PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
Doctorado en Neurociencias

Tesis Doctoral

Real-time Neurofeedback based on functional Magnetic Resonance Imaging as a new approach to study the Face Processing network in Autism Spectrum

Por

Jaime Andrés Pereira Quezada,

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Santiago, 20 de Diciembre 2019

Dedication

To my wife Macarena and my daughters Isidora and Leonor for their patience, time and love, and to my patients, who like my daughters, deserve to live in a friendlier world, one where they can develop to their full potential and be accepted as they are.

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During this process, I had the opportunity to meet several other outstanding people from whom I learned and gained a lot of technical experience. During this process, I had the opportunity to meet several other outstanding people from whom I learned and gained a lot

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ABBREVIATIONS

ASD	Autism spectrum disorder
rtfMRI-NF	Neurofeedback based on real-time functional MRI
FFA	Fusiform face area
FG	Fusiform gyrus
BOLD	Blood oxygenation level dependent
AG	Experimental group
TD	Typical neural development
CG1	Control group 1
CG2sham	Control group 2
ROI	Region of interest
EPI	Gradient echo planar imaging
SPM	Statistical parametric mapping software package
AAL	Anatomical automatic labeling atlas
ADOS-2	Autism diagnostic observational schedule version 2
ADI-R	Diagnostic interview-revised
CFMT	Cambridge face memory test
CCMT	Cambridge car memory test
FIR	Face recognition test
FER	Emotion recognition test

ABSTRACT

One of the most important and early impairments in autism spectrum disorder (ASD) is the abnormal visual processing of human faces. This deficit has been associated with hypoactivation of the fusiform face area (FFA), one of the main hubs of the face-processing network. Neurofeedback based on real-time fMRI (rtfMRI-NF) is a technique that allows the self-regulation of circumscribed brain regions, leading to specific neural modulation and behavioral changes. The aim of the present study was to train participants with ASD to achieve up-regulation of the FFA using rtfMRI-NF, to investigate the neural effects of FFA up-regulation in ASD. For this purpose, three groups of volunteers with normal I.Q. and fluent language were recruited to participate in a rtfMRI-NF protocol of eight training runs in two days. Five subjects with ASD participated as part of the experimental group and received contingent feedback to self-regulate bilateral FFA. Two control groups, each one with three participants with typical development (TD), underwent the same protocol: one group with contingent feedback and the other with sham feedback. Whole-brain and functional connectivity analysis using each fusiform gyrus as independent seeds were carried out. The results show that individuals with TD and ASD can achieve FFA up-regulation with contingent feedback. RtfMRI-NF in ASD produced more numerous and stronger short-range connections among brain areas of the ventral visual stream and an absence of the long-range connections to insula an inferior frontal gyrus, as observed in TD subjects. Recruitment of inferior frontal gyrus was observed in both groups during FAA self-regulation. However, insula and caudate nucleus were only recruited in subjects with TD. These results could be explained from a neurodevelopment perspective as a lack of the normal specialization of visual processing areas, and a compensatory mechanism to process visual information of faces. RtfMRI-NF emerges as a potential tool to study visual processing in ASD, and to explore its clinical potential.

Keywords: Autism Spectrum Disorder (ASD), Real-Time fMRI Neurofeedback (rtfMRI-NF), Fusiform Face Area (FFA), Facial Processing, Brain-Computer Interfaces, Neuromodulation.

1 INTRODUCTION

Autism spectrum disorder (ASD) is a chronic, burdensome (Beecham, 2014; Howlin et al., 2004; Weiss and Lunsky, 2011), highly prevalent neurodevelopmental condition (Fisch, 2012; Kim et al., 2011), and strongly associated with medical and psychiatric comorbidities (Lai et al., 2014). The presentation of ASD is heterogeneous, but is defined by certain clinical characteristics: 1) persistent deficits in communication and social reciprocity, and 2) patterns of repetitive and restrictive behaviors activities and interests, as well as sensorial integration disturbances that are of clinical significance (American Psychiatric Association, 2013). The social, adaptive and mental health prognosis improves with earlier diagnosis and treatment (Fernell et al., 2013). However, there is a subgroup of patients with ASD (patients with fluent language and normal or above normal cognitive capabilities) whose diagnosis usually occurs during late childhood, adolescence, or even in adulthood (Mandell et al., 2005). A better understanding of the neural substrates underlying the core ASD symptoms could help the development of biologically-based diagnostic tools to assist clinicians with this challenge (Lai et al., 2014; Varcin and Nelson, 2016).

One of the most important and early impairments in ASD is the abnormal visual processing of human faces (Baron-Cohen et al., 2001a; Calder et al., 2002; Klin et al., 2015; Weigelt et al., 2012a). This deficit has been associated with a lack of the typical attentional bias toward social stimuli - mainly faces - that is observed in people with typical neural development (TD) from early childhood and throughout life (Dawson et al., 2005; Simion and Giorgio, 2015). There is a deficit in processing visual information emanating from faces (Golarai et al., 2006). This lack of the typical specialization may be compensated by a slower and more cognitively demanding mechanism in ASD individuals with normal or above normal cognitive abilities (Clark et al., 2008; Livingston and Happé, 2017; Neumann et al., 2006; Santos et al., 2008; Weigelt et al., 2012b). However, rapid facial processing is necessary for the development of more complex socially relevant cognitive functions (García-Villamisar et al., 2010), such as inter-subjectivity (Yirmiya et al., 1992), pragmatic communication (Mundy et al., 1992) or Theory of Mind (Baron-Cohen et al., 2001a; Calder et al., 2002; Rogers and Bennetto, 2000). All of these are usually affected in ASD.

From a neurobiological point of view, progressive structural and functional neural specialization emerges during the visual experience of faces as an important part of typical development (Adolphs, 2009; Frith, 2007; Johnson et al., 2005). This process is characterized by right lateralization (Meng et al., 2012), global integration (Mišić et al., 2014), and local specialization of certain brain areas involved in processing the static, dynamic, emotional and contextual information associated with the visualization of faces (Haxby and Gobbini, 2010). The lateral area of the fusiform gyrus (FG), known as the fusiform face area (FFA) is considered a critical cortical node for face processing (Ganel et al., 2005; Huang et al., 2014; Jiang et al., 2013) and its hypoactivation is the most consistent finding in research on face processing deficits in ASD (Nickl-Jockschat et al., 2014). Despite the great advances in the description of the cerebral functioning that underlies the deficit of nuclear symptoms of ASD, it has not been possible to translate these findings into useful tools for use both for the diagnostic process in complex clinical settings and for new biologically-based therapeutic approaches to support the usual current treatment approaches. Neurofeedback based on real-time fMRI (rtfMRI-NF) is a closed-loop system in which the Blood Oxygenation Level Dependent (BOLD) signal from selected brain regions can be translated to an artificial output that gives contingent information in real-time to the subjects about their brain activity (Shih et al., 2012; Sulzer et al., 2013a). RtfMRI-NF has allowed healthy individuals as well as neurological and psychiatric patients to achieve self-regulation of circumscribed brain regions (e.g. Insula, Amygdala, Supplementary Motor Area, FFA), leading to specific neurobiological and behavioral changes (Caria et al., 2007; Habes et al., 2016; Paret et al., 2016; Sepulveda et al., 2016; Zotev et al., 2011a). This methodology has been used as a powerful tool to study addiction, schizophrenia, obsessive-compulsive disorder, depression and other brain disorders (Birbaumer et al., 2013; Ruiz et al., 2014; Sitaram et al., 2007b, 2017; Weiskopf, 2012b; Weiskopf et al., 2004a).

The present study is the first one to use rtfMRI-NF for the endogenous neuromodulation of one of the main hubs of face processing, i.e. FFA in autism. In this feasibility study, our first aim is to investigate the feasibility of training FFA up-regulation by means of fMRI-NF in people with ASD and to compare this capability with subjects with TD. The neural consequences of FFA self-regulation in both groups will be explored by whole-brain analysis and functional connectivity analysis using both FG as independent seed. In addition to the

above aim, the relation between clinical measures (and face processing performance, i.e. accuracy of face identity recognition and face emotion recognition) with self-regulation capability will be explored.

2 BACKGROUND

2.1 AUTISM SPECTRUM DISORDER

2.1.1 Definition

The term “autism” is derived etymologically from the Greek work *eaftismos* meaning “enclosed in one’s self”, which was coined by the Swiss psychiatrist Eugen Bleuler in his work “*Dementia praecox oder Gruppe der Schizophrenien*”, a psychiatric treatise published in Vienna in 1911 (Bleuler and Bleuler, 1986). Bleuler described autism as the self-absorption and loss of contact with the external reality presented by schizophrenic patients, a symptom that was more easily observed in the advanced stages of the disease. However, autism was first described as a childhood psychiatric pathology by Leo Kanner, an Austrian child psychiatrist who published "Autistic Disturbances of Affective Contact" in 1943, in which he described the psychopathology of eight boys and three girls, emphasizing the “profound lack of affective contact with other persons”, that these children suffer “innately”, as a core symptom of the disorder (Kanner, 1968). In 1944, Hans Asperger, an Austrian pediatrician and psychiatrist published his article "*Autistischen Psychopathen im Kindesalter*” or “*Autistic psychopathy in Childhood*”, which described a group of four children that, in contrast to Leo Kanner’s description, had language, but displayed important gaps in pragmatic communication and social reciprocity, describing them as “socially strange” (Asperger, 1991).

These seminal works were so important that “infantile autism” was identified as a clinical condition in the Diagnostic and Statistical Manual of Mental Disorders for the first time in its third edition (Rutter and Shaffer, 1980) and term it “autism disorder” (Wilson, 1993). The fourth edition of the manual described five categories under what was termed general developmental disorders (American Psychiatric Association, 2000): autism; Rett syndrome, childhood disintegrative disorder, Asperger syndrome; and Pervasive Developmental Disorder-Not Otherwise Specified. However, the fifth edition of the manual eliminated Rett syndrome and childhood disintegrative disorder because it was considered that both present distinct evolutions and characteristics from those of autism (Lai et al., 2013). Autism and Asperger are brought under the same umbrella of autism spectrum disorder, a term that had

been sketched out by different authors such as Lorna Wing and Allen. The latter author, who was the first to use the term autism spectrum in this publication "Autistic spectrum disorders: clinical presentation in preschool children" in 1988 (Allen, 1988).

Nowadays, autism spectrum disorder (ASD) is considered to be a heterogeneous group of neurodevelopmental conditions that tend to be chronic and that share certain clinical characteristics: 1) persistent deficits in communication, social reciprocity, and social interaction, and 2) patterns of repetitive and restricted behaviors, activities and interests (Lai et al., 2013).

