deployment of visuospatial attention. To this end, we used the line bisection task, that constitutes one of the most straightforward and commonly used tests for the assessment of visuospatial attention in the healthy and neurologically impaired brain (Ricci et al., 2000; Ricci and Chatterjee, 2001; Pierce et al., 2003; Savazzi et al., 2007; Laudate et al., 2013; Salatino et al., 2014; Chieffi et al., 2014). The observation of a specific directional bias in association with a specific form of the disease, for example toward the affected side (as shown in focal limb dystonia, Ricci et al., 2014), or opposite to it (as suggested by data in Parkinson's disease, Proctor et al., 1964; Starkstein et al., 1987), visuospatial might provide important insights into the mechanisms underlying differences in patients with CD, and then be crucial to the design of effective rehabilitation treatments.

### 2.3.1 Participants

Participants. Twenty-three participants (15 females and 8 males) with idiopathic cervical Dystonia (mean age 54.52 ± 11.35 years) were recruited from the Movement Disorders Centre of the University of Messina. Twelve

healthy controls (7 females and 5 males; mean age 49.16 ± 9.87 years) constituted the control group.

| Subject | Age | Gender | Ocular dominance | Handle dominance | Patterns | Affected muscles side | Disease duration (years) |
|---|---|---|---|---|---|---|---|
| S2 | 66 | F | RX | RX | LATEROCOLLIS | RX | 16 |
| S3 | 40 | M | RX | RX | LATEROCOLLIS | LX | 30 |
| S7 | 65 | F | LX | RX | LATEROCOLLIS | LX | 12 |
| S8 | 52 | F | RX | RX | LATEROCOLLIS | LX | 9 |
| S11 | 46 | M | RX | RX | LATEROCOLLIS | RX | 9 |
| S12 | 50 | F | LX | RX | LATEROCOLLIS | RX | 8 |
| S13 | 67 | M | RX | RX | LATEROCOLLIS | LX | 2 |
| S15 | 52 | F | RX | RX | LATEROCOLLIS | LX | 9 |
| S19 | 53 | F | LX | RX | LATEROCOLLIS | RX | 14 |
| S20 | 50 | F | RX | RX | LATEROCOLLIS | LX | 5 |
| S21 | 57 | F | RX | RX | LATEROCOLLIS | LX | 3 |
| S23 | 62 | F | LX | RX | LATEROCOLLIS | RX | 10 |
| S1 | 58 | M | LX | RX | TORTICOLLIS | LX | 36 |
| S4 | 63 | F | LX | RX | TORTICOLLIS | RX | 10 |
| S5 | 71 | F | RX | RX | TORTICOLLIS | RX | 7 |
| S6 | 53 | F | RX | RX | TORTICOLLIS | RX | 14 |
| S9 | 63 | M | LX | RX | TORTICOLLIS | RX | 4 |
| S10 | 61 | F | RX | RX | TORTICOLLIS | RX | 14 |
| S16 | 51 | M | RX | RX | TORTICOLLIS | LX | 10 |
| S17 | 47 | F | RX | RX | TORTICOLLIS | RX | 36 |
| S18 | 24 | M | RX | RX | TORTICOLLIS | RX | 21 |
| S22 | 36 | M | RX | RX | TORTICOLLIS | RX | 16 |
| S14 | 69 | F | LX | RX | TORTICOLLIS | LX | 19 |

**Table 1**: **a.** Demographic details of CD subjects recruited for this study.

All participants were right-handed according to Edinburgh Handedness Inventory, 28 right-eye dominant and 17 left-eye dominant according to ocular dominance test. Patients were further subdivided into two subgroups sub-groups according to the head movement pattern type derived from the prevalent subscore at the Tsui scale (Tsui et al., 1986) and Visual analog scale (VAS) Pain scale (Huskisson,1982): 12 Laterocollis and 11 Torticolis (see Table 1a.).

| Subject | Patterns | Toxin type injection | Therapy duration (years) | Toxin dose | Infiltration number | Tsui scale | Tremor (by Tsui scale) | VAS scale |
|---|---|---|---|---|---|---|---|---|
| S2 | LATEROCOLLIS | *BOTOX* | 3 | 180 | 10 | 7 | 0 | 1 |
| S3 | LATEROCOLLIS | *BOTOX* | 2 | 50 | 6 | 7 | 1 | 2 |
| S7 | LATEROCOLLIS | *DYSPORT* | 12 | 560 | 27 | 2 | 0 | 0 |
| S8 | LATEROCOLLIS | *BOTOX* | 2 | 800 | 9 | 9 | 0 | 0 |
| S11 | LATEROCOLLIS | *DYSPORT* | 6 | 900 | 22 | 3 | 1 | 1 |
| S12 | LATEROCOLLIS | *BOTOX* | 7 | 205 | 28 | 5 | 0 | 2 |
| S13 | LATEROCOLLIS | *DYSPORT* | 1 | 700 | 5 | 5 | 0 | 1 |
| S15 | LATEROCOLLIS | *BOTOX* | 6 | 190 | 23 | 8 | 1 | 0 |
| S19 | LATEROCOLLIS | *DYSPORT* | 9 | 600 | 31 | 8 | 1 | 0 |
| S20 | LATEROCOLLIS | *DYSPORT* | 2 | 80 | 8 | 10 | 0 | 0 |
| S21 | LATEROCOLLIS | *BOTOX* | 1 | 110 | 4 | 7 | 0 | 2 |
| S23 | LATEROCOLLIS | BOTOX | 8 | 110 | 27 | 10 | 0 | 1 |
| S1 | TORTICOLLIS | *DYSPORT* | 22 | 600 | 42 | 2 | 0 | 2 |
| S4 | TORTICOLLIS | *BOTOX* | 6 | 500 | 19 | 6 | 2 | 0 |
| S5 | TORTICOLLIS | *DYSPORT* | 6 | 600 | 21 | 8 | 2 | 2 |
| S6 | TORTICOLLIS | *DYSPORT* | 7 | 750 | 22 | 7 | 0 | 1 |
| S9 | TORTICOLLIS | *DYSPORT* | 3 | 950 | 10 | 4 | 0 | 1 |
| S10 | TORTICOLLIS | *DYSPORT* | 12 | 80 | 17 | 5 | 0 | 1 |
| S16 | TORTICOLLIS | *BOTOX* | 10 | 150 | 36 | 4 | 0 | 0 |
| S17 | TORTICOLLIS | *BOTOX* | 16 | 275 | 50 | 10 | 2 | 0 |
| S18 | TORTICOLLIS | *BOTOX* | 10 | 110 | 39 | 3 | 1 | 0 |
| S22 | TORTICOLLIS | BOTOX | 6 | 70 | 3 | 20 | 2 | 1 |
| S14 | TORTICOLLIS | *XEOMIN* | 10 | 110 | 34 | 4 | 0 | 0 |

**Table 1**: **b.** Clinical details of CD subjects recruited for this study.

Within the laterocollis sub-group, 5 of 12 patients (42%) mainly showed an involvement of the muscles of the right side of the body, while in the torticollis sub-group the involvement of the muscles of the right side of the body was evident in 8 of 11 patients (73%). Furthermore, 8 of 12 patients (67%) in the laterocollis sub-group were right-eye dominant, while in the Torticolis subgroup 7 of 11 patients (64%) were right-eye dominant. All patients underwent extensive neurological examination (see Table 1b.), laboratory and neuroimaging investigations to rule out acquired causes of dystonia. None of the enrolled patients had never been treated with drugs

blocking the dopamine receptor. All drugs affecting the central nervous system were discontinued at least 1 week prior to the study.

All patients were receiving botulinum toxin injections and were examined at least 3 months after the last injection and just before the periodic injection of botulinum toxin. Clinical features of dystonic patients are reported in Table 1 b.

The local ethical committee approved the research protocol and all participants signed an informed consent before examination.

### 2.3.2 Stimuli and procedure

Participants' hand dominance and eye dominance were first assessed. Then, they were asked to perform the Line Bisection Task.

*Assessment of Hand Preference*

The participants' hand dominance was assessed using the Edinburgh Inventory by Oldfield (1971).

*Assessment of Eye Dominance*

The preferred sighting eye was determined using the hole-in-the card test. A red cross (3 x 3 cm) was presented approximately 5 m in front of the participant. The participant held a sheet of paper with both hands, at arm's length, and moved the card until the cross was seen through a hole in the centre of the card (1.5 cm in diameter) with both eyes open. Then the participant was instructed to close one eye alternatively and report whether the cross remained in his/her line of view. The eye that allowed the observer to maintain the view of the cross while the other eye was closed was identified as the preferred sighting eye (Yang et al., 2009).

*Line Bisection task*

It has been used the same task of the first study.

On the line bisection Task, the deviation of the subjective midpoint from the true centre of the line was measured to the nearest millimetre. Rightward bisection errors were expressed, in millimetres, using positive values (i.e. they were preceded by +), and leftward errors using negative values (i.e. they were preceded by –).This measure constituted the dependent variable.

### 2.3.3 Statistical analysis.

On the line bisection Task, the deviation of the subjective midpoint from the true center of the line was measured to the nearest millimetre. The rightward bisection errors were expressed, in millimetres, using positive values (i.e. they were preceded by +), and the leftward errors using negative values (i.e. they were preceded by –).This measure constituted the dependent variable. The rightward and leftward bisection errors were analysed using repeated measures analysis of variance (ANOVA) with Group (Patients vs Controls) as the between-subjects factor and Hand (Right Hand/Left Hand) as the within-subjects factor.

For all analyses, age, gender and eye dominance were included as covariates in the model. Greenhouse-Geisser degrees of freedom (df) correction was used to account for potential assumptions violation in the model. When necessary, Bonferroni correction was applied on post-hoc tests to obtain a global significance threshold of 0.05.Before being administered cognitive tasks, TSUI (Tsui et al, 1986) and VAS (Huskisson,1982) scales were determined on CDs. At the time of the study, they were receiving different toxin types; moreover, disease duration and toxin therapy duration was quite variable. Thus, we tested whether those variables may influence deviation rates. To this end, for rates, we estimated Kendall's tau correlation coefficients between those measures and disease duration, as well as toxin therapy duration, TSUI and Pain scales. This analysis was performed both on

global measures obtained by pooling all tasks together, as well as for each separate task. Moreover, we tested whether systematic differences may exist due to toxin type injection.

## *2.4* FOURTH STUDY *"Spatial and temporal high processing of visual and auditory stimuli in Cervical Dystonia"*

In this study, the aim was the investigation of spatial and temporal cognitive processing in Idiopathic Cervical Dystonia by means of specific tasks based on perception in time and space domains of visual and auditory stimuli.

### 2.4.1 Participants

Clinical features of dystonic patients are given in Table 2. Twenty-one subjects (W/M, 14/7) with Idiopathic CD (mean age 55.2±11.01years) and twenty-two healthy controls (W/M, 11/10) (mean age 54.41±12.1years) were recruited at the Movement Disorders Centre of University of Messina.

All subjects were right-handed according to Edinburgh Handedness Inventory. Dystonic population was subdivided in three subgroups according to the head movement pattern type derived from the prevalent sub-score at the TSUI scale (Tsui et al., 1986 ): eight subjects were diagnosed as laterocollis, eight were diagnosed as torticollis, and five were diagnosed as tremulous CD (Tremor). All patients underwent extensive neurological examination, laboratory and neuroimaging investigations to rule out acquired causes of dystonia.

