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The deployment of visual attention in autism spectrum disorders

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To Beatrice and my family

ABSTRACT
(English)

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental condition that affects almost 1% of the population. One of the main challenges in the current ASD research is to define the early neurocognitive impairments that provide critical foundations for the core deficits in social and communication abilities. In particular, early attentional dysfunctions may play a critical role in the emergence of ASD. In this doctoral thesis I present six studies that give significant new insights into the nature of altered visual attention in individuals with ASD and their possible neural underpinnings.

In the first study we show that individuals with ASD are impaired in enlarging (i.e., "zooming-out") the attentional focus size relative to the control group and this deficit can impact the rapid orienting toward a cued location in the visual field. The second and the third studies show how parents without any history of ASD but with elevated autistic traits can transmit to their infants subtle deficit in visual attention (at the expense of both orienting and zooming mechanism) that may impact children's future socio-communicative abilities. In the fourth and the fifth studies we employed transcranial magnetic stimulation and dense-array electroencephalography, respectively, with typical adults participants and we show that a network of frontal (mainly FEF and IFG) and parietal (mainly IPS/SPL) brain areas are fundamental in regulating the size of the attentional focus. In the last study, we evaluated the spatial profile of the attentional focus in individuals with ASD and results show that the inhibitory ring outside the focus of attention – fundamental to attenuate processing of irrelevant information – is significantly weakened relative to the control group.

Overall, these findings show the importance of attentional impairments in the core manifestations of ASD and in its developmental course. Defining attentional abnormalities and their neural correlates is extremely important (i) to improve the early detection of the disorder and, (ii) to implement timely prevention programs to reduce the incidence of ASD.

ABSTRACT
(Italian)

Il disturbo dello spettro autistico (DSA) è un disturbo neuroevolutivo pervasivo che colpisce quasi l'1% della popolazione. Una delle principali sfide nell'attuale ricerca sul DSA è definire i deficit neurocognitivi precoci che costituiscono le fondamenta dei disturbi "chiave" nelle abilità sociali e comunicative. In particolare, precoci disfuzioni attentive potrebbero giocare un ruolo decisivo nell'emergere del DSA. Nella presente tesi di dottorato presento sei studi che contribuiscono significativamente alla comprensione delle alterazioni dell'attenzione visiva nei DSA e le loro possibili basi neurali.

Nel primo studio, mostriamo che gli individui affetti da DSA sono compromessi nell'abilità di allargare ("zoom-out") la dimensione del fuoco attentivo e che questo problema può avere un impatto negativo nell'orientamento rapido verso una posizione segnalata nel campo visivo. Il secondo e terzo studio mostrano come genitori senza alcuna storia clinica di DSA ma con elevati tratti autistici possano trasmettere ai loro infanti sottili alterazioni nell'attenzione visiva (a carico sia del meccanismo di orientamento che di quello di zoom) che possono avere conseguenze negative sul futuro sviluppo delle abilità socio-comunicative dei loro figli. Nel quarto e quinto studio, abbiamo utilizzato la stimolazione magnetica transcranica e l'elettroencefalografia ad alta densità, rispettivamente, in partecipanti adulti a sviluppo tipico e mostriamo che un network di aree frontali (principalmente FEF e IFG) e parietali (principalmente IPS/SPL) sono fondamentali nella regolazione della dimensione del fuoco attentivo. Nell'ultimo studio, abbiamo valutato il profilo spaziale del fuoco attentivo in individui con DSA e mostriamo come l'anulo inibitorio circostante al fuoco attentivo – fondamentale per attenuare il processamento d'informazioni irrilevanti – è significativamente più debole nel DSA rispetto al gruppo di controllo.

Complessivamente, queste evidenze mostrano l'importanza dei deficit attentivi nelle manifestazioni chiave del DSA e nel suo decorso evolutivo. Definire le anomalie dell'attenzione e i corrispondenti correlati neurali è estremamente importante (i) per migliorare la diagnosi precoce del disturbo e (ii) per implementare tempestivi programmi preventivi mirati a ridurre l'incidenza dei DSA.

PREFACE

"There are times, more often than not, in which she is completely oblivious to all but her immediate focus of attention." (Kanner, 1943, p. 231)

The essence of the term "autism" seems to be fully illustrated by these few words that Leo Kanner wrote in his original paper. He was referring to the striking characteristics of one of the children he visited, for which everything outside of the focus of attention seemed to be completely oblivious. This perfectly fit also to the origin of the term autism, derived from the term "autós" (αὐτός, a Greek word that mean "self") to indicate that persons affected were individuals who have very limited contacts with the outside world.

Despite the importance of *attention* was clear since the very first description of autism, much of the following research efforts in the field have historically been concentrated on trying to explain the disorder in term of altered "mind reading" capacities (more technically called "theory of mind"). Simply, persons with autism are missing core modules of the brain that are necessary for understanding the behavior of others, and consequently they found extremely difficult to interact with the outside world.

However, this seems to me as seeing only the tip of the iceberg. The ability to attribute mental states emerges gradually in the course of development and may depend on the integrity of several elementary (and at the same time essential) neurocognitive functions that constitute the fundamental bricks to build such a high-level constituent of human cognition. One of these fundamental brick is certainly constituted by attention. Attention allows us to select relevant input from the environment, avoiding to process irrelevant inputs and keeping only what is relevant for our current behaviour and future learning. Research on dysfunction

of attention in the field of autism has initially started to explore attentional abnormalities with the implicit idea that these deficits were only mere reflections and co-occurring factors of the disorder. Only recently this idea has started to be challenged, especially with the advent of longitudinal studies in infants at risk that showed how impairments in basic mechanisms of visual attention (e.g., disengagement) are closely related to the emergence of autism later in toddlerhood. A domain-general deficit, which can impact the attention network as well as other neurocognitive networks, is thus increasingly accredited as one of the main factor that could lead to the emergence of autism. This kind of model is also better fitting the nature of neural abnormalities that researchers have found in the autistic brain, abnormalities that are not confined into a single brain network but that involve the entire pattern of brain morphology and functional activity.

The better understanding of how basic attentional abnormalities can lead to social and communicative impairments that are the core symptoms of autism will be the *leitmotiv* of the present doctoral thesis.

CHAPTER 1 - INTRODUCTION:
CLINICAL CHARACTERIZATION, PREVALENCE AND CURRENT NEUROPATHOGENIC HYPOTHESES OF AUTISM SPECTRUM DISORDERS (ASD)

1.1 The origins of the scientific study of autism

The scientific study of autism, or what we called today autism spectrum disorder (ASD), started with the pioneers Leo Kanner and Hans Asperger who, independently, first published a description of the condition (Kanner, 1943; Asperger 1944). These publications contained detailed cases description and also offered the first theoretical attempts to explain the disorder. It is not a coincidence that both have chosen the word "autistic" for characterizing the nature of the underlying deficit. The word has been introduced by the eminent psychiatrist Eugene Bleuler in the 1911. It referred to a striking deficit that characterizes individuals with schizophrenia (another term coined by Bleuer), namely the narrowed relationships with people and the limited contact with the outside world. The narrowing is so extreme that seems to exclude everything except the person's own self. The words "autism" and "autistic" derived, indeed, from the Greek word *"autós"* that means "self". Both Kanner, working in Baltimore, and Asperger, working in Wien, studied several cases of children who had in common some fascinating behavioural features. These children seemed to be unable to established normal relationship with their peers. In contrast to Bleuer's schizophrenia, the disorder appear to have been there from the beginning. Furthermore, in contrast to schizophrenia, the deficit was not accompanied by progressive deterioration. If anything, behavioural improvements could be expected to occur with development and learning.

It is worth to note that both authors believed that a fundamental biological deficit was present from birth. Despite that, in the following years, around 1950, some child psychologists wrongly inferred that the parents' coldness was the cause of their children's autism. It is true that in his 1943 paper that first identified autism, Kanner called attention to what appeared to him as a lack of warmth among the fathers and mothers of autistic children. He wrote, in the original paper (Kanner, 1943, p. 250):

"This much is certain, that there is a great deal of obsessiveness in the family background. The very detailed diaries and reports and the frequent remembrance, after several years, that children had learned to recite twenty-five questions and answers of the Presbyterian Catechism, to sing thirty-seven nursery songs, or to discriminate between eighteen symphonies, furnish a telling illustration of the parental obsessiveness. One other fact stands out prominently. In the whole group, there are very few really warmhearted fathers and mothers. For the most parts, the parents, grandparents and collateral are persons strongly preoccupied with abstractions of a scientific, literary, or artistic nature, and limited in genuine interest in people."

But he also wrote, few lines below:

"The question arises whether or to what extent this fact has contributed to the condition of the children. The children's aloneness from the beginning of life makes it difficult to attribute the whole picture exclusively to the type of the early parental relations with our patient."

Notwithstanding the clear scepticism of Kanner in attributing the behaviors of children with autism to the type of early relations with parents, few years later Bruno Bettelheim, a University of Chicago professor and child development specialist facilitated the widespread acceptance of the so-called "refrigerators mothers" theory. In the absence of any biomedical explanation for what causes autism, Bettelheim and other leading psychoanalysts of the epoch supported the notion that autism was the product of mothers who were cold, distant and rejecting. The theory was embraced by the medical establishment and went largely unchallenged into the mid-1960s, with the apex of the Bettelheim's theory that was reached when his book *The Empty Fortress: Infantile Autism and the Birth of the Self* was published in 1967. Many articles and books published in that era blamed autism on a maternal lack of affection, but in 1969, Kanner tackled the refrigerator mother issue at the first annual meeting of what is now the Autism Society of America, by stating:

"From the very first publication until the last, I spoke of this condition in no uncertain terms as 'innate'. But because I described some of the characteristics of the parents as persons, I was misquoted often as having said that 'it is all the parents' fault'."

Fortunately, the modern consensus is that autism is a disorder of the neural development that has a strong genetic basis, although the genetic of autism is complex and not well understood yet (Abrahams and Geshwind, 2008). Even if recent studies have indicated that quality of relationship with mothers are associated with reductions of behavioural problems in adolescents and adults with autism, and that maternal criticisms are associated with maladaptive behaviours and symptoms, these ideas are distinct from the refrigerator mother hypothesis (Smith et al., 2008).

Today, precise behavioural criteria are used for the diagnosis of autism. The most detailed and recent scheme is the one described by the *Diagnostic and statistical manual of mental disorders: DSM-V* (American Psychiatric Association, 2013). There is substantial heterogeneity in the onset of autism. Some children manifest the disorder within the first 18 months of life. However, 25%-40% of children with autism initially demonstrate near-normal development until 18-24 months, when they regress into autism. Generally speaking, the early- and the late- onset types are indistinguishable (Werner and Dawson, 2005).

1.2 Diagnostic criteria for autism spectrum disorder in the DSM-V

In previous version of the *Diagnostic and statistical manual of mental disorders,* the DSM-IV, patients could be diagnosed with four separate disorders: autistic disorder, Asperger's disorder, childhood disintegrative disorder, or pervasive developmental disorder not otherwise specified (American Psychiatric Association, 1994). All these four categories, in the new DSM-V have been merged into a single category that is autism spectrum disorder (ASD).

The new diagnostic criteria for ASD (299.00 [F84.0]) (from the *Diagnostic and statistical manual of mental disorders: DSM-V,* pp. 50-51; American Psychiatric Association, 2013) are:

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):

    1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures: to a total lack of facial expressions and nonverbal communication.

3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 1.1).

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to

specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 1.1).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Table 1.1 Severity levels for autism spectrum disorder according to the DSM-V (American Psychiatric Association, 2013).

Severity level	Social communication	Restricted, repetitive behaviors
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and how has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-for conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

1.3 Co-morbid features of ASD

In addition to the core symptoms of autism, neurological disorders frequently co-occurred (DiCicco-Bloom et al., 2006). The prevalence of mental retardation when the autism spectrum is taken as a whole is closer to 30% (Fombonne, 2006). Epilepsy has long been associated with autism although estimates of the occurrence of seizure disorder vary from 5%

to 44% (Tuchman and Rapin, 2002). Anxiety and mood disorders are also very common (Lecavalier, 2006).

1.4 Prevalence of ASD and the enigma of climbing diagnoses

In the last fifty years there has been a frenetic rise in ASD diagnosis, as recently well reassumed by the freelance writer Karen Weintraub (2011), in a special issue of Nature dedicated to autism. An early study in the mid-60s examined eight- to ten-year-old children in Middlesex, UK, and estimated a prevalence of 4.5 cases per 10,000 children (Lotter, 1966). However, in 1992, 19 cases per 10,000 six-year-old Americans children were being diagnosed as autistic (Newschaffer et al., 2005), but it was in the first decade of the twenty-first century, that the growth in diagnoses has reached its highest peak. According to data from the US Centers for Disease Control and Prevention in Atlanta (Georgia), what is today known as ASD affect more than 90 in 10,000 eight-year-olds in the United States in the year 2006. In other words, ASD is currently affecting 1 in every 110 children (ADDMN Surveillance 2006).

Peter Bearman, a sociologist at Columbia University in New York, has been trying to figure out how much of the increase is driven by social forces. He analysed nearly 5 million California birth records and 20,000 records from the state's department of developmental
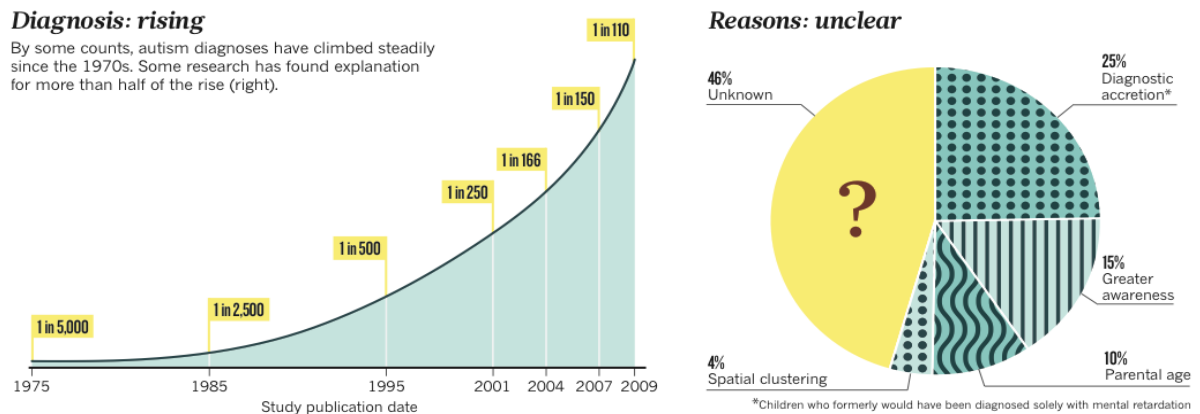
Figure 1.1 Left panel displays the ASD diagnoses increment from 1975 until now. Right panel displays the main factor that, however, only partially can explain the rise. Reproduced from Weintraub (2011).

services. By linking birth with detailed diagnostic data he was able to generate a rich picture of the demographics and life history of those with autism, which yielded clues to the social factors that influence diagnosis, which are summarized in Figure 1.1. Around 25% of the rise in autism can be ascribed to what he calls "diagnostic accretion", referring to the fact some children who would have been diagnosed as mentally retarded ten years ago are now diagnosed with both mental retardation and autism (King and Bearman, 2009). Another 15% can be accounted for by the growing awareness of autism. Simply, more parents and paediatricians are aware of what autism is (King and Bearman, 2011). Moreover, geographic clustering accounts for about 4%. The clearest example lies in and around the hills of Hollywood, California, where children living in a 900-square- kilometre area centred on West Hollywood are four times more likely to be diagnosed with autism than are those living elsewhere in the state (King and Bearman, 2011). The authors suggest the most plausible explanation for the cluster has to do with neighbourliness. Once a cluster of informed parents builds up, specialists are more likely to settle in that area, and as a consequence diagnosing are more common. The last piece of plausibly known reasons, accounting another 10% of the increase, may rely on specific social changes that have also biological implications. People tend to have their children when they are older. Some studies have found that children born to parents older than 35 have a higher risk of being diagnosed with autism (King et al., 2009). In the end, 46% of the increment in autism diagnoses is still far from being explained (Weintraub, 2011).

1.5 Neuropathogenesis of ASD: main hypotheses

Research into the biological basis of ASD is in its infancy; so, current etiological viewpoints are necessarily primitive (Geshwind and Levitt, 2007).

However, recent genetic findings, coupled with emerging anatomical and functional imaging studies, suggest a model that described autism in terms of altered brain connectivity (e.g., Belmonte et al., 2004; Frith, 2004; Geshwind and Levitt, 2007; Rudie and Dapretto, 2013; Casanova and Trippe, 2009). This hypothesis assumes that there is a developmental bias towards the formation of short-range connections due to disruptions of synapse development and function. This would result in excessive activity and overconnectivity within local networks. These networks might become partially isolated, and in turn this would affect the formation of long-range connections and systems governing top-down control and integration. Here after we will examine the main evidence supporting widespread alterations in brain of patients with autism that supports the altered connectivity hypothesis.

1.5.1 Brain overgrowth

One of the most robust findings in the neuropathology of autism is that the brain seems to undergo a period of precocious growth during early postnatal life (for a review see Amaral et al., 2008; see Figure 1.2). These findings have been demonstrated with head circumference measurements (that approximates the total brain volume) and also with magnetic resonance imaging (MRI). Collectively, these studies indicate a period of abnormal brain growth, which begins in the first year of life and results in a persistent enlargement at least through early childhood (Courchesne et al., 2001; Sparks et al., 2002; Courchesne et al., 2003; Dementieva et al., 2005; Hazlett et al., 2006; Dawson et al., 2007). Whether this enlargement persists into later childhood and adolescence is still not clear (Courchesne et al., 2001; Aylward et al. 2002). Similarly, it is not yet clear whether this overgrowth involve equally
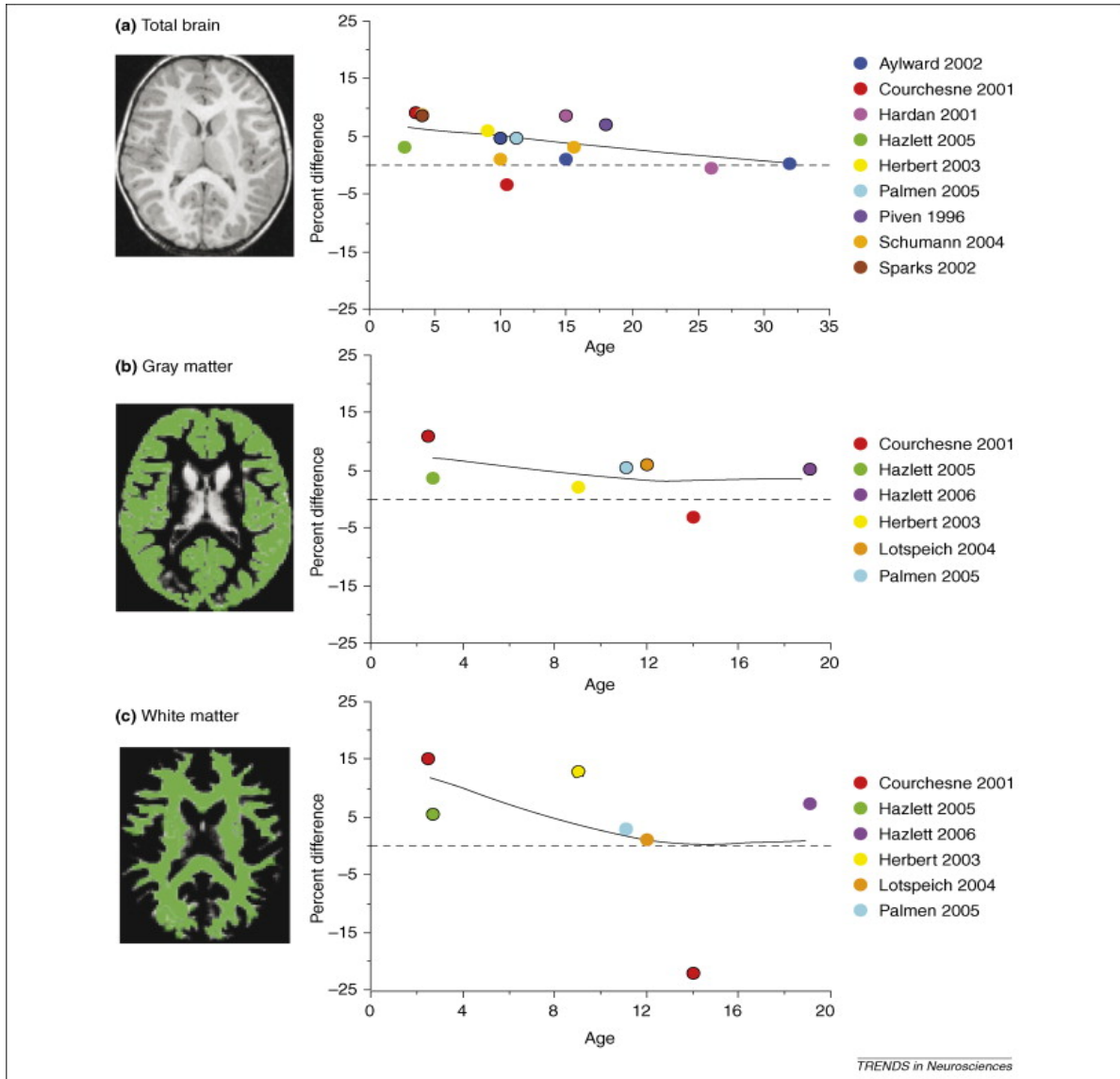
Figure 1.2 Percent difference between ASD and typical development groups with best-fit curves for (a) total brain volume, (b) gray matter and (c) white matter, based on existing MRI literature. Reproduced from Amaral et al. (2008).

the white and grey matter (Amaral et al., 2008). Herbert et al. (2003) postulated that the abnormal brain enlargement observed in children with autism is mainly accounted by an increment of white matter size, not grey matter (in accordance to Courchesne et al., 2001), even if it is not clear whether these increments persist into later childhood and adolescence (Hazlett et al., 2006).

It is important to underline that an ideal study would include a very large sample size of well-characterized individuals, tested at birth and followed longitudinally at least into late childhood or early adolescence. On the contrary, most of the studies in this field are

characterized by small sample sizes and the great majority is limited to cross-sectional design (Brambilla et al., 2003; Amaral et al., 2008).

1.5.2 Minicolumns alteration

As introduced above, current biological research hypothetically suggests that autism involves disruptions of synapse development and function. But how are such disruptions taking place during development? One possibility has been advanced by Casanova and colleagues. They postulated that there are an abnormal number and width of minicolumns in individuals with autism (Casanova et al., 2002, 2006; Buxhoeveden et al., 2006).

Minicolumns are radially oriented arrangements of cellular elements, which have a stereotypical morphometry and are distributed throughout the cortex. They share common input-output operations mediated by recurrent circuits linking translaminar columns of pyramidal neurons (Mountcastle, 1997; Buxhoeveden & Casanova 2002; DeFelipe, 2005). These modules have commonly been considered to represent a canonical microcircuit contained within a defined cylindrical volume (Casanova and Trippe, 2009). Minicolumn formation has been associated with early stages of cortical development when postmitotic neurons ascend in linear arrays along a radial glial scaffolding (Rakic, 1988).

Within the first year of life, there is a dramatic increase in dendritic growth. By 2 years of age, the minicolumns are spaced farther apart with a lower cell density in a given region of cortex. Dendritic bundles and axonal fascicles that extend throughout several layers of the cortex occupy the space between minicolumns. Within the first year of life, there is a dramatic increase in dendritic growth. By 2 years of age, the minicolumns are spaced farther apart with a lower cell density in a given region of cortex. Dendritic bundles and axonal fascicles that extend throughout several layers of the cortex occupy the space between minicolumns (Amaral et al., 2008).

As Amaral and colleagues (2008) recently reviewed, only 14 cases of autism (9 of which had seizures and at least 10 with mental retardation) have been examined for minicolumnar pathology so far. The most consistent finding in these studies is reduced intercolumnar width of the minicolumns (only layer III has been studied so far) in dorsolateral prefrontal cortex or Brodmann's area (BA) 9 (Casanova et al., 2002, 2006; Buxhoeveden et al., 2006). These findings, coupled with increases in neuronal density on the order of 23% noted by Casanova et al. (2006), imply that there should be a greater number of neurons in BA 9 of the autistic cortex. Given the narrower neuropil area between columns, one would also predict a decrease in the dendritic arborization of BA 9 neurons.
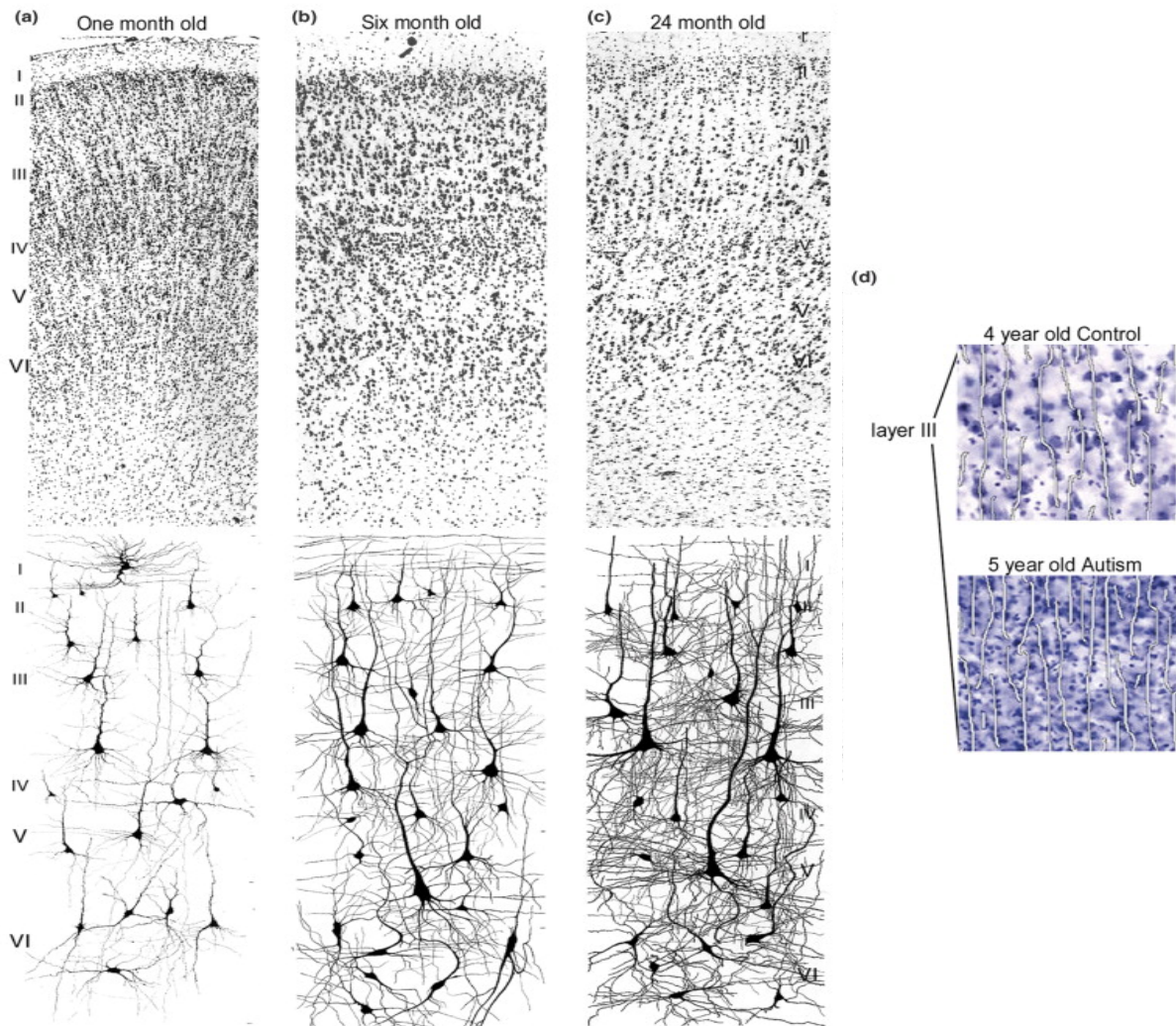
Figure 1.3 Features of neocortical organization potentially altered in ASD. Panels a–c depict cell body-stained sections of BA 9 at 1, 6 and 24 months of age. Below each is a representative Golgi-stained section showing the extent of dendritic growth in this same cortical area over these same ages. Panel d indicates aberrant columnar structure in autism in layer III with less space between cell body-defined minicolumns. Reproduced from Amaral et al. (2008).

It remains to be seen how these findings might relate to pathophysiological processes underlying ASD. One possibility is that the reduced volume of neuropil area between columns indicates reductions in the numbers of radially oriented inhibitory GABA neurons or in the extent of their axonal and dendritic processes. As a result, collateral excitation of neighbouring minicolumns would be increased leading to overconnectivity within local networks (Casanova and Trippe, 2009).

1.5.3 The altered connectivity hypothesis: a puzzling picture

Despite the challenges that remain, in particular the need of clarifying the underline neuronal mechanism that lead to the pattern of altered connectivity, there have been many progresses. As stated above, the original theory regarding brain connectivity in people with ASD claims that there is long distance under-connectivity and local over-connectivity (Belmonte et al., 2004; Frith, 2004; Just et al., 2004; Geshwind and Levitt, 2007; Casanova and Trippe, 2009; Rudie and Dapretto, 2013). This theory seems to be at least partially confirmed by findings of the past decade.

As reviewed by Vissers and colleagues (2012), consistent with the theory, a large body of evidence from fMRI studies showed reduced long-range cortico-cortical functional and structural connectivity appears to be weaker in people with ASD than in controls. On the contrary, in contrast to the theory, there is less evidence for local over-connectivity that was assumed for specific cortical areas, as the frontal cortex, following the results about minicolumns abnormalities (Amaral et al., 2008; Casanova and Trippe, 2009). Interestingly, a recent study by Keown et al. (2013) focused on the local connectivity issue. Several groups have hypothesized that enhanced local circuit connectivity may provide an explanation for the preservation or enhancement of certain cognitive functions in ASD, such as visual or auditory discrimination (Courchesne and Pierce, 2005; Geschwind and Levitt, 2007).

However, few studies have comprehensively addressed whole-brain local connectivity in ASD. Keown et al. (2013) tested adolescents with ASD with a resting state functional connectivity MRI and computed whole-brain maps of local connectivity. They showed an anterior-posterior gradient of local under- to over- connectivity in ASD. Specifically, reduced local connectivity was found in frontal regions and was more pronounced in ASD adolescents with less severe social impairments, whereas occipitotemporal regions showed diffuse overconnectivity, which was more pronounced in individuals with more severe social deficits.

In summary, even if the whole picture of the brain connectivity theory is still not completely delineated, this model offers a good framework to explain both the impairments and the preservation or even enhancement of certain functions, and can also clarify the specificity of deficits observed in the autisms. For this reason it will be one of the leading areas of research in ASD for the near future (Vissers et al., 2012; Rudie and Dapretto, 2013). However, despite some clues, mechanisms relating pathogenesis and altered cell function to the altered connectivity remain unclear (Casanova and Trippe, 2009).

CHAPTER 2 - STATE OF THE ART CONCERNING THE STUDY OF VISUAL ATTENTION IN ASD.