2.1.2 Prevalence

The prevalence of ASD has been increasing in recent decades, which may be due to laxity in applying diagnostic criteria (Fisch, 2012), greater diagnostic sensitivity among contemporary health providers (Heidgerken et al., 2005) and consequently earlier diagnoses and due to a real increase in prevalence due to environmental factors (Dietert et al., 2011). The prevalence is currently estimated in around 1 to 2% of the general population (Fisch, 2012), being four to five time more frequent in males than females (Werling and Geschwind, 2013). Its etiology is considered multifactorial, with a strong biological component that is modulated in a complex manner by the environment from very early life stages (DiCicco-Bloom et al., 2006; Gardener et al., 2009). Thus, protective environmental factors (e.g., therapeutic intervention) delivered at early stages of development may improve prognosis and prevent the mental health consequences that these people often experience.

2.1.3 Diagnosis

While it is known that early intervention improves the functional prognosis for adolescence and adulthood, there is wide variation in the age of diagnosis. The age of diagnosis depends on the country (Salomone et al., 2015), the health facility in which the diagnosis takes place (Shattuck et al., 2009) and possibly the level of training of the health providers (Mandell et al., 2005b). Other factors affecting the diagnosis age are gender, rural versus urban location and family income, with a more late diagnosis for women, rural residents and persons from low-income families (Mandell et al., 2005b; Salomone et al., 2015). The time of diagnosis also depends on the severity of the symptoms, such as the presence or absence of intellectual deficit or language use. Individuals with ASD with language and without intellectual deficit

or a history of global developmental delay, are not diagnosed until well into school age, adolescence or even adulthood (Howlin and Asgharian, 1999; Mandell et al., 2005b).

2.1.4 Comorbidity

Autism still implies a high level of stigmatism (Levy et al., 2009) and while there is a small percentage of individuals with ASD that can integrate socially and pursue academic studies, the great majority require a high degree of support from the health, educational and social systems. Three-quarters of individuals with ASD in adulthood present very poor results in measurements of independence (Howlin et al., 2004). It is estimated that 45% of individuals with ASD have intellectual deficits and 70% have some type of medical or psychiatric comorbidity. The main psychiatric comorbidities are attention deficit hyperactivity disorder (28- 44%), anxiety symptoms (42-56%), depression (12-70%) and sleep disorders (50-80%), tic disorder (14- 38%) and obsessive-compulsive disorder (7-24%). Psychotic disorders are much more common than in the general population (12- 17%) and presenting an autistic phenotype in childhood is a risk factor of a subsequent diagnosis of schizophrenia (Lugnegård et al., 2011; Simonoff et al., 2008).

2.1.5 Associated costs

A diagnosis of ASD not only means stigma and a complex handicap for the individual with the condition, but also a high emotional cost for the family. The primary caregivers of individuals with ASC have a higher risk of fatigue, stress, symptoms of personal dissatisfaction, anxiety and depression (Almansour et al., 2013; Buescher et al., 2014), symptoms that are more pronounced among parents or primary caregivers of individuals with other developmental (Beecham, 2014; Weiss and Lunsky, 2011). ASD is associated with high costs both for governments and families. In the United States, it is estimated that the cost per individual associated with ASD is 1.4 million dollars, while in the UK the estimated cost is one million Euros. The cost is approximately double when ASD is associated with an intellectual deficit. Most costs with ASD children are related to special education and the lost productivity of the parents (Buescher et al., 2014). The health costs for families have been estimated at around six thousand dollars per year per individual in the United States (Leslie and Martin, 2007), although there is considerable variability among studies (Beecham, 2014).

No studies have been published so far about the costs associated with an ASD diagnosis in Latin America.

2.1.6 Early diagnosis, treatment, and prognosis

There are no pharmacological or biological-based treatments to the core symptoms of the disorder and drugs have demonstrated effectiveness only for the comorbidities associated (Myers and Johnson, 2007). Intensive behavioral therapy at an early age has been the only therapy that has demonstrated effectiveness in improving the functional prognosis. In particular, good responses have been observed with this type of therapy in language, cognitive abilities and adaptive behavior (LeBlanc and Gillis, 2012). However, as we know, there is a subgroup of patients with ASD who are late diagnosed (i.e. patients with sentence language and without cognitive difficulty) and therefore do not have access to early intervention. These individuals constitute a high-risk subgroup for both social difficulties and mental health comorbidities so that therapy with a specialized health provider is recommended (Lake et al., 2014) and new diagnostic and therapeutic approaches for them is mandatory.

The neurobiological study of the symptoms that could be the basis of the pathophysiology of ASD can provide useful information for the development of novel diagnostic biomarkers or therapies to improve the prognosis and well-being of this population.

2.2 FACIAL PROCESSING DEVELOPMENT AND AUTISM

The development of the capacity to extract social information in real-time from the perception of faces is fundamental for the development of communication, social reciprocity, and social skills, which occurs naturally in typical development. Patients with ASD present a loss of such specialization. Thus, difficulties in facial processing are observable from early childhood in ASD and even correlate with the severity of symptoms in communication and socialization.

2.2.1 Innate preference for facial perception

The criteria for diagnosing ASC is currently divided into two major symptomatologic groups (American Psychiatric Association, 2013), communication deficits and deficits in social

interaction, symptoms considered central for diagnosis and included in the first phenomenological descriptions (Asperger, 1991; Kanner, 1968). Many of the social deficits that are observable in individuals with ASD from an early age, such as lack of eye contact, a deficit in joint attention, a deficit to recognize emotional expressions or identify faces (Zwaigenbaum et al., 2013). It reflects inadequate processing of perceptual information of faces or "facial processing" deficits. There is ample literature on the deficit in facial processing among individuals with ASD (Adolphs et al., 2001; Dalton et al., 2005; Hadjikhani et al., 2004; Teunisse and De Gelder, 2003)

The human face is an element of high interest and the basis for social interactions (Goren et al., 1975). Perception of the faces is considered to play an important role biologically and evolutionarily (Darwin, 1956). Consequently, the capacity to perceive faces is considered an innate human trait (Cassia et al., 2004; Turati, 2004) evidenced from birth (Goren et al., 1975). Individuals with ASD show less interest in faces than individuals with typical development, which is clinically evident at six months of age (Maestro et al., 2002). In fact, poor attention to social scenes and to faces at six months is a "red flag" for a possible subsequent diagnosis of ASD (Chawarska et al., 2013), being this symptom-diagnosis correlation higher at one year of age (Osterling et al., 2002). However, the fault in the processing of faces is not because of a general perceptual disturbance. The specific deficit in innate attentional focusing on elements of high social value -like the faces-, could reduce the probability of developing specialization in facial processing with observed consequences in the communication and social interaction deficits of individual with ASD and may explain the emergence of the unusual abilities too (Iuculano et al., 2014).

2.2.2 Milestones in the development of facial processing

In typical development, the ability to analyze information obtained from the faces becomes more and more advanced in a predictable way, being able to analyze more information, more complex and faster. A newborn with typical development can distinguish faces from other objects (Goren et al., 1975) being the recognition of faces faster than the other objects (Walton and Bower, 1993). At four months of age, infants recognize correctly oriented faces better than inverted faces (Fagan, 1972), which is not evidenced with other objects (Yin, 1969). At six months age infants with typical development can distinguish known and

unknown faces (de Haan and Nelson, 1999) and at one year of age can extract information from facial gestures and emotional expressions (Dawson et al., 2005). At 6, 8 and 12 years of age children recognize faces with the same precision as adults, but the speed of response for correctly oriented faces improves considerably over these years, while the speed for recognizing inverted faces or other non-social stimuli improves very slowly (de Heering et al., 2012; Dimitriou et al., 2014). Individuals with ASD do not have this evolutionary history of specialization in the perception of faces.

Children with ASD fail in multiple facial discrimination (Tantam et al., 1989) and recognition tests (Dawson et al., 2005; Weigelt et al., 2012b). Nevertheless, they may present higher levels of recognition of other things such as buildings (Boucher and Lewis, 1992), cats, horses and bicycles (Blair et al., 2002). The deficit to recognize faces is evidenced consistently in tests that include a mnemonic load (Serra et al., 2003) even with a lag under the second between the presentation of the stimulus and the test (Weigelt et al., 2012b). In addition, children with ASD have similar recognition levels for inverted and correctly oriented faces, and the performance in recognizing inverted faces can be better than that of individuals with typical development (Hobson et al., 1988; Langdell, 1978; Rose et al., 2007).

In addition to the effect of inverted faces, there is more evidence of the development of facilitating mechanisms to extract information from faces, which indicates specialization in facial processing in typical development. Individuals with typical development can more successfully recognize emotional expressions of basic and complex emotions by viewing the area of the eyes than viewing other parts of the face, indicating that the eyes represent a high information area (S Baron-Cohen et al., 2001; Calder et al., 2002; Pelphrey et al., 2009). Individuals with ASD spend less time observing central parts of the face like the eyes and nose (Klin et al., 2002; Pelphrey et al., 2002; Trepagnier et al., 2002) and fail to recognize complex emotions from observing eyes area (S Baron-Cohen et al., 2001; Calder et al., 2002), presenting a more erratic pattern observation to extract the social information from the faces (Dalton et al., 2005; Neumann et al., 2006).

2.2.3 The rapidity of facial processing in social interactions

Normal social interaction requires effective and rapid facial processing of social cues (Ekman, 1984) and the emotional state of the other (Dimberg et al., 2000). The natural

feedback of imitating changes in the facial expression of the other requires detecting such changes within 20 to 30 ms (Bartlett et al., 2006). Individuals with ASD fail to distinguish emotional expressions when expressions are presented for 20 to 30 ms (Clark et al., 2008). With intervals on the order of 200 ms or more, individuals with ASD can draw on top-down type compensatory cognitive mechanisms to extract facial information, such as interpreting the emotions of the other (Neumann et al., 2006; Santos et al., 2008). This partly explains the mixed results of facial and emotional expression recognition tests (Clark et al., 2008), in which performance depends on the length of exposure to the stimulus (test characteristic), the level of development (age group) and the presence or absence of an intellectual deficit (Weigelt et al., 2012b).

Effective and rapid facial processing is necessary for the development of more complex cognitive functions that are important for social interaction (García-Villamisar et al., 2010). Individuals with ASD fail in functions like spontaneous and flexible eye contact, initiation of joint attention, correspondence of joint attention and identification of emotional keys, all of which require effective and rapid facial processing (Clark et al., 2008). The absence of real-time facial processing at an early age can lead to altered development of inter-subjectivity (Yirmiya et al., 1992), that is, putting one's self in the situation of the other. Both inter-subjectivity and identifying the emotional state of the other in real-time have been proposed as the basis of developing pragmatic communication (Mundy et al., 1992).

Individuals with ASD fail inter-subjectivity tests (Rogers and Bennetto, 2000) and theory of mind tests (S Baron-Cohen et al., 2001; Calder et al., 2002) and present significant clinical deficits in pragmatic communication (American Psychiatric Association, 2013). There is a process of specialization in facial perception in normal development that is altered from an early stage in individuals with ASD, which results in the deficit of much more complex cognitive social functions that are important parts of normal communication and social interaction.