None of the enrolled patients has ever been treated with drugs blocking the dopamine receptor. All drugs affecting the central nervous system were discontinued at least 1 week prior to the study; all patients were receiving botulinum toxin injections and were examined at least 3 months after the last

injection. The local ethical committee approved the research protocol and all subjects signed an informed consent before examination.

| Subject | Age | Gender | Disease duration (years) | Toxin type injection | Toxin therapy duration (years) | Pattern (primary component) |
|---|---|---|---|---|---|---|
| S1 | 56 | F | 3 | *Onabotulinumtoxina* | 1 | Laterocollis |
| S4 | 26 | M | 9 | *Abobotulinumtoxina* | 8 | Laterocollis |
| S6 | 66 | F | 16 | *Onabotulinumtoxina* | 3 | Laterocollis |
| S8 | 46 | M | 33 | *Abobotulinumtoxina* | 20 | Laterocollis |
| S11 | 53 | F | 14 | *Abobotulinumtoxina* | 9 | Laterocollis |
| S12 | 62 | F | 13 | *Onabotulinumtoxina* | 6 | Laterocollis |
| S16 | 64 | F | 12 | *Abobotulinumtoxina* | 12 | Laterocollis |
| S18 | 46 | M | 9 | *Abobotulinumtoxina* | 6 | Laterocollis |
| S19 | 67 | M | 2 | *Abobotulinumtoxina* | 1 | Laterocollis |
| S2 | 61 | F | 13 | *Onabotulinumtoxina* | 13 | Torticollis |
| S5 | 58 | M | 36 | *Abobotulinumtoxina* | 22 | Torticollis |
| S9 | 71 | F | 7 | *Abobotulinumtoxina* | 6 | Torticollis |
| S10 | 52 | F | 14 | *Abobotulinumtoxina* | 7 | Torticollis |
| S13 | 66 | F | 18 | *Abobotulinumtoxina* | 18 | Torticollis |
| S14 | 64 | M | 4 | *Abobotulinumtoxina* | 3 | Torticollis |
| S15 | 61 | F | 14 | *Onabotulinumtoxina* | 12 | Torticollis |
| S17 | 50 | M | 27 | *Abobotulinumtoxina* | 27 | Torticollis |
| S21 | 47 | F | 36 | *Onabotulinumtoxina* | 16 | Torticollis |
| S3 | 45 | F | 22 | *Onabotulinumtoxina* | 6 | Tremor |
| S7 | 38 | F | 18 | *Onabotulinumtoxina* | 3 | Tremor |
| S20 | 61 | F | 16 | *Onabotulinumtoxina* | 13 | Tremor |

**Table 2**: Clinical details of CD subjects recruited for fourth study.

### 2.4.2 Procedure

All the tasks used in first three studies were involved in the fourth study: *Spatial attentional task, temporal attentional task, line bisection task.*

### 2.4.3 Statistical Analysis

For all the four tasks we measured accuracy (number of correct answers) and reaction times (interval between stimulus onset and response)

Linear mixed models (LMM) were run separately on spatial and temporal tasks using accuracy rates as dependent variable to investigate differences between controls and different forms of Dystonia (Pattern Type). For LMM on spatial tasks, three within-subject factors were considered: type of Stimulus (Visual vs Auditory), Congruency (Congruent vs Incongruent vs

Uninformative) and Position (Right vs Left vs Centred). Notice that, for visual task, performances related to stimuli presented either in the upmost or in the bottom part of the screen were averaged together to facilitate comparison with the "centred" condition of auditory task; this decision was taken after observing that results from those two conditions largely overlapped both in terms of accuracy and reaction times.

For LMM on temporal tasks, following within-subject factors were considered: type of Stimulus (visual vs auditory), Speed (fast vs slow), Duration (Shorter-Shorter vs Shorter vs Equal vs Longer vs Longer-Longer).

In both models, age and gender were treated as covariates. As our primary interest was investigating accuracy rates, we further included an interaction between Pattern type and reaction time as a covariate in the models; in this way we wanted to account for potential interaction effects, e.g. speed-accuracy trade-off. In LMMs, covariance structure of residuals related to repeated measurement is explicitly fitted together with parameter estimates; different structures were adopted, and compared by means of Akaike Information Criteria (AIC). The smaller the AIC the better the model fit (28, 29). For both spatial and temporal LMMs the best performances were obtained using a Heterogeneous Toeplitz structure. Random effect on subjects was not included in the final models as the percentage of variance explained in this way was negligible after modelling covariance structure of residuals. In all analyses, an alpha-value of 0.05 was considered as cut-off for significance; were needed, multiple comparisons were accounted for by applying Bonferroni correction.

Before being administered cognitive tasks, TSUI and Pain scales were determined on CDs. At the time of the study, they were receiving different toxin types; moreover disease duration and toxin therapy duration was quite variable. Thus, we tested whether those variables may influence either

accuracy rates or reaction times. To this end, for both accuracy rates and reaction times, we estimated Kendall's tau correlation coefficients between those measures and disease duration, as well as toxin therapy duration, TSUI and Pain scales. This analysis was performed both on global measures obtained by pooling all tasks together, as well as for each separate task. Moreover, we tested whether systematic differences may exist due to toxin type injection.

# Chapter 3

# Results and Discussions

## *3.1* FIRST STUDY *"Endogenous orienting of visual attention in auditory space"*

The first aim of this work has been explore how attentional bias are distributed on visual and auditory systems.

The second aim has been deepen the role of selective attention on cross modal interplay between endogenous visual cues and visual or auditory targets when manipulated spatially.

### 3.1.1 Results

Demographic characteristics of participants are reported in Table 3.

| **Age** | ***Mean (SD)*** | ***Minimum-Maximum*** |
|---|---|---|
| | 55.61 (9.52) years | 38-71 years |
| **Gender** | ***Females*** | ***Males*** |
| | 21/38 | 17/38 |
| **Hand dominance** | ***Left*** | ***Right*** |
| | ***0/38*** | ***38/38*** |
| **Eye dominance** | ***Left*** | ***Right*** |
| | 11/38 | 27/38 |

**Table 3:** Demographic data of the participants.

*Spatial tasks*

No significant effects were observed when analysing accuracy and reaction times of VST ($p>0.05$, data not shown).

We did not find significant effects when investigating RT in AST ($p>0.05$, data not shown).

Results of analysis of accuracy of AST are reported in Table 4 and shown in Figure 4. Both factors, *position* ($F=3.938$, $df=1.315$, p-value=0.042) and

*congruency* (F=8.283, df=1.690, p-value=0.001), were found to be significant. Post-hoc analyses on position revealed that sounds coming from right speaker yielded more accurate results if compared to trials when sounds were coming from the left speaker (mean difference=25.77%, SD=1.80%, corrected p-value<0.001), and sounds coming from both speakers (mean difference=10.75%, SD=2.78%, corrected p-value<0.001).

| FACTOR | Type III Sum of Squares | df | Mean Square | F | p-value |
|---|---|---|---|---|---|
| **Congruency** | 3662.784 | 1.690 | 2167.214 | 8.283 | 0.001** |
| **Position** | 3623.908 | 1.315 | 2755.204 | 3.938 | 0.042* |
| **Congruency * Position** | 1386.000 | 3.429 | 404.258 | 3.074 | 0.025* |

**Table 4**: Audio-spatial task. Results of rm-ANOVA performed on accuracy rates of AST. Asterisk indicate significance at 0.05 level. Double asterisks indicate accuracy at 0.01 level. Greenhouse-Geisser degrees of freedom correction was applied.

At the same time, accuracy was lower when sounds were coming from left speaker compared to trials during which sounds were presented through both speakers (mean difference=-15.02%, SD=3.65%, corrected p-value<0.001) (Figure 4.a).

Post-hoc analyses on congruency factor revealed that the best accuracy was achieved in presence of congruent cues with respect to incongruent (mean difference=14.80%, SD=1.57%, corrected p-value<0.001) and uninformative (mean difference=17.76%, SD=1.96%, corrected p-value<0.001) conditions (Figure 4.b).

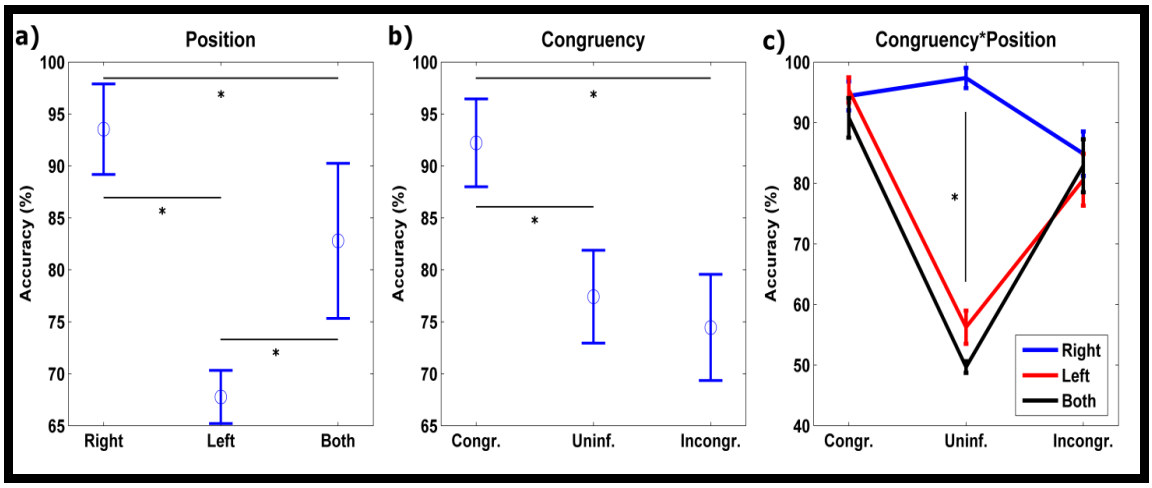



**Figure 4:** Accuracy rates for the audio-spatial (AST). Estimated marginal means for position (a) and congruency (b) factors, as well for interaction between congruency and position (c) coming from rm-ANOVA. Bars represent standard deviations. Asterisks indicate significant differences between sublevels at 0.05 threshold. Both=Sounds coming from both speakers; Congr=Congruent; Uninf.=Uninformative; Incongr.=Incongruent.

Post-hoc analyses performed on the basis of significant interaction detected between *position* and *congruency* factors showed that subjects were far less accurate when evaluating sounds coming from left (mean difference=-41.13%, SD=2.93%, corrected p-value<0.001) or both (mean difference=-47.70%, SD=1.51%, corrected p-value<0.001) speakers with respect to sounds coming from right speaker, but only during uninformative condition (Figure 4.c).

*Line Bisection task*

Statistical analyses revealed a significant *hand* effect (F=13.713, df=1.000, p-value=0.01), whereas no significance was reached neither for *repetition* nor for interaction between *hand* and *repetition* factors. Post-hoc analyses (corrected p-values=0.001) showed a leftward bias for left-hand trials (mean= -2.543 mm, SD= 0.463 mm) with respect to right ones (mean=-0.086 mm, SD=0.502 mm). Results of the line bisection task are shown in Figure 5.b.