"Millions of items of the outward order are present to my senses which never properly enter into my experience. Why? Because they have no interest for me. My experience is what I agree to attend to. Only those items which I notice shape my mind" *(William James, 1890)*

The visual system has to solve a variety of problems to make sense of a visual scene, and to this aim, we need to detect, localize and identify relevant information. Visual attention plays a fundamental role in this process and has been a matter of study from several centuries. It was originally discussed by philosophers, like Gottfried Leibniz (1646-1716), that introduced the concept of "apperception", referring to an act that is necessary for an individual to become conscious of a perceptual event (Shiraev, 2010).

What captures our attention spontaneously and what we decide to attend voluntary can influence the way we experience and perceive the world around us and impacts the course of brain and behavioural development (Keehn et al., 2013). The primary aim of this chapter is to summarize, without any pretension to be exhaustive, the major findings regarding visual attention in autism spectrum disorder (ASD), in order to progressively introduce the rationale of the present work and the theoretical framework underlying it. But before this, I will briefly introduce the main findings regarding the study of visual spatial attention in typical populations.

2.1 Models of visual spatial attention

Under normal circumstances, the direction of gaze and the direction of visual spatial attention are aligned. But since von Helmholtz (1910) and William James (1890) the potential dissociation between the point of gaze fixation and the focus of attention within the field of view was noted. The first experimental demonstrations of the phenomenon came more recently (Sperling and Melchner, 1978; Posner et al., 1980; Posner and Cohen 1984). The so-called "covert" deployment of spatial attention produces biases in behavioral performance and neural processing of relevant stimuli in the absence of "overt" orienting (i.e., head or eyes movement; Moore et al., 2003). Various model have been proposed by psychologists and neuroscientists to understand how relevant visual information is covertly selected by spatial attention. These models, with certain exceptions for some of their predictions, are not completely incompatible one with the others, but their relations have not been clarified yet.

2.1.1 The "spotlight" and the "zoom-lens" models of spatial attention.

Sokolov (1963) described what he called the "orienting reflex", a mechanism that allow us to identify new elements that has just occurred in the scene in order to prepare the whole organism to react toward it. A series of independent mechanisms would have allowed the orienting reflex to take place, and one of the most important is the orienting of attention to the region of the space where the new element has appeared. This idea by Sokolov gave a substantial contribution for the birth of the "spotlight" metaphor of visual attention, originally postulated by Posner, Snyder, and Davidson (1980). The spotlight model claims that information from one region of the visual field is selected by a mechanism analogous to a spotlight that can moves to a specific region in the visual space. This orienting of the attentional spotlight results in an improvement of information processing in the attended area at the expense of other locations, in other words stimulus detection is faster and its

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discrimination is more accurate (for reviews see Posner and Petersen, 1990; Corbetta and Shulman, 2002; Carrasco, 2011). Moreover, according to Posner (1980) and Jonides (1981), there are two different ways to control the spotlight of attention: i) endogenous (voluntary or sustained), which is determined and controlled voluntary by the subjects, and ii) exogenous (automatic or involuntary), that occurs imperatively following the abrupt onset of a peripheral stimulus.

However, because in everyday life objects have different dimensions, shapes and sizes, the focus of attention need also need to be adjusted in its size. Some years later, the idea that the attentional focus can process information from a broad or a narrow region of the visual field has been added by the "zoom-lens" model of attention (Eriksen and St. James, 1986; Castiello and Umiltà, 1990). This model also predicted an increase of processing efficiency within the focus when the attentional spotlight is decreased in size. In fact, reaction times are faster and discrimination are more accurate while the attentional focus size gets smaller (Eriksen and St. James, 1986; Castiello and Umiltà, 1990).
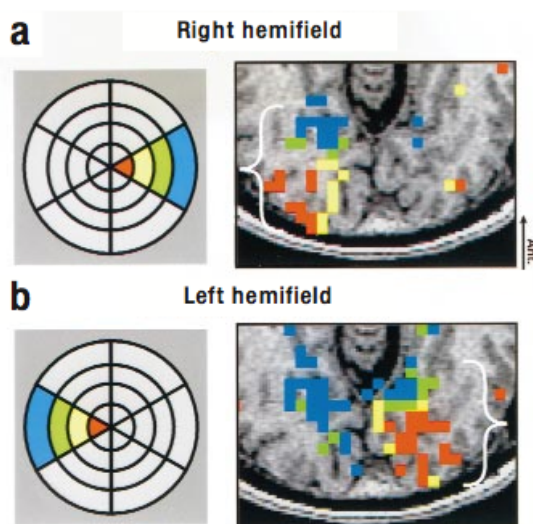
Figure 2.1 Characterization of attentional effects in early visual areas. (a) Retinotopically mapped activation due to shifts of attention into the right visual field. Colors of activated voxels (right panel) correspond to attentional focus (left schematic) that produced greatest modulation. (b) Activation produced by attentional shifts into the left visual field. Reproduced from Brefczynski and DeYoe (1999).

2.1.2 Neurophysiological correlates of the "spotlight" and the "zoom-lens" models.

Both the orienting and the zooming of the focus of attention lead to specific changes in the level of activation in the visual areas.

Neuroimaging (Brefczynski and DeYoe, 1999, Figure 2.1; Gandhi et al., 1999; Somers et al., 1999) and electrophysiological (Hillyard and Münte, 1984; Mangun and Hillyard, 1988; Neville and Lawson, 1987; Rugg et al., 1987; Eimer,

1994; for a review see Luck et al., 2000) studies in humans, as well as single-cell recordings in monkeys (Motter, 1993; Roelfsema et al., 1998; McAdams and Maunsell, 1999; Reynolds et al., 2000) suggest that the behavioral benefits of spatial attention are reflected in stronger activity in early visual areas for attended than unattended stimulus locations. Thus, when subjects orient their focus of attention to a spatial location, neural responses are enhanced for stimuli presented at the attended location, allowing for improved visual performance. Neurophysiological findings following variation of the attentional zoom-lens – though less investigated in the literature – are consistent in showing a precise retinotopic variations of neural activity in accordance to the portion of the visual field that subjects' are attending. Specifically, the spatial extent of activation increases whereas the level of neural activity decreased in the visual cortex as the size of the attended area becomes larger (Müller et al. 2003; Figure 2.2). Electrophysiological studies in human on this topic are only two (Luo et al., 2001; Fu et al., 2005), with discrepant findings (see Chapter 8 for a more extensive treatment of the topic).
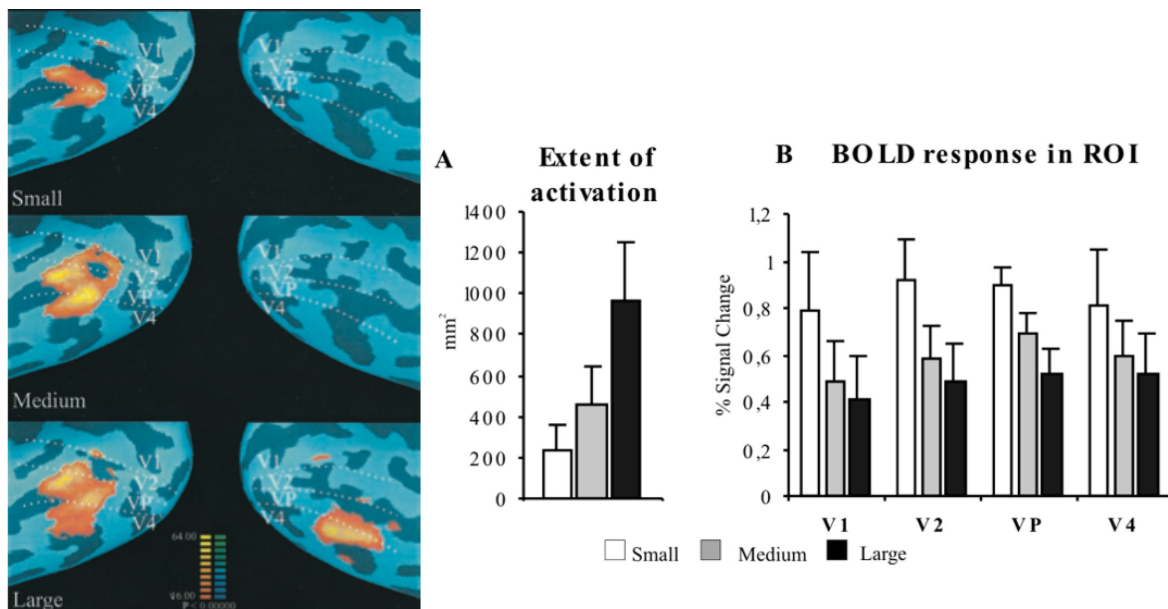
Figure 2.2 Left image: maps of activity in visual areas after the onset of the cue in an attentional zooming task (small cue, first row; medium cue, third row; large cue, fourth row). Right image: (a) extent of activated visual cortex (collapsed across visual areas); (b) peak blood oxygen level dependent (BOLD) responses as a function of the cue size. Reproduced from Müller et al. 2003.

2.1.3 Beyond the spotlight and the zoom-lens: the "Mexican hat" model of the attentional focus.

Both the spotlight and the zoom-lens models predict that the attentional resources decrease monotonically while the distance from the focus of attention increases. However, they do not represent the all picture of how attention selects relevant visual information in a real cluttered visual environment, where objects has to be discerned one another and in which fonts of relevant and irrelevant information may become mixed together. For this reason, in the last years researchers started to investigate how a combination of enhancement and suppression may effectively sharpen the demarcation of relevant from irrelevant inputs. The so-called "Mexican hat" profile of attentional modulation has been originally proposed by Müller and Kleinschmidt (2004), based on the observation that if observers attended to a location in space, responses in early visual areas were higher for stimuli farther from the attended location than relatively close to it. This and other findings are consistent with the idea that spatial attention, in order to enhance relevant visual information and attenuate irrelevant inputs, elicits a zone of attenuated excitability in the immediate surround of its focus (Slotnick et al., 2002; Müller and Kleinschmidt, 2004; Müller et al., 2005; Hopf et al., 2006; Boehler et al., 2011). A further demonstration of the existence of a zone of attenuation surrounding the focus of attention derives from a study by Hopf and colleagues (2006) that employed magnetoencephalographical (MEG) recordings. Observers were asked to attend to a colour pop-out target and probe stimuli appeared soon
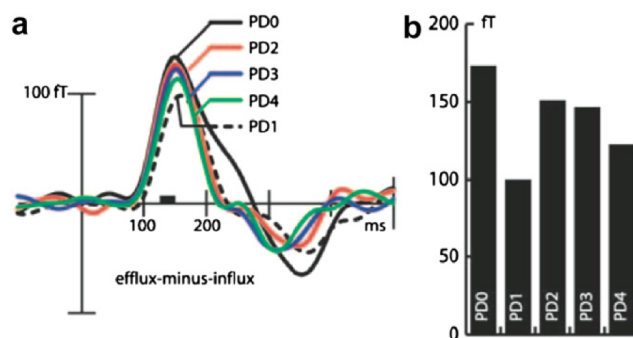
Figure 2.3 (a) Time course of the event-related magnetic field (ERMF) response for each probe distance; PD0: target and probe in the same spatial location; PD1: probe adjacent to the target; PD2-PD4: probe non-adjacent to the target (b) Mean size of the probe-related response between 130 and 150 ms, collapsed across corresponding probe-distance conditions. Reproduced from Hopf et al. (2006).

after at varying distances from the target (were the focus of attention was captured). The electromagnetic response to the probe stimulus was enhanced when the probe was presented at the location of the target, but was suppressed in a narrow zone surrounding the target and then recovered at more distant locations (Hopf et al., 2006; see Figure 2.3).

This centre-surround profile suggests that attending to a stimulus places a ring of inhibition around it, which would be optimal to attenuate the deleterious noise during target identification. These findings are also consistent with the selective tuning model proposed by Tsotsos and colleagues (Tsotsos, et al. 1995, 2001). According this model attention optimizes the search procedure by selectively tuning the visual processing network. Attentional selection operates in the visual cortex based on hierarchical winner-take-all (WTA) processes that propagate in a top-down direction from higher level of the visual hierarchy to lower levels. Connections representing input from irrelevant locations are pruned away from level to level, yielding a pass zone of enhanced activity for connections representing the target/attended input. Connections immediately surrounding the representation of the attended input become suppressed, leading to a profile of cortical responsiveness with an excitatory centre and an inhibitory surround.

2.2 Neural sources of the control of visual attention

Evidence of the network that control the ability to adjust the size of our attentional focus are limited and will be discussed in details on Chapter 8 and 9. Neural mechanisms that control the centre-surround profile of the attentional focus have never been investigated to the best of my knowledge. On the contrary, neural mechanisms controlling the orienting of spatial attention have been a central focus in cognitive neuroscience in the last decade and will be briefly summarized in the following two paragraphs.

2.2.1 Evidence from primate studies.

Much of what is known so far about the neural basis of attention comes from studies of the primate visual system, which has proven to be a highly valuable model (for a recent review see Noudoost et al., 2010; see Figure 2.4). In particular they aimed at identifying neural circuits controlling the "top-down" control (endogenous or voluntary) of spatial attention, which take place according to internal behavioral goals. Mechanisms of "bottom-up" (exogenous or involuntary) spatial attention, which occurs by virtue of a stimulus' physical salience, are less understood in the primate brain (Noudoost et al., 2010).

Figure 2.4 Bottom, Possible routes for attentional signals from frontal and parietal areas (FEF and LIP) to visual area V4. Direct corticocortical projections exist from both the FEF and LIP to most extrastriate areas in which signatures of attention have been observed, including well-studied area V4. Moreover, corticocortical feedback projections throughout the visual hierarchy could propagate a modulatory signal from higher (e.g. V4) to lower (e.g. V1) areas. Top, cytoarchitecture of area V4 and laminar patterns of afferent (left) and efferent (right) connections. Reproduced from Noudoost et al., 2010.

Moore and Fallah (2001) were the first to examine the effect of intracortical microstimulation on visual attention. They found that when neurons within the frontal eye fields (FEF) of the frontal lobe were stimulated using subthreshold currents (too low to evoke saccades), they could enhance a monkey's performance on an attention-demanding task. Another study found that subthreshold microstimulation of sites within the lateral intraparietal area (LIP) reduced reaction times in a cued target detection task, albeit in a non-spatially specific manner (Cutrell and Marrocco, 2002).

Consistent with the above evidence of attention-related effects of FEF microstimulation, a number of subsequent studies have observed modulation of visual cortical responses during microstimulation of the FEF. A brief enhancement of visually driven responses was observed

in receptive fields of area V4 neurons at locations overlapping the stimulated FEF representation (Moore and Armstrong, 2003). In another study that employed functional magnetic resonance imaging (fMRI) to examine the influence of FEF microstimulation on visual activation throughout cortex, Ekstrom and colleagues (2008) found that FEF microstimulation enhanced the visual activation of retinotopically corresponding foci within multiple visual areas, even V1 and V2, which receive little or no direct projections from the FEF (Stanton et al., 1995).

Studies comparing the latencies of top-down attentional modulation across different areas have yielded evidence that is consistent with a fronto-parietal source. FEF neurons achieve this activation first, followed shortly by dorso-lateral prefrontal cortex (dlPFC) neurons and then by LIP neurons (Buschman and Miller, 2007).

2.2.2 Evidence from human studies.

Several evidence indicate that two cortical neural systems are involved in attending to environmental stimuli (Corbetta and Shulman, 2002; Corbetta et al., 2008; see Figure 2.5).

One is the dorsal frontoparietal network, whose core regions include dorsal parietal cortex, particularly intraparietal sulcus (IPS) and superior parietal lobule (SPL), and dorsal frontal cortex along the precentral sulcus, where the frontal eye field (FEF) are located. The current idea is that dorsal system generates and maintains endogenous signals based on current goals and preexisting information about likely contingencies and sends out top-down signals that bias the processing of appropriate stimulus features and locations in sensory cortex. This conclusion is based mainly on the evidence that the dorsal network is preactivated by the expectation of seeing an object at a particular location or with certain features (e.g., movement in a specific direction) (Kastner et al., 1999; Corbetta et al., 2000; Hopfinger et al., 2000). Moreover, recent studies found that magnetic stimulation of FEF or IPS leads to a

retinotopically specific modulation of visual areas and parallel improvement of perception at corresponding locations of the visual field (Ruff et al., 2006, 2008, 2009).

A second system, the ventral frontoparietal network, responds – along with the dorsal network – when behaviourally relevant objects (or targets) are detected (Corbetta et al., 2000). Core regions of the ventral network include temporoparietal junction (TPJ) cortex – defined as the posterior sector of the superior temporal sulcus (STS) and gyrus (STG) and the ventral part of the supramarginal gyrus (SMG) – the ventral frontal cortex (VFC, including parts of middle frontal gyrus or MFG), inferior frontal gyrus (IFG), frontal operculum, and anterior insula (Corbetta and Shulman, 2002 for a review).

Both dorsal and ventral networks are also activated during reorienting of attention (disengagement from a previously cued location and orienting toward a new one), with enhanced responses during the detection of targets that appear at unattended locations. For example, enhanced responses are observed when subjects are cued to expect a target at one location but it unexpectedly appears at another (i.e., ''invalid'' targets in the Posner spatial cuing paradigm) (Arrington et al., 2000; Corbetta et al., 2000; Macaluso et al., 2002; Kincade et al., 2005; Vossel et al., 2006).

While segregation between dorsal and ventral attention networks is nearly complete, spontaneous activity in right posterior MFG correlates with both networks, indicating that right MFG may contain intermixed neuronal populations respectively connected with dorsal or ventral regions (Fox et al., 2006). This result raises the possibility that ventral and dorsal networks do not directly interact but are principally linked through prefrontal cortex (Fox et al., 2006).
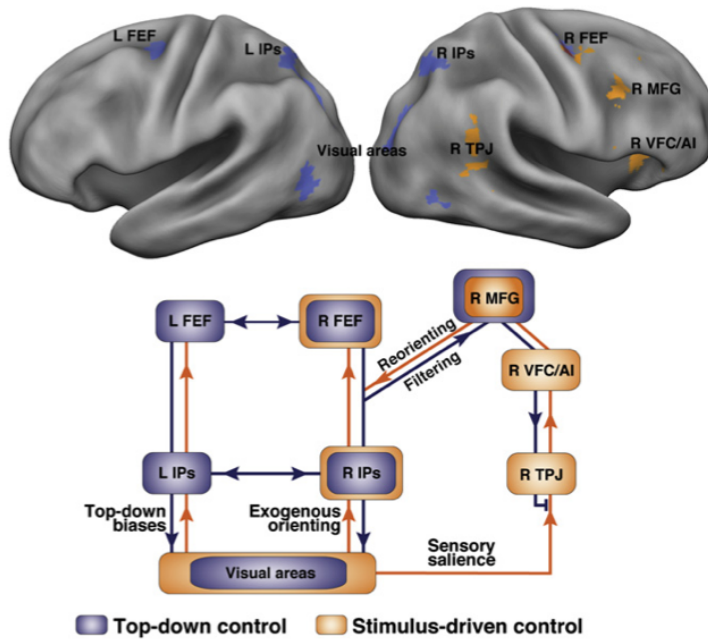
Figure 2.5 Definition of dorsal and ventral networks for the control of visual attention. (Top panel) Regions in blue are consistently activated by central cues, indicating where a peripheral object will subsequently appear or what is the feature of an upcoming object. Regions in orange are consistently activated when attention is reoriented to an unexpected but behaviorally relevant object. (Bottom panel) Model for the interaction of dorsal (blue) and ventral (orange) networks during stimulus-driven reorienting. Dorsal network regions FEF and IPS send top-down biases to visual areas and via MFG to the ventral network (filtering signal), restricting ventral activation to behaviorally important stimuli. IPS-FEF are also important for exogenous orienting. Overall, the dorsal network coordinates stimulus-response selection. Conversely, when a salient stimulus occurs, the ventral network sends a reorienting signal to the dorsal network through MFG. Reproduced from Corbetta et al. (2008).

Although an early theory of how the two networks interact (Corbetta and Shulman, 2002) proposed that the division between ventral and dorsal network may reflect the psychological distinction between exogenous (bottom-up) and endogenous (top-down) orienting, recent claims hypothesized that a more fundamental distinction appears to be between systems involved in orienting and those involved in re-orienting (Corbetta et al., 2008). While the orienting of attention, both exogenous and endogenous would recruit the dorsal attention system, when we have to reorient our attention because a relevant stimulus appear on the environment, the ventral and dorsal attention systems interact to perform this operation. Even if the nature of this interaction is still not completely clarified, according to Corbetta and colleagues (2008), the current idea is that when subjects focus on a task, TPJ (ventral network) is deactivated, thus preventing reorienting to distracting and irrelevant events (Shulman et al., 2007). When behaviourally-relevant environmental stimuli appear on the scene, the ventral network promote the reorienting (Downar et al., 2001; Serences et al., 2005) and the source of the filtering signal that distinguish between relevant and irrelevant inputs may be the dorsal network or other parts of pre-frontal cortex (Kastner et al., 1999; Corbetta et al., 2000; Shulman et al., 2003).

2.3 Why do we need to study visual attention in ASD?

Attentional abnormalities have been associated with the disorder since its first description by Kanner (1943). For example, reporting some notes on the behavior of his study case 6 (Virginia), Kanner (1943, p. 231) wrote:

"There are times, more often than not, in which she is completely oblivious to all but her immediate focus of attention."

This sentence perfectly depicts the fact that many patients with ASD appear to focus their attention intensely only on some element of the environment while ignoring surrounding contextual information (Schreibman & Lovaas, 1973; Lovaas et al., 1979).

After the first seminal investigations (for an early review see Lovaas et al., 1979), in the last two decades a large body of evidence has described attentional abnormalities in ASD, both in terms of dysfunctions and superiorities (for recent review see Ames and Fletcher-Watson, 2010; Keehn et al., 2013). Importantly, atypical attentional functioning has been shown in infants at-risk for ASD (because they have an older sibling diagnosed with ASD), and may be one of the earliest characteristics that distinguish infants who later receive an ASD diagnosis (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013).

These findings suggest that lower-level attentional processes may impact the development of higher-level sociocommunicative functions. Thus, understanding the nature of these abnormalities may help to elucidate atypical trajectories of attentional development in ASD, and furthermore, how these attentional abnormalities may contribute to the manifestation of the core symptoms in ASD. Understanding if early attentional impairments can be one of the factors that are causally involved in the development of ASD, is important for at least three reasons: i) attentional deficits may be used as an early marker to identify ASD in the first

year of life (Elsabbagh et al., 2013); ii) the development of attention-targeted early interventions that – even during infancy (Wass et al., 2011) – may remediate abnormal developmental trajectories and improve outcomes in children with ASD, and; iii) a precise clarification of attentional abnormalities can be the starting point for modelling atypical neural circuitries that characterize the autistic brain.

2.4 Abnormalities of visual spatial attention in ASD

2.4.1 The attentional spotlight in ASD: evidence for slow orienting and impaired disengagement.

As recently reviewed by Keehn and colleagues (2013), in children, adolescents, and adults with ASD orienting abilities have been measured using various spatial cuing paradigm derived from the original paradigm by Posner (1980). The common procedure is to compare response latencies to target at a validly cued versus an invalidly cued location ("cuing effect" or "validity effect"), so that we can measure the time course of the operations that the focus of attention performs.

Townsend et al. (1996) found slower orienting in adults with ASD compared to typical individuals. Automatic/exogenous orienting seems to be more impaired than voluntary/endogenous shifts of attention (Ristic et al., 2005; Renner et al., 2006; Grubb et al., 2013), although there is some conflicting evidence (Pruett et al., 2011). As theorized by Posner and colleagues (1980), attentional orienting involves also the ability to disengage attention from a previously
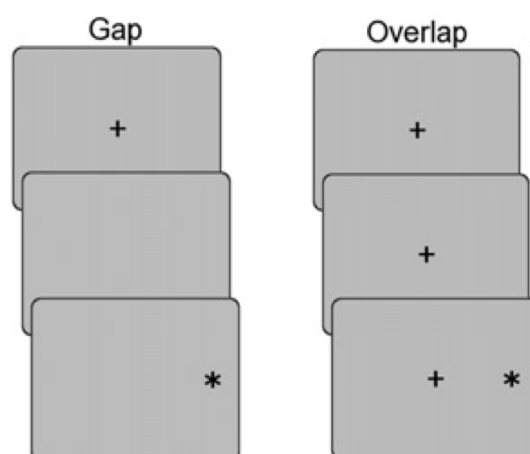
Figure 2.6 A gap-overlap task where a target can occur after fixation offset (gap), with the fixation remaining on screen (overlap). Readapted from Keehn et al. (2013).

cued location, in order to shift and re-engage our focus of attention onto a new location or object of interest. Disengagement efficiency in ASD has been tested mainly by examining saccadic responses in the "gap-overlap" paradigm (Kingstone and Klein, 1993; Figure 2.6). In this paradigm, targets appear in the periphery of the visual field under two different conditions. An overlap condition, when a central stimulus (e.g. the fixation cross) remains on the screen when the peripheral target appears, and a gap condition, when the central stimulus disappears prior to the target onset. These two conditions are usually compared (the measure is technically called "the gap effect") to obtain an index of the disengagement ability.

Landry and Bryson (2004) examined the disengagement ability in children with ASD, and two groups of age matched children with Down's syndrome or with typical development. The authors demonstrated that the ASD group showed significantly increased latencies to disengage visual attention (on overlap trials) compared to both comparison groups. Additionally, the authors report that the frequency of fast attentional shifts (i.e., the number of shifts with latency between 100 and 300 ms) for the gap condition was significantly reduced in the ASD group, suggesting that in addition to difficulty disengaging attention on overlap trials, children with ASD did not efficiently shift attention to the target, even when disengagement mechanisms were not competing with the central stimulus. Impaired disengagement has also been confirmed by other groups and in low-functioning adults with ASD (Wainwright-Sharp and Bryson 1993; Courchesne et al. 1994; Kawakubo et al., 2007).

Importantly, disengagement inefficiency has been demonstrated also in infants at risk for developing ASD (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013). In particular, a recent longitudinal study by Elsabbagh et al. (2013) demonstrated the relationship between disengagement of visual attention in infancy and later autism in toddlerhood. At 14 months, longer latencies to disengage was observed in a subset of the high-risk group later diagnosed with ASD at 36 months, relative to other infants at risk and the low-risk control group.

2.4.2 The attentional zoom-lens in ASD: evidence for a "zoom-out" impairment

Although several studies investigated the attentional orienting in ASD as summarized in the previous paragraph, less evidence exist on the ability to adjust the size of the attentional focus. In a first study by Burack (1994) participants (four mental-age matched groups composed by children with autism, with mental retardation and with no handicap) performed a forced-choice reaction time (RT) task to assess the filtering component of selective attention. The independent variables were the presence/absence of a window that narrowed the attentional focus (zoom-in), the number (zero, two, or four) and the location of distractors. The RTs of the subjects with autism improved relative to the other groups in the presence of the window without distractors, but this effect was negated when distractors were also presented. Performance of the autism group was, indeed, the most impaired in the presence of distractors. These findings represent a behavioral evidence of an inefficient broad attentional lens among persons with autism. In the second study, Mann and Walker (2003) employed a paradigm requiring participants to make a judgment about which one of the two pairs of cross-hairs was the longer. Participants with ASD were less able than comparison group in making this judgment only when the previous pair of cross-hairs was smaller than the one to be judged. The authors argued that individuals with ASD have a difficulty in the zoom-out of the attentional focus.

The findings of Mann and Walker (2003) were recently confirmed by a study performed in our laboratory. Ronconi and colleagues (2013b; Figure 2.7) tested participants with ASD in an attentional zooming paradigm where attentional resources were narrowed (zoom-in) or distributed (zoom-out) in the visual field with a small (containing only the nearest target eccentricity) or large (containing also the farthest target eccentricity) cue. Typically developing children, at the short cue-target interval, showed a "gradient effect" (i.e., increasing response latency with increasing eccentricity) in the small but not in the large

condition, indicating efficient zoom-in and zoom-out attentional mechanisms. In contrast, children with ASD showed a gradient effect also in the large focusing cue condition, suggesting a specific zoom-out attentional impairment. In addition, at the long cue-target interval the ASD group showed an atypical gradient effect in the small cue condition, suggesting a prolonged zoom-in and a sluggish zoom-out attentional mechanism.

In a following study (Ronconi et al., 2012), this zoom-out impairment was found to be associated with the inability to discriminate coherent motion information (for a review see Grinter et al., 2010). Moreover, the inability to zoom-out the attentional focus was found to be positively associated with ASD symptoms' severity (Ronconi et al., 2012). The finding of a relationship between poor coherent motion perception and zoom-out impairment is particularly important, since difficulties in perceiving coherent motion are representative of the so-called "weak central coherence" (Happé and Frith, 2006). In the visual domain the weak central coherence of individuals with ASD lead to a strong tendency toward the processing of details at the expense of the global configuration (for reviews see Dakin and Frith, 2005; Simmons et al., 2009).

Thus, the zoom-out attentional impairment can be one of the main factors underlying detail-oriented perception and poor integration abilities that characterizes the perception in ASD.
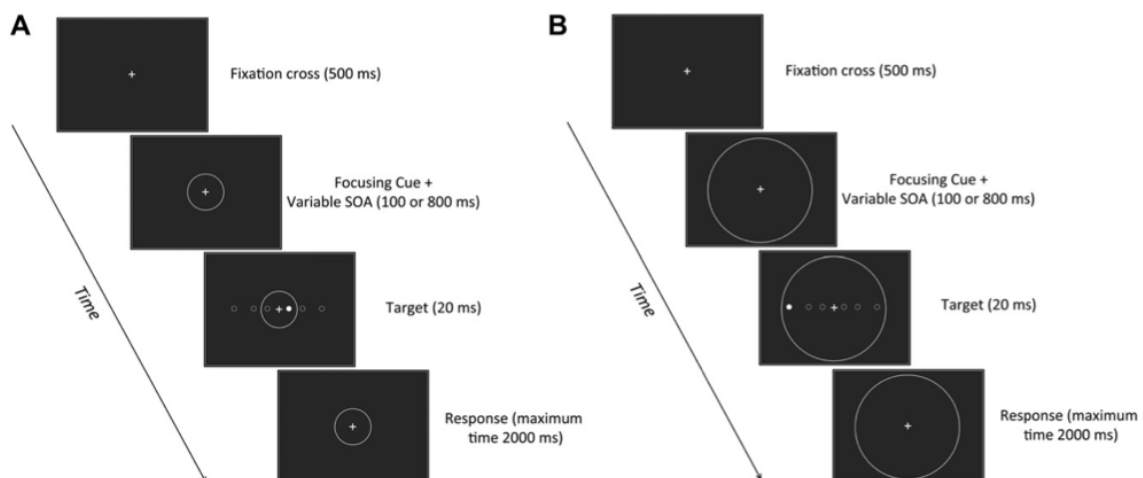
Figure 2.7 Attentional zooming paradigm. Representation of experimental sequences in the small (a) and in the large (b) cue condition, testing zoom-in and zoom-out attentional mechanisms, respectively. Target could appear in one of the six locations depicted along the horizontal axis and participants are required to simple detect it by pressing the response key. Reproduced from Ronconi et al. (2013b).

CHAPTER 3 - AIMS OF THE PRESENT STUDY

The general objective of the present doctoral thesis is to contribute to a better understanding of visual attentional abnormalities in individuals with autism spectrum disorder (ASD), both at behavioral and neurophysiological level. Each study will have its own specific introduction part with a clear statement of the hypotheses. Here, I would like just to briefly summarize the rationale behind each study.