2.2.4 Facial processing in social interaction

The lack of specialization to rapidly extract social information from faces can be compensated for by slower and more cognitively demanding top-down mechanisms (Clark et al., 2008; Neumann et al., 2006; Santos et al., 2008; Weigelt et al., 2012b). It is known that

persons on the autism spectrum who speak fluently and have normal IQs are often not diagnosed until their late childhood or later when more demanding social requirements surpass their social skills and compensatory mechanisms (Lai and Baron-Cohen, 2015; Mandy et al., 2018). In fact, individuals with ASD that achieve typical social interactions are those with better cognitive abilities and higher IQs, regardless of the severity of ASD symptoms (Livingston and Happé, 2017a). These non-automatic, consciousness-based compensation mechanisms require not only significant cognitive effort but also more time for information processing than individuals with normal development usually require. The dissociation between effort and social achievements partly explains feelings of frustration and anger, and finally symptoms of anxiety, depression and social isolation (Hull et al., 2017). This symptomatology is clearly evident among individuals on the autism spectrum, including those better adapted socially (Lugnegård et al., 2011). Thus, even late diagnosis is important from a mental health perspective in terms of allowing for a healthier redefinition of the social difficulties presented in childhood (Cassidy et al., 2014; Lewis, 2016; Roy-Byrne and Peter, 2014; Thienpont et al., 201ds5). A better understanding of the neural substrates underlying atypical development of facial processing in ASD can help in developing diagnostic biomarkers that assist clinicians to obtain an earlier diagnosis of these challenging diagnostic scenarios, as well to explore novel therapeutic avenues.

2.3 NEUROBIOLOGY OF FACIAL PROCESSING

Brain specialization can be theoretically divided into several general processes that occur in parallel. Thus, there is hemispheric lateralization of function (Nass and Gazzaniga, 2011) and functional specialization of brain areas that are hierarchically organized (Barrett, 2012) and integrated (Mišić et al., 2014). These developments are influenced by the interaction between biology and environment (Shakeshaft and Plomin, 2015), which is different in the case of individuals on the autism spectrum, especially in terms of developing the capacity to process visual facial information, which has its neural correlate. Studies of the neural correlate of processing facial information have mainly focused on describing specialized brain regions and integration among them, but there have been few studies on the process of specialization from childhood to adulthood of these brain areas and integration among them.

2.3.1 Core facial processing system

Functional neuroimaging studies have consistently identified three brain areas as having specialized responses to facial perception: the occipital face area, the fusiform face area (FFA) on the fusiform gyrus (FG) and the posterior part of the superior temporal sulcus. Taken together, these three brain areas are considered the core system of facial processing. The core system processes unvarying aspects of faces (the basis for recognizing individuals) and changeable aspects of faces, such as eye gaze and expressions (Haxby et al., 2000).

The FFA is considered a critical cortical area for facial recognition, facial discrimination, and identification of family relationships (Ganel et al., 2005). The FFA is activated more by emotional than neutral expression (Pessoa et al., 2002; Winston et al., 2004). As an adaptive phenomenon, activation in the FFA decreases when the same face is perceived repeatedly, but this does not occur with repeated exposure to emotional expressions (Winston et al., 2004). There is also a positive correlation between facial selectivity in the FFA and performance in facial memory recognition tests (L Huang et al., 2014). Furthermore, FFA dysfunction is the most commonly identified sign in ASD (Nickl-Jockschat et al., 2014). The posterior part of the superior temporal sulcus is thought to be the area where the dynamic characteristics of faces and gaze are processed. This brain area presents more activation in response to dynamic than to static emotional expressions (Hocking and Price, 2008), but activation decreases after repeated exposure to an emotion (Winston et al., 2004). However, it does not appear to be involved when subjects do facial memory assessment tests (L Huang et al., 2014). The occipital face area and the FFA are involved in identifying invariant facial features. As well, the visual analysis of faces is more complex as we move from the occipital cortex to the anterior temporal pole through the ventral face of the temporal cortex (Collins and Olson, 2014).

Right lateralization of the nuclear system has been described as part of the process of specialization in facial processing. The representation of a face in the left hemisphere (when observed in the right field of vision) can be processed, but only with the support of the right hemisphere. On the other hand, since the face is represented in the right hemisphere, the support of the contralateral hemisphere is not necessary. These results imply that facial representation information is transferred from the right hemisphere to the left (Verosky and

Turk-Browne, 2012) due to asymmetric recruitment in the early stages of processing, i.e. in the occipital cortex, rather than in the FFA (Frässle et al., 2016).

2.3.2 The extended facial processing system

The extended system consists of brain regions specialized in other cognitive functions that can act in concert with the central system to extract facial information (Haxby, Hoffman, and Gobbini 2000). Brain regions like the amygdala, insula and striate nucleus (reward system) participate in the emotional subsystem of facial processing, which contributes to giving emotional valence to perceived stimuli and probably also provides information about the biological and evolutionary valence of the stimuli (Barton et al., 2003). The amygdala is an anatomical and functional region that reacts rapidly to positive and negative emotional stimuli (Williams et al., 2005) that bypass the conscious mind (de Gelder et al., 1999; Whalen et al., 1998). It sends signals to the rest of the brain that assigns emotional valence and salience (LeDoux, 2012) and reacts differentially to familiar versus unfamiliar faces (Barrett et al., 2012; Gobbini and Haxby, 2007; Taylor et al., 2009). The amygdala is proposed to be part of a system of vigilance of stimuli of social and evolutionary importance (Davis and Whalen, 2001).

Brain areas like the prefrontal cortex, temporoparietal junction, precuneus, posterior cingulate cortex and anterior pole of the temporal lobe participate in an extended subsystem that provides top-down-type feedback to the core system and gives the background or information about the perceived face (Gobbini and Haxby, 2007). The "motor simulation or imitation" subsystem was subsequently incorporated, which participates in spontaneous motor imitation (facial expressions) and response to stimuli. This subsystem is composed of the inferior parietal cortex and frontal operculum, the intraparietal sulcus, and frontal eye fields (i.e related to eye gaze and spatial attention) (Haxby and Gobbini, 2010).

Interregional communication between brain areas or functional subsystems flows between local specialization and global integration (in development), where function reinforces functional connections independent of the distance between these areas (Mišić et al., 2014).

2.4 NEUROBIOLOGY OF FACE PROCESSING AND AUTISM

Hypoactivation of isolated regions of the brain such as the FFA, amygdala and superior temporal sulcus is a common finding in ASD, hypoactivation of the FFA being the most common. There are few studies on the neural development of facial processing in ASD, the amygdala-FFA hypothesis being one of the most cited.

2.4.1 Fusiform cortex and autism

Not only is cortical thickness reduced in the FFA of people with ASD (Wallace et al., 2010), as is the number of neurons (Van Kooten et al., 2008), but functional hypoactivation is also commonly observed when subjects with ASD do facial processing tests (Nickl-Jockschat et al., 2014). Selectivity in the FFA predicts the ability of participants with ASD to discriminate faces (Jiang et al., 2013), and the magnitude of activation in this area correlates with the symptomatic severity of individuals (Scherf et al., 2015). However, there are cases in which the FFA of subjects with ASD is exaggeratedly active, for example, with the perception of a stimulus for which the subject has a highly specialized discrimination, like animated characters (Grelotti et al., 2005), or when performing mathematical operations (Iuculano et al., 2014), which reinforces the idea of under-activation as a consequence of lack of specialization in processing faces rather than a problem inherent to the FFA.

2.4.2 The amygdala and autism

There is extensive literature on the association between deficits in different paradigms involving social cognition and amygdaline hypoactivation. Tests that infer mental states according to eye contact and gazes (S Baron-Cohen et al., 2001; Calder et al., 2002) or facial expressions (Critchley et al., 2000) have led authors like Baron- Cohen to argue that the amygdala fails to assign motivational value to such stimuli in subjects with ASD (Baron-Cohen et al., 2000). The amygdala of individuals with ASD has a larger than normal volume from the age of three. The degree of increased volume at this age correlates with symptomatic severity five years later (Munson et al., 2006; Schumann et al., 2004), which is consistent with the hypothesis that early alteration in assigning salience is probably due to a dysfunction in the amygdala in providing salience to stimuli of high biological valence, such as faces. In fact, patients with congenital prosopagnosia that cannot recognize family members present normal amygdalin activity and normal levels of functional connectivity between the

amygdala and the core facial processing system (Avidan et al., 2014). However, hypoactivation is observed in the two brain regions of individuals with ASD during facial processing tests (Baron-Cohen et al., 2000; Nickl-Jockschat et al., 2014). A strong inverse correlation was found between the severity of ASD symptoms and amygdala-FFA connectivity (Natalia M. Kleinhans et al., 2008).

2.4.3 Atypical face processing in Autism

Facial processing is a skill that emerges in development and is strongly mediated by early experience and exposure to faces. However, what happens when individuals cannot access this specialization process as infants and are forced to develop compensatory skills later at school age or adolescence, such as individuals on the autism spectrum that enter adolescent life in a regular school system? As we have seen, patients with adequate cognitive abilities manage to process facial information through atypical cognitive processes based on slower compensatory mechanisms, of greater cognitive load and mainly based on the processing of details.

Thus, in addition to hypoactivation and hypoconnectivity of brain areas of the core system of the facial processing network, which explain a lower level of specialization (Jason S Nomi and Uddin, 2015; Pierce et al., 2001), there is atypical recruitment and functional connections in this population which explains compensatory mechanisms and differentiated neurodevelopment. For example, hyperactivity in frontal brain areas (Ashwin et al., 2007) and connectivity between the FFA and lower frontal cortex (Natalia M Kleinhans et al., 2008) have been associated with cognitive efforts to process facial information in ASD (Livingston and Happé, 2017b). Atypical recruitment of parietal and occipital brain areas (Dapretto et al., 2006; Hubl et al., 2003), as well local overconnectivity of the occipitotemporal cortex (Keown et al., 2013), have been reported in ASD. In effect, there are neural findings that explain the failure to specialize, but we also find atypical recruitment and connections that are responsible for the particular neurodevelopment in this population (compensatory mechanisms and a particular way of processing information). We propose a novel neuroscience approach to explain these differences, an approach that can contribute to the development of tools for the early diagnosis of TEA in subpopulations in which diagnosis is

a major challenge (i.e. those with good cognitive and language development), thus improving the functional and emotional prognosis of these people.