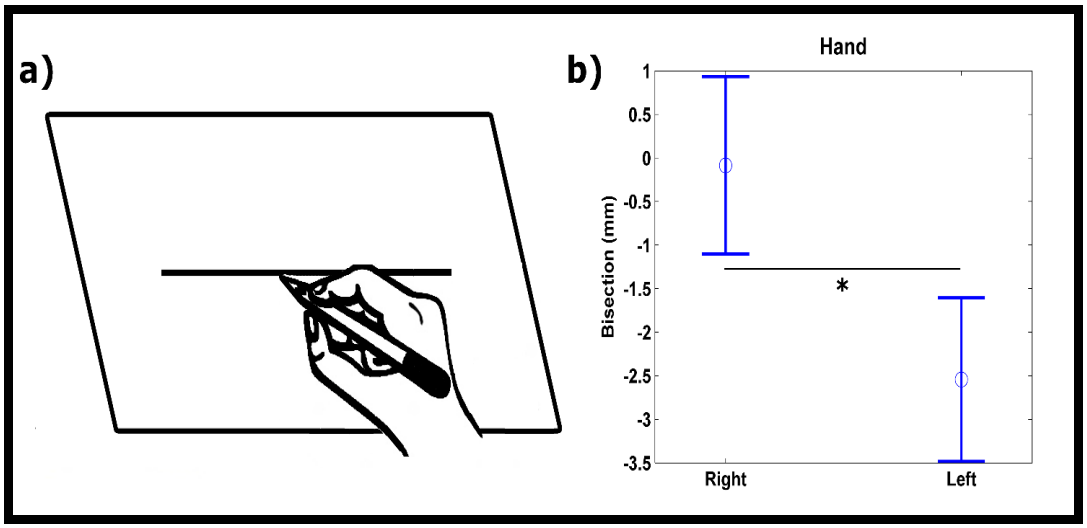



**Figure 5:** Line bisection task. a) Cartoon showing a trial. b) Estimate marginal means for hand factor.

*Correlation with line bisection task*

Results of correlation analysis between task features and bias factors are reported in Table 5 and shown for visualization purposes in Figure 6.

We found that, when analyzing incongruent trials, we observed a positive correlation between line bisection bias and reaction times when sounds were coming from the left speaker (r=0.372, corrected p-value=0.023, Figure 6.a). Moreover, when uninformative cues were given to subjects, measures obtained from line bisection task positively correlated with accuracy rates gathered from condition in which sounds were coming from both speakers (r=0.322, corrected p-value=0.049, Figure 6.b); no correlation was found for other positions during uninformative condition (Table 5).

| PARAMETER | Congruency | Position | SPEARMAN_S | CORR_PVAL |
|---|---|---|---|---|
| ACC | Congruent | Right | -0,142 | 0,799 |
| | | Left | 0,229 | 0,294 |
| | | Centre | 0,021 | 0,999 |
| | Incongruent | Right | -0,124 | 0,876 |
| | | Left | -0,198 | 0,479 |
| | | Centre | 0,017 | 0,999 |
| | Uninformative | Right | -0,116 | 0,898 |
| | | Left | -0,085 | 0,966 |
| | | Centre | 0,322 | 0,048* |
| RT | Congruent | Right | 0,151 | 0,755 |
| | | Left | 0,268 | 0,145 |
| | | Centre | 0,113 | 0,907 |
| | Incongruent | Right | 0,105 | 0,929 |
| | | Left | 0,372 | 0,017* |
| | | Centre | 0,195 | 0,500 |
| | Uninformative | Right | 0,147 | 0,779 |
| | | Left | 0,205 | 0,435 |
| | | Centre | 0,168 | 0,676 |

**Table 5**: Correlation analyses between audio-spatial task outcomes and line bisection bias. Asterisk indicate significance at 0.05 level. ACC=Average Accuracy Rates; RT=Average Reaction Times.

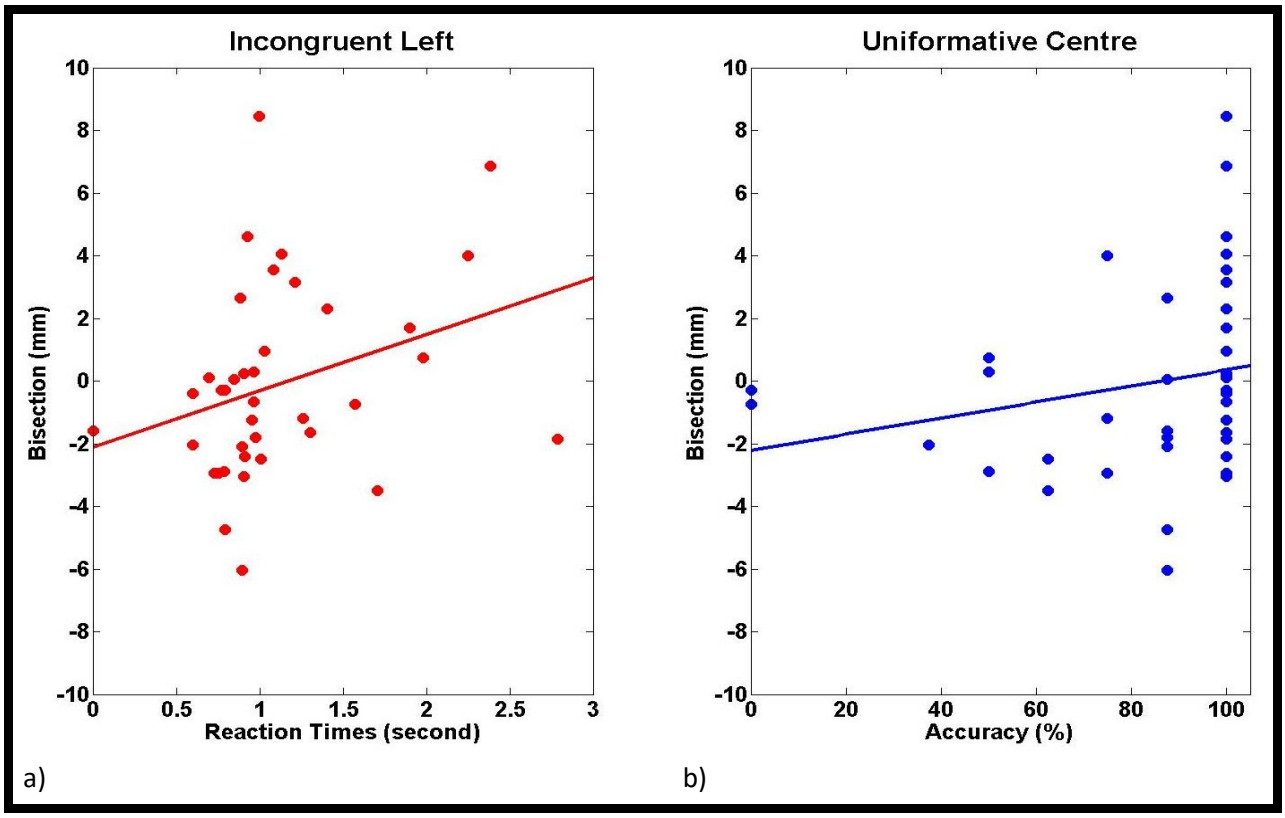



**Figure 6:** Correlation between audio-spatial task outcomes and line bisection bias. **a)** In the right side, we compared the AVG_Right and the Reaction time scores. **b)** In the left side, we compared the AVG_Right and the Accuracy rates.

### 3.1.2 Discussion

Our findings are consistent with the hypothesis that spatial attention is biased and modality specific. Moreover, they show that the visual cues influence the efficacy of orientation of audio spatial attention and modulate sounds localization.

On the visuo-audio spatial task, participants manifested a rightward bias (i.e. they detected more accurately sounds coming from the right speaker). Although the evidence about asymmetries in deployment of audio spatial attention is still controversial, our data are in line with previous findings showing a rightward preference for auditory spatial processing (Cusak et al., 2001; Dufour et al., 2007; Corral and Escera, 2008; Sosa et al., 2010). In our study, the interaction between 'position' and 'congruency' indicated that

participants were far less accurate when evaluating sounds coming from the left speaker in comparison with sounds coming from the right speaker, only during uninformative condition. In other words, the rightward advantage was present exclusively in absence of endogenous orienting of visuospatial attention. We may therefore speculate on the existence of a facilitation (i.e. involuntary transient attentional shift, Egly et al., 1994) effect toward the right hemispace rather than the left hemispace for the auditory modality. On the visuospatial task, the absence of significant findings was likely due to ceiling effects. However, we observed that participants, as a group, manifested a leftward bias on the line bisection task, confirming that, in this sample, visuospatial attention was asymmetrically distributed as well as leftward systematically deflected (Heilman and Van Den Abell, 1980; McCourt and Jewell, 1999). The leftward bias in the visual task and the rightward bias in the auditory task might be symmetrical manifestations of hemispheric dominance, supporting the hypothesis of a right hemispheric dominance for visuospatial attention and suggesting a left hemispheric dominance for audio spatial attention. There is strong evidence for a lateralized fronto-parietal network for visuospatial attention where the right hemisphere deploys attention into both hemispaces, while the left hemisphere attends primarily to the right hemispace (Corbetta and Shulman, 2002). However, it is still controversial the existence of a left hemisphere based network governing audio spatial attention (Cusak et al., 2001; Dufour et al., 2007; Corral and Escera, 2008, Sosa et al, 2010).

In our study, participants identified more easily sounds when a congruent visual cue was given. Such a result is consistent with the evidence that performance in detecting or discriminating a visual target is typically better (faster and/or more accurate) when it appears in the attended location, either for visual (Posner, 1980) as well as auditory cues (Schriiger and Eimer,

1996). This effect is known as the 'validity effect' (Giordano et al., 2009). Interestingly, here, the 'validity effect' on localization of auditory stimuli was induced by visual cues, suggesting an influence of the visual on the auditory spatial coding scheme (Kong et al. 2012).

On the visuo-audio spatial task, correlation analysis revealed that in presence of uninformative cue and sounds coming from the central position, the accuracy was higher in individuals with greater rightward bisection bias. In addition, when attention was directed toward the right side and the sound was coming from the opposite side (incongruent condition), reaction times were faster in individuals with greater leftward bisection bias. Thus, overall, individuals with greater leftward visuospatial bias were less efficient in localizing centrally presented sounds and less affected by endogenous orienting of visual attention. The results of this study are consistent with the evidence that right space is prominent when gathering auditory information (Sosa et al., 2010, Weintraub and Mesulam, 1987) and support the hypothesis that visual stimuli can facilitate sounds localization. Our findings showing a rightward bias for auditory attention together with the evidence of a leftward bias for visuospatial attention (Heilman and Van Den Abell, 1980; McCourt, 1999) support the idea that auditory and visual attentional systems are governed by modality-specific processes (Chambers, et al. 2004; Sosa et al., 2010). However, the findings that visual stimuli facilitated sounds localization and correlations between line bisection and performance on the visuo-audio task clearly suggest significant interactions between the two systems. Recent studies show that auditory localization accuracy improves if the cue is also visible to the subject (King, 2009). Repeated presentation of consistently misaligned visual cues results in a shift in the perception of auditory space that can last for tens of minutes once the visual stimulus is removed. This is known as the ventriloquism after-effect and has been

observed in both human (Radeau and Bertelson 1974; Recanzone 1998; Lewald 2002) and non-human (Woods & Recanzone, 2004) primates. Short-term changes in auditory localization can also be induced in humans by compressing the central part of the visual field for 3 days with 0.5 lenses (Zwiers et al. 2003). These studies highlight the dynamic nature of auditory spatial processing in the mature brain, which allows the perceived location of sound sources to be modified in order to conform to changes of visual space. Animal studies suggest that visual and somatosensory inputs can modulate the phase of oscillatory activity in the auditory cortex and potentially amplify the response to related auditory signals (Schroeder et al., 2009). Previously, we have argued that sounds localization was improved when the visual cue was congruent rather than incongruent or uninformative. Moreover, we observed a delay on left-side auditory processing when attention was previously driven toward the right hemispace but not when it was driven toward to the left hemispace or the visual cue was uninformative. These findings support the evidence of crossmodal links in spatial attention between vision and audition, when the visual cue orients attention to the right hemispace likely dominant for auditory targets: visual signal may increase the magnitude of attentional allocation over auditory target. Interestingly, the deployment of auditory attention and its modulation by visual cues was related to the degree of asymmetry of visuospatial attention. Furthermore, if as suggested by the activation-orientation theory (Kinsbourne, 1970; 1977; 1993) the left and right cerebral hemispheres compete for control of various cognitive functions (such as speech production or the deployment of visuospatial attention) via a process of mutual inhibition, then any phasic stimulation of the right hemisphere will up-regulate the activity of visuospatial networks leading to exacerbate the leftward shift in line bisection. On the other hand, the phasic stimulation of

the right hemisphere will also down-regulate the activity of audio spatial attention networks of the left hemisphere. Our finding are conformed to the activation-orientation theory and seem to suggest that the influence of visual cues on sounds localization is also affected by individual differences in the degree of hemispheric lateralization of visuospatial attention. Indeed, the size of individual bisection errors might be a marker of the degree to which right hemispheric (phasic) stimulation might up-regulate visuospatial and, putatively, down regulate audio spatial networks.