As we see in the previous Chapter, both orienting and zooming of visual attention have found to be compromised in ASD. In particular, deficits are present in rapid orienting and disengaging of attention (for a review see Keehn et al., 2013), as well as in zooming-out the size of the attentional focus (Mann and Walker, 2003; Ronconi et al., 2012; 2013b). Though the orienting and zooming components have always been investigated separately in ASD population (but the same could be said for the typical population), an ecological examination of the deployment of visual attention should involve both processes. The aim of the first study (Chapter 4) is to investigate the relationship between the orienting and the zooming components of the attentional system in a group of children and adolescents affected by ASD. Specifically, we aimed to evaluate possible differences in the time course of attentional orienting and re-orienting between ASD and typically developing (TD) groups as a function of the size of their attentional focus.

In Chapters 5 and 6, we present two studies that tested a new approach for the early identification of ASD neurocognitive markers. Attentional dysfunctions appear to be one of the earliest cognitive markers of children with ASD, and research in this area has greatly improved in recent years (for a review see Jones et al., in press). Early symptoms are evident not only when infants at-risk are compared with the control groups in their ability to attended

to the social scene (Chawarska et al., 2013), but also when they have to disengage visual attention in non-social context (Elsabbagh et al., 2013). The current strategy to identify early markers of the condition is to study infants siblings of older children with a diagnosis of ASD, which are at higher risk to develop the condition relative to the general population (Bolton et al. 1998). In two studies we tested a new and relatively lower cost strategy that together with study of infants sibling can inform this emerging area of research. Neurocognitive dysfunctions associated with autism can be found not only in affected individuals but also – thought in milder form – in individuals from the general population that has never received an ASD diagnosis and these findings support the idea that ASD is the upper extreme of a constellation of traits that may be continuously distributed in the general population (Dawson et al. 2002). For this reason, and considering the strong genetic basis of the disorder (Abrahams and Geshwind, 2008), we investigated in the general population, the relationship between infants' attentional functioning and the autistic traits measured in their parents. In the first infants study (Chapter 5) we employed a classical Posner cuing task to assess the orienting of visual attention in infants and their relationship with autistic traits in their parents. In the second infants study (Chapter 6), we used the same approach but this time the focus was on the infants' ability to adjust the attentional focus size. The attentional "zoom-lens" has never been tested in infants so far, so we created a paradigm suitable to evaluate this fundamental component of the attentional system at early stages of development.

Another major section of the present doctoral thesis (Chapters 7 and 8) is focused on the neural mechanisms involved in the control of the attentional focus size. As previously introduced, individuals affected by ASD show impairments when they have to enlarge their focus of attention in its size (i.e., attending a broad portion of the visual field). A precise clarification of neural areas underlying attentional abnormalities found in ASD can be the

starting point for modelling atypical attentional circuitries that characterize the autistic brain. That is why it is important to clarify the network of brain areas involved in the attentional operation that are compromised in ASD. Despite several studies investigated neural sources of the control of the attentional orienting (for reviews see Corbetta and Shulmann, 2002; Corbetta et al., 2008; Noudoost et al., 2010), limited evidence are present regarding the control of the attentional zoom-lens. In Chapter 7, we employed transcranial magnetic stimulation (TMS) in typical adult participants to elucidate the neural areas involved in the control of the attentional zoom-lens. TMS is a focal brain stimulation technique that can be used to induce a transient interference with normal brain activity in a relatively restricted area of the brain (Walsh and Cowey, 2000). We focused on the frontal eye fields (FEF) area, that it is clear from the evidence discussed in the previous chapter that in both humans and animals is vital for mediating spatial attention. In Chapter 8, neural dynamics involved in the control of the attentional zoom-lens was investigated with a more explorative approach with high-density electroencephalography (d-EEG). First, analysis of the event related potential (ERPs) allowed us to reveal the electrophysiological correlates of processing target with a narrow or broad attentional focus. Second, neural sources estimation from d-EEG was performed in the cue-target interval (where participants adjust their focus of attention to the cued dimension) to elucidate the network of brain areas, without strong a priori as in the TMS study, involved both in the zoom-in and the zoom-out of the attentional focus.

Finally, in Chapter 9, we went one step beyond the two models of visual spatial attention (spotlight and zoom-lens) mainly adopted so far in the study of ASD, in order to precisely define the spatial profile of the attentional focus in ASD. Both the spotlight and the zoom-lens models, indeed, predict that attentional resources decrease monotonically while the distance from the focus of attention increase. However, they don't represent the complete picture of how attention selects relevant visual information in the environment. Recent

neurophysiological evidence (Müller and Kleinschmidt, 2004; Hopf et al., 2006, 2010) demonstrate that visual search requiring spatial scrutiny for object recognition elicits – in the immediate surround of the attentional focus – a zone of attenuated excitability forming a "Mexican-hat" profile (Müller and Kleinschmidt, 2004; Müller et al., 2005). The attenuated excitability in the immediate surround of the attentional focus would be optimal to highlight relevant information and attenuate the deleterious noise during the selection of relevant visual target (Hopf et al., 2006).

CHAPTER 4 - RELATIONSHIP BETWEEN ORIENTING AND ZOOMING MECHANISMS IN ASD

4.1 Introduction

It is well known that perception of relevant information is mediated by visual attention, as extensively described in Chapter 2. Traditionally, the attentional focus has been compared to a "spotlight", that can moves to a specific region in the visual space, improving information processing in the attended area at the expense of other locations (Posner, 1980; Posner and Petersen, 1990; Corbetta and Shulman, 2002; Carrasco, 2011). In addition, the attentional focus can be adjusted in its size in order to process information from a broad or a narrow region of the visual field – as proposed by the "zoom-lens" model of attention (Eriksen and St. James, 1986; Castiello and Umiltà, 1990; Turatto et al., 2000).

ASD has been repeatedly associated with different types of dysfunctions in spatial attention (for reviews see Ames and Fletcher-Watson, 2010; Keehn et al., 2013) and the idea that people with ASD pay attention to the world differently, and that this might contribute to abnormalities in visual perception (Dakin and Frith, 2005; Simmons et al., 2009) and consequently in higher-level cognitive domains (Mundy, 2003; Mundy and Newell, 2007) is one of the most intriguing aspects of current ASD research. On the one hand, studies that evaluated the "spotlight" (i.e., orienting) efficiency in ASD found impairments in rapid orienting (Townsend et al., 1996) as well as in disengaging attention from a previously attended location (Wainwright-Sharp and Bryson, 1993; Courchesne et al., 1994; Landry and Bryson, 2004). Recently, a longitudinal study in a cohort of children at risk for ASD demonstrated that this disengagement deficit of visual attention discriminated 14-month-old infants who later manifest an ASD in toddlerhood (Elsabbagh et al., 2013). On the other

hand, studies that evaluated the "zoom-lens" (i.e., zooming) efficiency in ASD found that the disorder seems to be associated to impairment in "zooming-out" the attentional focus, namely the ability to spread attentional resources in a broad portion of the visual field (Mann and Walker, 2003; Ronconi et al., 2012, 2013b).

The orienting and the zooming mechanisms, though with a certain degree of independence (Castiello & Umiltà, 1992; Turatto et al., 2000; Fu et al., 2005), normally cooperate to select visual information that is relevant to our current behaviour. This cooperation allows us to plan accurate eye-movements, targeting the source of relevant information, as suggested by the premotor theory of attention (Rizzolatti et al., 1987). Although the orienting and the zooming components have been mainly investigated separately, an ecological examination of the deployment of visual attention should involve both the orienting and the zooming mechanism. First, because in the case of ASD impairments on both mechanisms have been documented as stated above. Second, because the deployment of visual attention is highly flexible and can adapt to various task demands to select relevant stimuli in a diverse range of spatial configurations (McMains and Somers, 2005). Previous studies by Castiello and Umiltà (1990, 1992) showed that typical adult subjects can maintain two attentional foci in non-contiguous regions of the visual field and can also vary their sizes in accordance with task demands. More recently, McMains and Somers (2004) confirmed the existence of multiple spotlight of attentional selection in visual cortex by using functional magnetic resonance imaging (fMRI). These findings determined that the orienting and the zooming mechanisms efficiency can be evaluated simultaneously in a single paradigm. To this aim, in the present experiment we modified the classical spatial cuing paradigm (Posner, 1980). Two small or large cues were initially presented at opposite sides of the visual hemifield. Subsequently, one of these cues was briefly flashed to manipulate its spatial validity. In valid trials the target appeared at the cued location while in invalid trials attention was captured in

the opposite hemifield. Neutral trials were also employed, and in this case both cues were flashed and consequently no information on the target location was provided. The two groups of participants comprised adolescents affected by ASD and typically developing (TD) peers matched for age and cognitive level. The analysis of the "cuing effect" (CE; i.e., difference in reactions times between invalid and valid trials) at different inter-stimulus interval (ISI) allowed us to evaluate possible differences in the time course of attentional orienting and re-orienting between ASD and TD groups as a function of the size of their attention foci. Since orienting and zooming of the attentional focus are not completely independent (Castiello and Umiltà, 1992; Fu et al., 2005), the deficit in zooming-out the attentional focus (Mann and Walker, 2003; Ronconi et al., 2012, 2013b) should amplify the problem in orienting and disengagement that was previously observed in ASD (Wainwright-Sharp and Bryson, 1993; Courchesne et al., 1994; Landry and Bryson, 2004; Elsabbagh et al., 2013).

4.2 Methods

4.2.1 Participants

Forty-four children took part in the experiment. Both the ASD and TD groups comprised 22 children each. All participants with ASD were recruited according to the following criteria: (i) full scale IQ > 70 as measured by the Italian version of Wechsler Intelligence Scale for Children-Revised (WISC-III, Wechsler, 1991); (ii) absence of gross behavioural problems; (iii) normal or corrected-to-normal vision and hearing; (iv) absence of drug therapy; and (v) absence of attention deficit hyperactivity disorder on the basis of DSM-IV criteria (American Psychiatric Association, 1994). Children with ASD were recruited at the Developmental Neuropsychology Unit of Scientific Institute "E. Medea" (Bosisio Parini, Italy) and at "Associazione La Nostra Famiglia" (Padua, Italy). Diagnosis of ASD was made by licensed clinicians experienced in the assessment of ASD in respect to DSM-IV diagnostic criteria and

to the Autism Diagnostic Observation Scale (ADOS; Lord et al., 2002). Children of the TD group were randomly sampled in Padua public schools. According to the parents' report, TD children did not have prior history of any psychiatric disorders. Both groups were matched for chronological age ($t_{(42)}$=-0.62, p=.535). Cognitive level in TD children was estimated with two Verbal (Vocabulary and Similarities) and two Performance (Block Design and Pictures Completion) subtests of the WISC-III (Wechsler, 1991). ASD and TD group did not differed in any of the four subtests (all ps>.113). The Social Communication Questionnaire (Rutter et al., 2003) was also administered to both groups. Children of the ASD group scored significantly higher in comparison to the TD group in both the Current ($t_{(42)}$=9.41, p<.001) and Lifetime ($t_{(42)}$=16.64, p<.001) forms. For details about participants' characterization see Table 4.1.

The entire research protocol was approved by the ethical committees of both Scientific Institute "E. Medea" and Department of General Psychology of Padua University. Informed consent was obtained from each child and their parents and the research was conducted in accordance to the principles elucidated in the declaration of Helsinki.

Table 4.1 Descriptive statistics of participants. ASD=Autism Spectrum Disorder; TD=Typically Developing.

	ASD (n=22)	TD (n=22)	p-value
	Mean (SD)	*Mean (SD)*	
Age	13.9 (2.7)	14.4 (2.6)	n.s
Gender	19 M	18 M	-
TIQ	95.5 (17.9)	-	-
WISC III - Vocabulary	9.8 (3.7)	10.0 (2.4)	n.s.
WISC III - Similarities	9.9 (3.4)	9.9 (2.4)	n.s.
WISC III - Picture completion	9.8 (3.8)	11.4 (2.4)	n.s.
WISC III - Block Design	9.8 (3.8)	10.8 (2.4)	n.s.
Social Communication Questionnaire (SCQ) - Current	12.5 (6.9)	3.14 (3.2)	<.001
Social Communication Questionnaire (SCQ) - Lifetime	19.3 (8.7)	2.7 (2.5)	<.001
ADOS - Communication	3.2 (1.8)	-	-
ADOS – Social Interaction	5.7 (3.1)	-	-

4.2.2 Apparatus and stimuli

The experiment was conducted in a dimly lit and quiet room. Participants were seated 50 cm far from an LCD screen (17 inch, 75 Hz). A chinrest was used to avoid head movement. Stimulus presentation and data acquisition were performed with E-Prime 2 (Psychology Software Tolls, Inc.). The choice about stimuli parameters was based on previous pilot observations.

All stimuli were middle grey (RGB: 128, 128, 128) presented on a black background. Fixation point consisted in a cross subtending a visual angle of 0.5 deg, presented on the screen center. To manipulate the size of the attentional focus two pairs of circle with different dimension were presented both on the left and right side of the fixation point, at an eccentricity of 9.6 deg from the fixation point. In the small cue condition there were two circles with a diameter of 2.17 deg, whereas in the large cue condition there were two circles with a diameter of 6.35 deg. The target stimulus was a small dot (diameter=1.5 deg) and appeared in the center of the two cues.

4.2.3 Procedure

Children were instructed to keep their eyes on the fixation for the entire duration of the trial. Each trial started with the onset of the fixation cross. After 500 ms, two small or large circles were presented at both the left and right side of the fixation. After 500 ms from the presentation of the circles, one or both of them were briefly thickened for 50 ms, resulting in a rapid flash. In the valid trials, the circle flashed on the same side of the target. In the invalid trials, the circle flashed on the opposite side of the target. In the neutral trials, circles flashed at both sides. The temporal interval or interstimulus interval (ISI) between the offset of the cue and the target onset was randomly chosen between 100, 400 or 700 ms. After this variable ISI, the target appeared on one side for 20 ms. Notably, the cue was completely not informative about the target location (valid cues indicated the correct target position with a probability of 50%). Participants were asked to press the space bar as soon as they see the target appearing. Catch trials, in which the stimulus was not presented and the participant did not have to respond, were intermixed with response trials.

The entire experiment consisted of 198 trials, randomly intermixed. Precisely, 180 response trials (2 cue-sizes by 3 cue-condition by 3 ISI, each repeated 10 times) and 18 catch trials. At the end of each trial a blank screen was presented until the experimenter pressed the mouse button to start the next trial.
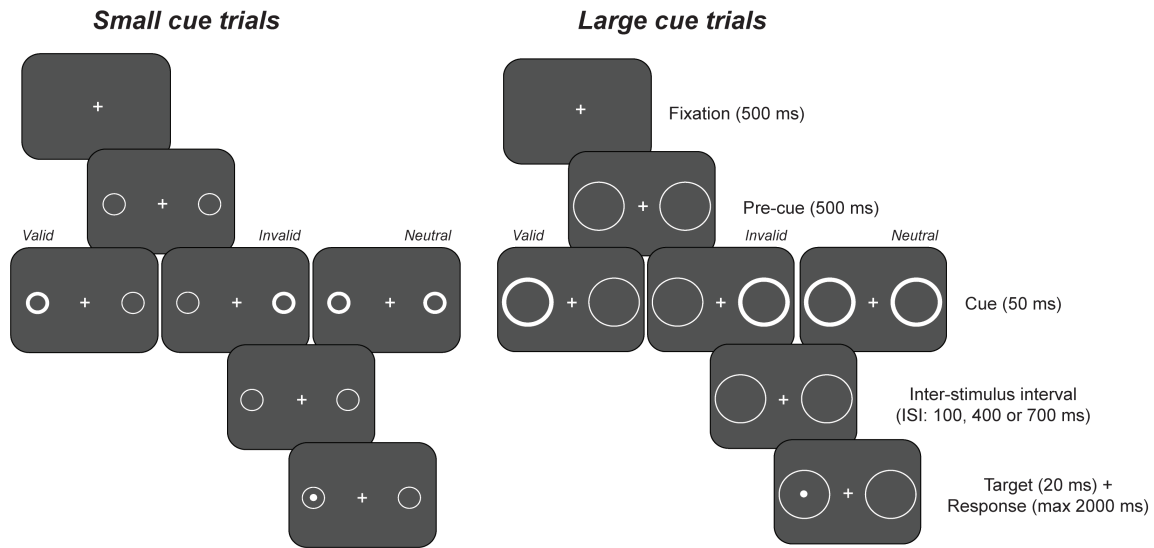
Figure 4.1 Schematic representation of the task procedure.

4.3 Results

4.3.1 Cuing effect

Reaction times (RTs) of accurate trials (filtered between 150 and 1200 ms) were used to compute the cuing effect (CE), that is the difference in RTs between invalid and valid trials and a commonly used index of the attentional orienting ability. The CE was then analysed with a 2×3×2 mixed design analysis of variance (ANOVA) with one between-subjects factor, the group (ASD vs. TD), and two within-subjects factors: the cue size (small vs. large) and the ISI (100, 400 and 700 ms). ANOVA revealed a main effect of ISI ($F_{(2, 84)}$=12.01, p<.001, η^2_p=.22), showing that overall mean CE varied as a function of the cue-target ISI (mean±SEM: ISI 100 = 13.61±6.18; ISI 400 = -2.24±6.97; ISI 700 = -31.81±6.53). Importantly, a significant cue size by ISI by group interaction emerged ($F_{(2, 84)}$=3.43, p=.037, η^2_p=.08), suggesting that the time course of the CE was different in the two groups relative to the cue size displayed. To further explore this three-way interaction we performed two distinct ISI by group ANOVA, one for the small and one for the large cue condition. ANOVA performed in the small cue condition showed only a main effect if ISI ($F_{(2, 84)}$=5.83,

p=.008, η^2_p=.11) but no interaction. In contrast, ANOVA performed in the large cue condition revealed both a main effect of ISI ($F_{(2, 84)}$=11.25, p<.001, η^2_p=.21) and a significant ISI by group interaction ($F_{(2, 84)}$=3.98, p=.022, η^2_p=.09; ; see Figure 4.2). A series of planned comparisons was then performed for both groups on the mean CE values to test the difference against μ=0 (absence of cuing effect, i.e. no difference between valid and invalid trials). In the TD group, trials with ISI=100 ms showed a significant positive difference as compared to 0 ($t_{(21)}$=2.03, p=.027), no difference at ISI=400 ms ($t_{(21)}$=-1.49, p=.152), and a significant negative difference at ISI=700 ms ($t_{(21)}$=-3.77, p=.001). In the ASD group, trials with ISI=100 ms did not show a significant difference as compared to 0 ($t_{(21)}$=.24, p=.812), while a positive difference emerged at ISI=400 ms ($t_{(21)}$=2.35, p=.028), and a significant negative difference at ISI=700 ms ($t_{(21)}$=-3.11, p=.005). Moreover, a significant difference emerged also when the CE at ISI=400 ms was compared between the two groups (t-test for independent sample: $t_{(42)}$=2.70, p=.010).
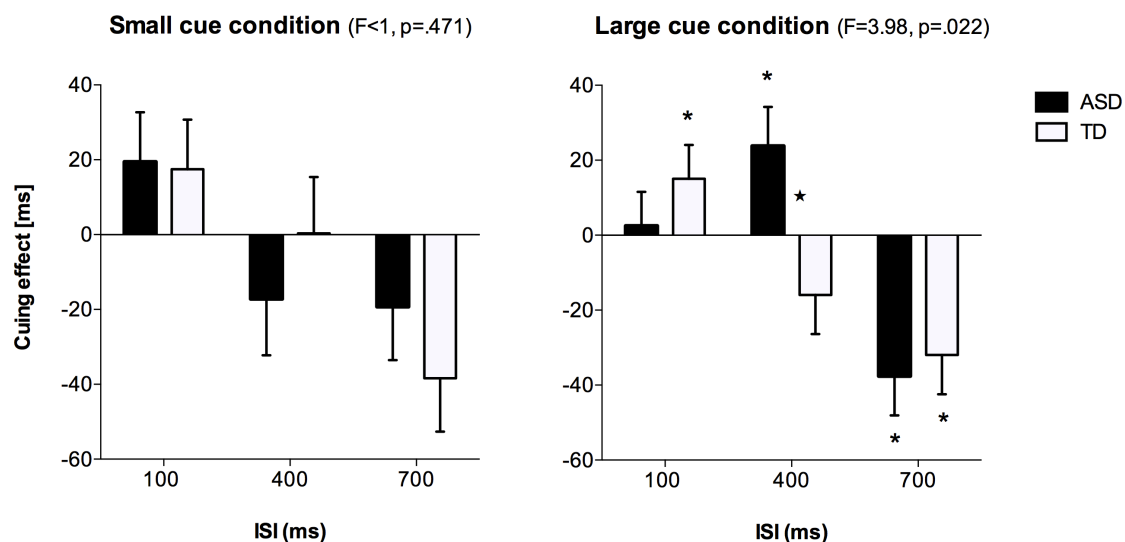
Figure 4.2 Bar plot showing the mean cuing effect (difference in RTs between the invalid and valid trials) as a function of group, inter-stimulus interval (ISI) and cue-size condition (small vs. large). In the large cue condition, the significant two-way interaction ISI by group was explored by the means of planned comparisons. *=p<.05 resulting from one-sample t-tests against 0; *=p<.05 resulting from independent sample t-test (ASD vs. TD).

4.3.2 Correlation between cuing effect and the autistic symptomatology

We considered the possible relationship between the individual cuing effects in the large cue condition and the ASD symptomatology measured by the ADOS (Lord et al., 2002). Partial correlation was performed to control for the effect of age, and the results showed that individual cuing effect at ISI=100 was negatively correlated with ADOS Social Interaction score ($r_{(22)}$ = -.422, p=.025; see Figure 4.3).

These results show that the sluggish attentional orienting exhibited by the ASD group in the large cue was associated with autistic symptomatology, so that slower attentional modulations corresponded to more severe problems in social interaction.
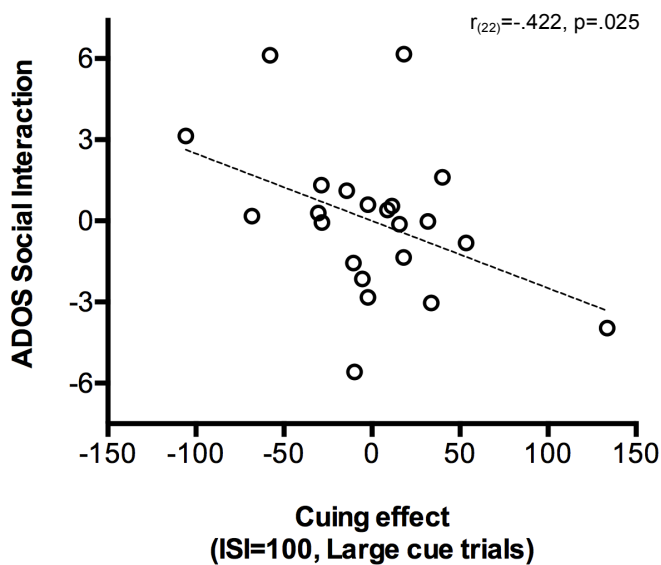
Figure 4.3 Scatterplot showing the relationship between individual cuing effect in the large cue trials (ISI=100 ms) and the ADOS Social Interaction subscore.

4.4 Discussion

In the present experiment we studied the relationship between orienting and zooming attentional mechanisms in adolescents affected by ASD and TD peers. Previous studies suggest that both functions are compromised in ASD, impaired rapid orienting and disengagement characterize the former mechanism (Wainwright-Sharp and Bryson, 1993;

Courchesne et al., 1994; Landry and Bryson, 2004; Elsabbagh et al., 2013), while an impaired zoom-out characterizes the latter one (Mann and Walker, 2003; Ronconi et al., 2012, 2013b).

Our results showed that in the small cue condition, where the two attentional foci had initially to be zoomed-in and then oriented toward the position indicated by the cue, the time course of attentional orienting was not different between the two groups. At the first ISI (100 ms), a positive cuing effect (RTs for valid trials were faster then RTs for invalid ones) suggests participants' attention was rapidly oriented toward the cued hemifield. At the intermediate ISI (400 ms), the cuing effect decayed (no difference between valid and invalid trials and at the third ISI (700 ms) a negative cuing effect emerged (invalid trials were faster relative to valid trials), thus resulting in the typical inhibition of return (IOR). IOR is a bias against directing attention to a previously cued location and it is a well-established sign of attentional re-orienting from the original cued position (first described by Posner and Cohen, 1984; for a review see Klein, 2000).

Interestingly, the two groups differed in their performance in the large cue condition. Here, the two attentional foci had initially to be zoomed-out and then oriented toward the cued position. In this case we found evidence of a different time course of attentional orienting between the two groups. The TD group showed a pattern of results very similar to what observed in the small cue condition: facilitation at the first ISI and a significant IOR at the third one, with a nulled cuing effect at the intermediate ISI. On the contrary, in the ASD group, the facilitation did not emerge at the first ISI but only at the intermediate one, thus revealing a specific sluggish attentional orienting only if an attentional zoom-out was required. At the third ISI, there was no difference between groups and both showed a significant IOR.

This evidence was supported also by a significant negative correlation between the individual rapid orienting ability in the large cue condition (individual cuing effect at ISI=100 ms) and the ADOS Social Interaction score, which measured the severity of autistic symptomatology in the social domain. The more impaired they were in orienting after the zoom-out the more severe was their impairments in social interaction. On the contrary, when the focus of attention had initially to be zoomed-in, no difference between ASD and TD groups emerged.

A plausible explanation of the present results is that while TD can efficiently orient their attentional focus both when narrow or broad portions of the visual field have to be attended, individuals affected by ASD suffer from a sluggish zoom-out of the attentional focus and this is likely to impact serially also other operations that focus of attention has to perform, in this case the orienting toward the cued location. Even if previous studies about zooming in ASD required the manipulation of the size of a single focus, the problem does not seem to rely on splitting attention between two foci (Castiello and Umiltà, 1992; McMains and Somers, 2004), since there was no difference between group when attention had initially to be zoomed-in, but only when it had initially to be zoomed-out.

To conclude, these results are important as they confirm previous findings of an impaired/sluggish zoom-out of the attentional focus in ASD obtained by other researchers (Mann and Walker, 2003) and in our own laboratory in an independent sample of children (Ronconi et al., 2012, 2013b). Moreover, the present findings have important implication for the studies of the orienting abilities in ASD. All attentional cueing paradigms, indeed, allow a fine grained analysis of the time course of attentional processing and enable researchers to identify components of attention that are impaired in ASD. However, as shown by Ames and Fletcher-Watson (2010; see also Keehn et al., 2013) in their recent review, there are a number of inconsistencies in this body of research. Potential methodological sources of this inconsistency, among others, may include the size of the attentional focus that participants

have to orient in the visual field. When a broad portion of the visual space has to be attended, difficulties in orienting the focus of attention can be only a mere consequence of difficulties in zooming-out the attentional focus size.

CHAPTER 5 - THE ORIENTING MECHANISM IN 8-MONTH-OLD INFANTS AND ITS RELATIONSHIP WITH THE BROADER AUTISTIC PHENOTYPE (BAP).

5.1 Introduction

As summarized in Chapter 2, people with ASD show dysfunctions not only when "zooming out" their attention to spread it over a broad portion of the visual field (Mann and Walker, 2003; Ronconi et al., 2012, 2013b), but also in quickly orienting (Townsend et al., 1996) or disengaging attention from a previously cued location (Wainwright-Sharp and Bryson, 1993; Courchesne et al., 1994; Landry and Bryson, 2004).

Attentional dysfunctions in ASD are not limited to visuo-spatial domains. Electrophysiological studies, among others, have demonstrated atypical alerting mechanisms in individuals with ASD (Courchesne et al., 1985; Ciesielski et al., 1990; Bruneau et al., 2003; Orekhova et al., 2009; for a review see Keehn et al., 2013), as well as in 10-month-old infants at risk of developing the disorder (McCleery et al., 2009).

These findings converge with the neuroconstructivist approach that suggests development plays a crucial role in phenotypic outcomes, and tiny variations in an initial state could cause marked differences in end states (Karmiloff-Smith, 1998). Some authors suggest high-level social impairment may spring from early impairments in other low-level attentional systems (Landry and Bryson, 2004; Elsabbagh et al., 2009). According to this view, inflexible spatial attention in early development could impair later visual orienting toward social stimuli (Mundy and Newell, 2007; Elsabbagh and Johnson, 2010). Therefore, current ASD research

has tried to identify neurocognitive markers for early detection of this disorder, studying the attentional mechanisms exhibited in infancy.

Since ASD is highly heritable, the most frequent approach is the study of infant siblings of older children with autism, which are at high risk of developing this disorder (Bolton et al., 1998). The infants show similar impairment to their siblings in disengaging visual attention in a "gap-overlap" paradigm (Elsabbagh et al., 2009).

Siblings are part of the broader autism phenotype (BAP), in which ASD represents the upper extreme of a constellation of traits that may be continuously distributed in the general population (Dawson et al., 2002). Therefore, neurocognitive dysfunctions associated with autism can be found not only in affected individuals but also in their genetic relatives (Dawson et al., 2005; Belmonte et al., 2010), many of whom have social and communication impairments similar to those in ASD, but in milder form.

Studies quantifying autistic traits have found that people score higher when they have a family history of ASD (Bishop et al., 2004). Importantly, children whose parents show high but subthreshold presence of autistic traits have, in turn, more prevalent autistic traits (Constantino and Todd, 2005).

People with elevated autistic traits show abnormalities not only in the high-level social domain, but also in low-level visual attention and perception. For example, they outperform individuals with low autistic traits in tasks requiring detail-oriented perception (Almeida et al., 2010), and tolerate a higher amount of perceptual load in visual tasks (Bayliss and Kritikos, 2011), but do not easily identify coherent motion (Grinter et al., 2010) or the global level of a hierarchical Navon stimuli with strongly salient local components (Sutherland and Crewther, 2010).

The present study aims to test a new approach to identify possible early markers of ASD. We hypothesized that traits for autism in adults from the general population could be related to

abnormalities in attentional functioning measured in their 8-month-old offspring. To verify this, we studied the relationship between infants' ability to deploy attention, in both space (visual orienting) and time (alerting), and autistic traits their parents self-reported in the Autism Quotient questionnaire (AQ; Baron-Cohen et al., 2001).

Efficiency of attentional systems is crucial to explore the environment for further processing and learning (Petersen and Posner, 2012). In particular, early dysfunction of orienting and alerting skills might contribute to the atypical development of joint attention and consequently to impairment in social cognition (Mundy, 2003). Orienting and alerting systems develop dramatically in the first year of life (Johnson et al., 1991; Hood, 1995). Infants get faster at paying attention to a location: the efficiency of neural circuits controlling these mechanisms improves over the first six months of life (Johnson and Tucker, 1996; Richards, 2003, 2005). Orienting and alerting have been consistently associated with the right ventral frontoparietal network in adults (Corbetta and Shulman, 2002, 2011)

Here, by using an eye-tracker system, we tested infants with a spatial cueing task (Posner, 1980). A visual target was presented after the onset of a spatiotemporal cue that could be: (i) valid, indicating where the target would appear; (ii) neutral, providing no information on the target location; and (iii) invalid, directing attention away from the target location. By calculating differences in the time to target fixation (TTF) between invalid and valid trials, we can estimate the efficiency of attentional orienting. We also employed two stimulus onset asynchronies (SOAs): short (84 ms) and long (168 ms). These measured the time course of orienting as well as the alerting system's efficiency, that is, the phasic arousal state that involves temporal preparation for response to an expected signal or event.