2.5 REAL-TIME NEUROFEEDBACK-BASED FUNCTIONAL MRI

2.5.1 Background

The conventional approach in contemporary cognitive neurosciences considers the brain as the dependent variable and behavior or a cognitive test as the independent variable. However, great strides have been made with the brain study by exploring behavior or neural impact following irreversible brain damage. Thus, the study of brain lesions (i.e. invasive non-reversible neuromodulation) led to great advances in the knowledge of the relationship between cognitive function and brain structure, opening new and important fields of research in cognitive neurosciences. For example, the case study of HM, an individual who required bilateral excision of the hippocampus, gave rise to the development of what we currently understand as implicit and declarative memory (Squire, 2009). With the development of non-invasive neuromodulation systems, the possibility was opened to study brain-behavior and brain-brain relationships without the repercussions an invasive or non-reversible neuromodulation system could have. There is a wide range of noninvasive neural stimulation devices available today that permit neuromodulation by exogenous stimuli (i.e. electroconvulsive therapy, transcranial electrical stimulation, transcranial magnetic stimulation, static magnet stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, focused ultrasound, peripheral nerve stimulation) or by endogenous neuromodulation (i.e neurofeedback based on electrical or metabolic/hemodynamic neural signals), all of which have their advantages and disadvantages (Davelaar, 2018; Lewis et al., 2016; Wagner et al., 2007; Watanabe et al., 2017; Zotev et al., 2014). Two major disadvantages of exogenous stimulation systems are the difficulty in modulating deep brain areas and evaluating neural activity during an intervention (Dmochowski and Bikson, 2017). Endogenous neuromodulation systems have been shown to be useful in modulating deep brain areas such as the midbrain (Sulzer et al., 2013), insula (Caria et al., 2007) and FFA (Habes et al., 2016), and it is also possible to evaluate neural activity in real-time, since this characteristic is a central part of the neurofeedback system.

2.5.2 Neurofeedback system

Neurofeedback systems are non-invasive and reversible neuromodulation systems in which subjects regulate their brain activity (i.e. endogenously) through operant conditioning training (Coben and Evans, 2011; Sulzer et al., 2013). Participants receive real-time information from their brain, which enables self-regulation of specific brain areas, functional connectivity between brain areas and modulation of specific neural networks (Ruiz et al., 2014). All neurofeedback systems are composed of at least four main components: 1) the participant, 2) acquisition unit brain signal 3) unit signal analysis and 4) the unit that provides the feedback. These components are part of the closed-loop system in which the brain signals of participants are translated into artificial output (e.g. visual or sound stimuli), which is provided to the experimental participant in real-time (Daly and Wolpaw, 2008; Weiskopf, 2012b). Early neurofeedback systems were based on electrical brain activity measured by electrodes placed on the skull (Spilker et al., 1969). These systems have a good temporal resolution, but a very low spatial resolution (Marzbani et al., 2016; Spilker et al., 1969). With technical improvements that have increased the speed of computer processing of information, it has been possible to develop neurofeedback systems with much better spatial resolution such as functional magnetic resonance (rtfMRI-NF).

2.5.3 Neurofeedback system based on functional MRI

Nuclear magnetic resonance provides high-resolution spatial imagery of the activity of the entire brain (superficial and deep brain areas) by recording the blood oxygen level-dependent response (BOLD) as an indirect measurement of neuroelectric activity (Logothetis et al., 2001).

This learning loop permits volitional control of circumscribed brain regions as complex neural networks (Watanabe et al., 2017), which can offer new treatments to restore dysfunctional brains and novel ways to explore the brain. In fact, this methodology has been used as a powerful tool to study addiction, schizophrenia, obsessive-compulsive disorder, depression and other brain disorders (Birbaumer et al., 2013; Ruiz et al., 2013b; Sitaram et al., 2017, 2007a; Weiskopf, 2012a; Weiskopf et al., 2004a). rtfMRI-NF makes it possible to neuromodulate small and functionally specific brain areas like FFA and be able to observe the consequences of this neuromodulation at both cognitive and neural levels in this clinical population. However, most studies involving rtfMRI-NF with clinical populations have

focused on the behavioral consequence of guided neuromodulation rather than neuronal consequences (Kim and Birbaumer, 2014; Ruiz et al., 2014; Watanabe et al., 2017). There are only two publications on autism and fMRI-NF, one being a narrative review that recommends studying the behavioral consequences of insula self-regulation among persons with autism (Caria and de Falco, 2015a). The other article, which was published while data for the present research was being analyzed, explored the behavioral effects on ASD participants of self-regulation of the functional connectivity among three brain nodes, the superior temporal sulcus, somatosensory cortex and inferior parietal cortex (Ramot et al., 2017). Thus, no studies have been published on the use of this technique to obtain a better understanding of the neural bases of the ASD. The present study is the first to use rtfMRI-NF to apply endogenous neuromodulation to one of the main hubs of face processing, the FFA, to study the neural functioning profile in ASD. It is hypothesized that FFA self-regulation among participants with ASD is associated with specific neural activation that can be explained from a developmental perspective.

3 OBJECTIVES

3.1 GENERAL OBJECTIVES

1. To implement a rtfMRI-NF system for the study of facial processing in ASD patients.

2. To study the neurobiological basis that underlies facial processing in ASD with rtfMRI-NF.

3.2 SPECIFIC OBJECTIVES

1. To determine the FFA self-regulation capability of individuals with ASD on a rtfMRI-NF training in comparison to individuals with typical development.

2. To evaluate the neuronal reorganization due to FFA self-regulation guided by rtfMRI-NF (by whole-brain analysis and functional connectivity analysis)

4. To look for potential predictors of FFA self-regulation ASD among clinical features or facial processing performance evaluated before the rtfMRI-NF training.

4 HYPOTHESES

4.1 GENERAL HYPOTHESES

1. Participants with typical and ASD development will achieve FFA self-regulation with rtfMRI-NF training.
2. FFA self-regulation with rtfMRI-NF will be associated with typical activation and functional connections of the face processing network on individuals with typical development.
3. FFA self-regulation with rtfMRI-NF will be associated with an abnormal pattern of activations and functional connections of the face processing network in individuals with ASD.
4. The abnormal pattern of brain activation and connections associated with the FFA self-regulation in ASD will be in concordance with the neurodevelopment of face processing of this population.
5. Face recognition accuracy will correlate positively with FFA self-regulation performance.
6. The severity of ASD symptoms will correlate with negatively with FFA self-regulation capability.

4.2 SPECIFIC HYPOTHESES

1. Individuals with ASD will achieve FFA self-regulation with rtfMRI-NF training.
2. FFA self-regulation training will carry extended neural activations. Particularly, the typical activation of the face processing neural network will be observed.
3. Modulations on face processing neural network with fMRI-NF will be different on participants with typical and ASD development (in concordance with the typical and ASD neural development of face processing).
    a. Participants with typical development will show a typical pattern of activations and functional connectivity associated with face processing. Particularly we expected:

i. Activation on the Core and the Extended Neural System of face processing.
ii. Right lateralization on the ventral visual stream.
iii. Functional connectivity between FFA and brain areas of the Extended Neural System of face processing (e.g. amygdala, insula, striatum, and inferior frontal gyrus).

b. Participants with ASD will show an atypical pattern of activations with rtfMRI-NF in concur with an ASD development of the face processing. Particularly, we expect:
    i. Similar activation on FFA and brain areas of early visual processing (temporo-occipital brain areas)
    ii. Hypoactivation on amygdala, insula, and striatum and more intense activations on PFC.
    iii. Hypoconnectivity between FFA and insula, amygdala, striatum and stronger connections with brain areas of the ventral visual stream and the prefrontal cortex.
    iv. Absence of right lateralization of the brain activity.

4. FFA self-regulation performance will correlate positively with the face recognition accuracy of the ASD participants.
5. The severity of ASD symptoms will correlate negatively with FFA self-regulation capability.

5 MATERIALS AND METHODS

5.1 PARTICIPANTS

Eleven male, right-handed volunteers, naïve to real-time fMRI experiments, underwent eight rtfMRI-NF training runs for volitional control of both FFAs. To evaluate the neural effects of this training in TD, six right-handed adult males with TD (i.e. without a clinical history of neurological, psychiatric nor neurodevelopmental disorders nor intellectual disability), and without autistic traits (i.e. negative family history of ASD, scores below 15 in the Social Communication Questionnaire (Rutter, M., Bailey, A., & Lord, 2003), and with Autism Spectrum Quotient (Simon Baron-Cohen et al., 2001)) below 32 were randomly distributed in two groups (Table 1). Those in the first control group (CG1) participated in a rtfMRI-NF training protocol with contingent information from the FFAs as feedback. The other three individuals participated in a similar protocol, but with non-contingent (sham) feedback (CG2sham).

	AG			CG1			CG2sham		
	M	SD	Range	M	SD	Range	M	SD	Range
AGE (years)	16,52	2,05	14,13-19,50	29,42	4,02	25,67-33,67	35,21	5,24	29,33-39,38
AQ (score)	28,80	5,81	22-34	9,67	6,81	2-15	9,67	4,17	5-13
SCQ (score)	21,80	1,92	19-24	8,33	5,13	4-14	6,33	3,05	3-9

Table 1. Demographical information of participants. SCQ: Social Communication Questionnaire; AQ: Autism Spectrum Quotient.

In a second instance, in order to evaluate the feasibility of this methodology in ASD and its neural effects, five participants with ASD with fluent speech and without intellectual disability (AG) participated in a rtfMRI-NF training protocol similar to that carried out by

the group CG1. Participants in the AG group were evaluated with a complete clinical battery of test to establish their clinical profiles and to evaluate if clinical characteristics could predict their performance in up-regulation of the FFA. Their I.Q. was evaluated with the FIX test, an abbreviated test standardized for the local population that correlates closely with the Wechsler Scale of Intelligence, 4th version (Riveros et al., n.d.; Rosas et al., 2014). The ASD diagnosis was made by two independent psychiatrists, based on the DSM 5 criteria (American Psychiatric Association, 2013) and confirmed by two standardized instruments, considered to be gold standard for diagnostic evaluation (the Autism Diagnostic Observational Schedule, ADOS-2 (Lord et al., 2012, 2000), and the Diagnostic Interview-Revised, ADI-R (Kim et al., 2013)). The Vineland Adaptive Behavior Scale, second edition (Klin et al., 2007) was used to assess adaptive behavior and social abilities not evaluated in ADOS-2 (Klin et al., 2007) or ADI-R (Lecavalier et al., 2006) (Table 1 and 2).

AG Group	M	SD	Range
FIX *	68,60	14,93	49-91
ADOS-2 **			
Communication (C)	4,00	1,22	3-6
Social reciprocity (S)	5,80	0,84	5-7
Total (C + S)	9,80	1,92	8-13
ADI-R subscales			
Social	19,00	3,74	13-22
Communication	13,00	3,74	8-18
Repetitive behavior	6,80	2,77	4-11
Vineland Scale ***			
Chronological Age	17,76	2,00	15,75-20,5
Social Age	15,66	2,45	11,70-17,8
Social Quotient	0,88	0,12	0,72-1

Table 2. Clinical information about AG group. ADOS-2: Autism Diagnostic Observational Schedule second version; ADI-R: Diagnostic Interview Revised; Vineland Scale: Vineland Adaptive Behavior scale, second edition. * FIX as a percentile for local population (normalized by age); ** ADOS-2, module 4 algorithm. *** Chronological age at Vineland scale performed time.

Exclusion criteria for all study participants included contraindications for participation in an MRI measurement. After giving a complete description of the study to the participants and to the parents of the adolescents, written informed consent and assent (required in the case of adolescent participants) was obtained. The experimental protocol was approved by the ethics committee of the Pontificia Universidad Católica de Chile.