In conclusion, our findings show an influence of endogenous orienting of visuospatial attention on sounds localization. Moreover, they suggest that individual differences in the degree to which visual attention improve performance in auditory space might be potential markers of brain recovery in neurological patients with disorders of spatial attention.

## *3.2* SECOND STUDY *"Spatially- driven temporal appraisals"*

The aim of this second work has been investigate the role of attention bias on cross-modal interplay between endogenous visual cues and visual or auditory targets when the distance between cue and target is manipulated temporally.

### 3.2.1 Results

Demographic characteristics of participants are reported up in Table 3.

*Temporal task*

No significant effects were observed when analyzing reaction times of VTT and ATT ($p>0.05$, data not shown).

Results of analysis of accuracy of VTT and ATT are reported in Table 6 and shown in Figure 6.

Visual temporal task: a significant interaction between reference-exposure time (RET) and target-exposure (TET) time factors was found to be

significant on VTT (F=2.837, df=3.445, p-value=0.034). Post-hoc analyses revealed that, for the Longer-longer TET condition (corrected p-value <0.001), fast RET (marginal mean=88.29%, SE=3.79%) yielded more accurate results if compared to slow RET (marginal mean=54.50%, SE=6.25%).

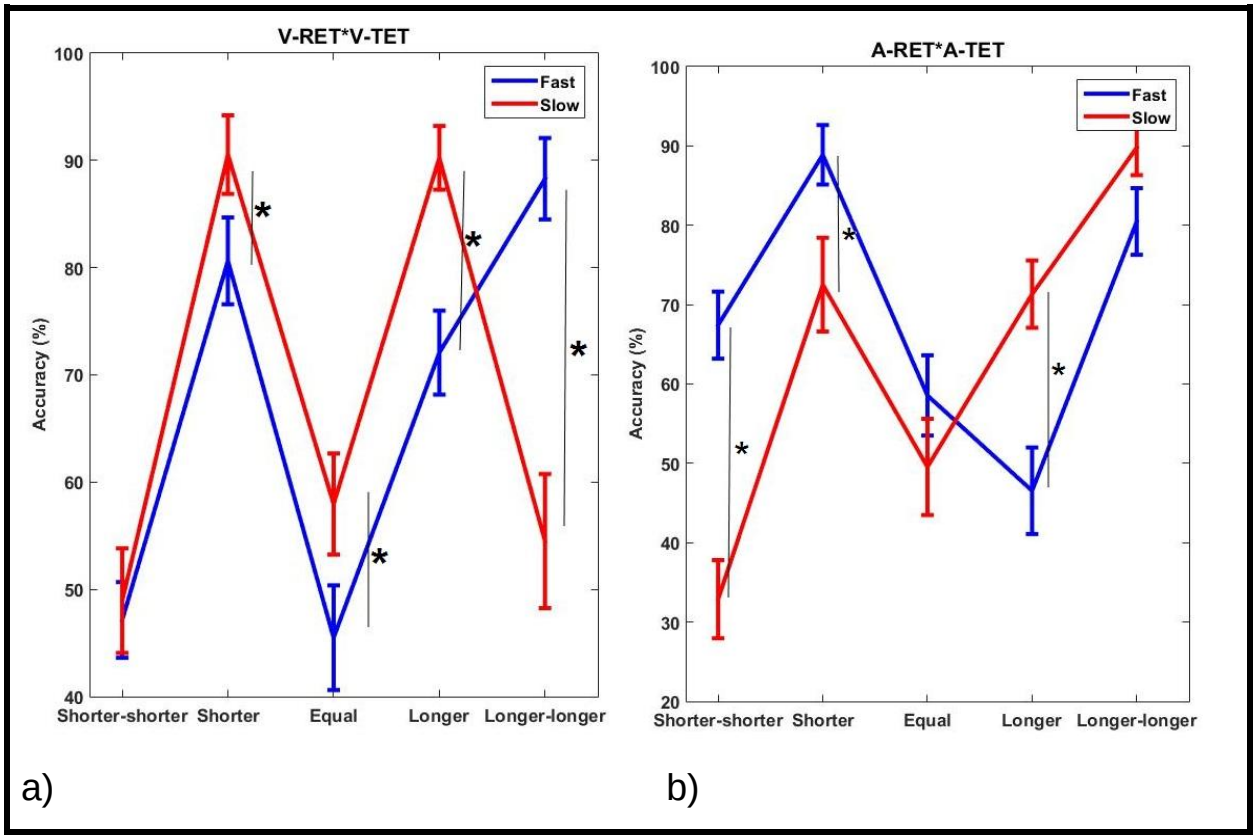



**Figure 6:** Interaction between Reference-exposure time and Target-exposure time in temporal task. a. In the left side accuracy rates on Visual temporal task. b. In the right part accuracy rates on Auditory temporal task.

A reversed trend was instead found when comparing the fast and slow condition in all the others target-exposure time conditions (except for shorter- shorter TET, whereas post-hoc analysis was not significant). Details are reported in Table 6 and Figure 6a.

Auditory temporal task: again, a significant interaction between reference-exposure time and target-exposure time factors was found to be significant on ATT (F= 5.897, df= 2.982, p-value<0.001). In the shorter-shorter TET,

post-hoc analyses (corrected p-value<0.001) revealed that subjects were more accurate during fast RET (marginal mean=67.42%, SE=4.22%) than the slow RET (marginal mean=32.88%, SE=4.93%). The same conclusions (corrected p-value<0.001) were obtained in the shorter TET, when comparing fast RET (marginal mean=88.89%, SE=3.75%) with slow RET (marginal mean=72.52%, SE=5.91%).

| | FACTORS | df | F | p-value |
|---|---|---|---|---|
| **VISUAL** | **RET** | 1.000 | 1.138 | .259 |
| | **TET** | 2.980 | 690.184 | .603 |
| | **RET*TET** | 3.445 | 1185.531 | .034* |
| **AUDITORY** | **RET** | 1.000 | .053 | .819 |
| | **TET** | 2.834 | 1.431 | .239 |
| | **RET*TET** | 2.982 | 5.897 | .001** |

**Table 6**: Temporal tasks. Results of rm-ANOVA performed on accuracy rates of VTT and ATT. Factors estimated were as Reference-exposure time (RET) and Target-exposure time (TET) as well as the interaction between mainly factors in both tasks. Asterisk indicate significance at 0.05 level. Double asterisks indicate accuracy at 0.01 level. Greenhouse-Geisser degrees of freedom correction was applied.

On the contrary, for longer and longer-longer TETs a reversed trend was observed: indeed fast RETs (marginal mean=46.55%, SE=5.46% and marginal mean=80.48%, SE 4.20% respectively) caused less accurate responses than slow RETs (marginal mean=71.32%, SE=4.24% and marginal mean=89.79%, SE 3.48% respectively). In both cases, corrected p-value was below 0.001 threshold. Details are reported in Table 6 and Figure 6 b.

*Line bisection task*

Results of statistical analyses are the same than those reported in the first study.

*Correlation with line bisection task*

Results of correlation analysis between task features and bias factors are reported in Table 7 and shown for visualization purposes in Figure 7.

No significant correlations were detected comparing line bisection task outcomes and reaction times in both tasks. We instead found significant correlations between line bisection tasks and ATT conditions: AVG_LEFT positively correlated with accuracy rates observed during fast RET condition, specifically in longer-longer TET condition (s=0.418, corrected p-value=0.003, Figure 7.a); moreover, for the slow RET condition, accuracy rates in longer TET condition positively correlated with line bisection data (s=0.366, corrected p-value=0.035, Figure 7.b).

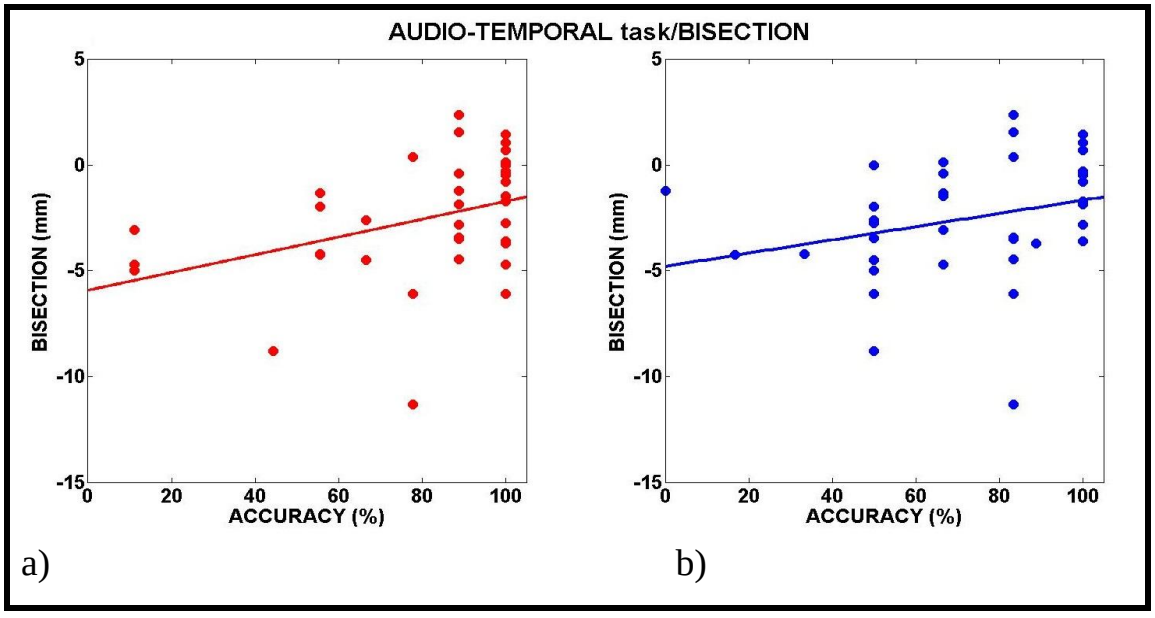



**Figure 7:** Correlation between Temporal tasks and line bisection task. In the plot, we observed the positive correlation between accuracy rates on auditory temporal task and leftward bias, when targets were and longer-longer and longer with fast and slow references respectively.

| Auditory_Temporal tasks/parameter | Reference-exposure time (RET) | Target-exposure time (TET) | SPEARMAN_S | CORR_PVAL |
|---|---|---|---|---|
| **ACC** | FAST | Shorter-shorter | -0,145 | 0,990 |
| | | Shorter | -0,047 | 1,000 |
| | | Equal | 0,120 | 0,998 |
| | | Longer | 0,240 | 0,647 |
| | | Longer-longer | 0,418 | 0,003* |
| | SLOW | Shorter-shorter | -0,073 | 1,000 |
| | | Shorter | -0,123 | 0,998 |
| | | Equal | 0,032 | 1,000 |
| | | Longer | 0,366 | 0,035* |
| | | Longer-longer | 0,043 | 1,000 |

**Table 7**: Correlation analyses between temporal tasks outcomes and line bisection task bias. Asterisk indicate significance at 0.05 level. ACC=Average Accuracy Rates; RT=Average Reaction Times.