As discussed above, we hypothesized that a high level of autistic traits in parents could be related to infants' impairment. More specifically, we looked for impairment in: i) rapid attentional orienting (measured by TTF difference between invalid and valid trials with the

short SOA); ii) disengagement of attention from a previously cued location (measured by invalid trials with the long SOA) and; iii) the alerting mechanism (overall difference between the two SOAs). Given that both ASD and sub-clinical autistic traits are more prevalent in male than female subjects (Baron-Cohen et al., 2001, 2011; Constantino and Todd, 2003; Amaral et al., 2008), it is reasonable to postulate that infants' attentional abilities will show stronger association with paternal autistic traits than maternal ones.

5.2 Methods

5.2.1 Participants

Twenty-six 8-month-old infants (13 females, mean age = 249 days, range = 235-262 days) and their parents comprised the final sample. Eight infants were observed but excluded from the final sample because of uninterpretable eye-movement data resulting from poor calibration of the point of gaze (n = 4) or general fussiness (n = 4). The mean parent age was 35 for mothers (range = 27-42 years) and 37 for fathers (range = 28-47 years), and all were biological parents. The inclusion criteria for all participants were that infants were born at full term, in good health, with no sensorial or neurological disorders. Infants were tested only after their parents gave informed consent. The departmental ethical committee approved the present study, and all research was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

5.2.2 Infants' spatial cueing task

5.2.2.1 Apparatus

The stimuli were presented with E-Prime 2.0 software on a 19-inch monitor (resolution 1024 x 768 pixels). A remote, pan-tilt infrared eye-tracking camera (Model 504, Applied Science Laboratory, Bedford, MA) using bright-pupil technology was directly below the stimulus

screen, recording participants'
eye movements at 50 Hz. An
experimenter guided the eye-
tracking camera by remote
control, keeping the
participants' eyes in focus. A
television monitor displayed
the eyes, simplifying this
procedure. To coordinate eye
movement data with respective
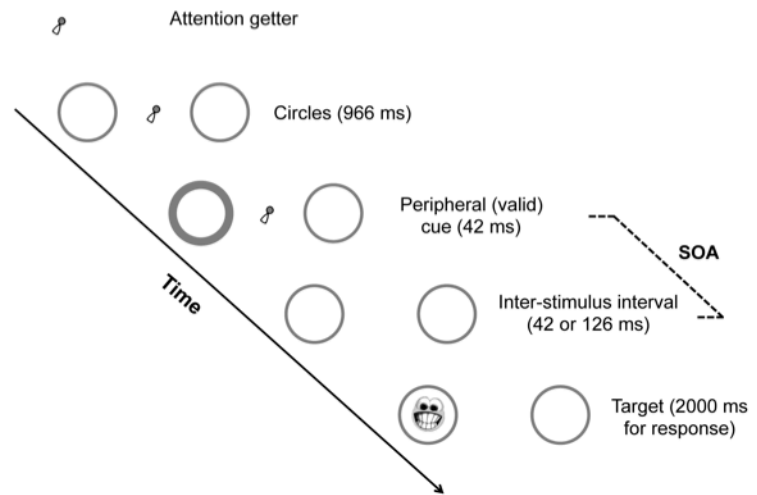
Figure 5.1 Schematic representation of a valid cue condition of the infants' spatial cueing task. Cue-target SOA = stimulus onset asynchrony = interval between cue and target.

stimulus displays, the stimulus-generating computer sent unique, time-stamped numerical

codes via parallel port to the data-collecting computer, indicating the onset and type of

stimulus display. The digital data, indicating the fixation locations and changes in locations

of the eye, were calculated in relation to the centroids of the pupils and the corneal

reflections, using the Applied Science Laboratories' algorithm.

5.2.2.2 Stimuli and Procedure

The infants sat in an infant car seat 60 cm from the stimulus monitor. Parents usually sat

behind the infant. Before experimental trials began, the stimulus monitor presented animated

cartoons (accompanied by a sound) at three different locations (centre, top left, and bottom

right) to calibrate the eye tracker. All subsequent eye data were calculated from these

calibration values. The cartoon directed the infant's gaze to the centre as the test began. A

dynamic stimulus is usually adopted with infants of this age because it easily triggers their

attention (e.g., Johnson & Tucker, 1996; Elsabbagh et al., 2009).

As soon as a participant looked at the central fixation point for 300 ms, two coloured circles (6°) were automatically presented peripherally (11° of eccentricity, with the two edges of the circles separated by 16°), one on the left and one on the right of the central attention-getter, on a black background (see Figure 5.1). Four different colours of circles (red, green, yellow and blue) and four different attention-getters, randomly presented during the trial, were chosen to sustain infants' attention. The circles appeared for 966 ms while the cartoon remained in the centre. It is worth to note that the cartoon's movement and sound made it much more triggering than the peripheral static circles. Therefore, central and peripheral stimuli were unbalanced, reducing the possibility of eye movements toward the peripheral circles. A cue, the thickening of one of the two circles (from 0.2° to 0.7°), then appeared for 42 ms in addition to the cartoon. This brief change did not let the infant orient eye movement toward the cue (i.e., covert attention; Richards, 2001). Moreover, the presentation of the cue at the same time as a dynamic central fixation stimulus helped prevent saccades to the peripheral cue (e.g. Johnson & Tucker, 1996). Valid cues (thickening in the same circle as the target), neutral cues (consisting in the thickening of both circles, providing no information on the target location), or invalid cues (thickening the circle that did not include the target), were randomly intermixed. Finally, the visual target, a smiling and flickering schematic face the visual target, consisting in a smiling and flickering schematic face (3.2°, flickering at 1 cycle of 168 ms, 64 ms on - 64 ms off, 5.95 Hz), appeared after one of two intervals (84 or 168 ms). One out of four different target types was randomly presented during each trial. The target remained visible until the participant glanced at it or for a maximum of 2 s. This terminated the trial, and another trial began at the central attention-getter. Each infant received 60 trials divided into three blocks. Each block consisted of 8 valid, 8 invalid and 4 neutral trials, for a total of 24 valid trials (12 for each cue-target SOA), 24 invalid trials (12 for each cue-target SOA), and 12 neutral trials (6 for each cue-target SOA).

5.2.2.3 Data analysis

The display was virtually divided into 3 square areas of interest (AOI); one surrounded the position of the central attention-getter, and two corresponded to the two circles. Each AOI measured approximately 7.8° on each side. Time to target fixation (TTF) was a dependent variable (fixation threshold settings: duration > 100 ms, max displacement < 1° of visual angle).

5.2.3 Evaluation of self-reported autistic traits in parents

Both parents of each participating infant completed a paper version of the AQ questionnaire (Baron-Cohen et al., 2001); higher scores correspond to elevated ASD traits. In addition to the *total score*, we also computed five sub-scores: (i) *social skill*; (ii) *attention switching*; (iii) *attention to detail*; (iv) *communication;* and (v) *imagination*.

5.3 Results

5.3.1 Infants' spatial cueing task

A mean of 27.5 trials (standard error mean, SEM = 1.97) were excluded from statistical analysis because: (i) the infant did not look at the central AOI at the onset of the cue and the target, (ii) the infant looked outside the AOI that contained the target, (iii) the infant oriented toward the peripheral target within the first 100 ms after its onset (anticipatory eye-movements), or (iv) the signal of the eye tracker was lost during the stimuli presentation. The final number of trials in which infants correctly detected the targets was (mean and SEM) 32.5 ± 1.97. For the shorter SOA (84 ms) valid trials were 6.31 ± 0.43, neutral ones were 3.08 ± 0.32, and invalid ones were 6.73 ± 0.46; for the longer SOA (168 ms), valid trials were 6.85 ± 0.42, neutral ones were 3.08 ± 0.28, and invalids ones were 6.58 ± 0.46. We analyzed corrected TTF using a repeated-measures ANOVA with a 3×2 design, in which the within

subjects factors were the cue condition (valid, neutral and invalid) and the cue-target SOA (84 and 168 ms). The ANOVA revealed a main effect of cue-target SOA ($F_{(1,23)}$ = 18.28, $p <$ .001, η^2_p=.44), showing that the mean TTF were faster (312 ± 10 ms) at the longer SOA than in the shorter one (362 ± 10 ms). The main effect of cue condition was also significant ($F_{(1.37,31.48)}$ = 13.2, $p < .001$, η^2_p=.36), showing that mean TTF varied with the condition of the cue (299 ± 8, 334 ± 15 and 379 ± 13 ms, respectively for valid, neutral and invalid cue condition). The SOA by cue condition interaction was not significant ($F < 1$, η^2_p=.001; see Figure 5.2).
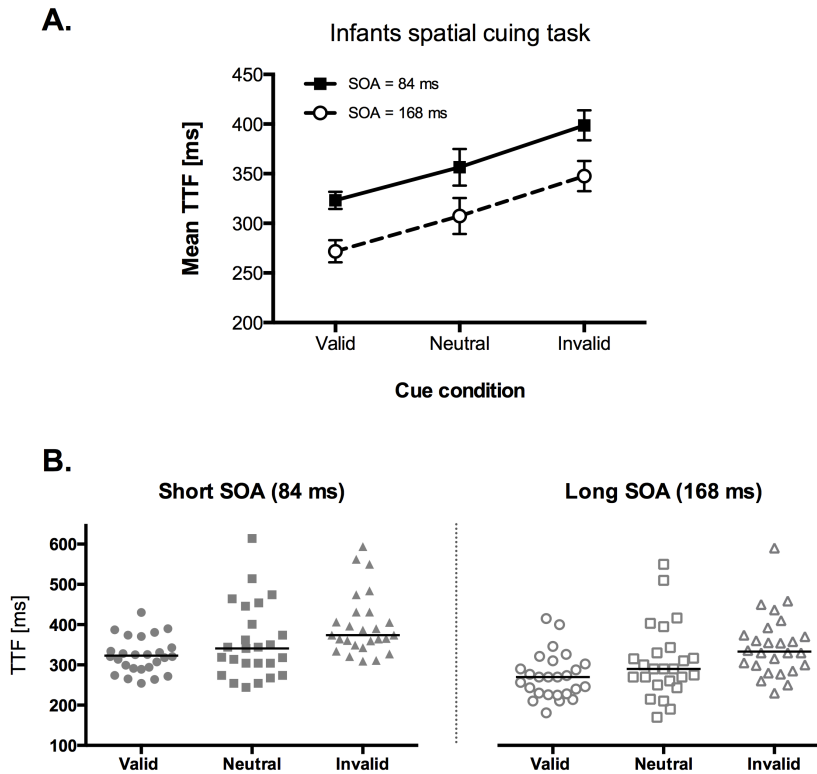
Figure 5.2 a) Results of the infants' spatial cueing task where TTF (time to target fixation) is plotted as a function of cue condition and cue-target SOA (stimulus onset asynchrony). Bars represent the SEM. b) Scatter plot showing the individual mean TTF separated for cue condition and SOA. Horizontal lines represent the medians.

5.3.2 Relationship between attention in infants and parents' autistic traits

Infants' TTF in the spatial cueing task were correlated to the amount of self-reported autistic traits exhibited by their parents. In line with the hypotheses in the Introduction, we used the following variables from the infants' cueing task: (i) the *rapid orienting index,* or the average difference between TTF under invalid and valid conditions at the short cue-target (SOAs, 84 ms), which measures the ability to use the spatial information provided by the peripheral cue to rapidly and automatically orient visual attention; (ii) the *raw TTF in the invalid condition* at the long cue-target SOAs (168 ms), which measures the ability to disengage attention from a previously cued location; and (iii) the *alerting index,* the difference in TTF across all cue conditions between short and long cue-target SOAs, which measures the ability to prepare a rapid response to the target stimuli after getting the temporal cue.

We found a significant positive correlation between the TTF on the invalid cue condition at the second SOA (168 ms) and AQ attention to details sub-scores ($r_{(24)}$ = .42, p < .05). The higher the attention to detail reported by fathers, the slower their infants were to look away from a previously cued location. We also found a negative correlation between the rapid orienting index and AQ communication sub-scores ($r_{(25)}$ = -.56, p < .05): higher communication problems reported by fathers corresponded to lower rapid orienting skill in their infants. Finally, a significant negative correlation between the alerting index and AQ attention to details sub-scores ($r_{(24)}$ = -.47, p < .05), shows that higher autistic traits corresponded to inefficient alerting skill.

In order to control for the paternal age effect (Parner et al., 2012) as a potential mediator or confounder of these relationships between paternal autistic traits and infants' attention, we performed three two-step fixed-entry multiple regression analyses, with paternal age always as a predictor in the first step.

In the first regression analysis, the predictor in the second step was the AQ attention to details sub-score, while the dependent variable was TTF in the invalid cue condition at 168 ms cue-target SOA. Overall the regression model accounted for 17% of the variance (p < .05). The AQ attention to details entered last accounted for 17% (F change$_{(1,23)}$ = 4.85, p < .05) of unique variance of TTF in the attentional disengagement index (see Figure 5.3, panel A).

In the second regression analysis, the dependent variable was the rapid orienting index, while the AQ communication was the predictor in the second step. The entire model accounted for 35% of the variance (p < .01). The AQ communication sub-scores entered last accounted for 19% (F change$_{(1,23)}$ = 6.45, p < .05) of the unique variance of the rapid orienting index (see Figure 5.3, panel B).

In the third regression analysis, the dependent variable was the alerting index, while the AQ attention to details was the predictor in the second step. The entire model accounted for 26%

of the variance ($p < .05$), and the AQ attention to details sub-scores entered last accounted for 19% (F change$_{(1,21)}$ = 5.22, $p < .05$) of the unique variance of the alerting index (see Figure 5.3, panel C).

Interestingly, we did not find any significant results (all $ps > 0.05$) when exploring the relationship between maternal autistic traits and their offspring's attentional indexes.
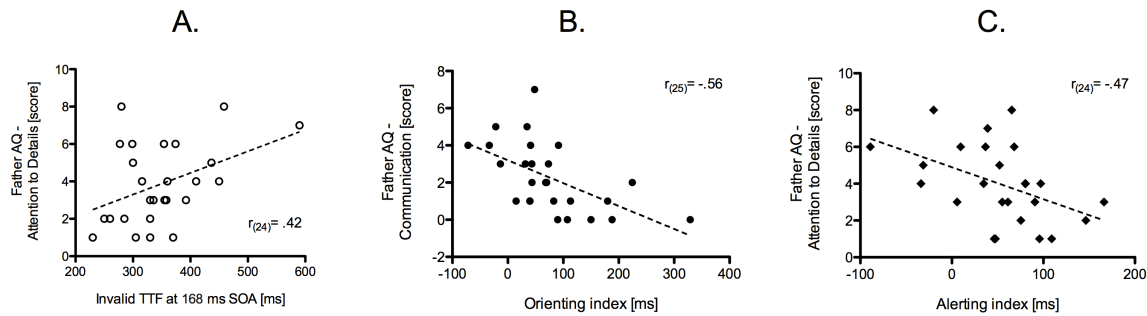
Figure 5.3 Correlation plots of: a) the relationship between the invalid cue condition of spatial cueing task in infants and the paternal AQ attention to details sub-score; b) the relationship between the rapid orienting index of spatial cueing task in infants and the paternal AQ communication sub-score; c) the relationship between the alerting index (difference between TTF at the first and at the second cue-target SOA) of spatial cueing task in infants and the paternal AQ attention to details sub-score.

5.4 Discussion

In the present study, we investigated a new approach for the identification of neurocognitive markers that, together with the study of infant siblings, might help to characterize the early developmental course of broader phenotype of autism. We hypothesized a relationship between the attentional functioning of 8-month-old infants and the autistic traits in their parents. Our results show that different aspects of attentional deployment in infants were related to autistic traits in their fathers.

Specifically, we found that TTF on the invalid cue condition at the long cue-target interval was associated with higher levels of attention to details in the fathers. Since the invalid cue condition measures the ability to disengage and re-orient the focus of attention (Posner, 1980), this evidence agrees with findings of impairments in that ability, demonstrated not

only in the ASD population (Wainwright-Sharp and Bryson, 1993; Courchesne et al., 1994; Landry and Bryson, 2004), but also in infant siblings of children with ASD (Elsabbagh et al., 2009), and, more importantly, in infants who later develop ASD (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013; Sacrey et al., 2013). Trying to identify the possible mechanism connecting the infants' ability to disengage/re-orient the focus of attention and the greater attention to details manifest in fathers is not easy, given that also within the ASD population this relation in not fully understood (for a discussion see Keehn et al., 2013). Fischer and Breitmeyer (1987) showed that the exploration of visual environment by the means of saccadic eye movement is strictly in relation to mechanisms of visual attention. During the engagement phase of visual attention, indeed, saccades are inhibited, thereby providing steady fixation. The inefficiency of the attentional disengagement could therefore be linked to "sticky" attention in a limited portion of the visual field, that could lead in turn to greater attention to the detailed aspects of visual input. Accordingly, children affected by ASD show a specific impairment in zooming out the attentional focus (Mann and Waler, 2003; Ronconi et al., 2013b), which is linked to their social-communicative impairments and global integration deficit of dynamic information (Ronconi et al., 2012).

Paternal autistic traits were also related to the rapid orienting index (i.e., TTF difference between the invalid and the valid trials at the short cue-target SOA), which measures the ability to use a peripheral and transient spatial cue to rapidly shift visual attention to the cued location. Higher communication difficulties reported by fathers were related to smaller rapid orienting indexes in their infants. This evidence agrees with Wainwright-Sharp and Bryson (1993), who found that a group of high-functioning adolescents with autism did not show a cueing effect when the cue was presented for 100 ms, indicating an inability to process rapidly presented spatial cues. This absence of cueing effect suggests a possible disorder of right frontoparietal network in children with ASD (Belmonte et al., 2010; Ronconi et al.,

2012, 2013b). Visual sensitivity to peripheral cues, indeed, induces automatic orienting of attention mainly controlled by the right frontoparietal network (Saalmann et al., 2007; Corbetta and Shulman, 2011; Ronconi et al., 2014a). Visual orienting is a basic element for the development of joint attention (Mundy and Newell, 2007). This idea is supported by previous studies showing that the degree of which attention is captured by changes in the visual environment (Butterworth and Jarrett, 1991) – as well as by changes in head/gaze direction of the caregiver (Butterworth and Grover, 1990) – influence joint attention abilities. Moreover, joint attention have been linked to language and communication development, as research in typically developing infants and toddlers demonstrated (Carpenter et al., 1998). In sum, we can reasonably speculate that parents with poor communication abilities transmit to their offspring subtle deficits in visual attention that in turn affect joint attention and communication development.

Our results were not limited to the spatial dimension of attention. We also found a relationship between alerting efficiency and paternal autistic traits: the alerting index (i.e., difference in TTF between the shorter and longer cue-target SOAs) was inversely related to attention to details in the father, suggesting that the ability to react to high-priority stimuli was lower in infants whose fathers had higher attention to details. This result is compatible with the relationship between alerting system disorder and social impairment recently found in children with ASD (Keehn et al., 2010). Some authors (Gold and Gold, 1975; Dawson and Lewy, 1989) hypothesized that abnormal alerting would have developmental consequences in a variety of domains. Particularly, if the attention system is not adequately prepared to process incoming information with a proper level of phasic arousal, novelty can lead to stressful reaction. To avoid this it may be preferable to persist in the ongoing state ("insistence on sameness"). Thus, overfocused and detail-oriented attention could be partially due to the inefficiency of the alerting system that disrupts responses to novel stimuli. An

alternative explanation of the relationship between inefficiency in alerting and overfocused attention could rely on the close interplay between orienting and alerting systems. Even if classical theoretical frameworks claim for an independency between these two systems (Posner and Petersen, 1990; Petersen and Posner, 2012), recent evidence suggest an intensive interplay (for a review see Corbetta and Shulman, 2011). Callejas and colleagues (2004), in particular, demonstrate that increasing phasic alerting can exert a positive influence on attentional orienting, by accelerating its time-course. Thus, alerting inefficiency could amplify the deficit in attentional orienting and re-orienting that contributes to sticky attention typically associated to ASD and its broader phenotype (Zwaigenbaum et al., 2005; Keehn et al., 2010).

Overall, these findings suggest that inefficient rapid orienting of visual attention in space, as well as poorer ability to use the temporal cue to program an action in time, characterized infants whose fathers showed higher presence of autistic traits.

By contrast, maternal autistic traits were not related to any attentional measures of their children. This result is consistent with the evidence that ASD is four times more prevalent in males than in females (Baron-Cohen et al., 2011) and similarly sub-clinical autistic traits are more common in males (Baron Cohen et al., 2001; Constantino and Todd, 2003). However, this lack of a relationship should not be taken as definitive, because of the small sample size in the present study.

The main innovative aspect of the present research is that early attentional markers of the broader autism phenotype shared not only in infant siblings of children affected by ASD, but also in infants whose parents show high presence of autistic traits. The infants' early deficits in attention systems may be related to future deficits in higher-level domains, such as responses to social and non-social stimuli and communication skills (Chawarska et al., 2013; Hutman, 2013). Accordingly, various studies in individuals with ASD found that basic visual

anomalies, in particular the performance in visual search task (Joseph et al., 2009), biological motion processing (Koldewyn et al., 2010), and visual fixation pattern (Klin et al., 2002) predicted communication and social interaction impairments.

However, our results, and similar findings reported above, derive from studies with a purely correlational design. Thus, it is not possible to exclude that poor development of both social and non-social domain derives from a common developmental pathogenic process causing ASD. A recent longitudinal study seems to go one step forward to clarify this question. Studying a cohort of children at risk for ASD, Elsabbagh and colleagues (2013) demonstrate the relationship between disengagement of visual attention in infancy and later autism in toddlerhood.

In conclusion, the present research highlights the potential of studying infants whose parents exhibit elevated autistic traits to improve the identification of early ASD markers. Employing larger samples and using research with longitudinal design could improve the identification of early attentional dysfunction that might undermine typical social-communication development.

CHAPTER 6 - THE ZOOMING MECHANISM IN 8-MONTH-OLD INFANTS AND ITS RELATIONSHIP WITH THE BROADER AUTISTIC PHENOTYPE (BAP)

6.1 Introduction

A wide range of studies investigated the orienting component of visual attention in infanthood (e.g., Clohessy et al., 1991; Johnson et al., 1991; Hood, 1993; Valenza et al., 1994; Johnson & Tucker, 1996; Richards & Hunter, 1998; Ronconi et al., 2014b). It has been shown that its efficiency develops dramatically in the first year of life (Johnson et al., 1991; Hood, 1995), with neural circuits responsible for the spatial orienting getting faster over the first 6 months (Johnson & Tucker, 1996; Richards, 2003, 2005). On the other hand, the ability to modulate the attentional focus size – hereafter, "attentional zooming" – has yet to be explored in infants.

In the present study, we developed the first paradigm to measure attentional zooming in infancy. In previous works the efficiency of attentional zooming was evaluated in children affected by developmental dyslexia (Facoetti et al., 2000; Facoetti & Molteni, 2001) and autism spectrum disorder (Ronconi et al., 2012, 2013b), and the neural underpinnings of this process was clarified using neurophysiological, neuroimaging and transcranial magnetic stimulation in human adults (e.g., Fu et al., 2005; Chen et al., 2009; Ronconi et al., 2014a). Here, an attentional zooming paradigm was readapted and an eye-tracker system was employed to measure saccadic latencies (SLs), defined as the time to initiate a saccade toward the target. SLs are the most reliable measure of covert visual attention deployment in infanthood.

SLs were measured in response to a visual target appearing at two possible eccentricities (central and peripheral) from the central fixation along the horizontal axis. Attentional resources were focused or distributed by using a small or large cue, respectively. In the small cue condition, the central target appeared inside the cue, while the peripheral target appeared outside. In the large cue condition, instead, both the central and peripheral target appeared inside the cue.

Our prediction was that if the attentional zooming mechanism is already developed in 8-months-old infants, SLs should vary between the small and the large cue condition as a function of target eccentricity. Specifically, if in the small cue condition infants can zoom-in their attentional focus, then the detection of central targets should be accelerated relative to the large cue condition (i.e., cue-size effect; e.g., Eriksen & St. James, 1986; Castiello & Umiltà, 1990; Turatto et al., 2000). Furthermore, if in the large cue condition infants can zoom-out their attentional focus, then the detection of peripheral targets should be accelerated relative to the small cue condition. We tested this hypothesis performing two different experiments. In the Experiment 1 visual target had the same dimension for both the central and the peripheral eccentricity, while in the Experiment 2 peripheral target was enlarged according to the cortical magnification factor (Daniel & Whitteridge, 1961), ensuring a balanced perceptual saliency between eccentricities. Manipulating the cue-target interval (100 or 300 ms), we could also evaluate what was the optimal time to adjust the focus of attention at this stage of development. Evidence of the time-course of the attentional zooming in adults have shown that the mechanism takes between 33 and 66 ms to be initiated (Benso et al., 1998). Previous data on both typically developing school-aged children and adults showed that an optimal cue-target interval to perform the attentional zooming is 100 ms, while at longer cue-target intervals (e.g., 500-800 ms) the attentional focus "collapsed" (Benso et al., 1998; Ronconi et al., 2013b, 2014a).

6.2 EXPERIMENT 1

6.2.1 Method

6.2.1.1 Participants

Twenty-five healthy and full-term infants participated in the Experiment 1. Nine infants were tested but not included in the analyses, as they had less than 50% valid trials. This was due to fussiness or drowsiness (n=4), excessive movement of the infant, such that we were unable to record eye movements (n=1), or poor calibration in detecting with the eye tracker the infant's gaze direction in a reliable way (n=4). The final sample was composed by sixteen infants (11 males and 5 females) with a mean age of 8 months and 13 days (mean age=253 days, SD=7.83, range=243-265). Infants were recruited from a database of new parents and were tested only after their parents had given their informed consent. The entire research protocol was approved by the ethic committee of the Department of Developmental and Socialization Psychology of the University of Padua and was conducted in accordance to the principles elucidated in the Declaration of Helsinki.

6.2.1.2 Stimuli

The computer screen showed the stimuli on a black background. The attention getter was a coloured dynamic cartoon with a musical soundtrack. The cue was a central empty grey circle, concentrically displayed relative to the fixation point, with a ray of 4° in the small and 12.5° in the large cue condition.

The target was a coloured (green, red, or yellow) smile that could appear at two possible eccentricities, 3° (central) or 9° (peripheral) from the fixation along the horizontal axis. Targets at both eccentricity measured 2 cm (1.9°) in width and 2 cm (1.9°) in height. In the small cue condition, the central target appeared inside the cue, while the peripheral target

appeared outside. In the large cue condition, both the central and peripheral target appeared always inside the cue (see Figure 6.1, panel A and C).

6.2.1.3 Apparatus

The stimuli were presented with E-Prime 2.0 on a 19-inch monitor with a resolution of 1024x768 pixels. A remote, pan-tilt infrared eye-tracking camera (Model 504, Applied Science Laboratories, Bedford, MA) using bright-pupil technology, placed directly below the stimulus screen, recorded the participant's eye movements at a temporal resolution of 50 Hz. Infrared light emitted from diodes on the camera was reflected back from the participant's retina through the pupil, producing a backlit, white pupil from the corneal surface of the eye. An experimenter guided the eye-tracking camera by means of a remote control, so that the eye of the participant was always in focus. The image of the eye on a television monitor made this procedure easier. To coordinate the eye-movement data with a specific stimulus display, the stimuli-generating computer sent a unique, time-stamped numerical code via a parallel port to the data-collecting computer, indicating the onset and the type of the stimulus display. The digital data indicating the fixation locations and change of locations of the eye (the eye movements themselves) were calculated in relation between the centroid of the pupil and the corneal reflection by using the Applied Science Laboratories' algorithm.

Four main areas of interest (AOI) that corresponded to the possible positions of the target (left and right central targets; left and right peripheral targets) were selected. Each AOI measured 2.5 cm in width and 2.5 cm in height.

6.2.1.4 Procedure

The infant sat in an infant car seat placed 60 cm distant from the stimulus monitor. Parents usually were seated behind the infant seat, slightly moved randomly to the right or left side of

the infant, so they could see the monitor and be close to their baby. The room lights were first lowered, and the infants shown a dynamic cartoon with a musical soundtrack to engage his or her interest toward the predetermined locations, as the experimenter directed the pupil camera toward the participants' eye with the remote control.

The experimental session began with the calibration procedure that allowed the eye-tracker system to subsequently determine the precise direction of the infants' gaze. The eye tracker was calibrated by showing to participants three markers on the screen presented one by one on the top-left, on the centre and on the bottom-right, and recording the eye-tracker readings for the eye-fixation location. If the recorded gaze position did not remain stable within the area covered by the calibration stimulus, a new calibration was conducted. Calibration usually lasted between 1 and 2 minutes. All subsequent eye data were calculated from these calibration values.

An experimental trial began with the presentation, in the middle of the screen, of the central dynamic attention getter (a coloured moving clown). As soon as the participants looked at this central fixation point, one of the two types of cue – the small or the large circle – was presented. After a variable interval of 100 or 300 ms from the cue presentation (Stimulus Onset Asynchrony or SOA), the target appeared randomly on the left or on the right of the central attention getter, at two different eccentricities (central=3° or peripheral=9°). The probability of the target locations was balanced in the two sides. The target remained visible until the participant made a saccade toward it or for a maximum of 2 seconds, after which the trial terminated.

A total of 48 trials (6 repetitions × 2 cue size × 2 SOA × 2 target eccentricities) were administered to each infant, randomly intermixed and arranged in two blocks, so they could take a break halfway trough. The entire experiment lasted about 15-20 minutes.

Software E-Prime allowed us to elaborate the raw data coming from the eye-tracker system, calculating participants' SLs. Trials were considered valid and were analyzed only if saccades started from the central fixation point, were directed toward the target and reached it.