5.2 EVALUATION OF FACE PROCESSING

To evaluate the relationship between different aspects of facial processing and FFA up-regulation, four tasks were included at the beginning of the first day of rtfMRI-NF training outside the scanner. First, to evaluate long-term memory of faces, the Cambridge Facial Memory Test (CFMT) (Hedley et al., 2011; Wilson et al., 2010) was applied, along with its counterpart, the Cambridge Car Memory test (CCMT) (Dennett et al., 2012). Second, to evaluate Theory of Mind and recognition of complex emotions from the eyes, the Reading the Mind in the Eyes task, revised version of "the Eyes task" (S Baron-Cohen et al., 2001) was used. In addition, two tasks were included to evaluate early visual processing of faces, reducing reliance on higher-level cognitive skills: a 4-Alternative Forced Choice task to evaluate the ability to recognize faces ("FIR" task), and a 5-Alternative Forced choice task for the recognition of facial expression of basic emotions ("FER" task). FIR and FER tasks were composed of 32 concatenated trials of the identical temporal organization (320 seconds for each task), screened on a 13.3-in. LCD-monitor (Resolution: 1366 x 768; Frame Rate 60 Hz; Viewing distance: 50 cm. app.; PresentationVR 17.1 software, Neurobehavioral Systems, USA). See Box for a complete description.

The tasks to test the speed of recognition of emotions and identity by the observation of faces (FER and FIR task, respectively) begin with a fixation block to ensure attentional resources are directed to detect the stimuli, followed by a stimulus image (a neutral face for FIR and a face with an expression of negative emotion for FER) presented for 67 milliseconds, i.e., slightly above the identification threshold, but with enough duration to ensure their detection (Calvo and Lundqvist, 2008; Clark et al., 2008; Inuggi et al., 2014; Or and Wilson, 2010). The stimulus presentation was followed by a black screen of 500 milliseconds, followed by the task to be answered (button press) for 5.5 seconds. The FIR task was composed of 3 new neutral faces plus the target (Lai et al., 2012; Serra et al., 2003;

Weigelt et al., 2012b). The FER task consisted of a five-choice display with the words "Fear", "Disgust", "Anger", "Sadness" and "Surprise" (Ashwin et al., 2006). **Stimuli**: Faces for the FIR and FER tests were obtained from the Karolinska Directed Emotional Faces (Goeleven et al., 2008). 21 male and 21 female faces (168 images in total) were cropped so that each stimulus fit within an oval window of 15 x 11 cm. and the images of the task fit in an oval of 10 x 7,33 cm. In the FIR task, the stimulus images consisted of 32 neutral faces (sex balanced) and in the FER task, the stimulus images consisted of 32 images of basic emotions of negative valence.

Box 1. The tasks for the rapid recognition of emotions and identity by faces.

5.3 REAL-TIME FMRI TRAINING

All subjects participated in two days of rtfMRI-NF sessions, with 1 or 2 days of separation between sessions. Each training session began with one localizer run (lasting 4.15 minutes) to bilaterally localize the FFA to be used as the region of interest (ROI1) from where the BOLD activity was extracted for the next four training runs (each lasting 3.75 minutes). An anatomical T1 image was acquired at the end of each training day.

5.3.1 Functional localizer

The functional localizer consisted of a block-based paradigm to contrast neutral faces and houses in order to localize left and right FFA (ROI1) (Tong et al., 2000). Four blocks of faces and three blocks of houses were alternating with each other and separated by 21 seconds of rest between two consecutive blocks (166 volumes; 4.15 minutes). Each block of houses and faces were composed of 40 images obtained from a pool of 60 images of houses without background and from 60 images of neutral faces obtained from the Karolinska Directed Emotional Faces database (Goeleven et al., 2008) respectively. Each image was presented for 650 milliseconds and separated by 100 milliseconds (black screen) from the next image. A black screen with a white cross in the middle was used for the rest blocks.

The software Turbo Brain Voyager 3.0 (Brain Innovations, The Netherlands) was used to select the brain areas of interest that were incorporated into the feedback calculation of the training runs. Feedback information was obtained from ROI1, specifically from the voxels with the greatest activation (Faces > Houses) within the ventral part of each temporal lobe,

lateral to the parahippocampal cortices (two cuts of around 5x3 voxels each). To cancel the effects of global activation, a transversal slide (9 x 3 voxels) positioned in advance of the third ventricle was used as reference (ROI2).

5.3.2 The Real-Time fMRI System

we implement an fMRI-NF system similar to those used in similar studies (Ruiz et al., 2014; Sitaram et al., 2007a; Weiskopf, 2012a; Weiskopf et al., 2004b) (Figure 1). At the beginning of each measurement, participants were positioned in the scanner and reference scans were acquired. Later, using a gradient echo-planar imaging (EPI) sequence (see MR acquisition), functional brain volumes were generated. During image acquisition, brain volumes were transferred in real-time directly from the scanner's image reconstruction system using the Direct Reconstructor Interface application (Philips Healthcare, Best, The Netherlands) to an external computer to analyze it in real-time (Sitaram et al., 2011). A standard personal computer running Turbo Brain Voyager software read the incoming brain volumes to perform real-time 3D motion correction and statistical analysis (Weiskopf et al., 2003). Turbo Brain Voyager parameters were set to match parameters of the EPI acquisition and to obtain the BOLD signal coming from the ROIs at each repetition time (TR: 1.5 seconds). Custom MATLAB scripts used the signals from the ROIs to compute the feedback by comparing blocks of up-regulation and baseline (Equation 1). The feedback output was stored in a shared text file in the Turbo Brain Voyager computer, which was accessed from the personal computer with PresentationVR 17.1 software (Neurobehavioral Systems, USA). Presentation software read the feedback output file continuously and updated the feedback on the screen at an interval of 1.5 seconds. The feedback was presented in the form of thermometer bars in an MR compatible visual display system (NordicNeuroLab AS, Norway).

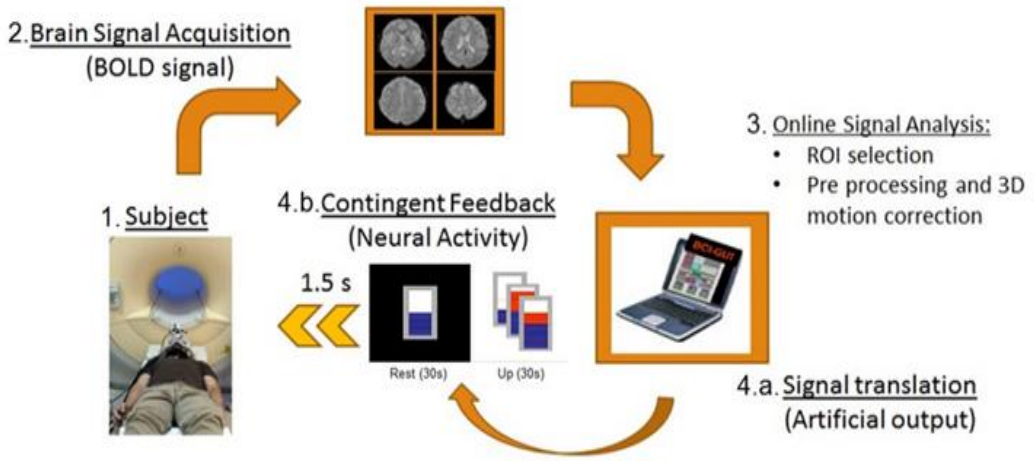

Figure 1. Schematic of the rtfMRI-NF components. RtfMRI-NFs are based on a circular re-entry system in which the BOLD signals of the participants are translated into artificial outputs (i.e. visual contingent feedback). It is compound by four main components: 1) the participants, 2) brain signal acquisition unit, 3) signal analysis unit and 4) feedback unit.

5.3.3 Training Runs and feedback calculation

Each participant went through two training sessions. Each training session consisted of four training runs. Each training run started with 10 dummy scans (duration of 15s) at the beginning of the run to reach T1 steady state, followed by 4 baseline blocks and 3 up-regulation blocks (each block of 30s). The dummy scans were later discarded from the analysis. The total duration of training runs was 3 minutes 45 seconds. During up-regulation blocks, participants of AG and CG1 groups received contingent visual feedback from their FFAs. Feedback (F) was calculated as:

$$F = \left(BOLD_{Upreg} - BOLD_{Base}\right)_{ROI\ 1} - \left(BOLD_{Upreg} - BOLD_{Base}\right)_{ROI\ 2} \qquad \textit{Equation 1}$$

Where $BOLD_{Upreg}$ is the average BOLD signal of a moving window of the last three scans of the up-regulation block, and $BOLD_{Base}$ is the average BOLD signal of the preceding baseline block. ROI 1 represented bilateral FFAs selected during the Localizer Run, and ROI 2 was the brain area anterior to the third ventricle which was selected to cancel the effects of global brain activation. Signal artifacts (due to head movement or swallowing) was corrected by replacing any abrupt increases in the BOLD signal by the mean BOLD signal from the

preceding time points. Participants of CG2sham were also provided with thermometer feedback but without contingent information, i.e., "sham" feedback (i.e. pseudorandom movement of the thermometer bars).

All participants were instructed to observe the thermometer and to increase the bars. Participants were informed that the movement of the thermometer bars was contingent with the activity of a brain area related to the visual processing of faces. They were also instructed about the 4-6 seconds delay in the movement of the bar (due to slow hemodynamic response as well as to restrictions imposed by data acquisition and processing). During baseline blocks, a thermometer with stationary bars in the center of the screen was provided to participants, and they were asked to remain at rest (with open eyes) in order to return the BOLD signal to the baseline level.

5.3.4 MR Acquisition

The rtfMRI-NF system was implemented using a Philips Achieva 1.5T MR scanner (Philips Healthcare, Best, The Netherlands) at the Biomedical Imaging Center of the Pontificia Universidad Católica de Chile. A standard 8-channel head coil was used. For functional image acquisition, we used the Fast Field Echo EPI sequence (TR/TE = 1500/45 ms, matrix size = 64 x 64, flip angle α=70°, FOV: RL = 210 mm, AP = 210 mm, FH = 79 mm). Sixteen slices (voxel size = 3.2 x 3.3 x 4 mm^3, gap = 1 mm) were used, oriented with AC/PC alignment to cover the entire temporal and most of the frontal and parietal lobes (Figure 2). 150 and 166 scans (10 dummy scans for each one) were performed in each training and functional localizer run respectively. For the superimposition of functional maps on brain anatomy, anatomical T1-weighted brain volumes were acquired, using T1W-3D Turbo Field Echo (magnetization-prepared gradient-echo also known as MPRAGE) sequence (TR/TE = 7.4/3.4 ms, matrix size = 208 x 227, α = 8°, 317 partitions, voxels size = 1.1 x 1.1 x 0.6 mm3, TI = 868.7ms). To prevent discomfort during MRI sessions, pads and air cushions were used to secure the head. Relatives of the ASD participants were asked to accompany the researcher and follow the MRI sessions.