## Discussion

Using novel and simple tasks, we found evidence that temporal selective attention of visual and auditory stimuli may be spatially driven by visual leftward and auditory rightward biases, respectively.

These results were obtained using novel but simple tasks, in a healthy cohort of thirty-eight subjects.

By means of line bisection task, we observed a clear leftward bias with the left hand. This finding confirms that visuospatial attention is asymmetrically distributed as well as leftward systematically deflected (Heilman and Van Den Abel, 1980; McCourt and Jewell, 1999).

Results of visual task are in accordance with existing literature on object-based attention. We indeed observed that it was easier to compare targets when slow references were provided. This finding is in accordance with a previous study on visual system (Shomstein and Behrmann, 2006); there, authors found that longer exposure times of visual stimuli allowed the best

object representation. Moreover, Shomstein and Behrmann (2008) found that effects of the object's representation diminished with longer delay occurring between references and targets. Moving from here, and in accordance with (Liu et al. 2007), we may hypothesize that the object exposure times are important when comparing short stimuli that are temporally close. We also observed that overall in the auditory task the fast references were identified more accurately than slow ones, in other word exhibited a reversed trend than visual task. Such finding may be in accordance with the fact that spatial and temporal processing are independently processed (Mackay, 2007).

Interestingly, in the visual task, in presence of a clear difference in terms of exposure times between target and reference stimuli, fast references were more easily identified than slow ones. It is worthy to remark that the overall time interval between the end of the reference and the end target presentations in fast condition were clearly shorter than the same time interval during the slow condition. In this case, the time interval between the end of the reference and the end target presentations in slow condition were clearly longer than the same time interval during the slow condition. On the other hand, we observed in auditory task that when a shorter difference in terms of exposure times between target and reference stimuli was exhibited, fast references were more easily identified than fast ones. In this perspective, our findings show that it is easier to estimate stimuli duration when processing short distances with visual stimuli and long distance with auditory ones. That is notably, the spatial representation of lager magnitudes is on the right side whereas the smaller ones is on the left side with respect the finding by Dehaene et al (2003).This in turn may pose the accent on the existence of a leftward and a rightward biases for visual and auditory stimuli respectably in timing judgment for such distances.

Surprisingly, we observed relevant significant correlations for the auditory tasks and data obtained from line bisection task. Indeed, we found that lower accuracy rates correspond to subjects with increased leftward bias for longer-longer and longer TETs with fast and slow RET respectively. Again, these results confirmed rightward bias in auditory temporal processing. If the differences in deployment of auditory temporal attention were related to individual differences in visual spatial attentional processing, then the temporal domain might be spatially driven. Indeed, our findings may be in accordance with evidence suggesting that models of auditory cortical processing can be conceived by analogy to the visual cortex, with both the visual and auditory cortex using spatial coordinates to detect stimuli (Rauschecker, 2015).

Overall, our results on temporal processing together with other finding on spatial processing (Chillemi, Calamuneri, et al., accepted) may thus underlie that the visual information processing is facilitated on the left in space, whereas it may be facilitated on the right when processing auditory information. In other words, whilst we may be in presence of a leftward bias for visual attention and a rightward bias may exist for the auditory attention. These findings could be useful to develop individual treatments for patients with different neurological disorders.

# Chapter 4

# Results and Discussions

## 4.1 THIRD STUDY "Biased visuo spatial attention in cervical Dystonia"

There is increasing evidence of non-motor, sensory features, mainly involving the spatial domain in cervical dystonia (CD). The aim of this study has been to investigate visuospatial attention in patients with cervical dystonia.

### 4.1.1 Results

The mean bisection errors for the three groups and the relative differences are presented in Table 8 and 9. The two factors ANOVA on the bisection errors showed a significant effect of the Hand [F (1.49) = 7.36, p<0.001].

| FACTORS | Numerator df | Denominator df | F | Sig. |
|---|---|---|---|---|
| **Intercept** | 1 | 366157.092 | 4.790 | .036* |
| **Disease** | 2 | 308604,728 | 4.037 | 0.027* |
| **Hand** | 1.495 | 395719.709 | 7.364 | <0.001** |
| **Hand*disease** | 2.990 | 25413.666 | .473 | .702 |

**Table 8**: Bisection line task. Results of rm-ANOVA performed on accuracy rates of BLT. Asterisk indicate significance at 0.05 level. Double asterisks indicate accuracy at 0.01 level. Greenhouse-Geisser degrees of freedom correction was applied

Post-hoc analysis revealed all participants (corrected p-values=0.001) showed a greater leftward deviation when the task was performed with the left hand (LH mean= -102.61 mm, SD= 246. 33) with respect to when the task was performed with the right hand (RH mean= 48.44 mm, SD= 243. 88). Moreover, a significant Group effect [F (2) = 4.03, p=0.027] was found. Post-hoc analyses revealed that, overall, TC patients (corrected p-values p=

0.02, see Figure 8) showed a greater leftward deviation (TC mean= -234.9 mm, SD= 235. 32) than the control group (C mean= -10.69, SD= 147.81). No differences were observed between LC and TC or C.

For CD patients, no significant correlations were observed between the bisection bias and clinical features. No other significant difference was found.

| (I) disease | (J) disease | Mean Difference (I-J) | Errore std | Sig. | 95% confidence interval for difference | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Higher Bound |
| **Controls** | **TC** | 187.521 | 66.631 | .025* | 19.184 | 355.859 |
| | **LC** | 67.377 | 65.166 | .927 | -97.260 | 232.014 |
| **Torticollis** | **C** | -187.521 | 66.631 | .025* | -355.859 | -19.184 |
| | **LC** | -120.144 | 66.631 | .242 | -288.482 | 48.193 |
| **Laterocollis** | **C** | -67.377 | 65.166 | .927 | -232.014 | 97.260 |
| | **TC** | 120.144 | 66.631 | .242 | -48.193 | 288.482 |

**Table 9:** Results of pairwise comparisons between groups. Bonferroni correction was applied. Asterisk indicate significance at 0.05 level.

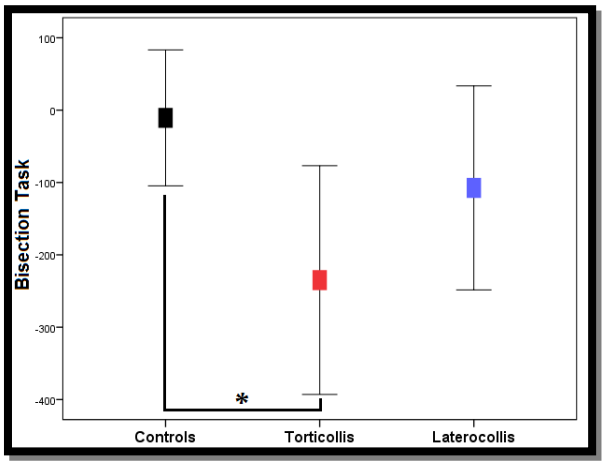



**Figure 8:** Bisection Task average results. Asterisks indicate significant differences between sub-levels at 0.05 threshold. Bars represent standard error.

We did not identify, within CD group and after correcting for multiple comparisons, significant correlations between measured task outcomes and clinical features. No other significant differences were found.

### 4.1.2 Discussions

With the present study, we provide evidence of consistent leftward attentional bias in patients with asymmetric symptoms of idiopathic cervical dystonia, and in particular in Torticollis patients (TC). In accordance with the literature, healthy controls manifested a leftward bias on the line bisection task, confirming that visuospatial attention is asymmetrically distributed as well as leftward systematically deflected in normal individuals (Heilman and Van Den Abell, 1980; McCourt and Jewell, 1999, Chillemi, Formica, et al., 2016 a.). Interestingly, the bisection bias, indexing asymmetrical distribution of visuospatial attention toward the left space (i.e. pseudoneglect), was stronger in TC patients than healthy controls. In TC patients, dystonia was mainly affecting right-sided muscles. While, based on findings in focal limb dystonia (Ricci et al., 2014), we expected to observe an attentional bias in the direction of the dystonic/affected muscles; here we observed an opposite pattern. However, this directional bias is consistent with data in Parkinsonian patients mainly affecting the left side, who showed a rightward bisection shift (Davidsdottir et al., 2008; Lee et al., 2001; Laudate et al., 2013). A line bisection bias toward the unaffected side of the body is thought to reflect hyperactivity of the attentional cerebral circuits contralateral to the unaffected side (Kinsbourne, 1977). In line with this suggestion, de novo PD patients, during the performance of a motor task (opening and closing the right hand), showed increased activation of pre-SMA, contralateral M1 and lateral premotor cortex, right inferior parietal cortex as well as ipsilateral (right) and contralateral (left) superior cerebellum (Eckert et al. 2006). Thus in our TC patients the leftward bias would imply hyperactivity of the right hemisphere attentional circuits (and/or hypoactivity of the left hemisphere). This hypothesis is also consistent with a model of crossed cerebello-cortical interactions, according to which the

cerebellar hemispheres and contralateral cortical regions are interconnected via thalamus (Clower et al., 2001; Middleton and Strick, 2001; Dum and Strick, 2003) and with the evidence of altered cerebellar activity in dystonic patients (Ghilardi et al., 2003). There are reciprocal projections from the ventral thalamus to other brain regions known to be involved in spatial attention, including posterior parietal and precentral frontal cortex (Carpenter, 1985; Nieuwenhuys et al., 1988; Middleton and Strick, 1994). Picazio and colleagues (2015) propose the idea that the left cerebellar hemisphere and the right parietal lobe work together for directing attention toward the left visual field. Whereas the right parietal lobe directs attention toward the left visual field, the right cerebellum inhibits the activity of the left parietal cortex, producing an attentional vector of greater strength than the contralateral attentional vector. Considering that spatial attention is controlled by the posterior parietal cortex and frontoparietal circuits, but also by contralateral cerebellum, the data of the present study bring further evidence of a pivotal role of these circuits in the pathophysiology of idiopathic dystonia.