6.2.2 Results

A mean of 8.6 trials (SD=7) for each infant was excluded from the statistical analysis for the following reasons: infants looked outside the defined AOI (mean=3.1 trials; SD=3.7), or the signal of the eye tracker was lost during the stimuli presentation (mean=4.5 trials; SD=4.2), or the saccadic latencies were lower than 100 ms (i.e., anticipations; mean=0.6 trials; SD=0.7), or the saccadic latencies were greater than 500 ms (mean=0.4 trials; SD=0.8). The final number of valid was on average 39.4 (SD=7.0). Table 6.1 shows mean SLs and other collected measures for all infants' valid responses, as a function of the cue size, SOA and target eccentricity.
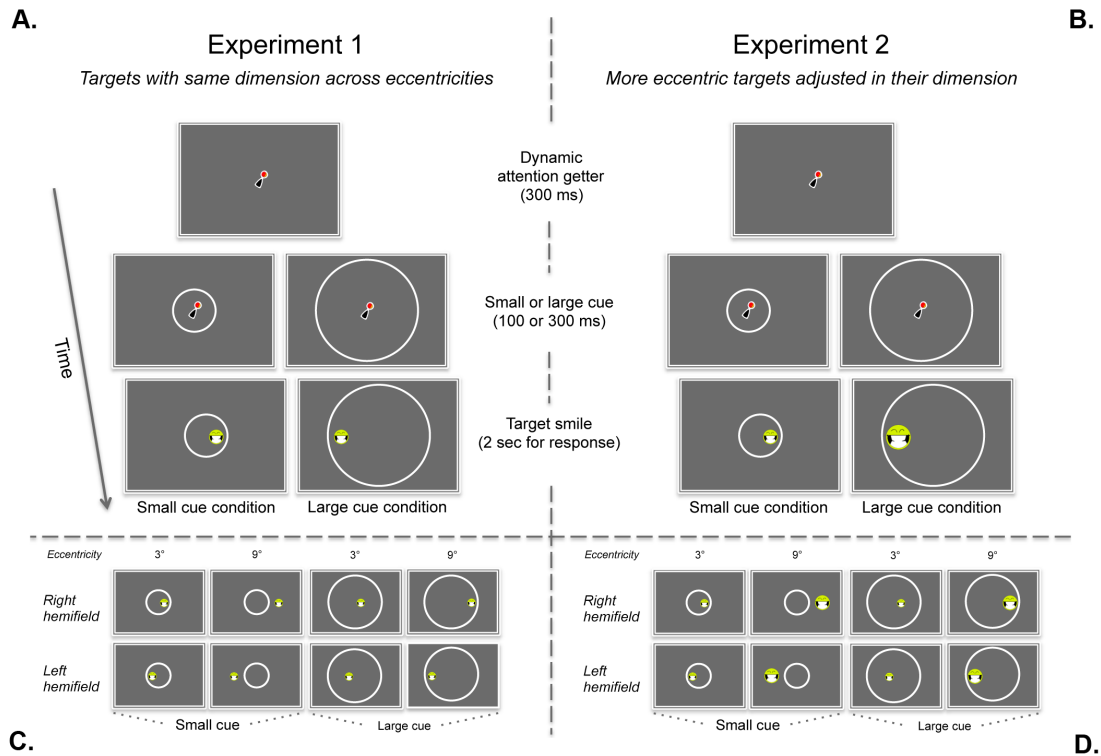
Figure 6.1 Schematic representation of the attentional zooming task for Experiment 1 (panel A) and Experiment 2 (panel B). The two bottom panels C and D represent possible targets location in Experiment 1 and 2 respectively, for every combination of visual hemi-field, cue size and target eccentricity.

SLs were analyzed using a repeated measure 2×2×2 analysis of variance (ANOVA) with the following within-subjects factors: Cue size (small vs. large), SOA (100 vs. 300) and Target eccentricity (central vs. peripheral). The results showed a significant main effect of SOA ($F_{(1,15)}$=22.14, p<.001, η^2_p=.60; mean±SEM SLs were 246±5 ms and 263±6 ms at the two SOA, respectively), and Target eccentricity ($F_{(1,15)}$=26.63, p<.001, η^2_p=.64; mean SLs were 238±5 and 271±8 ms at the central and peripheral eccentricity, respectively), and a significant SOA by Target eccentricity interaction ($F_{(1,15)}$=6.55, p<.05, η^2_p=.30; at SOA=100 ms SLs were 236±6 and 257±7 ms for the central and the peripheral eccentricity, respectively; at SOA=300 ms SLs were 241±5 and 286±9 ms for the central and the peripheral eccentricity, respectively).

Importantly, a Cue size by Target eccentricity interaction emerged ($F_{(1,15)}$=5.61, p<.05, η^2_p=.27; see Figure 6.2). Planned comparisons showed that SLs for peripheral target were

significantly faster in the large (257±8) relative to the small (285±12) cue condition ($t_{(15)}$=-2.23, p<.05, η^2_p=.25), while SLs for central target were faster in the small relative to the large cue condition, but this difference was not statistically significant (234±5 vs. 242±6; $t_{(15)}$=1.16, p=.26, η^2_p=.08). In addition, SLs were faster for central (234±5) versus peripheral target (285±12) in the small cue condition, ($t_{(15)}$=-4.57, p<.001, η^2_p=.58), but no difference emerged in the large cue condition (242±6 vs. 257±8; $t_{(15)}$=-1.71, p=.11, η^2_p=.16). The main effect of the Cue size and the other interactions were not significant.

Figure 6.2 Graph displaying the results of the Experiment 1, with mean saccadic latencies (SLs) plotted as a function of cue type and eccentricity (averaged across SOAs). In this case, target had always the same dimension across eccentricity. Error bars represent SEM. n.s.= not significant, ***=p<.001; *=p<.05.
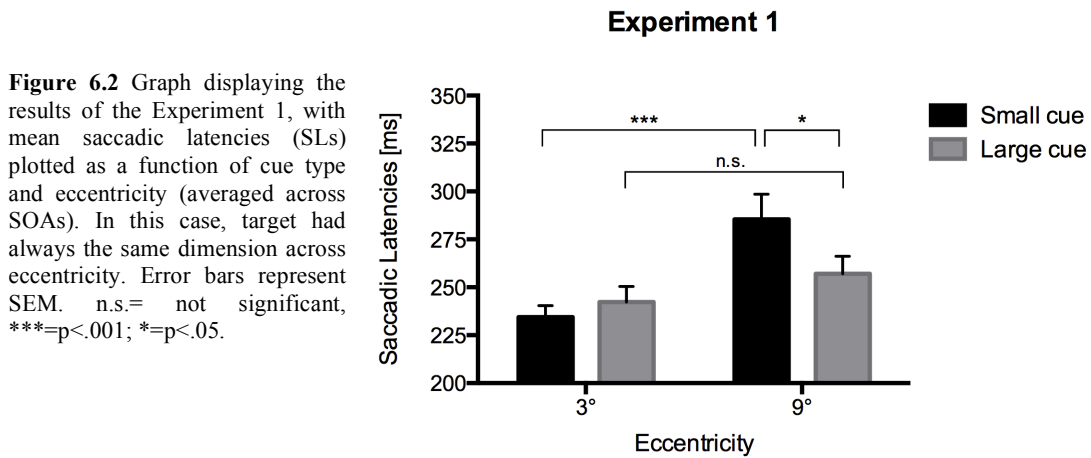
Table 6.1 Descriptive statistics (mean and SD) of the main measures collected in Experiment 1, separated for each level of each independent variable.

	Experiment 1															
	SOA=100 ms								SOA=300 ms							
	Small cue				Large cue				Small cue				Large cue			
	Eccentr. 3°		Eccentr. 9°		Eccentr. 3°		Eccentr. 9°		Eccentr. 3°		Eccentr. 9°		Eccentr. 3°		Eccentr. 9°	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Saccadic Latency (ms)	236.73	28.66	271.56	45.10	235.33	26.20	241.79	29.43	232.06	19.84	300.11	61.50	249.40	38.50	272.33	43.33
Time to target fixation (ms)	295.58	42.36	451.29	58.29	317.23	58.82	430.13	72.23	298.58	50.14	492.51	86.43	318.17	64.33	465.15	75.80
Duration (ms)	35.85	12.23	98.31	26.21	44.02	10.94	91.85	29.50	40.29	15.06	86.91	25.74	39.39	16.85	97.37	28.17
Angle (°)	2.58	0.44	8.97	0.97	2.89	0.44	8.63	0.88	2.57	0.43	8.94	1.15	2.72	0.58	8.94	1.31
Speed (°/sec)	88.77	10.80	101.74	14.56	80.06	11.56	102.53	9.07	85.45	14.47	105.35	13.21	85.82	16.80	101.62	19.42

6.2.3 Discussion

Results of the Experiment 1 are in agreement with a proper modulation of the attentional focus size, demonstrating that zoom-in and zoom-out attentional mechanisms are already developed in 8-month-old infants. In particular, peripheral target detection was faster in the large relative to the small cue condition, whereas central target detection was slower (although not statistically significant). Accordingly, target anticipated by a small cue led to the rise of a significant "attentional gradient" (i.e., slower detection of peripheral than central targets), suggesting that attentional resources were focused inside the narrow area delimited by the small cue and fall off progressively outside the focus. On the other hand, for targets anticipated by a large cue – containing both possible target locations – the attentional gradient was nullified, because of the spreading of attentional resources in the entire cue-delimited visual space. These results are congruent with previous studies employing manual reaction times to investigate the attentional zooming in children and adults (Castiello and Umiltà, 1990; 1992; Benso et al., 1998; Greenwood and Parasuraman, 1999; Facoetti et al., 2000; Luo et al., 2001; Müller et al., 2003; Ronconi et al., 2013b, 2014a; Turatto et al., 2000). Although the cue was effective in modulating the target detection relative to the eccentricity, peripheral (vs. central) targets were detected systematically slower independently from all the other factors (as suggested by the significant main effect of the target eccentricity), revealing that peripheral target were perceptually less salient than central ones, particularly for longer cue-target SOA (as suggested by the significant SOA by target eccentricity interaction).

We aimed to remove the perceptual bias by adjusting the size of the peripheral target in agreement to the cortical magnification factor (Daniel & Whitteridge, 1961), which states that there is a larger representation in the visual cortex of the foveal and parafoveal retinal portions compared to peripheral regions. In the Experiment 2, the perceptual saliency of visual targets was balanced across eccentricities.

6.3 EXPERIMENT 2

6.3.1 Method

6.3.1.1 Participants

Twenty-eight healthy and full-term infants participated in the experiment and none of them took part in the Experiment 1. Eighteen infants (9 males and 9 females) with a mean age of 8 months and 11 days (mean age=250 days, SD=7.45, range=240-264) comprised the final sample. Ten infants were observed but not included in the statistical analyses, as they had less than 50% valid trials. This was due to fussiness or drowsiness (N=4), excessive movement of the infant, such that we were unable to record eye movements (N=3), or poor calibration in detecting with the eye tracker the infant's gaze direction in a reliable way (N=3). The recruitment method was the same of the Experiment 1.

6.3.1.2 Stimuli and apparatus

The stimuli and the apparatus were identical to those used in the Experiment 1, with the following exceptions: (i) target at the peripheral eccentricity was scaled following the procedure elucidated by Rovamo and Virsu (1979) and Virsu and Rovamo (1979), resulting in a 5 cm (4.8°) width and 5 cm (4.8°) height target; (ii) the dimensions of the four main AOI measured 2.5 cm in width and 2.5 cm in height at the central eccentricity and 5.5 cm in width and 5.5 cm in height at the peripheral eccentricity.

6.3.1.3 Procedure

The procedure was exactly the same of the Experiment 1.

6.3.2 Results

Trials were considered valid and were analyzed only if saccades started from the central fixation point, were directed toward the target and reached it. A mean of 10.2 trials (SD=7.3) for each infant was excluded by the statistical analysis for the following reasons: because infants looked outside the defined AOI (mean=2.4 trials; SD=2.3), or because the signal of the eye tracker was lost during the stimuli presentation (mean=6.4 trials; SD=6.5), or the saccadic latencies were lower than 100 ms (i.e., anticipations) (mean=0.4 trials; SD=1.0), or the saccadic latencies were greater than 500 ms (mean=0.9 trials; SD=1.3). The final number of trials in which infants correctly detected the target was on average 37.8 trials (SD=7.3). Table 6.2 shows mean SLs and other measures collected for all infants' valid responses, as a function of the cue size, SOA and target eccentricity.

As for the Experiment 1, SLs were analyzed using a repeated measure 2×2×2 ANOVA with the following within-subjects factors: Cue size (small vs. large), SOA (100 vs. 300 ms) and Target eccentricity (central vs. peripheral). Main effects were not significant. It is worth to note that the absence of a significant effect of the factor Target eccentricity demonstrated that the manipulation of peripheral target size was effective in balancing the perceptual saliency between the two eccentricities. Importantly, a significant Cue size by SOA by Target eccentricity interaction emerged ($F_{(1,17)}$=10.62, p<.01, η^2_p=.38; see Figure 6.3). This three-way interaction was further explored with two 2×2 ANOVA performed at each SOA. At the first SOA (100 ms) ANOVA revealed a significant Cue size by Target eccentricity interaction ($F_{(1,17)}$=22.49, p<.001, η^2_p=.57). Planned comparison revealed that SLs at the central eccentricity were faster when anticipated by a small than by a large cue (235±6 vs. 249±5; $t_{(17)}$=2.69, p<.05, η^2_p=.30), while the opposite was obtained for targets appearing at the peripheral eccentricity, that were detected faster when anticipated by a large then a small cue (230±5 vs. 245±7; $t_{(17)}$=-2.39, p<.05, η^2_p=.25).

ANOVA performed at the second SOA (300 ms) did not revealed any significant main effect or interaction between factors.

Experiment 2
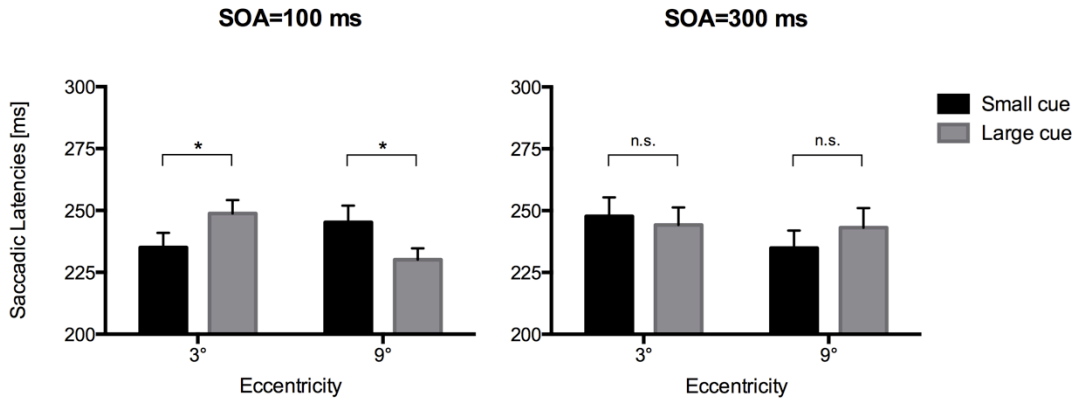
Figure 6.3 Graph displaying the results of the Experiment 2, with mean saccadic latencies (SLs) plotted as a function of SOA, cue type and eccentricity. In this case, the target dimension at the second eccentricity was adjusted accordingly to the cortical magnification factor (see Figure 6.1). Error bars represent SEM, n.s.= not significant, *=p<.05.

Table 6.2 Descriptive statistics (mean and SD) of the main measures collected in Experiment 2, separated for each level of each independent variable.

	Experiment 2															
	SOA=100 ms								SOA=300 ms							
	Small cue				Large cue				Small cue				Large cue			
	Eccentr. 3°		Eccentr. 9°		Eccentr. 3°		Eccentr. 9°		Eccentr. 3°		Eccentr. 9°		Eccentr. 3°		Eccentr. 9°	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Saccadic Latency (ms)	235.00	25.12	245.21	28.45	248.77	22.90	230.09	19.49	247.71	32.67	234.90	29.77	244.17	30.25	243.11	33.57
Time to target fixation (ms)	300.39	58.45	372.94	63.71	324.72	48.67	386.91	73.49	318.65	60.04	392.91	81.76	368.94	85.54	414.94	108.77
Duration (ms)	42.09	29.74	89.20	19.55	37.48	23.97	100.00	46.16	39.59	19.57	92.39	22.70	44.31	27.51	105.18	44.42
Angle (°)	2.49	0.30	8.36	0.67	2.54	0.36	8.58	0.53	2.48	0.31	8.26	0.86	2.83	0.75	8.46	0.95
Speed (°/sec)	87.59	18.51	100.92	13.10	89.77	20.18	100.05	14.52	78.54	25.29	101.20	13.80	88.16	19.62	97.95	16.04

6.3.3 Discussion

In the Experiment 2 we balanced the perceptual saliency between the two target eccentricities by enlarging the peripheral target size according to the cortical magnification factor (Daniel & Whitteridge, 1961). Thus, the only comparisons that can be done are between the two types of cue at each of the two target eccentricities. Results showed that at the central eccentricity SLs were faster in the small relative to the large cue condition (i.e., the cue size effect on central target). Target at the peripheral eccentricity on the other hand were faster when anticipated by a large cue (i.e., the cue size effect on peripheral target). Overall these results corroborate the hypothesis tested in the Experiment 1, in which infants were able to automatically adjust the size of the attentional focus in accordance with the cue size. Moreover, in the Experiment 2 there was a specific temporal window to perform the attentional zooming. Only at the first SOA (100 ms), indeed, the small cue induced infants to narrow their attentional focus (zoom-in), while the large cue induced them to broaden their attentional focus (zoom-out). In contrast, at the longer SOA (300 m), infants' attentional focus collapsed and returned to a "default" state.

6.4 Relationship between infants' zooming mechanism and parents' autistic traits

Similarly to what we did in the previous study (Chapter 5), we explored the relationship between infants' attentional functioning – in this case the ability to adjust the size of the attentional focus – and the autistic traits self reported by their parents by using the Autism Quotient questionnaire (Baron-Cohen et al., 2001).

In order to maximize the statistical power of our analysis, we decided to consider the entire group of infants that took part in the present study. Thus, we putted together in a unique analysis infants from Experiment 1 and 2. Since the peripheral target was magnified in

Experiment 2, while the central target remain with the same dimension, we limited our analysis SLs at the first target eccentricity.

We computed an index of attentional zoom-in, by subtracting SLs in the small cue condition from SLs in the large cue condition (averaged between SOAs). Higher zoom-in indexes correspond to stronger focusing of attention. We found that both fathers' ($r_{(30)}$=.314, p=.028) and mothers' ($r_{(32)}$=.440, p=.005) individuals AQ scores in the Attention Switching subscale were positively correlated with the zoom-in indexes of their offspring (see Figure 6.4).
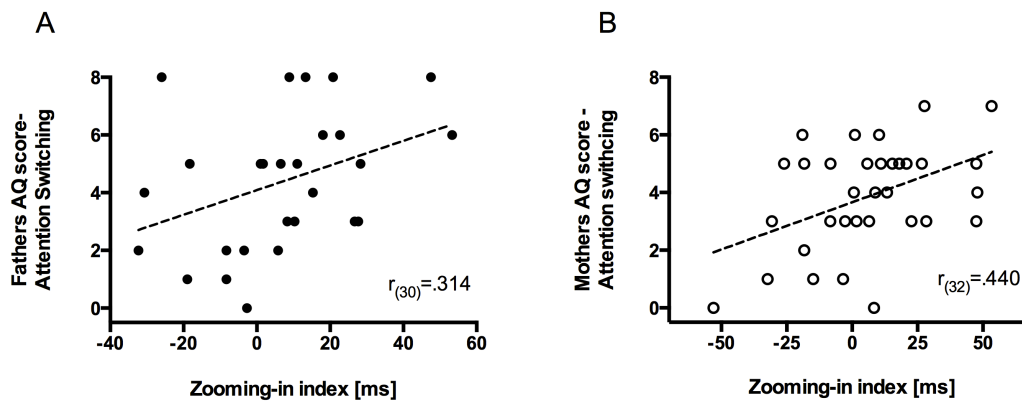
Figure 6.4 Graph displaying the relationship between fathers' (a) nad mothers' (b) individual score on the Attention Switching subscale of the Autism Quotient (AQ) questionnaire and their infants' attentional zoom-in indexes.

6.5 General Discussion

In the developed human brain, the focus of attention can be adjusted in its size to process information from a narrow (zoom-in) or a broad (zoom-out) region of the visual field (Ericksen and St. James, 1986; Müller et al., 2003; Chen et al., 2009). This mechanism is fundamental to select relevant information from the complex visual environment. Attentional zooming ability has never been investigated in infants. In two different experiments we demonstrated, for the first time, that 8-month-old infants were able to accurately adapt the size of their attentional focus.

Results of the Experiment 1 – where we employed targets of the same size across eccentricities – show that peripheral target detection was faster in the large relative to the small cue condition, whereas central target detection was slower (although not statistically significant). In addition, when targets were preceded by a small cue a significant attentional gradient (difference in SLs between central and peripheral eccentricity) emerged, indicating an efficient focusing of attentional resources (zoom-in). On the contrary, when targets were preceded by a large cue the attentional gradient was nullified (SLs did not differ across eccentricities), indicating an efficient spread of attentional resources (zoom-out).

In Experiment 2, we controlled for the perceptual saliency of peripheral targets by adjusting their dimension according to the cortical magnification factor. Results show that for central targets SLs were faster in the small relative to the large cue condition (i.e., the cue size effect; Eriksen & St. James, 1986; Castiello & Umiltà, 1990; Turatto et al., 2000). Conversely, for peripheral target SLs were faster in the large relative to the small cue condition. These findings demonstrate that infants were able to zoom-in and zoom-out their attentional focus, respectively. Since these findings were found only at the short cue-target SOA, we propose that attentional zooming mechanism was rapidly adapted to the object size but collapsed shortly after, accordingly to an exogenous deployment of visual selective attention (see Posner and Petersen, 1990; Petersen and Posner, 2012 for reviews).

The validation of this paradigm and the evidence that the zooming mechanism is already developed in infants at 8 months of age have important implications for the study of developing cognition. According to the neuro-constructivist approach (Karmiloff-Smith, 1998) and interactive specialization approach (Johnson, 2011), indeed, development itself plays a crucial role in phenotypical outcomes, and tiny variations in the initial state could give rise to marked differences in the end states. Thus, the ability to control the attentional

zooming mechanism can be related to higher order cognitive function such as joint attention, as previously suggested also for the orienting mechanism (Mundy & Newell, 2007). Importantly, this paradigm could be use in future studies as a tool for the early diagnosis of autism spectrum disorder (ASD). Previous studies found an impaired zoom-out attentional mechanism in children with ASD (Mann & Walker, 2003; Ronconi et al., 2012, 2013b; see Chapter 2). This impairment in spreading the attentional resources has been confirmed also by results of the first study exposed in the present thesis (Chapter 4). Future longitudinal studies will have the possibility to assess if the deficit in enlarging the attentional focus size is present also in infants at-risk for developing the condition that are later diagnosed with ASD in toddlerhood. The correlational analyses that we performed with the approach of the broader autistic phenotype seem to confirm a possible relationship between higher risk of autistic phenotype and a deficit in spreading attentional resources. Autistic traits of parents in the AQ - Attention Switching subscore were indeed related to infants' deployment of attention. Those parents with higher autistic traits have infants with higher zoom-in indexes, which could be considered the flip side of the coin relative to the zoom-out dysfunction. Prolonged zoom-in was indeed coupled with sluggish zoom-out of the attentional focus in our previous study in individuals with ADS (Ronconi e al., 2013b). However, these data have to be considered preliminary, as we do not have the possibility to correlate parents' autistic traits with infants' attentional zoom-out (because the peripheral target eccentricity had different dimensions across the two experiments, thus only central target eccentricity was considered).

In conclusion, for the first time, the current study showed that the essential ability to control the size of the attentional focus is present in 8-month-old infants. The relationship between this attentional mechanism and higher order visual perception (e.g. local/global stimulus analysis, spatio-temporal visual integration) and attentional processes (e.g. joint attention)

remains to be fully explored. Moreover, having a tool to assess the modulation of the attentional focus size in infancy is extremely important for its potential application as an early marker of ASD.

CHAPTER 7 - THE NEURAL UNDERPINNINGS OF THE ZOOMING MECHANISM – PART I: TMS ON THE RIGHT FRONTAL EYE FIELDS INDUCES AN INFLEXIBLE ZOOM-LENS OF ATTENTION*.

7.1 Introduction

As summarized in Chapter 2, the selection of relevant visual information is controlled by spatial attention. The focus of attention can be moved to a particular region in the visual space, also in absence of eye movements (i.e., covert orienting of attention; Posner, 1980). Moreover, it can be adjusted in its size, like a "zoom-lens" (e.g., Eriksen and St. James, 1986; Castiello and Umiltà, 1990), in order to be spread in a broader portion (zoom-out) or focused in a narrow region (zoom-in) of the visual field. Neuroimaging and neurophysiological data supported this hypothesis, suggesting that the neural activity preceding the target presentation was finely modulated by the attended region in early visual areas (Vidyasagar, 1998; Brefczynski and DeYoe, 1999; Müller et al., 2003; McAdams and Reid, 2005), and that the attentional zooming modulated both P1 and N1 component of the visual event related potentials (Luo et al., 2001; Fu et al., 2005).

It is widely demonstrated that a fronto-parietal network, composed of superior frontal cortex (in particular Frontal Eyes Fields - FEF) and intraparietal sulcus, plays a crucial role on covert orienting of attention (see Corbetta and Shulman, 2002, 2011 for reviews). However, the brain areas devoted to control the attentional focus size have not been specifically investigated yet. In particular, there is no evidence regarding the role of FEF. The predominant view of visual cognition associated FEF with eye movement programming (see Tehovnik et al., 2000 for a review). The hypothesis of a strict link between covert spatial

attention and eye movement programming was originally suggested by Rizzolatti and colleagues (1987). After this proposal, the role of FEF has been increasingly recognized to go beyond the programming of eye movements. Previous studies showed that the FEF area of the macaques was involved in visual target selection during a visual search task (e.g., Bichot and Schall, 1999, 2001; Murthy et al., 2001). Further evidence came from transcranial magnetic stimulation (TMS) studies in human participants, which demonstrated the FEF fundamental role in covert orienting of attention (e.g., Ro et al., 2003; Taylor et al., 2007) and in serial visual search (see O'Shea et al., 2006 for a review). Importantly, recent concurrent TMS and functional neuroimaging studies suggest the casual role for FEF in the fronto-parietal modulation of neural activity in both striate and extrastriate visual areas (Ruff et al., 2006; 2008).

The aim of the present study was to investigate the role of FEF in the modulation of the attentional focus size. Single pulse TMS was used to interfere with the cue processing that induced subjects to narrow or to broaden the attentional focus. We measured simple reaction times (RTs) to a visual target that could appear at one out of three eccentricities from the fixation. We used the term "attentional gradient" to indicate the specific RTs pattern, dependent on target eccentricity, that is influenced by the two different cue-sizes employed (LaBerge, 1983; see LaBerge and Brown, 1989 for a review). When a small cue (containing only the first target eccentricity) preceded the target onset, subjects are induced to zoom-in their focus of attention, generating a significant attentional gradient in RTs (i.e. increasing RTs with increasing target eccentricity). On the other hand, when a large cue (containing all possible target eccentricity) anticipated the target onset, subjects automatically zoom-out their attentional focus to cover all the possible target locations. Consequently, the attentional gradient in RTs is usually reduced or even nullify (equal RTs across eccentricities) in presence of a large cue. This prediction should be valid only within a limited cue-target time

window, as suggested by previous studies that investigated the specific time course of the attentional focusing (e.g., Benso et al., 1998; Turatto et al., 2000; Ronconi et al., 2013b; 2012b). In particular, Turatto and colleagues (2000) provided evidence of automatic and voluntary attentional mechanisms controlling the size of the focus. When a new object suddenly appears in the visual field, the focus automatically adjusted its size. Accordingly, Benso and collegues (1998) showed that the focusing mechanism takes between 33 and 66 ms to be initiated but for long SOAs the focus collapses.

Since it is a widely held view that the right hemisphere is dominant for spatial attention (Corbetta and Shulman, 2002, 2011), our prediction is that only TMS of the right FEF would interfere with the attentional zoom-lens control.

7.2 Materials and Methods

7.2.1 Participants

Fifteen adult participants (age range 22-27, mean age=24.33, all right-handed) without any history of neurological or psychiatric disorder took part in the present study as paid volunteers. Six participants took part in the "No TMS experiment" (Experiment 1), while the other 9 participants performed the "TMS experiment" (Experiment 2). All had normal or corrected to normal vision and provided informed consent before participation. The entire research protocol was conducted in accordance to the principles elucidated in the Declaration of Helsinki and the ethical committee of the Department of General Psychology of the University of Padua approved the study.

7.2.2 Apparatus and Procedure

7.2.2.1 No TMS Experiment (Experiment 1)

The experiment was conducted in a dimly lit and quiet room. Participants were seated 40 cm away from a 19-in. CRT monitor. A chinrest was used to stabilize the head, fixation was binocular. All stimuli were middle gray displayed on a black background. The fixation point was a cross of 0.5 deg placed in the screen center. One circle was presented concentrically to the fixation point and the dimension of its ray was manipulated according to the two cue conditions: 4 deg in the Small and 12.5 deg in the Large cue condition (Figure 7.1). The target stimulus was a dot of 0.5 deg, which could appear at one out of three possible horizontal eccentricity (i.e., 2, 6 and 12 deg, namely: Eccentricity 1, Eccentricity 2 and Eccentricity 3, respectively). In the Small cue condition, the target was displayed inside the focusing cue at Eccentricity 1, whereas at Eccentricity 2 and 3 it felt outside. In the Large cue condition the target was always displayed inside the focusing cue. The target was randomly presented either in the left or in the right visual hemifield. Similar experimental paradigms have already been employed in other studies (Facoetti and Molteni, 2001; Ronconi et al., 2012, 2013b).

At the beginning of each trial, a central fixation point appeared for 1000 ms. Subsequently, a non-informative Small or Large cue was presented (i.e., the probability of the target location was equal in the two focusing cue conditions). After a variable stimulus onset asynchrony (SOA: 100, 300 or 500 ms), the target was displayed for 20 ms. A short target duration was chosen to prevent eye movements after the stimulus onset. Participants were instructed to press the space bar with their right hand as fast as possible at the target onset. If no response was provided within 1000 ms from the stimulus onset, participants were warned with a 800 Hz sound played for 500 ms. At the end of each trial, a blank screen for an inter-trial interval of 1500 ms was presented before starting the following trial. The entire experiment consisted

of 1440 trials, run in two separate sessions of 720 trials, with a few hours of break between them. Both sessions were identical, and consisted in three different blocks of 240 trials. Each block contained 216 response trials (108 trials for the 2 focusing cue sizes; 36 trials for each target location) and 24 catch trials (target absent).

7.2.2.2 TMS Experiment (Experiment 2)

Experiment 2 used the same behavioral procedure of Experiment 1, but TMS stimulation was included. Single-pulse TMS was performed using a Magstim Rapid² stimulator and a 70mm figure-8 shaped coil (The Magstim Company Ltd) combined with the Brainsight frameless stereotactic navigation system (Rogue Research Inc., Montreal, Canada).

Single-pulse TMS was delivered on the right FEF (r-FEF, experimental condition) and on the left FEF (l-FEF, control condition). The stimulation was time-locked to each trial, either 0 or 70 ms after the cue onset, and randomized across trials. We separated the two stimulation sites (r-FEF and l-FEF) into different blocks. The same administration order was repeated for the two sessions and was randomly counterbalanced across participants.
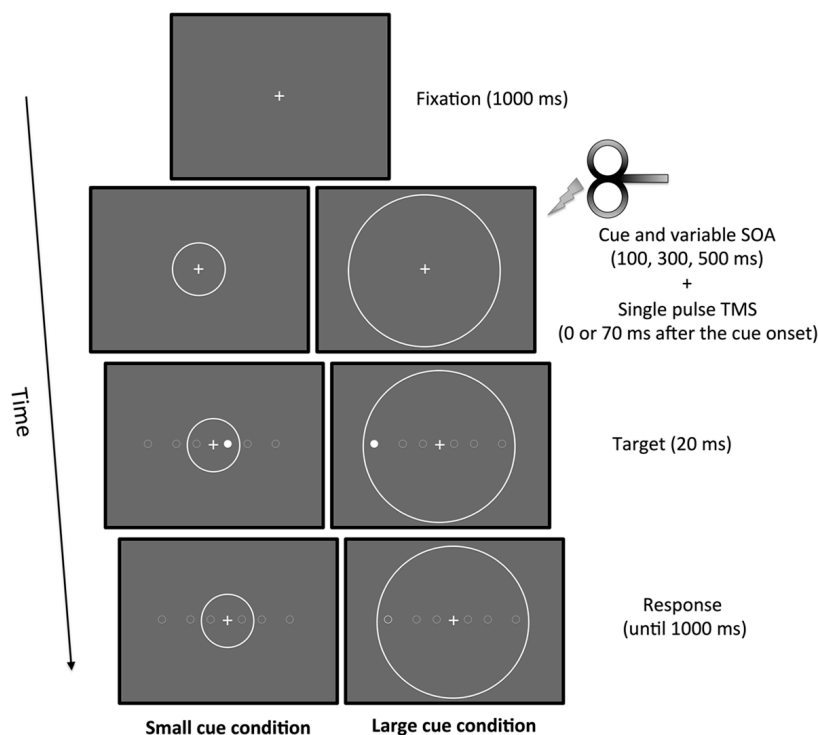

Figure 7.1 Schematic illustration of the task design (SOA: stimulus onset asynchronies, TMS: transcranial magnetic stimulation). Target appeared randomly in one of the six position depicted along the horizontal axis (not shown while participants performed the task).