5.4 OFFLINE BRAIN IMAGING ANALYSIS.

5.4.1 Preprocessing

For brain imagining and ROI analysis, spatial and temporal pre-processing steps were performed with the version eight of the Statistical Parametric Mapping software package, SPM (Wellcome Department of Imaging Neuroscience, London, UK), using 140 functional volumes. The first 10 volumes were discarded to ensure steady-state. Preprocessing included motion correction, realignment, and slice-timing correction. Functional EPI images were co-registered with the acquired T1-weighted image and normalized to Montreal Neurological Institute coordinates. In addition, functional volumes were smoothed with a Gaussian kernel of Full-Width Half Maximum of 8 x 8 x 8 mm.

5.4.2 FFA Up-regulation calculation

The smoothed and normalized brain volumes were used to evaluate the up-regulation of the BOLD signal separately in the left and right FFAs. The ROI analysis was performed using a sphere of 5 mm^3 obtained from the left and right parts of ROI1 of each participant (Table 3). The magnitude of the left and right FFA (r_{FFA}) up-regulation was calculated using the mean BOLD values of regulation and baseline blocks of each run per participant as a percentage as follows:

$$r_{FFA} = 100 * \frac{Mean(BOLD_{Upreg}) - Mean(BOLD_{Bas})}{Mean(BOLD_{Bas})} \qquad \textit{Equation 2}$$

Where $BOLD_{Upreg}$ and $BOLD_{Bas}$ represent vectors whose values are extracted from the time-series of regulation and baseline (no feedback) blocks of each training run. The average value of the r_{FFA} during each training session was used as the main measurement of up-regulation performance (one-sample t-test compared to zero, p two-tailed, 95% confidence). We verified the normality of the data using the D'Agostino & Pearson (omnibus k2) test, and non-parametric tests were used when appropriate.

PARTICIPANT	Day 1	Day 2
AG.1	[-43 -55 -23] ; [48 -58 -22]	[-54 -64 -2] ; [47 -62 0]
AG.2	[-54 -62 0] ; [52 -66 0]	[-51 -58 -10] ; [52 -66 -2]
AG.3	[-39 -67 -19]; [43 -65 -18]	[-39 -67 -19] ; [43 -65 -18]
AG.4	[-56 -56 -10]; [56 -56 -10]	[-56 -56 -10]; [56 -56 -10]
AG.5	[-39 -67 -19]; [43 -65 -18]	[-39 -67 -19]; [43 -65 -18]
CG1.1	[-45 -53 -21];[40 -50 -20]	[-39 -50 -20]; [35 -56 -18]
CG1.2	[-48 -60 -18]; [34 -66 -15]	[-40 -47 -23]; [41 -46 -20]
CG2.3	[-47 -67 -8]; [37 -76 -13]	[-48 -71 -12]; [40 -63 -12]
CG2.1	[-35 -54 -20]; [36 -64 -18]	[-37 -54 -20]; [44 -63 -20]
CG2.2	[-47 -65 -16];[42 -71 -17]	[-50 -68 -13]; [42 -70 -17]
CG2.3	[-39 -67 -19]; [43 -65 -18]	[44 -55 -20]; [-40 -60 -18]

Table 3. Region of interest (ROI) localization (MNI) for offline analysis.

The "training effect" on up-regulation performance was assessed for each group using two approaches. The difference between the mean r_{FFA} of training session 2 and of training session 1 (Δr_{FFA}) was calculated for each subject and then compared against zero by group (one-sample Wilcoxon Signed Rank Test compared with zero, p two-tailed, 95% confidence). Second, the slope of the group average of r_{FFA} through the runs, i.e. the "learning slope" of up-regulation was calculated for left and right FFAs (Spearman correlation coefficient, p two-tailed, 95% confidence).

5.4.3 Variability in FFA Up-regulation

Given that the variability of the BOLD signal has been associated with neural flexibility and specialization of some brain areas (Nomi et al., 2017), the variability to self-regulate left and right FFAs (as standard deviation (SD) of the BOLD magnitude on each run) was evaluated in the three groups. First, the SD of the r_{FFA} values (SD-r_{FFA}) were calculated, and a group comparison (considering all training runs) was carried out for left and right FFA separately (Kruskal–Wallis test, with Dunn's multiple comparison test as a post-hoc analysis). Second, the training effect on SD-r_{FFA} values was evaluated for each group, using two approaches. First, the difference between the mean SD-r_{FFA} of session 2 and the mean SD-r_{FFA} of session 1 was calculated for each subject (ΔSD-r_{FFA}) and then compared against zero by group (one-sample Wilcoxon Signed Rank Test compared to zero, p two-tailed, $p < .05$). Second, the

slope of the group average of SD-r_{FFA} through the 8 runs or "learning slope" of the variability was calculated for left and right FFA separately (Spearman correlation coefficient, p two-tailed, 95% confidence).

5.5 FUNCTIONAL ANALYSIS OF THE BRAIN AND FFA UP-REGULATION

The whole-brain activations and the functional connectivity profile of each fusiform gyrus during FFA up-regulation with rtfMRI-NF were evaluated to obtain a better understanding of the neural networks associated with up-regulation of FFA in ASD.

5.5.1 Whole-brain analysis

A whole functional brain analysis using all the preprocessed functional images was carried out to evaluate neural activations during the FFA up-regulation guided by the rtfMRI-NF training. A first-level analysis was performed with the SPM. General Linear Modeling was defined considering Regulation and Rest blocks as two independent conditions to map the brain regions recruited. In addition, six generated motion confounds were added to the model and convolution of the regressor with the canonical hemodynamic response function was carried out. A second-level analysis was performed with SPM considering the contrast between regulation blocks and rest blocks (contrast = [Regulation > Rest]) to evaluate specific activations resulting from up-regulation training in each group (one-sample t-test per group, $P < 0.001$ & FWE $P < 0.05$; $K = 10$). For the visualization of the brain activations, anatomical automatic labeling or AAL atlas (Tzourio-Mazoyer et al., 2002) and XjView toolbox (http://www.alivelearn.net/xjview) were used.

5.5.2 Functional connectivity analysis

To investigate the network changes during up-regulation, a functional connectivity analysis was carried out. For this purpose, a linear relationship between BOLD activity of different brain regions (AAL atlas) inside of the field of view (Whole brain without the cerebellum and the upper middle part of both parietal and frontal lobes, Figure 2) was computed from their correlation coefficients (Friston, 2011) using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) with left and right fusiform gyrus (FG) as the seed regions. FG was chosen as seed given the wide interindividual variability of FFA reported in ASD (Scherf

et al., 2010) and replicated in this study (Table 3). We used FG as the seed as it encloses our ROI (FFA) due to its greater spatial extent and hence would give us the possibility of making an anatomical and functional comparison between the groups.

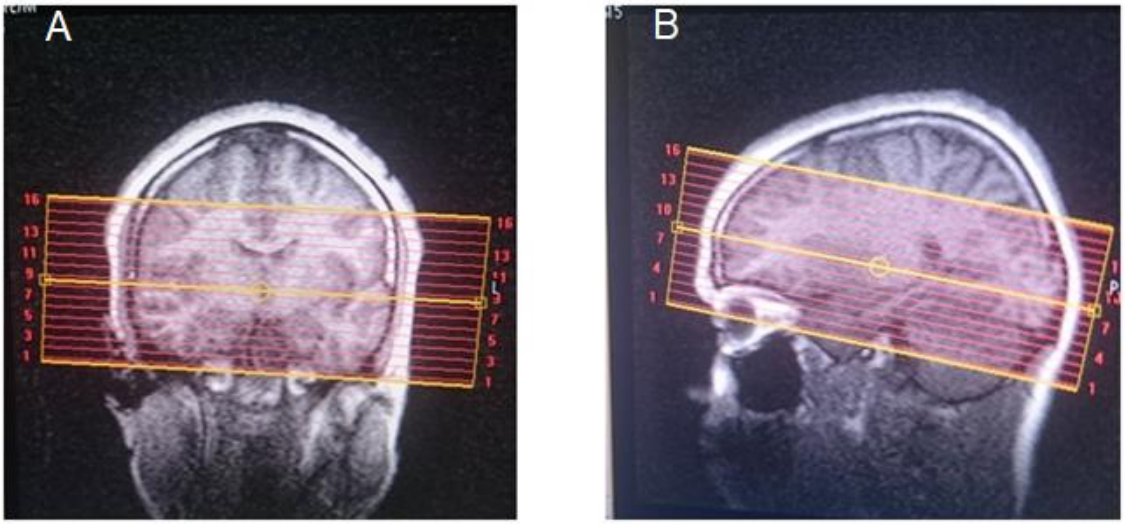

Figure 2. Image of the field of view (FOV) used on fMRI-NF. For functional image acquisition, we used the Fast Field Echo EPI sequence (TR/TE = 1500/45 ms, matrix size = 64 x 64, flip angle α=70°, FOV: RL = 210 mm, AP = 210 mm, FH = 79 mm). Sixteen slices (voxel size = 3.2 x 3.3 x 4 mm^3, gap = 1 mm) were used, oriented with AC/PC alignment to cover the entire temporal and most of the frontal and parietal lobes. The anteroposterior and lateral view is showed in figure A and B respectively.

Pre-processing consisted of denoising, bandpass-filtering (0.008–0.09 Hz), the inclusion of estimated head motion parameters, use of white matter and cerebrospinal fluid as covariates, linear detrending, and despiking. Bivariate correlations between different brain regions were calculated for regulation blocks taking left and right FGs as seed regions separately. The correlation coefficients between each pair of regions (seed-target) were considered as independent measurement values as follows (Whitfield-Gabrieli and Nieto-Castanon, 2012):

$$r = (x^t x)^{-\frac{1}{2}}(x^t y)(y^{\,t} y)^{-\frac{1}{2}} \qquad \textit{Equation 3}$$

Where *x* and *y* are vectors of the BOLD time-series for seed ROI and target ROI respectively. To assess similarities and differences of functional connectivity among the participants of

different groups, mean pairwise correlation coefficients of functional connectivity (mean z_{FC} values) through all training runs were considered. Results are reported for all significant connections (threshold P-FDR (seed corrected) <0.01, one-sided (positive)) and a group description by lobe is presented.

Group differences in connection strength (mean z_{FC} values) of left and right FGs were evaluated for all brain areas and for the ventral visual stream (i.e. brain areas of the occipital lobe, lingual cortex, FG, parahippocampal cortex, inferior temporal gyrus and ventral area of the temporal pole) (Collins and Olson, 2014; Kravitz et al., 2013) using all significant connections. The late analysis was carried out due: First, based on the importance of the ventral visual stream for specialized visual processing (Kravitz et al., 2013), in particular of faces (Collins and Olson, 2014). Second, due to the particular connection profile described for ASD namely that there are stronger short-range and weaker long-range functional connections (Barttfeld et al., 2011). In particular, higher values of local functional connectivity (Keown et al., 2013), regional activity coherence (Paakki et al., 2010) and degree of centrality (Di Martino et al., 2013) have been found between brain areas of the ventral visual stream in ASD. Both group analyses were performed by one-way ANOVA and the Kruskal-Wallis test, using Tukey's and Dunn's multiple comparisons test, respectively, for post-hoc analysis. All data were checked for normality using D'Agostino & Pearson (omnibus k2) test, and non-parametric tests were used when appropriate. For the visualization, the thickness of the lines connecting the ROIs was represented proportionally to the magnitude of t values.