Although idiopathic cervical dystonia has long been considered to be related to dysfunction of the basal ganglia, an increasing amount of evidence implicates a relationship between dystonia and the cerebellum (Ghilardi et al., 2003). Indeed, abnormalities in circuits involving the cerebellum have been observed in clinically unaffected carriers of the DYT1 dystonia mutation, during learning of visuo-motor sequences (performed with the right hand) with a compensatory increased activation in the left ventral prefrontal cortex (Quartarone et al., 2014), and decreased activation in the posterior medial cerebellum (Ghilardi et al. 2003). In a review of 143 cases of posterior fossa tumour, 23% of patients developed cervical dystonia with Torticollis pattern (Extremera, 2008). The surgical removal of the cerebello-

pontine angle tumour improved cervical dystonia symptoms in two case reports (Krauss, 1997). Another important piece of evidence is provided by the finding that bilateral cerebellar stroke (O'Rourke, 2006), or encephalomalacia affecting the cerebellum, especially of the right side (Waln and LeDoux, 2010) can produce blepharospasm and oramandibular dystonia. Consistent with the above hypothesis, in neurophysiological studies, dystonia patients do not show any effect of reduced MEP, decreased SICI or increased ICF when treated with right or left cerebellar stimulation, as usually shown by normal subjects (Brighina et al, 2009). Finally, some preliminary evidence supports the idea that while sensory abnormality might be mainly present in Laterocollis patients, higher level cognitive impairment might specifically affect Torticollis patients (Chillemi, Calamuneri et al, accepted). Differences in non-motor features are likely to reflect differences in the involvement of specific structures/circuits. We suggest that the presence of an attentional leftward bias in patients with TC might be explained by alteration of cortico-subcortical circuits involving the cerebellum. On the other hand, the cerebellar structure would not be crucially involved in Laterocollis pathophysiology.

Thus, on the basis of previous evidence (Ghilardi et al., 2003), we speculate that, in patients with Torticollis mainly affecting the right-sided muscles the leftward attentional bias might be the expression of abnormal right cerebellum hyperactivity, leading to inhibition of left posterior parietal activity (and, consequently, to increased right posterior parietal activity).

In line with this hypothesis, induction of rightward bisection bias by single-pulse TMS over the right posterior parietal cortex in healthy subjects is associated with decreased activity of ipsilateral parieto-frontal circuit and increased activity of contralateral cerebellum (Ricci, 2012). In addition, suppression of the left but not the right cerebellum with theta burst cTMS

significantly affects swift behavioural adjustment to changes in the environment driven by spatial attention during sensorimotor integration activities (Bijsterbosch, 2011). In this study (Bijsterbosch et al., 2011) using fMRI, the authors observed a psychophysiological interaction between error correction and enhanced connectivity of the left and right cerebellum with frontal, auditory, and sensory cortices.

To sum up, the notion that the cerebellum is part of a distributed network involved in the regulation of spatial attention (Picazio et al., 2015), and our finding showing a directional attentional bias in idiopathic cervical dystonia, likely indexing contralateral cerebellar dysfunction, might offer a rationale for targeting a specific cerebellar site with non-invasive brain stimulation in prospective rehabilitative interventions in Torticollis patients. In future rehabilitation studies, the efficacy of the intervention will need to be assessed not only on movement disorders but also on visuospatial (Ricci et al., 2014); cognitive (Lange et al., 2016) as well as psychological symptoms (Stamelou et al., 2011; Berardelli et al 2015) that may significantly affect diverse aspects of daily life in patients with dystonia (Müller et al., 2002; Cano et al., 2006; Perozzo et al., 2016).

## 4.2FOURTH STUDY "Spatial and temporal high processing of visual and auditory stimuli in Cervical Dystonia"

Previous psychophysiological studies have investigated temporal and spatial characteristics of neural processing of sensory stimuli (mainly somatosensorial and visual) in focal dystonia. Abnormalities at higher cognitive level have not yet been sufficiently addressed. The aim of this work has been Investigation of spatial and temporal cognitive processing in idiopathic cervical dystonia by means of specific tasks based on perception in time and space domains of visual and auditory stimuli.

### 4.2.1 Results

Table 2 shows the clinical features of dystonic patients. Correlation analyses performed between task outcomes and clinical features did not show significant differences within dystonic group, neither when pooling al subjects together, nor when separately analyzing subjects belonging to different dystonic Patterns (corrected p-values>0.05).

*Spatial Tasks*

Results of LMM performed on spatial tasks are detailed reported in Table 10. A main effect of PATTERN TYPE was observed ($F=22.404$, $p<0.001$); however post-hoc comparisons did not reveal significant differences after correcting for multiple comparison. Furthermore, a significant interaction between pattern type and STIMULUS was observed ($F=5.431$, $p=0.002$); post-hoc analyses revealed that subjects diagnosed as Laterocollis were significantly less accurate than controls when processing auditory stimuli (average diff = 10.75%, std error=3.502, corrected $p=0.021$, see Figure 9.a). Moreover, a significant interaction with Reaction time was observed ($F=36.989$, $p<0.001$).

Post hoc analyses, after applying Bonferroni correction, showed that subjects with pre-dominant torticollis and laterocollis were consistently slower than controls (Z=-2.976, corrected p=0.018 and Z=-3.702, corrected p=0.001 respectively). No significant differences were detected between controls and Tremor group, likely due to lack of statistical power.

| FACTORS | Numerator df | Denominator df | F | Sig. |
|---|---|---|---|---|
| Intercept | 1 | 155.795 | 4013.412 | <0.001 |
| Pattern Type | 3 | 149.945 | 22.404 | <0.001 |
| Stimulus | 1 | 83.831 | 224.248 | <0.001 |
| Congruency | 2 | 152.911 | 38.834 | <0.001 |
| Position | 2 | 132.204 | 121.565 | <0.001 |
| PatternType * Stimulus | 3 | 81.993 | 5.431 | 0.002 |
| PatternType * Congruency | 6 | 153.751 | 1.531 | 0.171 |
| PatternType * Position | 6 | 132.531 | 0.733 | 0.624 |
| Stimulus * Congruency | 2 | 151.894 | 38.449 | <0.001 |
| Stimulus * Position | 2 | 133.673 | 122.449 | <0.001 |
| Congruency * Position | 4 | 120.589 | 59.004 | <0.001 |
| PatternType * RT | 4 | 170.724 | 36.989 | <0.001 |

**Table 10**: Results of LMM applied on Spatial Tasks. RT stands for reaction times. Asterisks represent interaction between factors included in the model.

*Temporal Tasks*

Results of LMM performed on temporal tasks are detailed reported in Table 11. We found a significant interaction between the factors pattern type and duration (F=2.585, p=0.003); post-hoc analyses revealed, after applying

Bonferroni correction, that subjects diagnosed with torticollis were significantly less accurate than controls when detecting target stimuli whose duration with respect to reference sound was longer (average diff= 18.362%, std error=6.616, corrected p=0.043, see Figure 9.b). Unlike for the spatial task, no significant interaction was observed with reaction times.

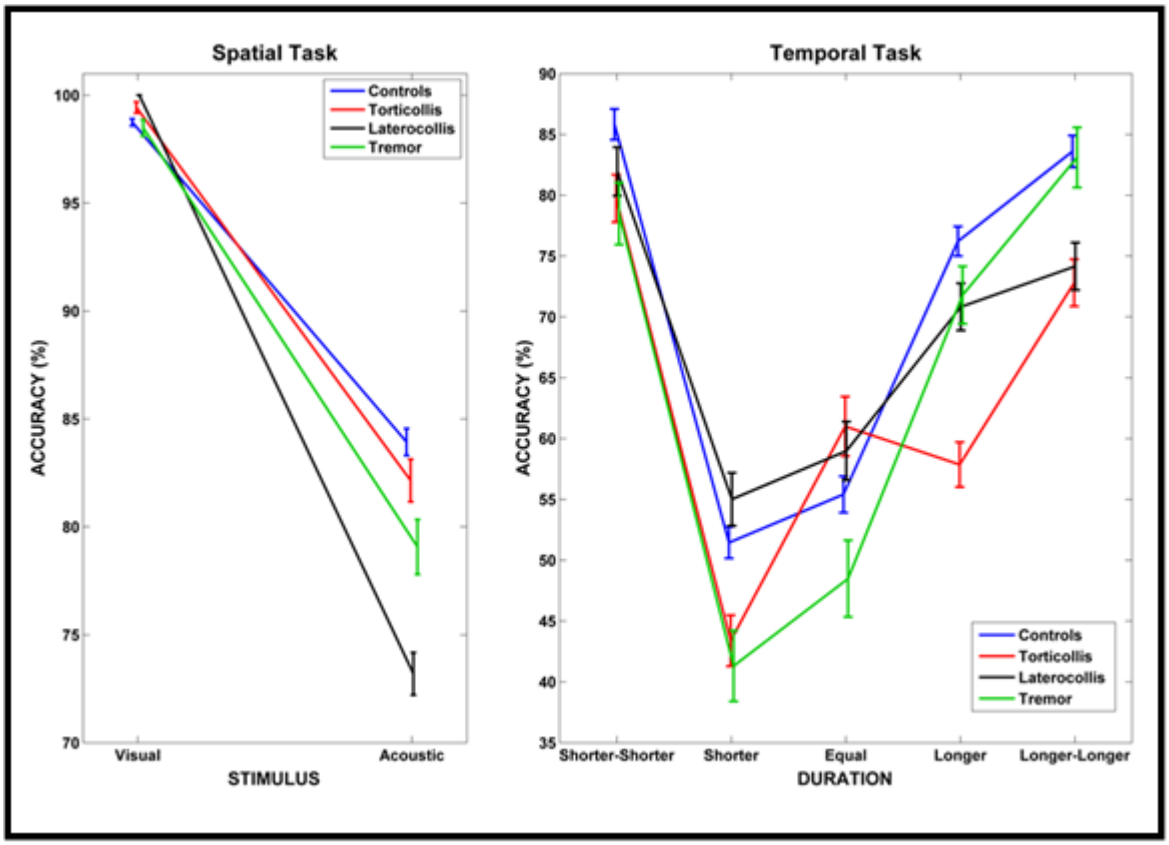
| FACTORS | Numerator df | Denominator df | F | Sig. |
|---|---|---|---|---|
| Intercept | 1 | 168.010 | 337.059 | <0.001 |
| Pattern Type | 3 | 167.912 | 0.067 | 0.977 |
| Stimulus | 1 | 478.628 | 0.090 | 0.765 |
| Speed | 1 | 471.246 | 0.329 | 0.567 |
| Duration | 4 | 198.448 | 31.700 | <0.001 |
| Pattern Type * Stimulus | 3 | 481.074 | 0.187 | 0.905 |
| Pattern Type * Speed | 3 | 472.068 | 1.078 | 0.358 |
| Pattern Type * Duration | 12 | 201.289 | 2.585 | 0.003 |
| Stimulus * Speed | 1 | 483.565 | 6.993 | 0.008 |
| Stimulus * Duration | 4 | 184.750 | 5.664 | <0.001 |
| Speed * Duration | 4 | 173.508 | 6.775 | <0.001 |
| Pattern Type * RT | 4 | 264.348 | 0.592 | 0.669 |

**Table 11**: Results of LMM applied on Temporal Tasks. RT stands for reaction times. Asterisks represent interaction between factors included in the model.

We did not identify, within CD group and after correcting for multiple comparisons, significant correlations between measured task outcomes and clinical features. It is however worth to mention that average accuracy rates in audio spatial task showed a negative correlation with TSUI scale (kendall's tau=-0.408, uncorrected p=0.016); this result did not come

unexpected, and may reflect increased difficulty for CDs to achieve good accuracy in audio-spatial processing when degree of impairment increases.