The r-FEF and the control (l-FEF) sites were localized moving the coil 3 cm rostrally from each subject's motor hotspots and 5 cm laterally of the sagittal midline. These positions were then marked with the Brainsight software. The handle of the coil was oriented posteriorly. The precise location of the FEFs varies from individual to individual (Ro et al. 2002) and this could be a possible source of error. However, the same procedure has been successfully employed in previous TMS studies (e.g., Muri et al., 1991; Ro et al., 1999; Leff et al., 2001; O'Shea et al., 2006). When participants reported discomfort caused by TMS-evoked blinks and facial twitches, the orientation of the coil was altered slightly, without any change in position. Stimulation was delivered at 100% of the motor threshold, considered as the minimal intensity necessary to elicit a visible movement of the hand in 5 out of 10 stimulation pulses produced on the contralateral motor hotspot (mean intensity for the r-FEF was 51.22 ± 4.26; mean intensity for the l-FEF was 50.67 ± 4.47, $t_{(8)}=.73$, $p>.05$).

7.3 Results

7.3.1 No TMS Experiment (Experiment 1)

Mean RTs for the correct response trials were used as the dependent variable for a three-way repeated-measures ANOVA with the following within subject factors: Cue (Small and Large), SOA (100, 300 and 500 ms) and Eccentricity (2, 6 and 12 deg). The main result is a significant Cue × SOA × Eccentricities interaction ($F_{(4, 20)}=2.91$, $p<.05$, $\eta^2_p=.37$; Figure 7.2). This interaction showed the specific time course of the cue size effect on the RTs at the three eccentricities. Planned comparisons at 100 ms SOA ($F_{(2, 10)}=20.37$, $p<.05$, $\eta^2_p=.80$) showed that RTs difference between Eccentricity 1 and Eccentricity 3 was significant in the Small Cue condition (306 ms; SE=7 and 335 ms; SE=10 respectively; $F_{(1, 5)}=39.3$, $p<.05$, $\eta^2_p=.89$), but not in the Large Cue condition (310 ms; SE=8 and 313 ms; SE=8 respectively; $F_{(1, 5)}<1$, $\eta^2_p=.07$). In contrast, planned comparisons at the other SOAs did not reveal any significant

Cue × Eccentricity (SOA=300 ms: $F_{(1, 5)}<1$, $\eta^2_p=.04$; SOA=500 ms: $F_{(1, 5)}=2.25$, n.s., $\eta^2_p=.31$).

These results show that an automatic control of the attentional focus is present only when the target appeared 100 ms after the cue.

The ANOVA revealed also a main effect of Cue ($F_{(1, 5)}=18.17$, $p<.01$, $\eta^2_p=.78$), SOA ($F_{(2, 10)}=23.49$, $p<.05$, $\eta^2_p=.82$), and Eccentricity ($F_{(2, 10)}=37.28$, $p<.05$, $\eta^2_p=.88$). No other main effect or interaction was significant.
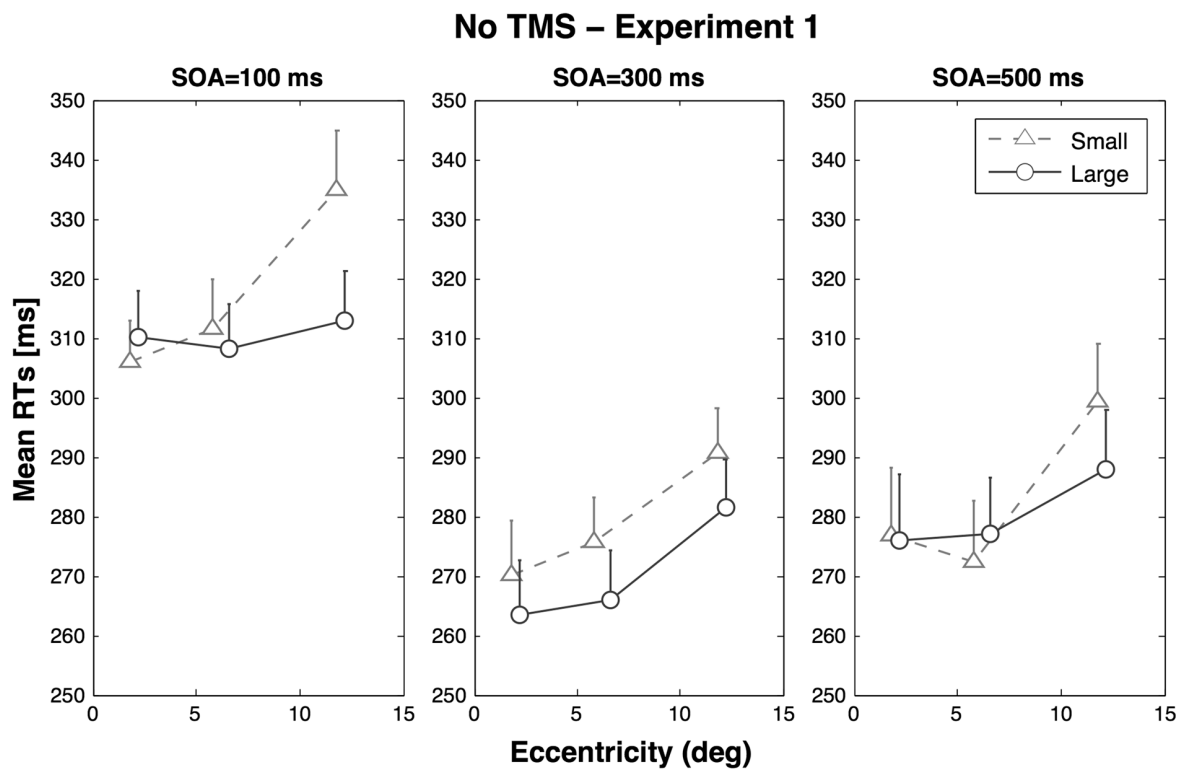

Figure 7.2 Results of the behavioral experiment (Experiment 1 – No TMS), showing mean RTs as a function of the Cue (small vs. large), Eccentricity (2, 6 and 12 deg) and stimulus onset asynchronies (SOAs: 100, 300 and 500 ms). Error bars represent the SEM.

7.3.2 The "Attentional Gradient" (AG) as a measure of the attentional focus modulation

According to the results of the Experiment 1, we calculated an Attentional Gradient (AG) index (Ronconi et al., 2012; 2013b) for the 100 ms SOA. The AG was obtained separately for the Small and Large cue conditions, subtracting the Eccentricity 1 from the Eccentricity 3 RTs. As can be seen from the (panel A), in the Experiment 1 the AG was significantly different between the Large (mean AG=2.62 ms, SE=4) and the Small cue condition (mean AG=29.01 ms, SE=5; $F_{(1, 5)}$=37.52, p<.05, η^2_p=.88; Figure 7.4, panel A). This difference was not significant at the other SOAs (300 and 500 ms, all ps>.05). In the light of these results, we focused the analysis of the Experiment 2 on the AG calculated at the first SOA.

7.3.3 TMS Experiment (Experiment 2)

In Experiment 2, we used the raw RTs mean of the correct response trials (see Figure 7.3) to compute the AG values mean, and performed a three-way repeated-measures ANOVA (2×2×2) with the following within subjects factors: Cue (Small and Large), Site (l-FEF and r-FEF) and TMS Timing (0 and 70 ms from the cue onset). The main result is a significant Cue × Site × TMS Timing interaction ($F_{(1, 8)}$=7.17, p<.05, η^2_p=.47; see Figure 7.4, panels B and C) which was explored by the following planned comparisons. For the l-FEF site (Figure 7.4, panel B), comparison revealed that the AG was significantly different between the Small and the Large cue condition, regardless of the TMS Timing (0 ms TMS Timing: mean AG=1.17 ms for the Large cue, SE=5; mean AG=19.75 ms for the Small cue, SE=5; $F_{(1, 8)}$=12.78, p<.05, η^2_p=.61; 70 ms TMS Timing: mean AG=-.86 ms for the Large cue, SE=9; mean AG=26.76 for the Small cue, SE=3; $F_{(1, 8)}$= 10.69, p<.05, η^2_p=.57). This result indicates that participants automatic adjusted their focus of attention when the single-pulse TMS was delivered at the l-FEF site, as we found in the No-TMS Experiment.

When TMS was delivered at the r-FEF site (Figure 7.4, panel C) simultaneously with the cue onset (TMS Timing=0 ms), participants continued to automatically adjust the focus of attention. The AG was still different between the two cue conditions (for the Large cue: mean AG=-5.13 ms, SE=6; for the Small cue: mean AG=26.13 ms, SE=7; $F_{(1, 8)}$=8.08, p<.05, η^2_p=.50). In contrast, when TMS was delivered to the r-FEF 70 ms after the cue onset, the AG did not differ between the Large and the Small cue condition (mean AG=12.97 ms in the Large cue, SE=5; mean AG=13.81 ms in the Small cue, SE=6; $F_{(1, 8)}$<1, n.s., η^2_p=.001). Furthermore, in the r-FEF TMS condition, the AG differed significantly between the two TMS Timing, for both the Large ($F_{(1, 8)}$=12.60, p<.05, η^2_p=.61) and the Small cue condition ($F_{(1, 8)}$=7.84, p<.05, η^2_p=.49). These results suggest that benefits associated with automatic control of the size of the attentional focus were selectively disrupted by TMS delivered 70 ms after the cue onset on the right FEF.

The ANOVA revealed also a main effect of Cue ($F_{(1, 8)}$=10.29, p<.05, η^2_p=.56). No other main effect or interaction were significant.
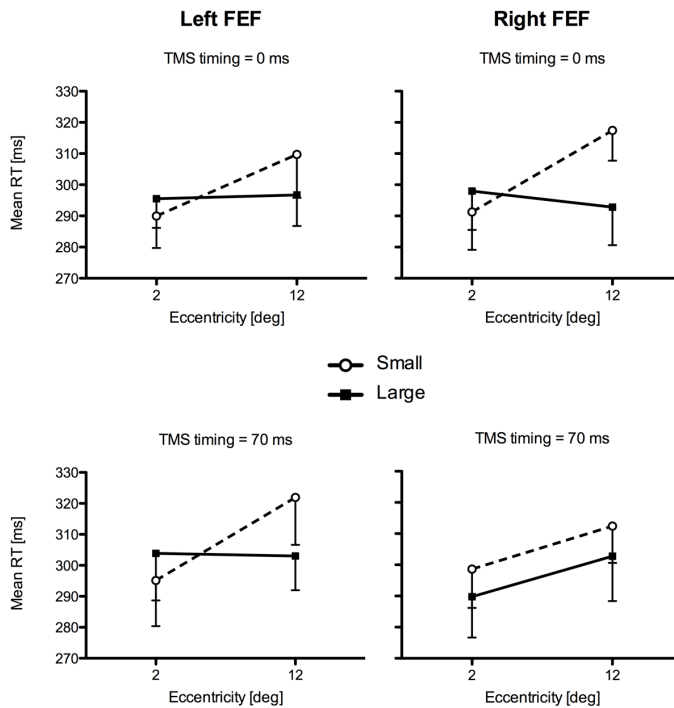

Figure 7.3 The mean raw reaction times are depicted as a function of TMS Sites (left FEF vs. right FEF), Cue (small vs. large) and Eccentricity (2 vs. 12 deg). Error bars represent the SEM.
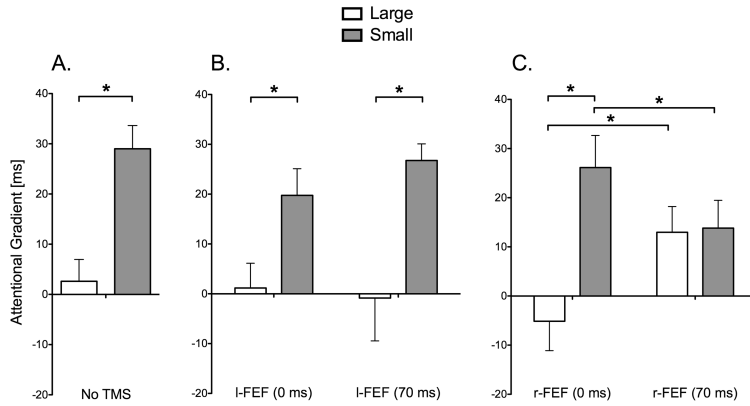
Figure 7.4 The mean Attentional Gradient (AG; i.e., difference between RTs at Eccentricity 3 [12 deg] and RTs at Eccentricity 1 [2 deg]) is depicted as a function of cue and TMS condition: **(A)** No TMS, **(B)** TMS on the left FEF (control site) and **(C)** TMS on the right FEF. Error bars represent the SEM. * indicates a significant difference as revealed by planned comparisons (p<.05).

7.4 Discussion

The focus of attention can be adjusted in its size in order to process information from a narrow (zoom-in) or a broad (zoom-out) region of the visual field. Two processes control the attentional zooming: an early, short-lasting process that automatically adjusts the focus of attention to the object size and a later, long-lasting process that voluntarily maintains attention on a focus (Turatto et al., 2000). However, the brain areas devoted to control the size of the attentional focus in striate and extrastriate visual cortex (Müller et al., 2003) have not been clarified yet. Our findings are the first prove that FEF plays a causal role in the automatic modulation of the attentional focus size.

Our behavioral results showed that when participants were induced to broaden their focus of attention onto a large cue, the "attentional gradient" (i.e., difference in RTs between the farthest and the nearest eccentricity) was nullified, indicating an efficient spread of attentional resources. On the other hand, when participants were induced to narrow their focus of attention onto a small cue, the attentional gradient arose, indicating an efficient zoom-in mechanism.

It is important to note that we observed a focus size-dependent modulation only at 100 ms cue-target SOA, while with longer SOAs the attentional zooming mechanism decayed,

supporting the existence of a short-lasting process that automatically adjusts the focus of attention (Turatto et al., 2000). The same time course is present also in typically developing children (Ronconi et al., 2012, 2013b). These results show that the modulation of the attentional focus size were measured, rather than a simple perceptual facilitation due to the lateral small or large cue boundary. No theoretical reasons suggest that this perceptual facilitation should be present only at the first SOA. One could argue that the cue did not operate to focused or spread attentional resources, but simply served as an exogenous lateralized cue. This alternative hypothesis seems unfounded given the pattern of results we observed. A lateralized facilitation in the large cue condition should induce an inverse attentional gradient (e.g. slower RTs near the fixation and faster RTs at the locus of the cue boards), whereas we found a flattened detection speed across eccentricities when participants spread their focus of attention.

In Experiment 2 we applied single-pulse TMS to interfere with the control of the attentional focus size. Our results clearly show that only TMS to the right FEF interferes with the modulation of the attentional focus size at the first cue-target SOA. When single-pulse TMS was delivered on right FEF 70 ms after the large cue onset, the attentional gradient persisted, demonstrating that the zoom-out of the attentional focus was impaired. Similarly, when single-pulse TMS was delivered on right FEF 70 ms after the small cue onset, the zoom-in mechanism was inhibited. On the contrary, when TMS was delivered simultaneously to the cue onset participants succeed in the automatic modulation of the size of their attentional focus according to the area delimited by the spatial cue.

The use of two different TMS timings was important because it allowed us to exclude indirect and non-specific effects of FEF stimulation in early visual areas (Ruff et al., 2006, 2008). Only single-pulse TMS delivered 70 ms after the cue onset inhibited the regulation of the attentional focus size. The efficacy of the 70 ms TMS timing in interfering with the focus

size modulation is compatible with the latencies of FEF neuron response after the onset of a visual stimulus (Bullier, 2001). In contrast, the stimulation of the left FEF did not interfere with the modulation of the attentional focus size. The fact that TMS affects the attentional focus only when delivered on the right FEF, appears to be another strong argument against the interpretation of our results in terms of perceptual facilitation.

Since attentional zooming modulates visual search (e.g., Greenwood and Parasuraman, 1999), right hemisphere specialization in controlling the size of the attentional focus is consistent with previous studies revealing the causal role of the right FEF in visual conjunction search performance (e.g., Ashbridge et al., 1997; Muggleton et al., 2003). The present results are also in agreement with the evidence revealing the causal role of the right FEF in modulating the activity of the striate and extra-striate visual cortices (Ruff et al., 2006; Taylor et al., 2007).

Although our results demonstrated the role of the right FEF area in controlling the adjustment of the focus size, other areas could also be involved. Another possible candidate in playing a role in the attentional focus modulation could be the right posterior parietal cortex (PPC; e.g., Halligan and Marshall, 1993; Ruff et al., 2009; Taylor et al., 2007). This area is an important component of the attentional network in human and non-human primates (e.g., Bisley and Goldberg, 2003; Saalmann et al., 2007; see Vidyasagar, 1999 for reviews) and it is strongly interconnected with the FEF (e.g., Buschman and Miller, 2007; Kveraga, et al., 2007; see Corbetta and Shulman, 2002, 2011 for reviews). Future researches could directly investigate the role of the PPC in the attentional focus control, employing a similar paradigm, but varying the TMS timing. In support of the role of PPC in the modulation of the attentional focus, Chen and colleagues (2009) employed a different experimental paradigm with fMRI and revealed shared activations for both zoom-in and zoom-out conditions in the right posterior temporoparietal junction. The combination of our findings and the previous

literature suggest that a right network of brain areas, including the FEF and PPC, could be involved not only in attentional orienting (Corbetta and Shulman, 2002, 2011) but also in the attentional focus size control.

These findings have important implications autism spectrum disorders (ASD) that as we have seen in Chapter 2 have been associated with an impaired zoom-out attentional mechanism (Mann and Walker, 2003; Ronconi et al., 2012, 2013b). One of the leading hypotheses about the neural disorders in ASD proposes that autistic brain is characterized by a short-range hyper-connectivity (i.e., within local neural districts) and long-range hypo-connectivity (i.e., across different brain areas; Belmonte et al., 2004). In particular, one of the most impaired long-range connections is between frontal and occipital lobe (e.g., Courchesne and Pierce, 2005; Barttfeld et al., 2010). Thus, the present study, showing the critical role of right FEF in the attentional focus size control, supports the dysfunctional fronto-occipital connection hypothesis for the attentional zoom-out deficit in children with ASD.

The importance of these findings for ASD will be more extensively discussed in the final chapter.

CHAPTER 8 - THE NEURAL UNDERPINNINGS OF THE ZOOMING MECHANISM – PART II: NEURAL DYNAMICS OF THE ATTENTIONAL ZOOM-LENS AS REVEALED BY DENSE-ARRAY EEG.

8.1 Introduction

In the previous experiment (Chapter 8), we showed that TMS applied to the right frontal eye fields area can disrupt the zoom-lens mechanism in typical adults participants. However, this result gives only a limited picture of the more complex neural network that is recruited when we have to adapt the size of the attentional focus. In the present experiment, we used dense-array electroencephalography (d-EEG) to better investigate neural events associated to the modulation of the attentional focus size. EEG is a powerful tool to investigate with high temporal resolution neural events that characterized a certain cognitive process. With recent advances in technology and the advent of d-EEG (i.e. multi-channels, usually 64 or more channels in a cap), we can now apply a big quantity of electrodes quickly and without painful scalp abrasion. Increasing the number of electrodes turns directly in better spatial resolution of the neuroelectric signal. Consequently, d-EEG, can be used on the one hand to investigate large scale response of neuronal population locked to an event, commonly referred as event-related potential (ERP), and on the other hand to finally estimate deep neural sources at the cortical level that are the generators of electrical activity measured outside the scalp.

Studies that attempted to identify the neurophysiological correlates of the orienting mechanism demonstrated that target appearing in the attended location, where attentional resources are invested, elicits larger P1 and N1 as compared to the unattended location, where attentional resources are withdrawn (see Luck et al., 2000 for a review). According to

these findings it is reasonable to postulate that for central targets, P1 and N1 in the small cue trials should be larger relative to large cue trials. Conversely, for peripheral targets, P1 and N1 in the large cue trials should be larger relative to small cue trials.

Only a few studies, to the best of our knowledge, have investigated ERPs associated to changing in the zoom-lens of attention (Luo et al., 2001; Fu et al., 2005). In a first study, Luo and colleagues (2001) tested the ERP correlates of the attentional zooming in a visual search task in which they varied the size of a cue that circumscribed the target region. They found that the amplitudes of the posterior P1 and N1 components of the ERP evoked by the target were affected in opposite ways by the cue size: P1 amplitude increased whereas N1 amplitude decreased as cue size increased (i.e., broader attentional focus). Their results, therefore, are partially coherent with predictions that can be made according to attentional orienting studies findings. Later, Fu and colleagues (2005) reported that attentional focusing modulated only the amplitudes of the P1 component, with zoom-in trials eliciting a larger P1 than zoom-out trials at both contralateral and ipsilateral sites. Thus, the picture of the ERP correlates of the attentional zooming is still fuzzy and the first aim of the present experiment is to clarify how different dimension of the attentional focus affect target-related ERP.

Evidence about the neural network controlling the zoom-lens of attention is also very limited. Only one study, to our knowledge, have tried to locate neural areas underliyng the control of the attentional zoom-lens with functional magnetic resonance imaging (fMRI) (Chen et al., 2009). This study highlighted that when compared with zoom-out condition, zoom-in differentially implicated the activation of the left anterior intraparietal sulcus (IPS), which may reflect the functional specificity of left anterior IPS in focusing attention on local object features. By contrast, zooming out differentially activated the right inferior frontal gyrus (IFG), which may reflect higher demands on cognitive control processes associated with enlarging the attentional focus (Chen et al., 2009). However, fMRI has really low temporal

resolution, thus providing limited evidence on the dynamics of neural operations involved in the attentional zooming. The second goal of the current study is, therefore, to investigate with very high temporal precision the neural network and the timing of neural operations that underlies the control of the attentional zoom-lens. To this aim, scalp-recorded EEG data were analyzed with a source reconstruction method in the cue-target interval.

8.2 Method

8.2.1 Participants

Twenty adult participants took part in the present study as paid volunteers. Three participants were excluded from analysis because less than 60% of their experimental trials were retained after artefact rejection procedures. Seventeen adult participants comprise the final sample for which EEG analysis was computed (8 male, mean age=23.7, age range=20-27). Participants provided informed consent, had normal or corrected-to-normal vision and normal hearing. They reported no history of psychiatric/neurological disorders. The study was approved by the Ethics Committee of the Department of General Psychology at the University of Padua and was conducted according to the principles elucidated in the Declaration of Helsinki.

8.2.2 Stimuli and procedure

The experiment was presented on a Dell LCD monitor (19 inch, refreshing at 75 Hz). Stimuli presentation and data acquisition were performed using E-Prime 2.0 (Psychology Software Tools, Inc.).

Stimuli and procedure were mostly identical to those used in the previous experiment (see Chapter 7), except for the stimulus onset asynchronies (SOA) used that was uniquely set to 500 ms and the response device that was an electrically shielded response pad. Experimental

trials were totally 328: 288 real trials (2 cue size × 2 SOA × 2 target eccentricity × 36 repetitions) and 40 catch trials in which no target was presented).

8.2.3 EEG Recording and pre-processing

Testing occurred individually in a dimly lit and electrically isolated room. EEG was recorded using the Electrical Geodesics system and a 128-channel Hydrocel Geodesic Sensor Net (Electrical Geodesics, Inc.). The sampling rate was 500 Hz, and input data were analog-filtered between 0.01 and 100 Hz.

Data analysis was performed with EEGLAB 12.0.2 (Delorme and Makeig, 2004), a freely available open source software toolbox (Swartz Center for Computational Neurosciences, La Jolla, CA; http://www.sccn.ucsd.edu/eeglab) running under Matlab (MathWorks, Inc, Natick, MA). Offline, data were down-sampled at 250 Hz, recomputed to an average reference, notch-filtered at 50 Hz and band-pass filtered between 0.1 and 30 Hz. Continuous EEG data were then segmented to -200 +500 ms relative to the target onset – for target-related analysis – and -200 +700 ms relative to the cue onset – for the cue-related analysis (see following paragraphs). Interpolation was carried out on individual bad channels if required (3.3% and 2.7% channels interpolated on average for target- and cue- locked trials respectively, range 1.5-8.6% and 0-8.6%). Epochs containing eye movements were discarded. Activity evoked by eye-blinks or electrocardiogram was detected using the Independent Component Analysis (ICA). ICA-derived components that clearly were artifactual in their nature were removed. Moreover, epochs containing voltage deviation that exceeds ±100 μV were also removed. Across participants, 88.9% and 90.4% of trials were retained after artifact rejection for the target-locked and the cue-locked analysis, respectively.

8.2.4 Data Analysis – Behavioral performance

Reaction times (RTs) of correct responses were analyzed by using a repeated measures ANOVA, with the following within-subjects factors: type of cue (small vs. large) and target eccentricity (2 deg vs. 12 deg).

8.2.5 Data Analysis – Target-locked ERP

As stated in the previous paragraph, the time-window for the analysis of the target-locked activity ranged from -200 to +500 ms relative to the target onset. Data were analyzed with a classical ERP approach. Regions of interest (ROI) were located in two parieto-occipital clusters of electrodes above the left (channels: 59, 60, 65, 66, 67, 70, 71) and the right hemisphere (channels: 76, 77, 83, 84, 85, 90, 91). Peak amplitude for P1 (100-150 ms) and N1 (175-225 ms) in the identified electrodes' cluster was subjected to two repeated-measures ANOVA (one for left-displayed and one for right-displayed targets) with the following within-subject factors: ROI (left vs. right), type of cue (small vs. large) and target eccentricity (2 deg vs. 12 deg).

8.2.6 Data Analysis – Cue-locked activity and estimation of neural sources

Since this is the first study that investigates the neuroelectric events associated to the zooming of visual attention in the cue-target period, we had no *a priori* assumptions about possible ROI and time windows. For this reason, we used a mass univariate approach in the analysis of cue-related activity. This approach is superior to conventional ANOVA-based analysis of event-related brain potentials (ERPs) in that it requires fewer a priori assumptions and can provide greater temporal and spatial resolution of the phenomenon under investigation (Groppe et al., 2011).

To detect reliable differences between the ERPs elicited by the small and the large cue, we performed a series of two-tailed repeated measures permutation tests based on the "tmax" statistic (Blair & Karniski, 1993), with a family-wise alpha level of 0.01. The tmax statistic was chosen for this permutation test because it has been shown to have relatively good power for data (like ERPs) whose dimensions are highly correlated (Hemmelman et al., 2004). The time window between 0 and 500 ms (corresponding to the cue and target onset, respectively) was divided in ten 50 ms-windows. Thus, 10 time windows at all 128 scalp electrodes were included in the test (i.e., 1280 total comparisons), and 5000 random within-participant permutations of the data were used to estimate the distribution of the null hypothesis. Based on this estimate, critical t-scores of ±6.11 were derived. In other words, any differences in the original data that exceeded a t-score of ±6.11 (corresponding to a p-values<.0096 with df=16) were considered reliable.

Source reconstruction was then performed with Brainstorm (Tadel et al., 2011), an open source software for the analysis of EEG and MEG data which is documented and freely available for download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm). Individual averaged ERP were used to estimate neural activity by applying a depth-weighted minimum-norm estimation inverse solution (Baillet et al., 2001) with constrained dipole orientation (i.e., at each vertex of the cortex surface, there is only one dipole, and that its orientation is the normal to the cortex surface at this point). A cortical mesh template surface, composed by 15000 vertices and derived from the default anatomy of the Montreal Neurological Institute (MNI/Colin27), was used as a brain model to estimate the current source distribution. To compute the forward model we employed a symmetric boundary element method (symmetric BEM) with the OpenMEEG software (Kybic et al., 2005; Gramfort et al., 2010; http://www-sop.inria.fr/athena/software/OpenMEEG/).

8.3 Results

8.3.1 RT data

ANOVA performed on corrected mean RTs revealed a main effect of target eccentricity ($F_{(1,16)}$=40.17, p<.001, η^2_p=.71), and importantly a significant type of cue by target eccentricity interaction ($F_{(1,16)}$=23.50, p<.001, η^2_p=.59; Figure 8.1). Planned
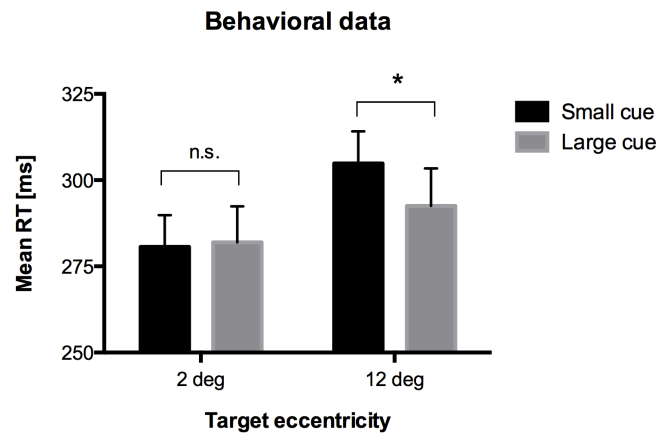

Figure 8.2 Behavioural data. Mean RTs are displayed as a function of target eccentricity and cue size.

comparisons revealed that for target displayed at 2 deg there were no difference in RTs for the two cue conditions (small: 280±9 ms; large: 282±10 ms; $t_{(16)}$=-0.36). In contrast, the large cue led to faster RTs relative to the small cue (small: 305±9 ms; large: 292±11 ms; $t_{(16)}$=3.73, p=.002) for target displayed at 12 deg.

8.3.2 Target-locked ERP – P1

ANOVA performed on the P1 peak amplitude elicited by target displayed on the right visual hemifield revealed main effects of eccentricity ($F_{(1,16)}$=7.56, p=.014, η^2_p=.32) and ROI ($F_{(1,16)}$=12.31, p=.003, η^2_p=.43). P1 elicited by target at 2 deg (mean±SEM: 1.20±.29 µV) were larger than P1 elicited by target at 12 deg (0.48±.22 µV), and the P1 registered left parieto-occipital electrodes (0.50±.22 µV) was smaller than P1 registered at right parieto-occipital electrodes (1.19±.22 µV). No significant interaction emerged.