5.6 AUTISM SPECTRUM DISORDER AND UP-REGULATION PERFORMANCE

To evaluate if clinical aspects such as chronological age, IQ, Social Age of Vineland scale, ADOS-2 and ADI-R scores or some aspects of the facial processing performance (i.e., accuracy of FER, FIR, CFMT and Eye-Task and reaction-time of CFMT) are associated with FFA up-regulation performance in subjects with ASD, correlations between these clinical data and r_{FFA} of all training runs were calculated (Spearman correlation coefficient, p two-tailed, 95% confidence).

6 RESULTS

6.1 CLINICAL AND FACIAL PROCESSING PROFILE OF PARTICIPANTS

Initially, six participants with ASD were recruited for the study. However, one ASD participant declined to participate in the training due to hearing and tactile discomfort in the scanner. Participants with TD participated in both training days without any sensorial inconvenience. A demographic and clinical summary of the participants can be seen in Tables 1 and 2. Although there were no significant group differences in the accuracy achieved in the visual processing tasks (Table 4), participants with TD (the participants in CG1 + CG2sham) showed a faster reaction time in the standardized face memory task (CFMT) compared to the non-social memory task (CCMT) (CFMT Mdn = 3291; CCMT Mdn = 5054; U = 5 , p = .0411, Mann–Whitney U test). Participants with ASD showed no such difference (CFMT Mdn = 4436; CCMT Mdn = 4762, U = 7, p = .310, Mann–Whitney U test).

Task	AG Mdn.	CG1 + CG2sham Mdn.	statistics
FER task			
Accuracy	(0.781)	(0.719)	*U* = 12, *p* = .658
FIR task			
Accuracy	(0.781)	(0.750)	*U = 9.5, p =* .342
CFMT			
Accuracy	(0.667)	(0.688)	*U = 13, p =* .792
Reaction Time (msec.)	(4436)	(3291)	*U = 7, p =* .178
CCMT			
Accuracy	(0.736)	(0.757)	*U = 13.5, p =* .833
Reaction Time (msec.)	(4762)	(5054)	*U = 13, p =* .792
the Eyes task			
Accuracy	(0.780)	(0.720)	*U = 9.5, p =* .366

Table 4. Facial processing performance on participants with ASD (AG) and with typical development (participants of CG1 and CG2sham groups).

6.2 TRAINING SESSIONS

All participants underwent eight training runs in two training sessions. Two runs of one participant with ASD had to be discarded from the analysis, as the participant moved his head significantly during the first training run and reported after completing the run that he was using head and eye movements as a strategy to control the thermometer bars. Furthermore, there was a communication loss between the computers due to a temporary hardware problem. In total, 94 training runs (13160 functional images) were used in the analysis.

6.2.1 FFA up-regulation magnitude

Both AG and CG1 were able to self-regulate left and right FFAs during all training (left FFA: AG: Mdn = 0.277, W = 655, p< .001; CG1: Mdn = 0.2058, W = 292, p< .001, one-sample Wilcoxon Signed Rank Test compared to zero / right FFA: AG: M = 0.286, t(37) = 7.55, p< .001; CG1: M = 0.191, t(23) = 8.10, p< .001, one-sample t test, compared to zero). Moreover, the performance of these groups to self-regulate left and right FFA was significantly high in training session 1 (AG: left FFA: M = 0.287, t(18) = 3.48, p = 0.003; right FFA, Day1: M = 0.261, t(18) = 5.343, p < .001 / CG1: left FFA: Mdn = 0.226, W = 76, p < .001; right FFA: M = 0.244, t(11) = 7.114, p < .001) and training session 2 (AG: left FFA: Mdn = 0.3546, W = 188, p < .001; right FFA: M = 0.311, t(18) = 5.297, p < .001 / CG1: left FFA: M = 0.185, t(11) = 5.294, p < .001; right FFA: M = 0.139, t(11) = 5.406, p < .001). In contrast, participants of CG2sham failed to achieve up-regulation in either left or right FFA when both training sessions were taken together (left FFA: Mdn =-0.1417, W = -106, p = .136), or separately (Session 1: left FFA: M = -0.131, t(11) = 1.553, p = .149; right FFA: Day1: M = -0.0349, t(11) = 0.394, p = .701 / Session 2: left FFA: Mdn = -0.1246, W = -22, p = .424; right FFA: M = -0.0294, t(11) = 0.240, p = .814) (Figure 3).

Differences between the up-regulation performance of the groups were found on left FFA (H(2)23.35, p < .001, Kruskal-Wallis test) and right FFA (F (2, 83) = 11,69, p < .001, one-way ANOVA). The post-hoc analysis for left FFA and right FFA showed better performance in the up-regulation of left and right FFAs in AG and CG1 than in CG2sham (left FFA: AG vs. CG2sham: p < .001; CG1 vs. CG2sham: p = .002 / right FFA: AG vs. CG2sham: p < .001; CG1 vs. CG2sham: p = .008). On the other hand, no differences were found between AG and CG1 (left FFA: p > .999; right FFA: p = .332) (Figure 3).

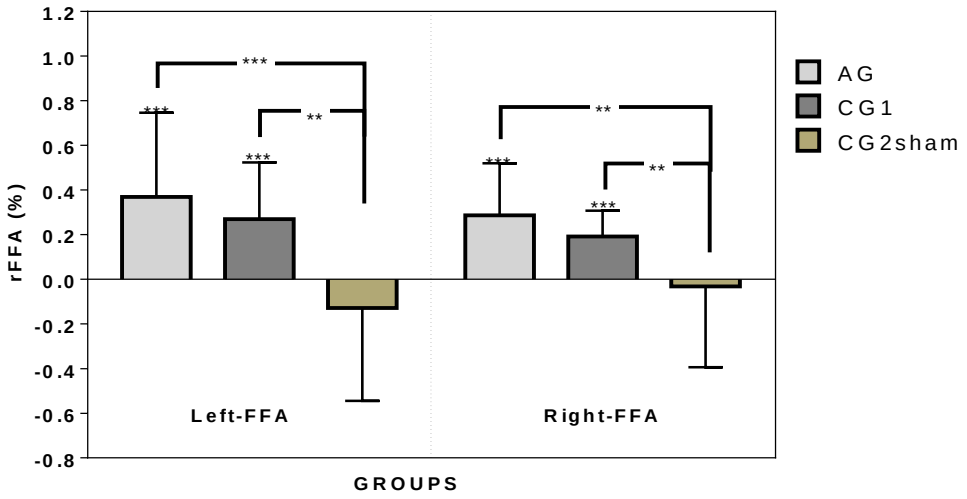

Figure 3. Up-regulation performance (rFFA) by group on left and right FFA (*p<0.05, **p<0.01, ***p<0.001).

6.2.2 FFA up-regulation learning process

Up-regulation learning in left and right FFAs was evaluated using the following two approaches. First, we evaluated the individual difference in r_{FFA} between session 2 and session 1 (Δr_{FFA}) and these values were then compared against zero for each group. Second, the slope obtained from the group mean r_{FFA} of each run (the "activation learning slope") was estimated. No differences in self-regulating left or right FFA between sessions was found in any group (AG: left Δr_{FFA}: Mdn = 0.137, W = 13, p = .125; right Δr_{FFA}: Mdn = 0.0691, W = 9, p = .313/ CG1: left Δr_{FFA}: Mdn = 0.108, W = -6, p = .250 ; right Δr_{FFA}: Mdn = -0.0443, W = -6, p = .250/ CG2sham: left Δr_{FFA}: Mdn = -0.0150, W = 0, p > .999; right Δr_{FFA}: Mdn = -0.0302, W = 0, p > .999). No significant learning slope was found in any group (AG: left FFA: r_s: 0.405, p = .327; right FFA: r_s= -0.238, p = .582/ CG1: left FFA: r_s= -0.619, p = .115; right FFA: r_s= -0.476, p = .2431 / CG2sham: left FFA: r_s= -0.333, p = .428; right FFA: r_s= -0.239, p = .977).

6.2.3 FFA up-regulation variability

Group differences between SD-r_{FFA} were found on right FFA but not on left FFA (right FFA: H(2)10.67, p = .005; left FFA: H(2)5.495, p = .064). In a post-hoc analysis of the right FFA, less variability was found in CG1 than in CG2sham (p = .004). However, no differences between AG and CG1 (p = .078), or with CG2sham (p > .999), were found (Figure 4).

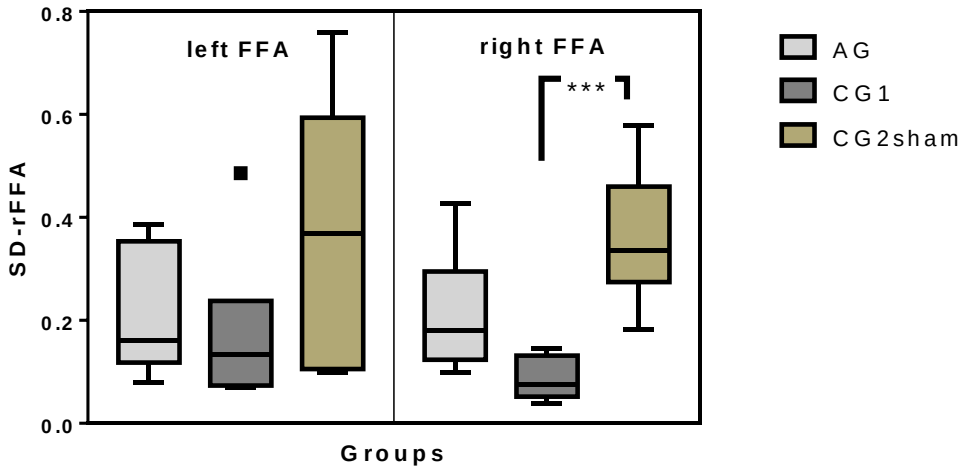

Figure 4. A box-and-whisker plot of the inter-subject variability of up-regulation performance *(SD of BOLD magnitude) by group on left and right FFA. (*p<0.05, **p<0.01, ***p≤0.001).*

6.2.4 Learning process and up-regulation variability

No differences between ΔSD-r_{FFA} and zero was found for any group (AG: left FFA: Mdn = .040, W = 9, p = .313, right FFA: Mdn = -.0885 , W = -11, p = .188; CG1: left FFA: Mdn = .0425, W = 2, p = .750, right FFA: Mdn = .0663, W = 4, p = .50 ; CG2sham: left FFA: Mdn = -.211, W = -4, p = .50, right FFA: Mdn = -.140, W = -4, p = .50). On analysis of the changes in SD-r_{FFA} during the training runs, a negative correlation between Run progression and SD-r_{FFA} was found on left FFA of the CG1 (left FFA: r_s= -.857, p = .011; right FFA: r_s= .095 p = .840, ns). No correlation was found between SD-rFFA and run progression on AG or

CG2sham (AG: left FFA: r_s = -.024, P = .977, ns; right FFA: r_s= -.0714, P = .882, ns. / CG2sham: left FFA: r_s= .048, P = .935, ns; right FFA: r_s= 0, P >.999, ns).