**Figure 9**: Interaction between dystonic patients and tasks. In the left side accuracy rates for controls and dystonic subtypes highlight the lower accuracy for Laterocollis with respect to controls when spatially detecting acoustic stimuli. In the right part we observe decreased accuracy




for Torticollis with respect to controls when detecting target sounds that lasted "longer" than reference sounds in temporal tasks. Bars represent Standard Error of the Mean (SEM).

### 4.2.2 Discussion

We found that patients with idiopathic cervical Dystonia showed perceptive dysfunctions of different level with respect to neurophysiologic pattern type: a double dissociation in the performance between lateorcollis and torticollis undergoing spatial and temporal tasks was indeed detected.

*Spatial task*

In visuo spatial task we observed that all dystonic patients were on average slower than controls, although significant differences were detected only for Torticollis and Laterocollis subtypes. This result likely reflects the motor features of the disorder, resulting from involuntary concomitant contraction of agonist and antagonist muscles, with overflow of unwanted muscle contractions into adjacent muscles (Tarsy and Simon, 2006). The abnormal movements may indeed occur during the execution of a task slowing execution.

When investigating accuracies in spatial tasks, we found that Laterocollis were worse than healthy subjects in auditory but not visual task. It is known that a sound lasts in short term memory for about 4sec while a visual stimulus persists for only 0.25sec (Grice and Gwynne, 1985); thus, we may hypothesize that the first sound mask the second one interfering on the response accuracy of the second auditory stimulus. This result may therefore indicate a perceptual abnormality on auditory recognition for Laterocollis.

Recent studies using intracranial recordings (Liegeois-Chauvel et al., 2004) and functional imaging (Zatorre and Belin, 2001) have provided compelling evidence for a hemispheric specialization in the auditory processing. It has been suggested that the processes associated with identification of linguistic auditory objects are lateralized toward the left hemisphere (Parker et al, 2005) while the paralinguistic aspects of vocal processing are lateralized toward the right hemisphere (Belin et al. 2004). According to this theory, in the left hemisphere anterior brain structures are involved in expressive tasks, whereas posterior areas contribute to stimulus perception (Ross et al., 1997).

It is well known that idiopathic Dystonia is mainly attributed to basal ganglia dysfunction (Peller et al., 2006). Hence, a greater left damage involving these structures may explain perceptual abnormality observed on the performance of the Laterocollis. It is important to highlight that this result

was not confirmed neither for Torticollis, who were on average 1.78% less accurate than controls (std err 3.5%), nor for subjects diagnosed as Tremor, who were on average 4.86% less accurate than controls (std error 4.42%).

*Temporal tasks*

When investigating temporal tasks, we found that subject diagnosed as Torticollis were less accurate than healthy subjects when the duration of stimulus (exposure times) was in the condition "longer" with respect to reference sound.

It is supposed that the representation of numbers is arranged along a mental line, called mental number line (MNL) (Umiltà et al, 2009; Oliveri et al., 2008). In people who read from left to right, the MNL is spatially oriented from left to right, with small magnitude numbers represented on the left-hand side of the line and numbers of larger magnitude represented on the right-hand side (Dehaene et al., 2003). Moreover, it is known that two numbers that are numerically distant are more easily and quickly detected with respect to when they are closer; this phenomenon is referred to as the distance effect (Moyer and Landauer, 1967). In accordance to these theories, we observed that for all subjects it was easier to temporally discriminate reference from target sounds in presence of a clear temporal difference (Jolicoeur and Lefebvre, 2015). This situation can be visualized in Figure 7.b, where it can be clearly evinced that best performances were reached when target sounds were in "shorter-shorter" and "longer-longer" condition with respect to reference ones. The condition "equal" was the most difficult to detect, while "shorter" and "longer" duration performances ranged in between extremal conditions and this latter on. Of importance, such pattern did not hold for Torticollis, who did not show an advantage for "long" condition (see Results section).

Shomstein and Behrmann (2008) found that longer exposure times of stimuli allowed more time for perceptual grouping and figure-ground segmentation, leading to the best representation of the object. On other hand, the effects of this representation diminished with long SOA (time between the onsets of reference and target components). This effect may explain the loss of accuracy of Torticollis in our temporal task. In fact, in our study we have SOA longer for long exposure times. Hence, we might hypothesize that the longer the time interval, the greater the likelihood that Torticollis could make mistakes, since they are less able, compared to other subjects to maintain the temporal representation of the object due to deficit of selective attention object-based.

A similar situation was observed in a study by Sadnicka et al. (2012): there, an important observation consisted in the fact that cervical dystonic patients and the spinocerebellar ataxic patients, in addition to poor performance, had abnormal timing adjustment. In another study by Filip et al. (2013), it was observed a lower accuracy for dystonic patients in comparison to a control group in a specific motor-timing task in association with significantly slower reaction time to a simple color change in the dystonic group. In our study, we observed that only Torticollis pattern showed an impairment in time estimation of stimuli with long exposure times. Dystonic group of Filip and colleagues included both Torticollis and Laterocollis; however, they did not explicitly compared different dystonic patterns in search of differences within subtypes: it might be the case that it was the Torticollis subgroup to mostly drive their result.

It is noteworthy that patients by Filip (2013) showed motor disorders connected with cerebellum dysfunctions. The same dysfunctions may explain the deficit observed on our patients.

# Chapter 5

# Conclusions

## 5.1 Neurophysiology of selective attention

In the healthy human brain, neuroimaging studies have identified activations over specific dorsal and more ventral frontoparietal networks during a wide variety of visuospatial attention tasks (Kastner and Ungerleider, 2000; Corbetta, 2002; Ricci et al 2012). This network includes several areas along the intraparietal sulcus (areas 1-5) and the superior parietal lobule (area 1) as well as the putative human frontal eye fields and supplementary eye field (Silver, 2009). Behavioural studies with patients suffering from visuospatial neglect provide evidence on how human frontal and posterior parietal circuits guide spatial attention (Robertson, 1993; Corbetta et al., 2002). Other studies observed that the severity and the direction of inattention for visual and auditory stimuli is positively correlated with the side of the brain injury in neglect patients (Pavani, 2004), leading to the inability to orient toward or attend to the contralateral side of space. Notably, this syndrome is more frequently associated with right than left hemisphere lesions (Vallar, 2001). To account for these observations, the "hemispatial" theory (Heilman and Van Den Abell, 1980) has proposed that the right hemisphere directs attention to both visual hemifields, whereas the left one directs attention to the right visual field only. Thus, although the right hemi visual field can compensate for left hemisphere damage, such compensation is not possible with right hemisphere damage, thereby resulting in stronger neglect of the left visual field. Moreover, the anatomical basis of the right hemispheric dominance for visuospatial attention is largely observed in animal studies (Sperry, 1974; Mesulam, 1981). Nevertheless, some evidence exists of right visuospatial bias in patients with left hemisphere damage (Beis et al., 2004), suggesting that visuospatial attention is probably a bilateral function (Heilman and Van Den Abell, 1980; Corbetta and Shulman, 2002; Salatino

et al., 2014). Moreover, a few and more recent studies showed a larger connections of parietofrontal network in the right than left hemisphere and a correlation between the degree of anatomical lateralization and an unbalanced speed of visuospatial processing (Thiebaut De Schotten et al., 2011; Ricci et al., 2012). Then, an alternative account, "interhemispheric competition" theory (Kinsbourne, 1977, 1993; Cohen et al., 1994), has proposed an opponent processor systems, wherein each hemisphere directs attention toward the contralateral visual field and is balanced through reciprocal inhibition. Szczepanski and Kastner (2013) found that, by interfering with TMS on the activity of the intraparietal sulcus (areas 1-2), is possible to induce a temporary shift of attentional weights toward the ipsilateral visual field. The authors explained these result on the basis of the interhemispheric competition theory of attention. Indeed when they applied TMS on left side attention shifted leftwards and vice versa.

The "interhemispheric competition" theory (Kinsbourne, 1977, 1993; Cohen et al., 1994) might be the best explanation for some our findings. We found a delay on left-side auditory processing when attention was previously driven toward the right space. This delay might be accounted for by reciprocal interhemispheric inhibition used to balance the bilateral attentional system, whereas left cerebellar hemisphere may inhibit right parietal lobe (see figure 10), both working together for directing the attention toward the left visual hemifield with greater strength than the contralateral attentional vector (Picazio, 2015).

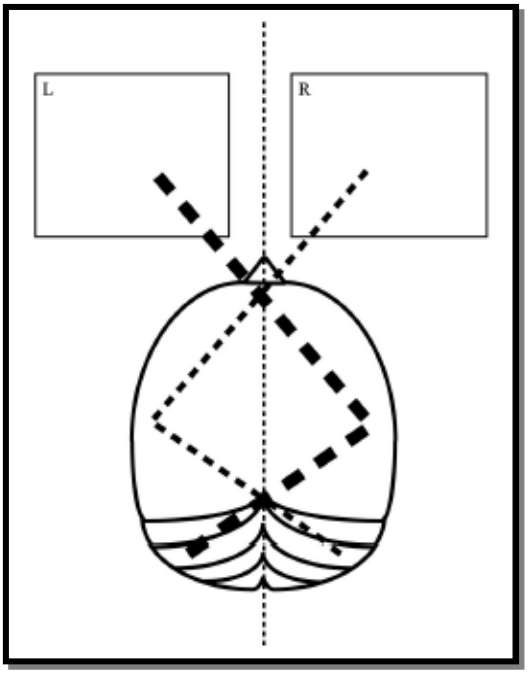



**Figure 10**. By Picazio (2015), a model of cerebellar involvement in Visuospatial lateralized attention. Left cerebellar hemisphere works in network with the right cerebral hemisphere for directing the attention toward the left visual hemifield. Right cerebellar hemisphere works in network with the left cerebral hemisphere for directing the attention toward the right visual hemifield. The attentional vector for the left visual hemifield (thickdashedline) is naturally stronger than the one for the right visual hemifield (thindashedline).

Finally, we showed some evidence that selective attention is modality specific. It should be noted that most research on spatial attention has focused on visual processing, and only scant evidence of putative asymmetries of audiospatial attention (although still controversial) seems to suggest a rightward bias (Sosa et al., 2010) according to our results. Furthermore, it is known that sound sources can be localized exclusively on the basis of auditory cues. Nonetheless, sound localization accuracy improves if the cue is also visible to the subject (Shelton and Searle 1980; Stein et al., 1989; King, 2009). Facilitation of sound localization by visual information (Schroeder et al., 2009), has been mainly observed in animals studies (Bizley and King 2008) and insufficient evidence exists on humans (Sosa et al., 2010). It is also known, in term of anatomical basis of auditory processing, that central auditory projections have a large ipsilateral component that is absent in the visual system (Bellmann et al., 2001). In addition, there is substantial evidence that sounds confined to the left hemispace activate only the contralateral hemisphere, whereas sounds located in right hemispace produce bihemispheric activation (Krumbholz et

al., 2005; 2007; Petit et al., 2007; Schonwiesner et al. 2007; Hine and Debener, 2007). However, it is not clear which brain regions are mainly involved in audio spatial attention. There is some evidence showing that audiospatial attention does not involve visuotopic maps of the intraparietal sulcus that are instead implicated in visuospatial attention. On the other hand, it activates the superior temporal gyrus and the supramarginal gyrus, suggesting that audiospatial and visuospatial attention utilize distinct spatial coding schemes (Kong et al., 2012). To sum up, it could reasonable be that spatial attention and temporal attention involve similar cerebral networks to control of attention, but different primary sensory areas to selection of specific stimuli although they can interact each other.