ANOVA performed on the P1 peak amplitude elicited by target displayed on the left visual hemifield revealed no significant main effects, but a significant type of cue by eccentricity by ROI interaction ($F_{(1,16)}$=7.25, p=.016, η^2_p=.31). This interaction was explored by the means of

planned comparisons, but no significant difference emerged when target at the same eccentricity were compared between the two cue conditions, neither for P1 elicited in the contralateral nor in the ipsilateral ROI.

8.3.3 Target-locked ERP – N1

ANOVA performed on the N1 peak amplitude elicited by target displayed on the right visual hemifield revealed a main effect of eccentricity ($F_{(1,16)}$=21.72, p<.001, η^2_p=.58), showing that overall central targets elicited a larger N1 amplitude relative to peripheral targets (2 deg=-2.72±.25 µV; 12 deg=-1.83±.22 µV). Also the main effect of ROI was significant, indicating that the N1 amplitude was larger for the parieto-occipital left (-3.36±.28 µV) relative to the parieto-occipital right (-1.19±.28 µV) cluster of electrodes ($F_{(1,16)}$=34.24, p<.001, η^2_p=.68). Importantly, a type of cue by eccentricity by ROI emerged ($F_{(1,16)}$=6.92, p=.018, η^2_p=.30). This interaction was explored by the means of planned comparisons. Target appearing at 2 deg elicited a larger N1 when anticipated by a small relative to a large cue in the contralateral ROI (parieto-occipital left ROI: $t_{(16)}$=-2.39, p=.029; parieto-occipital right ROI: $t_{(16)}$=-1.15, n.s.). Target appearing at 12 deg, on the other contrary, elicited a larger N1 when anticipated by a large relative to a small cue in the contralateral ROI (parieto-occipital left ROI: $t_{(16)}$=2.73, p=.015; parieto-occipital right ROI: $t_{(16)}$=1.50, n.s.).

ANOVA performed on the N1 peak amplitude elicited by target displayed on the left visual hemifield revealed only a main effect of eccentricity ($F_{(1,16)}$=5.07, p=.039, η^2_p=.24; 2 deg=-2.31±.22 µV and 12 deg=-1.57±.28 µV). However, if we test the same comparisons performed for left hemi-field target, they reveal that target appearing at 12 deg elicited again a larger N1 when anticipated by a large relative to a small cue in the contralateral ROI (parieto-occipital right ROI: $t_{(16)}$=2.26, p=.038; parieto-occipital left ROI: $t_{(16)}$=.93, n.s.).
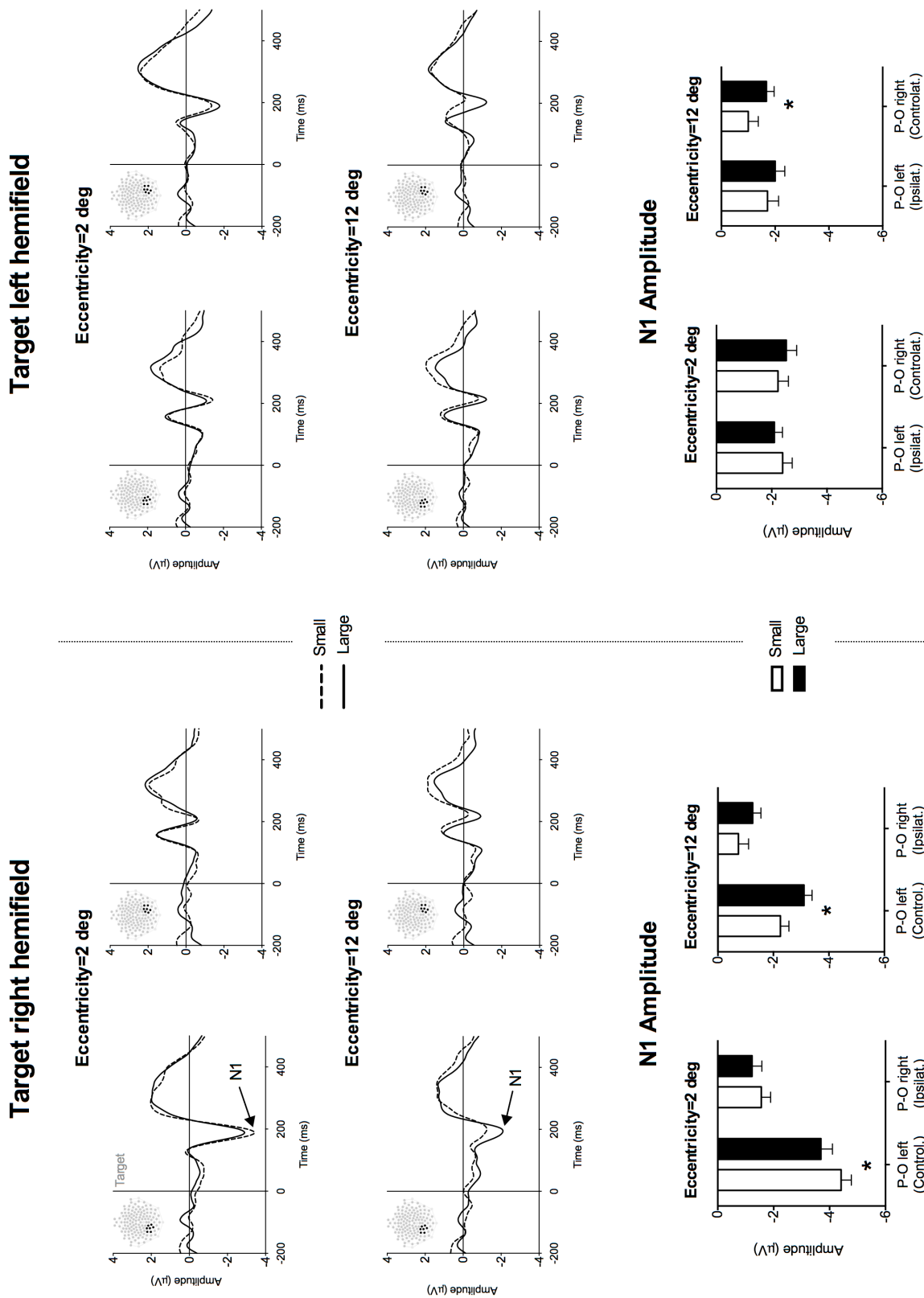
Figure 8.2 Waveforms elicited by left- and right- displayed target for each combination of cue size (small vs. large) and target eccentricity (2 vs. 12 deg). Bar plots depicted the N1 peak amplitude with * denoting a significant difference (p<.05) between the large and the small cue condition. Clusters of channels used to compute waveforms and N1 peak amplitudes are marked in black.

8.3.4 Scalp recorded neural activity and related brain sources in the cue-target interval

Our general approach was to analyze the difference between the large and the small cue condition both at the channels and the sources level. Mass univariate analysis using permutation tests with the t-max correction for multiple comparisons revealed that three out of ten temporal windows showed a significant difference when the large and the small cue condition were compared: i) 150-200 ms (channels: 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 21, 22, 53, 60, 61, 62,66, 71, 72, 128); ii) 250-300 ms (channels: 4, 5, 6, 7, 9, 11, 12, 15, 16, 18, 19, 22, 23, 65, 66, 70, 84, 89, 90, 96, 97, 112); and iii) 300-350 ms (channels: 3, 4, 9, 10, 11, 12, 16, 18, 19, 20, 22, 24, 27, 28, 60, 66, 67, 70, 71, 73, 74, 75, 81, 82, 88, 89, 124). Figure 8.3 show the butterfly plot of all 128 channels obtained from the difference between the large and the small cue condition for all the ten temporal windows, with related scalp maps. Channels that showed significant difference in the two cue conditions are marked in white. Two neural events are clearly discernable, one more transient activity in the 100-200 ms temporal window and one more sustained activity after 200 ms.

Estimated neural sources are displayed in Figure 8.4. Red/yellow area depicted greater activation for the large as compared to the small cue condition, whereas dark/light blue area depicted greater activation for the small as compared to the large cue condition. To use a conservative approach to sources data, we consider as reliable only significantly activated neural sources in the three temporal windows (i.e., 150-200; 250-300 and 300-350 ms) that differed between the two cue conditions at the channels level. Moreover, we considered as reliable only cortex activations that emerged significantly for at least 24 neighboring vertices.
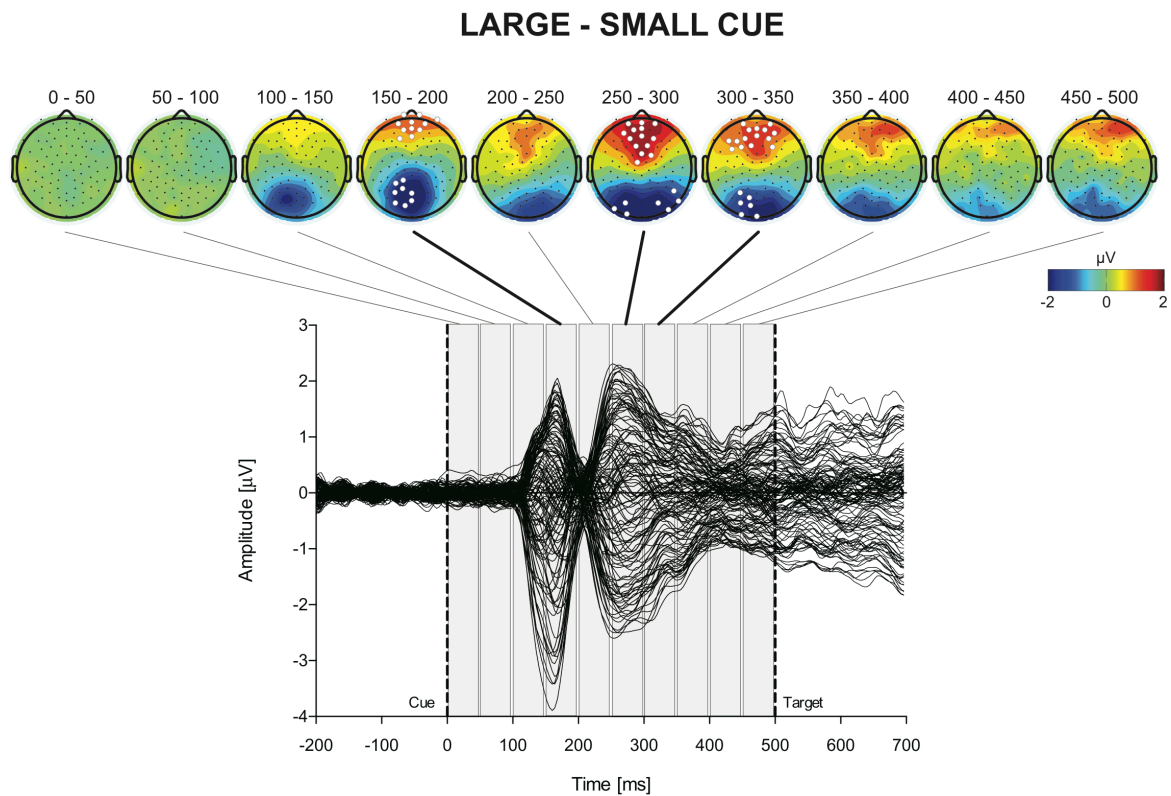
LARGE - SMALL CUE

Figure 8.3 Butterfly plot of all 128 electrodes and related scalp maps obtained by subtracting small cue trials (zoom-in) from large cue trials (zoom-out). For the scalp maps, neural activity was averaged over ten 50ms-time windows between the cue and the target onset. White-marked channels are channels that showed a significant difference between the two cue conditions as revealed by permutation tests with the "t-max" correction.

In the 150-200 ms temporal window, large cue led to significantly increased activation in the superior parietal lobule of the left hemisphere, and bilaterally in the superior/middle frontal gyrus and in the inferior frontal junction/gyrus. On the contrary, small cue led to significantly increased activation in the left intraparietal sulcus. In the 250-300 ms temporal window, bilateral activation of the middle temporal gyrus were observed, that persist in the right middle temporal gyrus also during the 300-350 ms window. Moreover, in both the 250-300 and 300-350 ms temporal windows, we found neural sources in the inferior frontal gyrus and insula of both hemispheres. Interestingly, increased activation for the zoom-out condition in the IFG was observed in all the three temporal windows. Table 8.1 reports coordinates of the points of maximum activation in the three significant temporal windows.

Table 8.1 Area labels, coordinates [x,y,z] in the MNI and Talairach systems and Brodmann areas relative to the points (vertices) of maximum activation in the cortex surface.

AREA LABELS	MNI COORDINATES	TALAIRACH COORDINATES	BRODMANN AREAS
Zoom-in > Zoom-out			
Left IPS	-24, -73, 40	-24, -69, 37	7
Zoom-out > Zoom-in			
Left SPL	-18, -44, -68	-17, -48, 56	7
Right IFG/J	51, 1, 18	48, 0, 20	9
Left IFG/J	-36, 5, 31	-35, 4, 30	6
Right FEF	26, 9, 49	26, 11, 46	6
Left FEF	-25, 27, 43	-25, 25, 40	8
Right MTG	43, -64, 20	44, -62, 21	39
Left MTG	-42, -61, 22	-42, -59, 23	39
Right Insula	33, -29, 15	32, -28, 16	13
Left Insula	-41, -10, 19	-39, -10, 19	13
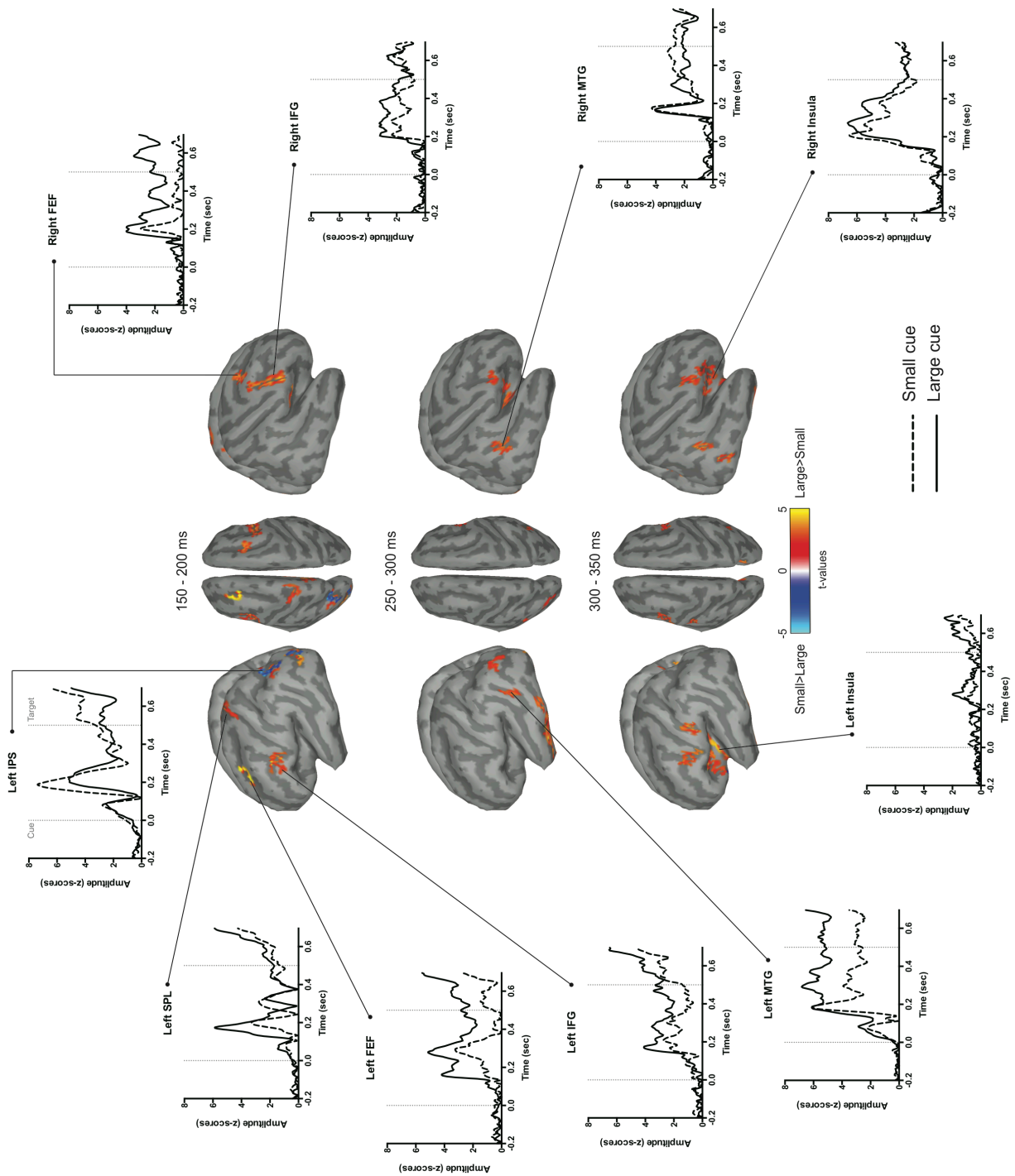
Figure 8.4 Source activations in the cue-target time interval for the three temporal windows in which the two cue conditions differed one each other are displayed. In the cortical maps, red/yellow activations represent greater activity for large relative to small cue trials, whereas dark-/light-blue activations represent greater activity for small relative to large cue trials. The entire time course of activations (z-scores of the point of maximum activation normalized by the -200/+0 baseline period) are also plotted for each significantly activated region.

8.4 Discussion

The present experiment clarifies both the effect of processing visual target with different sizes of the attentional focus at the ERP level and the cortical sources underlying the control of the attentional zoom-lens.

The ERPs results show that the effect of the cue-size was reflected in the amplitude of the target-related N1 registered at posterior electrodes. Targets appearing in the central position evoked a larger N1 when anticipated by a small cue as compared to a large one. Conversely, targets appearing in the peripheral position elicited a larger N1 when anticipated by a large cue as compared to a small one. This is in agreement with the zoom-lens model of the attentional focus (Ericksen and St. James, 1986; Castiello and Umiltà, 1990; see also the gradient model of attentional resources by La Berge and Brown, 1989) that predict that when participants see the small cue before the target appearance, their attentional resources are focused onto the narrow portion of the visual field delimited by the cue, with very rarefied resources outside the attentional focus. On the contrary, the large cue led attentional resources to be spread almost uniformly in a broader portion of the visual field. The larger target-evoked N1 amplitude in our paradigm was directly reflecting the degree of attentional resources deployed for target processing, with more attentional resources (i.e., when central targets were preceded by a small cue or when peripheral targets were preceded by a large cue). These results is in agreement with a wide literature concerning the effect of attentional orienting on target related ERPs, that largely demonstrate that N1 elicited for attended targets are larger as compared to N1 elicited by unattended targets (see Luck et al., 2000 for a review). The evidence of N1 modulation induced by different sizes of the attentional focus is also consistent with one of the two studies that in the past aimed to test the ERPs correlates of the scaling of the attentional focus size. Luo et al. (2001) found that in a visual search task where the target appeared always inside the cue, the amplitude of the N1 decreased as the cue

size increased. Our results, contrarily to those reported by Luo et al (2001) and Fu et al. (2005), that however reported opposite findings, did not revealed a clear modulation of the P1 amplitude. Further studies are probably necessary to clarify the P1 modulation by attentional zooming.

The second aim of the present high-density EEG study was to analyze neural events in the cue-target time interval to better understand the neural mechanisms that allow us to change the ongoing size of the attentional focus. The results show that two clearly discernable neural events characterized the cue-target time interval, one in the 100-200 ms time range and one that extended after the 200 ms until the target appearance, confirming previous claims of a dissociation between a transient (automatic) and a sustained (voluntary) control of the attentional zooming mechanism (Turatto et al., 2000). With a data-driven and statistically robust approach we demonstrated that large and small cue differed in the neural evoked response in three out of ten selected time windows (150-200, 250-300 and 300-350 ms) and the effect was extensively visible in both parieto-occipital and frontal electrodes. Analysis of the neural sources in these three time windows showed that when compared to the zoom-out condition, the zoom-in of the attentional focus was associated to greater activations of the left intra-parietal sulcus (IPS). This result is in agreement with what reported by Chen and colleagues (2009) with fMRI. On the other, when compared to the zoom-in condition, the zoom-out of the attentional focus was associated initially to greater activations in the right superior parietal lobule (SPL) and bilaterally in the superior/middle frontal gyrus – including the frontal eye fields (FEF) – and in the inferior frontal gyrus (IFG). After this initial pattern of activity, the zoom-out condition led to greater activations bilaterally in the middle temporal gyrus (MTG) and in the insula (INS). Notably, increased activation for the zoom-out condition in the IFG was observed in all the three temporal windows, and is consistent with what was previously reported by the fMRI study of Chen and colleagues (2009).

Although not observed in the study by Chen et al. (2009), FEF activation is consistent with what we reported in the previous experiment, where we found that TMS applied over the right FEF area disrupted both the zoom-in and the zoom-out of the attentional focus (see Chapter 7; Ronconi et al., 2014a). Here, activation of the FEF area was bilateral, and this can be explained in different ways. One possibility could rely on the employment of a longer SOA in the present study. While a more automatic (transient) control of the zoom-lens – as in the case of the previous TMS study, where the SOA was 100 ms – involve especially the right FEF, a more voluntary (sustained) control of the zoom-lens – as in the present experiment, where the SOA was 500 ms – could recruit also FEF of the left hemisphere. Another possibility is that, given the right hemisphere dominance for spatial attention control (Kinsbourne, 1987; Corbetta and Shulmann, 2002, 2011), when disrupting the left FEF activity, the right FEF is still strong enough to control the size of the attentional focus by itself, while when disrupting the right FEF, the activation of the left FEF alone is not sufficient to perform the zoom-lens modulation.

The critical difference between the zoom-out and the zoom-in mechanisms in the current experiment is that attentional resources are more widely spatially distributed in the former case. This should be reflected in a spatially broader activation in occipital visual areas, as demonstrated by Müller and colleagues (2003). It is largely demonstrated that frontal cortex modulates the neural processing in the posterior visual cortex with direct top-down feedback (Miller and D'Esposito 2005; Rowe et al. 2005; Ruff et al., 2006, 2008), and the greater degree of activations in various parts of the frontal lobe (FEF and IFG) that we found in the zoom-out condition could be due to increased top-down modulation of visual cortex. Importantly, our data suggest also that two phases of activation in the cue-target interval are clearly discernable. The activity was initially distributed in a more dorsal network (150-200 ms), and subsequently there was a clear shift toward activations mostly distributed in a

ventral network (250-300 and 300-350 ms). Recent neurophysiological models obtained by examining correlations in spontaneous fluctuations of the fMRI signal while neurologically intact adult participants were in a resting state (i.e., absence of a cognitive task) showed the existence of two distinct attentional network (Fox et al., 2006; He et al., 2007; Corbetta and Shulmann, 2011): i) a dorsal attention network that includes IPS and FEF of both hemispheres and is thought to control the spatial mechanism of attention (i.e., spatial coding), and; ii) a ventral attention network, largely right-lateralized, that includes the region of temporo-parietal junction and ventral frontal cortex (including IFG) and is thought to control the non-spatial mechanisms of attention (i.e. response preparation, arousal and temporal attention). The location and timing of activations we found in the present study seems to be consistent with the dorsal/ventral attention network model. The initial activations we observed were mainly located in the dorsal regions (IPS, SPL and FEF). These regions may be the generators of the spatial coordinated for the size of the attentional focus. Subsequently, activations moved to a more ventral network (IFG, MTG and Insula), which may operate to maintain high level of alertness until the target appearance. The current dimension of the attentional focus modulated the ventral network activation (i.e., larger activations in the zoom-out condition), suggesting that a broader attentional focus size required higher level of alertness and response preparation. Interestingly, the only activation that persists for all the three temporal windows is the activation in the IFG, a region that shows resting-state connectivity with both dorsal and ventral networks (He et al. 2007), and that some authors proposed may act as a pivot area between to attentional networks (Corbetta and Shulmann, 2011).

The importance of these results in understanding the zoom-out attentional impairments found in ASD will be discussed in the last chapter of general discussion.

CHAPTER 9 - BEYOND THE SPOTLIGHT AND THE ZOOM-LENS MODELS: THE "MEXICAN HAT" OF THE ATTENTIONAL FOCUS IN ASD

9.1 Introduction

As we have seen in Chapter 2, many efforts have been made to understand the way in which individuals with ASD deploy their visual attention to select relevant information in the environment (for a review see Ames and Fletcher-Watson, 2010). The focus of spatial attention has been traditionally viewed as a simple "spotlight", that can moves to a specific region in the visual space, improving information processing in the attended area at the expense of other locations (Posner et al., 1980; Posner and Petersen, 1990; Corbetta and Shulman, 2002). In addition, the attentional focus can be adjusted in its size in order to process information from a broad or a narrow region of the visual field – like a "zoom-lens" (Eriksen and St. James, 1986; Castiello and Umiltà, 1990; Turatto et al., 2000). Several investigations used these two theoretical accounts to investigate how individuals with ASD deploy their attention in the visual field. It has been consistently reported that ASD is associated to impairment in disengaging attention from a previously cued location (Courchesne, Townsend, Akshoomoff, Saitoh, Yeung-Courchesne, Lincoln, et al., 1994; Landry and Bryson, 2004; Wainwright-Sharp and Bryson, 1993), and a recent longitudinal study revealed that this deficit in the disengagement of visual attention measured in infants at risk for developing ASD is associated to the later emergence of autism in toddlerhood (Elsabbagh et al., 2013). Moreover, increasing evidence demonstrate that individuals with ASD manifest an overfocused attention and an impairment in "zooming-out" the attentional focus, that is the ability to spread the attentional resources in a broad portion of the visual

field (Mann and Walker, 2003; Roberston et al., 2013; Ronconi et al., 2012; 2013b; Study 1 - Chapter 4 of the present thesis).

In the light of these evidence, some authors suggest that high-level deficit in social orienting may originate from early impairments in low-level attentional systems (Landry and Bryson, 2004; Elsabbagh et al., 2009). For example, the inability to flexibly shift the locus of spatial attention could lead to problems in visual orienting toward social stimuli (Mundy and Newell, 2007; Elsabbagh and Johnson, 2010). Similarly, the difficulties in broadening the focus of attention could cause abnormalities in the spatio-temporal visual integration, with cascade effect in the processing of dynamic stimuli, as faces and actions with biological meaning (Mann & Walker, 2003; Ronconi et al., 2012).

Both the spotlight and the zoom-lens models predict that the attentional resources are concentrated at their maximum at the center of the attentional focus, and then shade progressively (with a linear spatial gradient) while the distance from the attentional focus increases. However, these models do not represent the all picture of how attention selects relevant visual objects in an ecological environment. The focus of attention, indeed, is not always characterized by a simple spatial gradient that falls off monotonically with increasing distance from the focus center. On the contrary, recent neurophysiological model demonstrate that visual selection requiring spatial scrutiny for object recognition elicits – in the immediate surround of the attentional focus – a zone of attenuated excitability, forming a profile that resembles a "Mexican hat" (Caputo & Guerra, 1998; Slotnick et al., 2002; Müller and Kleinschmidt, 2004; Müller et al., 2005; Hopf et al., 2006; Boehler et al., 2011). Hopf and colleagues (2006) argued that this inhibitory ring surrounding the focus of attention is optimal to highlight relevant information and attenuate the deleterious noise during visual object selection.

The aim of the present study was to evaluate the spatial profile (i.e., the Mexican hat) of the attentional focus in individuals with ASD. This question is particularly important to understand the way in which individuals with ASD deploy spatial attention in the visual space and how they select relevant visual information. A huge amount of evidence associated ASD with higher performance in detail-oriented task (for reviews see Simmons et al., 2009; Dakin & Frith, 2005; Pellicano & Burr, 2012). Individuals with ASD display faster detection of targets in visual search tasks (O'Riordan et al., 2001; Joseph et al., 2009) and in the Embedded Figure Test (Jolliffe & Baron-Cohen, 1997; Manjaly et al., 2007), and show also a better tolerance to visual crowding (Baldassi et al., 2009; Keïta et al., 2010). One might expect a detail-oriented perception to be associated also to a reduced interference from incongruent/irrelevant information. However, both clinical and experimental reports are fairly clear in showing that this is not the case. One of the first studies that highlighted this contradictory aspect was made by Burack (1994). Participants performed a forced-choice reaction time (RT) task to assess the filtering component of selective attention. The manipulated variables were the presence/absence of a window that narrowed the attentional spotlight and the presence of a variable number of distractors. The RTs of the subjects with ASD improved relative to the other groups in the presence of the window without distractors, but the performance of the ASD group was the most impaired in the presence of distractors. A recent study employing an Eriksen flanker task manipulated target-flanker distance and showed an increased interference effect across all distances in individuals with ASD (Adams and Jarrold, 2012). Moreover, in a recent study we showed that when lateral competing information is presented close in time to a central target, children with ASD suffered for a deeper and prolonged backward interference (that we referred as an "attentional masking" effect) in respect to controls (Ronconi et al., 2013a). In addition to these experimental evidence, visual sensory overload is traditionally associated to ASD, and has been well

documented not only in autobiographical reports (Grandin, 2009) but also with caregiver-report questionnaires (Kern et al., 2006; Leekam et al., 2007) and electrophysiological studies (Pritchard et al., 1987; Belmonte, 2000).

Thus, the central question of the present study is: How individuals affected by ASD process visual information at different degrees of proximity from the attentional focus? The answer to this question can be particularly relevant to understand the discrepancy between strong attention to details and deeper interference by irrelevant visual objects in ASD. To measure the spatial profile of the attentional focus we readapted the behavioral paradigm developed by Hopf and colleagues (2006). Children with ASD and an age- and IQ- matched sample of typically developing (TD) peers were asked to perform a computerized task in which they were asked initially to fixate the center of the screen. Their attention was captured onto a color pop-out target (red C) among an array of non-target stimuli (blue Cs). In half of the trials (baseline condition), their task was to recognize the orientation of the red C that changed position from trial to trial. In the other half of the trials (probe condition), after the red target C a probe circle circumscribed a region containing a non-target C at various distances from the red target C. This latter condition allowed measuring the spatial profile (i.e., the inhibitory ring or Mexican hat) of the attentional focus.

9.2 Methods

9.2.1. Participants

Forty-six children took part in the experiment. Both the ASD and TD groups comprised initially 23 children each. Four participants from the ASD group and 1 from the TD group were excluded from statistical analyses because they did not achieve 40% of overall accuracy in the probe condition. Thus, the final samples comprised 19 children for the ASD group and 22 for the TD group.

All participants with ASD were recruited according to the following criteria: (i) full scale IQ > 70 as measured by the Italian version of Wechsler Intelligence Scale for Children-Revised (WISC-III, Wechsler, 1991); (ii) absence of gross behavioural problems; (iii) normal or corrected-to-normal vision and hearing; (iv) absence of drug therapy; and (v) absence of attention deficit hyperactivity disorder on the basis of DSM-IV criteria (American Psychiatric Association, 1994). Children with ASD were recruited at the Developmental Neuropsychology Unit of Scientific Institute "E. Medea" (Bosisio Parini, Italy) and at "Associazione La Nostra Famiglia" (Padua, Italy). Diagnosis of ASD was made by licensed clinicians experienced in the assessment of ASD in respect to DSM-IV diagnostic criteria and to the Autism Diagnostic Observation Scale (ADOS; Lord et al., 2002; see Table 9.1). Children of the TD group were randomly sampled in Padua public schools. According to the parents' report, TD children did not have prior history of any psychiatric disorders. Both groups were matched for chronological age ($t_{(39)}$=0.21, p=.831). Cognitive level in TD children was estimated with two Verbal (Vocabulary and Similarities) and two Performance (Block Design and Pictures Completion) subtests of the WISC-III (Wechsler, 1991). ASD and TD group did not differed in any of the four subtests (all ps>.272). The Social Communication Questionnaire (Rutter et al., 2003) was also administered to both groups. Children of the ASD group scored significantly higher in comparison to the TD group in both the Current ($t_{(39)}$=6.40, p<.001) and Lifetime ($t_{(39)}$=8.85, p<.001) forms.

The entire research protocol was approved by the ethical committees of both Scientific Institute "E. Medea" and Department of General Psychology of Padua University. Informed consent was obtained from each child and their parents and the entire research protocol was conducted in accordance to the principles elucidated in the declaration of Helsinki.

Table 9.1 Descriptive statistics for the two groups of participants (ASD=autism spectrum disorder; TD=typically developing).

	ASD (n=19)	TD (n=22)	p-value
	Mean (SD)	*Mean (SD)*	
Age	14.6 (2.7)	14.4 (2.6)	n.s
Gender	17 M	18 M	-
TIQ	100.11 (14.6)	-	-
WISC III - Vocabulary	10.17 (3.4)	10.1 (2.4)	n.s.
WISC III - Similarities	10.8 (2.8)	9.91 (2.4)	n.s.
WISC III – Picture completion	10.5 (3.3)	11.4 (2.4)	n.s.
WISC III – Block Design	10.33 (3.9)	10.77 (2.4)	n.s.
Social Communication Questionnaire (SCQ) - Current	13.0 (6.4)	3.05 (3.2)	<.001
Social Communication Questionnaire (SCQ) - Lifetime	18.8 (8.1)	2.6 (2.6)	<.001
ADOS - Communication	2.7 (1.3)	-	-
ADOS – Social Interaction	5.3 (3.0)	-	-

9.2.2 Apparatus and stimuli

The experiment was conducted in a dimly lit and quiet room. Participants were seated 50 cm far from an LCD screen (17 inch, 75 Hz). A chinrest was used to avoid head movement. Stimulus presentation and data acquisition were performed with E-Prime 2 (Psychology Software Tolls, Inc.). The choice about stimuli parameters was based on previous pilot observations.

All stimuli were presented on a middle grey background (RGB=142,142,142). Fixation point consisted in a black cross subtending a visual angle of 0.5 deg, presented on the screen center. The search array consisted on nine blue non-target Cs stimuli (RGB=4,61,245), while the target C was colored in red (RGB=242,18,42). Both target and non-target Cs subtended a

visual angle of 1.2 deg, and were presented at an isoeccentric distance of 8 deg from the fixation. All Cs were obtained by removing a portion subtending 45° of angle from a ring-shape stimulus. The gap of each C varied randomly in position (up, down, left, right).

One C was presented aligned with the horizontal axis, and the other Cs were presented four in the upper and four in the lower quadrant, separated by an angle of 0.26 rad one each other. The stimulus used as a probe consisted in a white circle with a diameter of 2.12 deg. Masks stimuli were obtained from the complete ring used to create the Cs stimuli.

9.2.3 Procedure

The procedure was adapted from previous studies on typical adults (Hopf et al., 2006, 2010). Children were instructed to keep their eyes on the fixation for the entire duration of the trial. The entire experiment was proposed to the children as a game ("The Naughty Turtle" game). Each trial started with the onset of the fixation cross, which lasted for 1000 ms. The array of nine randomly oriented non-target Cs then appeared unpredictably to the left or to the right side of the fixation. After 50 ms, a target C was colored in red for 100 ms, while the other Cs remained blue. On 50% of the trials (baseline condition, Figure 9.1, panel A), children were instructed search the red target C among the other eight blue non-target Cs. The target C appeared randomly at one of the nine possible stimulus locations, so that children were forced to focus their attention in different positions from trial to trial.

In the other 50% of the trials (probe condition, Figure 9.1, panel B), the appearance of the target red C was followed by the probe circle appearing around the central C for 50 ms. As the probe position was kept constant and the target position varied, there were five target-to-probe distances, called Probe Distance (PD), ranging from probe distance 0 (PD0; probe at the target location) through probe-distance 4 (PD4; probe at the farthest distance from the target; see Figure 9.1, panel C). Trials for the Baseline and the Probe condition were

randomly intermixed during the experiment, so that was impossible for participants to predict in advance the type of trial that they had to perform.

Subsequently, all Cs were replaced by the mask ring for 13 ms (one refresh of the monitor). After a blank screen displayed for 1000 ms, the response screen with the four possible orientation of the Cs was presented for an unlimited time. Participants then indicated the correct response, corresponding to the orientation of the red C in the baseline condition and to the orientation of the blue C surrounded by the probe circle in the probe condition. The experimenter than entered the selected choice by pressing the one of the four arrow keys on the pc keyboard. Children were specified that only accuracy was important and that no reaction times were collected.

The entire experiment consisted in 144 trials, 72 for the baseline and 72 for the probe condition, each one composed by 36 trials presented in the right and 36 trials in the left visual field, 4 for each of the nine position in the array. A practice session of 12 trials – accompanied by correctness feedbacks – was performed before starting the experiment, with stimuli presented at half of the speed and separated by wider spaces.
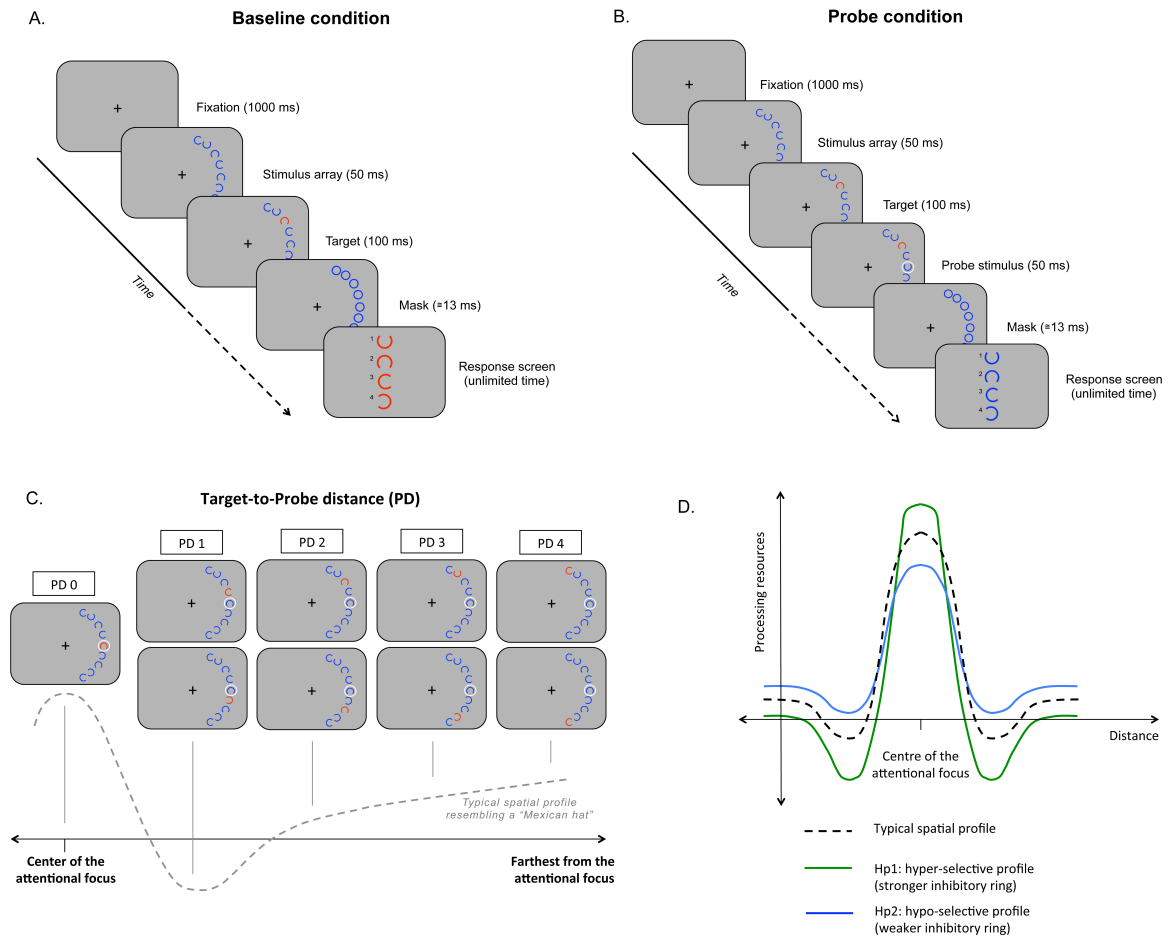
Figure 9.1 Schematic representation of the task procedure for: (a) baseline and (b) probe condition. (c) Relation between target-to-probe distance (PD) distances and the prediction of the Mexican hat model (Müller et al., 2005; Hopf et al., 2006) of the attentional focus. (d) Graph representing the two alternative hypotheses (Hp1 and 2) of the current study.

9.3 Results

Response accuracies were analyzed by two 5×2 mixed design ANOVA, one for the baseline and one for the probe condition. Both ANOVAs had as within-subjects factor the probe distance (or PD, with 5 levels: PD0, PD1, PD2, PD3, PD4), and as between-subjects factor the group (ASD vs. TD). Note that for the baseline condition, the variable PD – since the probe stimulus is absent – is used to identify the position of the target in the array (PD0 represents a target aligned with the horizontal axis, while PD1 to PD4 are progressively farther from it).

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9.3.1 Comparable performance between groups in the baseline condition

ANOVA performed in the baseline condition revealed a main effect of Probe Distance ($F_{(4, 156)}$=12.96, p<.001, η^2_p=.25), revealing that overall accuracy varied as a function of the position of the C in the array (mean±SEM were: PD0=89.2%±2.5, PD1=84.4%±2.3, PD2=82.1%±2.1, PD3=74.3%±2.2, PD4=83.3%±2.6). On the contrary, the main effect of Group and the interaction were not significant (p=.33 and p=.59, respectively; see Figure 9.2, panel A). These results show that both group were equally efficient in orienting and zoom-in attention in a small cue (see also Chapter 4 study in the small cue condition). The main effect of probe distance in this case it is to consider the result of a combination of visual anisotropy (i.e., stimuli placed along the vertical and horizontal axes are discriminated better than stimuli placed in the oblique ones; Maffei and Campbell, 1970) and crowding. For both group, the task was easier at PD0, because in this case the target was placed aligned with the horizontal axis. A gradient of decreased accuracy, instead, was observed from PD1 to PD3, caused by an increasing level of visual crowding. Contrarily, in the outer position PD4, visual crowding was reduced since no other stimuli were externally presented.

9.3.2 Weak surround suppression of the attentional focus in ASD

ANOVA performed in the probe condition revealed a main effect of Probe Distance ($F_{(4, 156)}$=17.40, p<.001, η^2_p=.31; mean±SEM were: PD0=80.4%±3.1, PD1=58.4%±2.7, PD2=64.1%±2.7, PD3=68.7%±2.3, PD4=73.3%±2.5). Importantly, a significant Probe Distance by Group interaction emerged ($F_{(4,172)}$=4.38, p=.002, η^2_p=.10). To further explore this two-way interaction we performed planned comparisons, comparing the performance of the two groups in the five different Probe Distance (PD). As shown in the Figure 9.2 (panel B), ASD showed a higher accuracy as compared to the TD group both at PD 1 ($t_{(39)}$=2.17,

p=.036) and PD 2 ($t_{(39)}$=2.15, p=.038). Comparisons at the other PDs did not result significant (all ps>.15).

These results show that the ASD group, at PD1 and PD2, where the effect of surround suppression should be the strongest, show a significant weaker suppression – relative to the TD group – as reflected by higher accuracy rate.
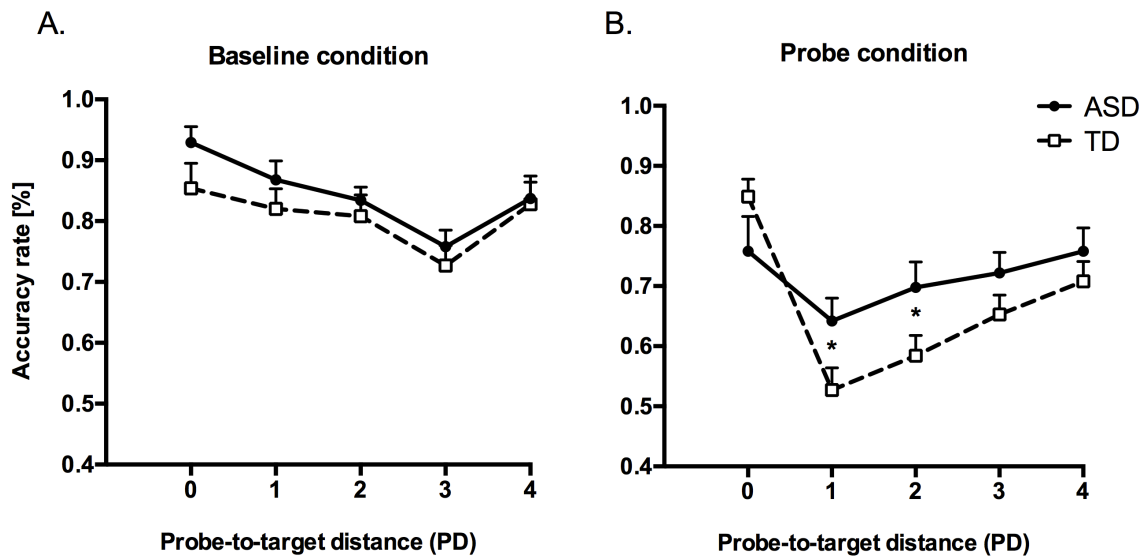

Figure 9.2 Plots showing mean accuracies in the (a) basene and (b) probe conditions, as a function of group and target-to-probe (PD) distances. *=p<.05. Bars represent the SEM.

9.3.3 Weak surround suppression correlates with autistic symptomatology

We considered the possible relationship between the individual measure of surround suppression and the ASD symptomatology measured by the SCQ. Individual Surround Suppression Index (SSI) was calculated as the mean of accuracy rate in PD1 and PD2, subtracted from the accuracy rate at PD0 (SSI = PD0 – Mean [PD1, PD2]). A lower SSI corresponds to a weaker suppression outside the focus of attention, and vice versa. Partial correlation was performed to control for the effect of age, and the results showed that individual SSI was negatively correlated with SCQ scores (Current version; $r_{(16)}$=-.418, p=.042; see Figure 9.3).

These results show that this low-level attentional dysfunction in the ASD group is associated with symptomatology defined at a higher behavioral level, so that weaker suppression in the surround of the attentional focus corresponds to higher symptoms severity.
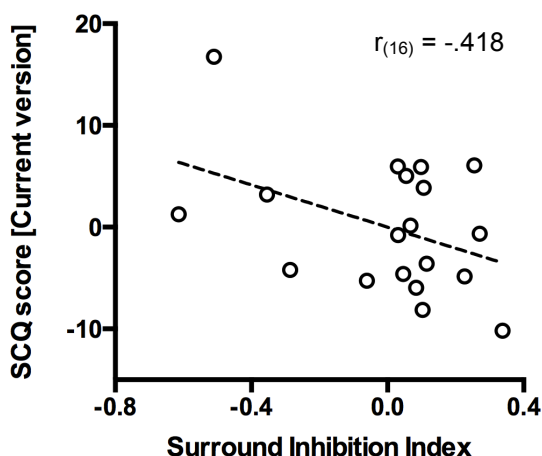

Figure 9.3 Partial correlation plot. Scatter plot showing the correlation between individuals Surround Inhibition Indexes and the Social Communication Questionnaire (SCQ) score. The effect of chronological age has been controlled for.

9.4 Discussion

The present study is the first that systematically assess the spatial profile of the attentional focus in individuals with ASD. Results clearly demonstrate that the ASD group exhibits a weaker suppression in the surround of the attentional focus relative to the TD group. Further, the degree of inefficiency in inhibiting visual information outside the focus of attention was associated with higher ASD symptoms severity.

A weaker suppression surrounding the focus of attention suggests an unbalanced relationship between neural mechanism of enhancement and suppression at the locus of visual attention and is likely to dramatically impact the way in which persons with ASD engage to the visual environment. Weak surround suppression may also explain different aspects of their visual perception, both in term of strengths and weaknesses. On the one hand, a weak suppression surrounding the focus of attention can lead to a better representation of visual information (e.g. enhancing local contrast sensitivity) in the vicinity of the attentional focus. This can

translate into better performance in task such as the visual search (O'Riordan et al., 2001; Joseph et al., 2009), the Embedded Figure Test (Jolliffe & Baron-Cohen, 1997; Manjaly et al., 2007) and visual crowding (Baldassi et al., 2009; Keïta et al., 2010). Accordingly, Joseph and colleagues (2009) studied the factors underlying superior visual search performance in ASD. Their findings showed that neither differences in eye-movements nor enhanced visual memory can account for better performance in search. They claim, on the contrary, that non-search factors, specifically related to an anomalously enhanced perception of stimulus features, are the key factor behind this advantage. On the other hand, less inhibition of the visual information outside the focus of attention could lead to tremendous problem when irrelevant information are concurrently presented with relevant ones. One case that clearly demonstrates this phenomenon has been described by Burack (1994). The author found that individuals with ASD have better performance relative to the control groups when a window circumscribed the target and no distractors were on the scene. Conversely, the performance of the ASD group was clearly impaired in the presence of distractors outside the window cue. An anomalous interference from irrelevant information has been found also using an Eriksen flanker task in a more recent study by Adams and Jarrold (2012). Interestingly, the same sample of individuals with ASD showed no evidence of impaired prepotent response inhibition, leading Adams and Jarrold to conclude that the nature of impaired distractor inhibition found in the Eriksen flanker task is not due to a real inhibitory problem, but may in fact be related to an increased perceptual representation of distractors. In addition and coherently with these findings, in our previous work we demonstrated that people with ASD suffered for a deeper and prolonged backward interference (i.e., attentional masking), relative to controls, when a laterally displayed irrelevant object was presented after a central target. The same impairment was not observed when the second irrelevant masking object followed the target in the same spatial position (Ronconi et al., 2013a).

The present findings suggest also an important theoretical question that needs to be solved to better understand the peculiar nature of visual selection in ASD and their cognition more generally. The question is: how the present findings of a weaker suppression surrounding the focus of attention are related to evidence of an impaired zoom-out and hyper-focused attention previously reported (Mann and Walker, 2003; Robertson et al., 2013; Ronconi et al., 2013b)? In other words, how persons with ASD can show at the same time a narrowly focused attention (which should predict less resources outside the attentional focus) and a stronger interference from information outside the attentional window? One plausible answer relies on the nature of experimental paradigm previously used to asses the distribution of attentional resource. Previous studies have never systematically address – as we did in the present study – the processing resolution as a function of the distance from the locus in space where attention has been captured. In particular, previous experiments have never specifically tested attentional resources outside but near to the attentional focus (although results of Ronconi et al., 2013a are in line with present findings). Another possible answer could be that the zoom-out problem may be a consequence of a weaker inhibition outside the attended area. To avoid visual sensory overload caused by an inefficient suppression at unattended locations, people with ASD may develop a tendency to avoid the zooming-out of their attentional focus, as the load of information that they have to deal with may become excessive and overwhelming. Of course, this latter interpretation remains just speculative at the present state, but we believe that future studies need to asses in parallel the modulation of the attentional resources as a function of the spatial position or size of the attended area (i.e., orienting and zooming), and the spatial profile of the attentional focus (i.e. the surround suppression). Evaluating the developmental trajectory and the mutual influence of these two mechanisms, we can reach a better understanding of the nature of visual processing and related abnormalities that characterize ASD.

Possible neural correlates of a weak suppression surrounding the focus of attention can rely on diminished top-down modulation coupled with an augmented neural representation of visual objects in visual areas. Hopf and colleagues (2006, 2010), indeed, showed that the inhibitory ring surrounding the attentional focus arises with a substantial delay relative to the initial feed-forward visual flow, suggesting that it is the consequence of top-down attentional selection in the early visual system (Tsotsos, 1990, 2005; Hopf et al., 2006, 2010).

Accumulating evidence, furthermore, support the idea that ASD is characterized by reduced functional connectivity between distant neural areas (Rubenstein and Merzenich, 2003; Just et al., 2004; Belmonte et al., 2004; Minshew and Williams, 2007; Di Martino et al., 2013; Khan et al., 2013; see Vissers et al., 2012 for a review), with a conspicuous reduction in fronto-occipital connection (Courchesne and Pierce, 2005; Bartffeld et al., 2011; Jou et al., 2011). On the other hand, recent reports assessing local connectivity alterations in ASD lend support to the hypothesis of diffuse local overconnectivity in occipitotemporal region, where the object representation is formed (Keown et al., 2013). Thus, the inefficient surround suppression of individuals with ASD is likely to result from impaired feedback projections from the attentional network (i.e., frontoparietal areas) – caused by underconnectivity – coupled with an augmented visual representation of irrelevant object in visual associative areas (i.e., occipitotemporal areas) – caused by local regional overconnectivity.

In sum, the present findings show that individuals with ASD manifest a spatial profile of the attentional focus characterizes by a weak suppression surrounding the attended area. This altered inhibitory ring is likely to derive from an inefficient top-down selection of information in visual areas and can be the main factor underlying the profile of strengths and weaknesses in the visual sensory domain typically associated with ASD. Importantly, as attention is known to be a supramodal neurocognitive function that operates on different sensory modalities (Farah et al., 1989; Banerijee et al., 2011; Green et al., 2011), this deficit

in suppression of irrelevant information can be postulated also for the sensory overload present in tactile and auditory domains (Kern et al., 2006; Leekam et al., 2007).

The experiments conducted so far in the present thesis investigated the deployment of visual attention in ASD according to the spotlight (Posner, 1980) and the zoom-lens (Eriksen and St. James, 1986; Castiello and Umiltà 1990) models. These models predict that the attentional resources are concentrated at their maximum at the center of the attentional focus, and then shade progressively (with a linear spatial gradient) while the distance from the attentional focus increases. Considering the zoom-out deficit (but the same could be valid for the disengagement deficit), one would expect an overfocused attention to be associated also to a reduced interference from incongruent/irrelevant information. However, both clinical and experimental reports are fairly clear in showing that individuals with ASD suffer often from an increased interference from irrelevant and distracting information (e.g. Burack, 1994; Belmonte, 2000; Leekam et al., 2007; Ronconi et al., 2013a).

CHAPTER 10 – GENERAL DISCUSSION AND CONCLUDING REMARKS

The six studies reported in my Ph.D. thesis give new insights into the nature of altered visual attention in individuals with autism spectrum disorder (ASD).

In the first study (Chapter 4), we evaluated possible differences in the time course of attentional orienting and re-orienting between ASD and typically developing (TD) peers as a function of the size of their attention focus. We found that performance of the two groups was comparable when the attentional focus had to be scaled in a small portion of the visual field. On the contrary, when participants had initially to enlarge their attentional focus size, the ASD group showed a sluggish attentional orienting relative to the TD group. This evidence was also supported by a significant correlation that suggests that slower orienting abilities in the large cue condition were related to higher autistic symptomatology. These findings suggest that while TD group can efficiently orient their attentional focus both when narrow or broad portions of the visual field have to be attended, individuals affected by ASD suffer from a sluggish zoom-out of the attentional focus and this is likely to impact consecutively also other operations that visual attention has to perform, in this case the orienting toward the cued location. Moreover, these results confirm previous evidence of an impaired zooming-out of the attentional focus (Mann and Walker, 2003; Ronconi et al., 2012, 2013b).

In the two following studies (Chapter 5 and 6) we tested a new strategy that together with study of infants at-risk (sibling of older children with ASD) can inform about the neurocognitive dysfunction that characterizes ASD and the broader autistic phenotype in the very early stage of development. We found that autistic traits in parents from the general

population without any history of ASD were related to the attentional functioning of their 8-month-old infants. In one study (Chapter 5), orienting and alerting attention systems were measured in infants using a spatial cueing paradigm and an eye-tracker. Results showed that paternal autistic traits were linked to their infants': (i) attentional disengagement; (ii) rapid attentional orienting and (iii) alerting. In the other study (Chapter 6), we tested a new paradigm that allows evaluating the attentional zooming mechanism in infanthood, always by the means of an eye-tracker. Attentional zooming has never been tested in infanthood before. The first important result was that 8-month-old infants can automatically adjust the size of their attentional focus in a pre-saccadic temporal window. Moreover, higher autistic traits both in fathers and mothers were related to a narrower focus of attention in their infants (probably the flip side of the zoom-out attentional impairment associated with ASD). Overall, these findings suggest that an early dysfunction of orienting and zooming mechanisms might alter the developmental trajectory of future ability in social and communication domains. It suggests also that attentional abnormalities can be found not only in infants who have a "strong" biological risk for developing the condition – as they are siblings of older children with a diagnosis of ASD – but also in infants who have a "mild" biological risk since born from parents with high autistic traits.

Two other studies presented in this work (Chapter 7 and 8) were conducted in order to better understand the zoom-out attentional impairment found in ASD and in infants of the broader autistic phenotype (Chapter 4 and 6; Mann and Walker, 2003; Ronconi et al., 2012, 2013b). We investigated, in the typical population, the neural underpinnings of the attentional zooming. While the neural sources of the control of attentional orienting have been widely investigated in cognitive neuroscience (see Corbetta and Shulmann, 2002, 2011; Corbetta et al., 2008 for reviews), limited evidence are present regarding the neural areas that control the attentional focus size. In a first study, we delivered single-pulse transcranial magnetic

stimulation (TMS) on the frontal eye fields (FEF) while participants performed an attentional zooming task. Results showed that TMS delivered on the right FEF, but not on the left FEF, was able to interfere with both zoom-in and zoom-out attentional mechanisms. In a second study, we used dense-array electroencephalography (d-EEG) to better investigate neural events associated to the modulation of the attentional focus size. Neural sources estimation were performed in the cue-target interval, revealing that when compared to the zoom-out condition, the zoom-in of the attentional focus was associated to greater activations of the left intra-parietal sulcus (IPS). On the other hand, when compared to the zoom-in condition, the zoom-out of the attentional focus was associated to long-lasting increased activation in the inferior frontal gyrus (IFG) accompanied by: (i) initially, activations in right superior parietal lobule (SPL) and bilaterally in superior/middle frontal gyrus – where the frontal eye fields (FEF) are located; (ii) secondly, activations bilaterally in middle temporal gyrus (MTG) and insula (INS).

Overall, these two studies reveal clearly a massive involvement prior to the target onset of different part of the frontal lobe, especially FEF and IFG, when subjects had to zoom-out their focus of attention. What these results in typical population can tell us about the zoom-out dysfunction observed in ASD? We saw in Chapter 2 that one of the leading hypothesis about neural abnormalities in ASD claims that the autistic brain is characterized by long distance under-connectivity (Belmonte et al., 2004; Frith, 2004; Just et al., 2004; Geshwind and Levitt, 2007; Casanova and Trippe, 2009; Rudie and Dapretto, 2013), presumably due to defect in the development of the minicolumns during early stages of post-natal life (Casanova et al., 2002, 2006; Buxhoeveden et al., 2006;). Interestingly, increasing evidence show that that long-range connectivity is particularly disrupted between frontal and occipital areas in ASD (e.g., Courchesne and Pierce, 2005; Barttfeld et al., 2010; see Belmonte et al., 2004 for a review). Accordingly, two fMRI studies have shown, in individuals with ASD, a

dysfunction of the dorso-lateral prefrontal cortex during visual attention task (Ring et al., 1999; Manjaly et al., 2007), and atypical prefrontal activations when testing visual attention seem to be present also in unaffected sibs (Belmonte et al., 2010). These findings, along with TMS and d-EEG results presented here, give increased consistency to the hypothesis that underconnectivity between frontal areas – where top-down attentional processes are controlled – and visual areas are the main factor underlying the altered deployment of visual attention in ASD.

In the last study reported here (Chapter 9) we went one step forward the main models of visual spatial attention (orienting and zooming) and we investigated the spatial profile of the attentional focus in individuals with ASD, according to the so-called "Mexican-hat" model (Müller et al., 2005; Hopf et al., 2006). This model, supported by strong neurophysiological data, claim that the selection of relevant visual objects produces an area of neural attenuation surrounding the focus of attention, a sort of inhibitory ring which is optimal to highlight important information and attenuate the deleterious noise (Hopf et al., 2006, 2010). We tested this model in ASD in order to clarify why detailed oriented perception and overfocused attention – largely demonstrated in ASD (see Happé, 1999; Happé and Frith, 2006; Dakin and Frith, 2005; Mottron et al., 2006 for reviews) – coexist with stronger interference from irrelevant information (e.g. Burack, 1994; Adams and Jarrold, 2012; Ronconi et al., 2013a), which often leads to sensory overload in most individuals with ASD (Kern et al., 2006; Leekam et al., 2007). Results showed that in the ASD group the attenuation surrounding the focus of attention was markedly reduced, suggesting an unbalanced relationship between neural mechanisms of enhancement and suppression at the locus of attention. Moreover, weaker suppression outside the focus of attention correlated with higher autistic symptomatology.

The inefficient surround suppression of individuals with ASD is likely to result from at least two different neural abnormalities. Precisely, impaired feedback projections from the top-down attentional network (i.e., frontal and parietal areas) caused by long-range underconnectivity coupled with an augmented representation of objects outside the attentional focus in visual associative areas (i.e., occipitotemporal areas) – presumably caused by a local regional overconnectivity. While evidence in favor of the former alteration has been already discussed above, the latter alteration is supported by a recent study that demonstrated local connectivity alterations in occipitotemporal region of individuals with ASD (Keown et al., 2013). Local overconnectivity in visual areas was suggested also by previous results of psychophysical lateral and attentional masking paradigm in individuals with ASD (Kéïta et al., 2011; Ronconi et al., 2013a).

To conclude, the present doctoral thesis gives significant new insights to define the altered deployment of visual attention in persons with ASD. Specifically: (i) it confirms deficit in enlarging the attentional focus previously reported (Mann and Walker, 2003; Ronconi et al., 2012, 2013b); (ii) it shows how parents with high autistic traits can transmit to their infants subtle deficit in visual attention that are likely to impact their future socio-communicative abilities; (iii) it confirms the validity of visual attention abnormalities as an early marker of ASD; (iv) it shows the importance of frontal (especially, FEF and IFG) and parietal (especially IPS/SPL) brain areas in regulating the size of the attentional focus and consequently the portion in the visual cortex activated in preparation to a stimulus via top-down modulatory connections; and, lastly (v) it demonstrate that the inhibitory ring outside the focus of attention is markedly reduced in ASD, providing a fundamental insight into the understanding of both superior performance in detail-oriented tasks as well as sensory overload characterizing persons with ASD.

The question that remains to be solved is whether these impairments are a cause or a consequence of ASD. Only future longitudinal studies carried out in infants at risk can help to solve this question. However, whatever will be the case, our evidence in infants with high-autistic-traits parents – along with recent longitudinal studies in infants at biological risk for developing the condition (e.g., Elsabbagh et al., 2013; Chawarska et al., 2013) – suggests that alterations of the attention network play a central role in the development of ASD. Since attention can be trained efficiently also in infanthood (Wass et al., 2011), the time for early and inexpensive prevention programs to reduce the incidence of ASD is getting closer.

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