## 5.2 Multisensory integration in the selective attention

Multisensory integration has often been characterized as an automatic process (Santangelo et al., 2009), nerveless recent findings suggest that it can occur across various stages of stimulus processing that are linked to attentional bottom-up (stimulus-driven) mechanisms as well as it can be modulated by top-down attention systems (Busse et al, 2005).

These findings may be linked to Lee and Shomstein's findings (2013), providing evidence that spatial processing is attentional mechanisms independent by object-based attention. Using a variant of the two-rectangle paradigm by Egly (1994) (see figure 11), they obtained behavioural and neuroimaging results that spatial attentional allocation is mandatory, integrating reward information over time, whereas object-based attentional allocation is a default setting that is completely replaced by the reward signal (Lee and Shomsteim, 2013). The first finding dovetails with attentional selection research demonstrating automaticity of spatial attention (Posner, 1980).

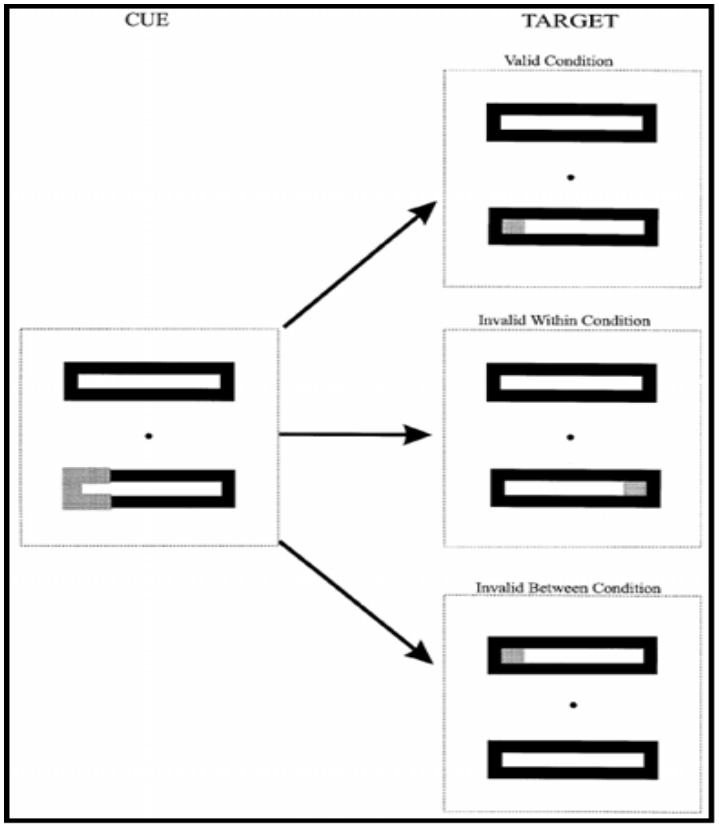



**Figure 11**. Stimulus display for the Egly paradigm (1994). Examples of cue and target displays are shown for valid, invalid-within object and invalid-between object conditions.

On the other hand, it highlights that spatial attention effects are eventually modulated by reward. Thus, they observed that albeit spatial attention is automatic, when a reward is given, its effects are added to spatial guidance, increasing the accuracy on valid location. The second conclusion is that object-based attention, rather than interacting with reward, is completely abandoned in favour of the reward contingency. Indeed, reward-based modulation emerged immediately after a cue and persisted until target identification, suggesting that perceptual efficiency is determined exclusively by reward and object-based effects are not automatic (Chen and Cave, 2008; Yeari and Goldsmith, 2010).

Interestingly, we observed results that allowed similar observations but on the auditory system (Chillemi et al. 2016 b.). We found a rightward bias for

auditory stimuli (see figure 12b.), that means the attention may be automatically biased toward the greater attentional vector, likely in the right hemisphere for auditory system.

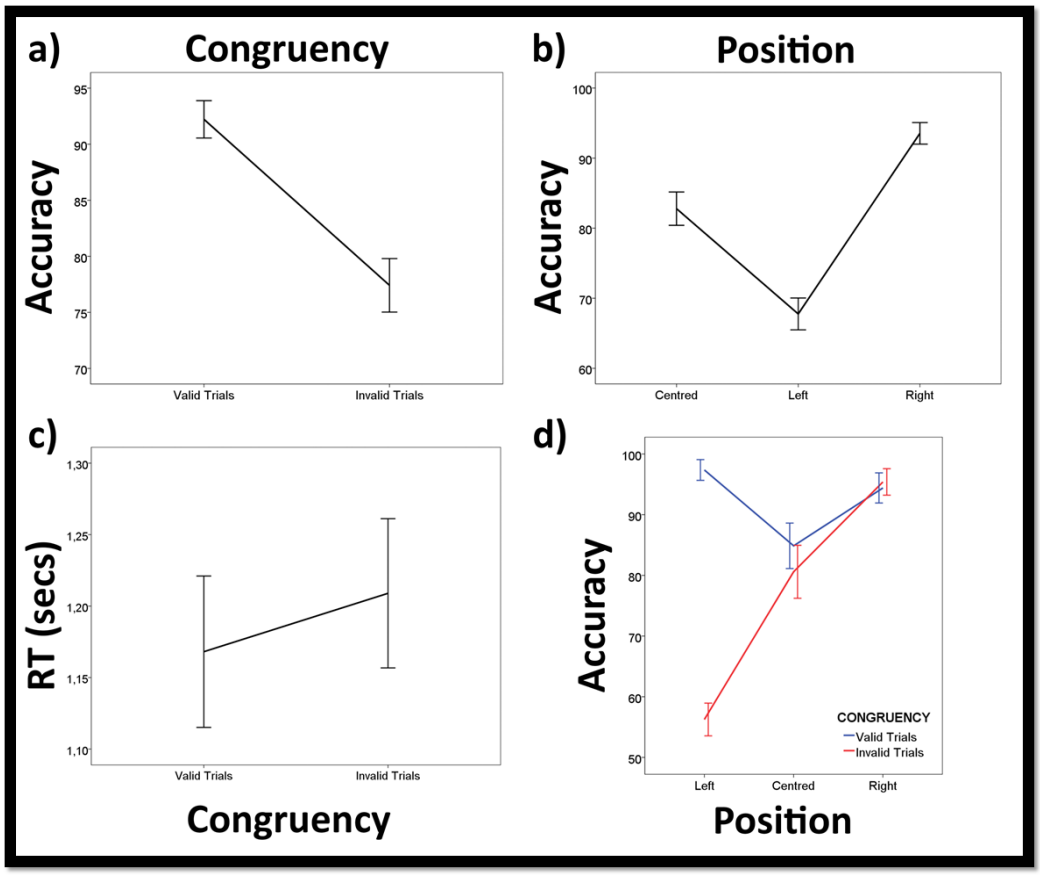



**Figure 12:** Spatial visuo-audio task results. Rates were more accurate for stimuli appearing in the attended than in the unattended locations (Figure 12.a, $p<0.001$). They also showed greater accuracy for right-sided stimuli (Figure 12.b, $p<0.001$). However, the rightward advantage disappeared for correctly cued attended locations (Figure 12.d, $p=0.285$). Reaction times were faster for valid trials (Figure 12.c, $p=0.036$) and for left-sided stimuli ($p<0.019$).

Nevertheless, it might be modulated by visuo-valid cue. We showed that when the auditory spatial attention was invalidity driven by visual cue the performance fell down dramatically. In other words, the visual cue might influence the spatial guidance of auditory information similarly to reward mechanism, facilitating the allocation. Details of the preliminary work are reported in figure 12.

These findings support the evidence of crossmodal links in spatial attention between vision and audition, when the visual cue orients attention to the right hemispace likely dominant for auditory targets. Moreover, as discussed in third capitol, these seem to suggest that the influence of visual cues on sounds localization is also affected by individual differences in the degree of hemispheric lateralization of visuospatial attention.

## 5.3 Pathophysiological correlates of Visuospatial and audio spatial impairment in focal cervical dystonia

Abnormalities have been observed on posterior parietal cortex (PPC) and ventral frontoparietal circuits in clinically unaffected carriers of the DYT1 Dystonia mutation during learning of visuo-motor sequences with a compensatory increased activation in the left ventral prefrontal cortex, and lateral cerebellum (Fiorio et al., 2003). Furthermore, abnormal connectivity between PPC and primary motor cortex (M1) may be present in Cervical Dystonia, an abnormality that is associated with slower reaching movements (Koch et al. 2008; Ricci et al. 2014). The interaction between PPC and M1 is crucial for the preparation and planning of movements directed to visual targets (Vicario et al, 2013; Koch et al., 2010), as it regulates visuospatial mechanisms that affect performance, accuracy and variability. On the other hand, increasing evidence the cerebellum is implicated in a wide spectrum of different process controls extending far beyond the typical cerebellar domain. These include, for example, attention (Perloy et al., 2010; Bledsoe et al., 2011), associative learning (Timman et al., 2010), and time assessment (Bares et al. 2007).

Considering that spatial attention is controlled by posterior parietal cortex (PPC) and ventral frontoparietal circuits as well as contralateral cerebellum, the data of the present thesis may confirm a pivotal role of these circuits in

the pathophysiology of idiopathic Dystonia. A consistent body literature supports a major role of the basal ganglia in Dystonia; however, more recent findings explore the causative role of other regions, in particular the cerebellum (Manganelli et al., 2013), but no previous study has linked the respective basal ganglia and cerebellar networks with different patterns of Dystonia. The differences observed in our study between Laterocollis and Torticollis might be explained by involvement of different brain structures in these groups of patients. We might hypothesize that the difficulty of identifying the stimuli as result of spatial selective attention deficits may be more marked in dystonic patients with major impairment of the basal ganglia, as we found in the case of Laterocollis. On the other side, it may be supposed that problems in time estimation of stimuli are due to difficulty of selective attention based on the object in dystonic patients with major cerebellar involvement, as we observed in the case of Torticollis. Finally, it may be postulated that the abnormal auditory and visual processing might also have a reflection on movement programming and planning (Blauert, 1996). It is well known that Dystonia, apart for being a movement execution disorder and a sensory disorder, is also a disorder of movement preparation. Movement preparation involves a number of factors, including the process of sensorimotor integration (Hallett, 2000). The human nervous system prefers to be anticipatory rather than reactive and a disordered preparation for movement will certainly be a crucial factor in faulty execution.

The heterogeneity as well as in the small size of the population under study have to be considered limitations of the present work. In addition, due to the small number of subjects, we could not stratify the patients according to the side (i.e. right or left) of the affected muscles. Future studies will be necessary to better explore parieto-motor-cerebellum connectivity during audio-motor or visuo-motor tasks by means, for instance, of fMRI or dual-

coil TMS approaches, and to further clarify the differences we observed within subtypes of Dystonia.

## 5.4 Future approaches

In conclusion, our results suggest that the individual differences observed among subjects are functionally meaningful. Indeed, the perceptual biases manifested on line bisection as well as spatial and temporal task might be measures of how individuals allocate their attention across the as visual field as well as auditory one. This is especially important to consider when dealing with individuals who have sustained damage to portions of the fronto-parietal-cerebellum attentional network and may be suffering from various attentional deficits.

Therefore, our data suggest that examination of individual differences in attention control system should be performed by innovative behavioural tasks, eventually deepen with neuroimaging tools, in order to develop treatment options for individual patients with different neurological disorders. In this perspective, new insights by interdisciplinary approaches are needed.

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