6.3 FUNCTIONAL ANALYSIS OF THE BRAIN AND FFA UP-REGULATION

6.3.1 Whole Brain analysis

Activation profiles in each group (contrast = up > rest; one-sample t-test, P < 0.001 & FWE P < 0.05; K = 10) showed clear differences. Although both groups that received contingent feedback (CG1 and AG) showed recruitment of the left FG, left lingual cortex, and left inferior frontal gyrus, recruitment of these brain areas tends to be weaker in AG than in CG1 (Table 5 and Figure 5).

Group	AAL region	peak T	peak p(FWE-corr)	cluster equivk	cluster p(FWE-corr)	x,y,z {mm}	x,y,z {mm}	x,y,z {mm}
AG								
	Cerebellum_6_R	6,8508	0,000286	98	4,36E-08	7,280004	-79,2	-15
	Calcarine_R	6,0926	0,002275			20,4	-75,92	5
	Vermis_7	5,8632	0,004139			-2,56	-75,92	-20
	Frontal_Inf_Orb_L	5,7737	0,005221	37	3,46E-05	-32,08	22,48	-10
	Frontal_Inf_Orb_L	5,6847	0,006573			-45,2	22,48	-10
	Fusiform_L	5,5197	0,010055			-32,08	29,04	5
	Cerebellum_6_L	5,7160	0,006062	10	0,002421	-28,8	-69,36	-20
	Calcarine_L	5,2525	0,019846	11	0,001982	-5,84	-75,92	5
	Lingual_L	5,1958	0,02289			-12,4	-75,92	0
CG1								
	Lingual_R	12,349	9,84E-08	728	0	13,84	-82,48	-10
	Fusiform_R	12,136	1,4E-07			26,96	-79,2	-15
	Lingual_R	10,695	1,67E-06			7,280004	-79,2	-5
	Insula_L	12,271	1,12E-07	169	1,11E-16	-28,8	29,04	0
	Frontal_Inf_Orb_L	7,6874	0,000667			-35,36	22,48	-15
	Frontal_Inf_Tri_L	7,3467	0,001416			-51,76	22,48	15
	Frontal_Inf_Orb_R	9,2211	2,73E-05	49	1,43E-08	36,8	29,04	-5
	Insula_R	8,5149	0,000114	53	6,37E-09	43,36	19,2	20
	Frontal_Inf_Tri_R	8,4055	0,000144			49,92	22,48	15
	Frontal_Inf_Tri_R	7,6552	0,000716			56,48	32,32	20

	Fusiform_L	7,8604	0,000458	15	5,41E-05	-35,36	-39,84	-25
	undefined	7,7325	0,000605	150	7,77E-16	17,12	-7,04	5
	Caudate_L	7,5439	0,000914			-15,68	-3,76	20
	L_Thalamus*	7,4661	0,001086			10,56	-0,48	5
	L_Thalamus*	7,3197	0,001504	15	5,41E-05	-2,56	-30	-5
	Temporal_Mid_R	6,5764	0,008211	12	0,00014	40,08	-69,36	20
	Temporal_Mid_R	6,5569	0,008592			46,64	-59,52	10
CG2sham								
	Calcarine_L	11,40644	9,77E-07	66	7,14E-09	0,720004	-85,76	10

Table 5 Significantly activated regions related to self-regulation training (contrast: up-regulation > rest) in the whole brain, univariate analysis, considering the three groups independently (one sample t-test, P < 0.001 & FWE P < 0.05; K = 10).

Activations of the right FG, right lingual cortex, right middle temporal gyrus, right inferior frontal gyrus, right insula, and left caudate were found only in CG1. In contrast, bilateral activations of the cerebellum (cerebellum area 6 and vermis area 7) were observed only in AG. The CG2sham group showed activation only in the primary visual cortex (Table 5 and Figure 5).

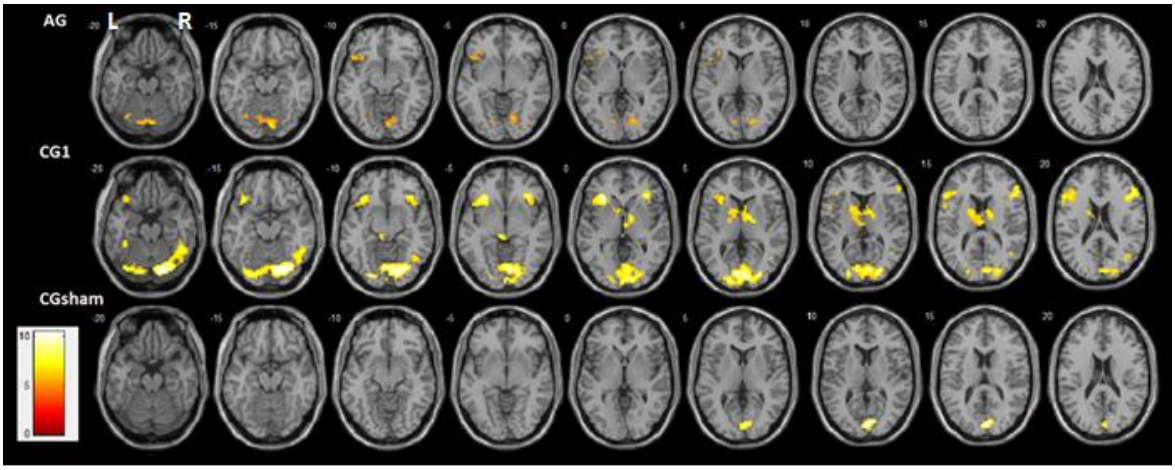

Figure 5. Activation maps of up-regulation of FFAs (Contrast: = up > rest) obtained from whole-brain analysis statistical parametric mapping (SPM) of all runs by group (one-sample t-test, P < 0.001 & FWE P < 0.05; K = 10; neurological convention). Bilateral ventral face of the occipitotemporal cortex and bilateral inferior Frontal gyrus activations were found in CG1. In contrast, the left ventral face of the occipitotemporal cortex and left inferior Frontal gyrus activation was found in AG. The right posterior part of the Middle Temporal Gyrus and left Insula were found

only in CG1. In addition, cerebellum activation was only present in AG. CG2sham showed only a bilateral Calcarine cortex activation.

6.3.2 Functional connectivity analysis.

Functional connectivity analysis to evaluate the neural modulation associated with FFA self-regulation in each group was performed using each FGs as two independent seeds (based on the AAL atlas). First, significant functional connections (threshold P-FDR (seed corrected) <0.01, one-sided (positive)) between the FG and brain areas inside of the field of view were described by lobe for each group. Second, group differences between the functional connectivity strength (mean z_{FC} values) of all significant connections and of connections inside of the ventral visual stream were evaluated taking each FG separately (see section 5.5.2 for more information).

Abundant functional connections between the cerebral areas of the occipital lobe (the occipital, lingual and cuneal cortex) and the FG was observed in all three groups, but with interesting differences. GC1 participants showed an ipsilateral and contralateral connection between the occipital brain areas and the right FG, but only ipsilateral connections with the left FG. In contrast, ipsilateral and contralateral connectivities were observed between the occipital lobe and both FGs in AG and CG2sham (Figure 6). Concerning the temporal lobe, although the three groups showed functional connectivity between both FGs, group differences in the connectivity profile were found in this lobe too. Ipsi and contralateral connections between FG and brain areas of the ventral visual stream were observed in AG. In contrast, only ipsilateral connections between the FGs and the inferior Temporal gyrus and parahippocampal cortex were observed in the temporal lobe of CG1. Functional connections to the frontal cortex (ipsilateral connection to right inferior frontal gyrus) and insula (ipsilateral connection to the right insula) were found only in CG1 (Figure 6 and Table 6).

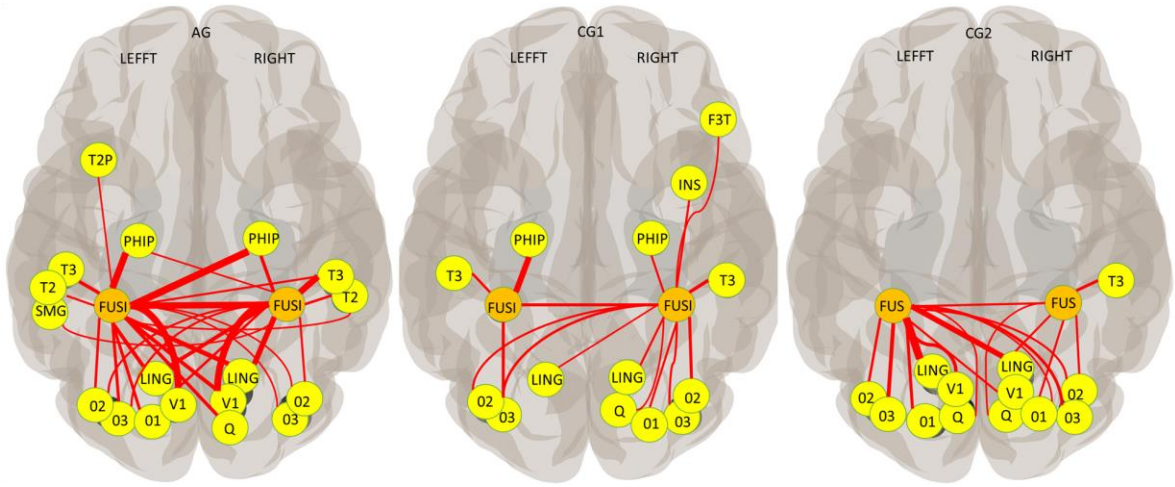

Figure 6. Functional connectivity across all training blocks *(*AAL Atlas; Seed: each FG; P-FDR (seed corrected) <0.01; one-sided (positive); thickness proportional to T magnitude). V1 (Calcarine cortex); O1, O2 and O3 (Superior, Middle and Inferior Occipital gyrus, respectively); Q (Cuneus cortex); LING (Lingual cortex); FUSI (FG); SMG (Supramarginal gyrus); T2 and T3 (Middle and Inferior Temporal gyrus); T2P (Temporal Pole, Middle Temporal gyrus); PHIP (Para hippocampus); SMG (Supramarginal gyrus); INS (Insula); F3T (inferior Frontal gyrus, pars triangularis).

Group AG	Seed: Fusiform L				Seed: Fusiform R			
	Targets	T(7)	p-unc	p-FDR	Targets	T(7)	p-unc	p-FDR
	ParaHippocampal R'	16.98	0.0000	0.0000	Temporal Inf R'	14.91	0.0000	0.0000
	Calcarine L'	15.80	0.0000	0.0000	Fusiform L'	14.89	0.0000	0.0000
	ParaHippocampal L'	15.39	0.0000	0.0000	Lingual R'	12.89	0.0000	0.0000
	Fusiform R'	14.89	0.0000	0.0000	Calcarine R'	10.22	0.0000	0.0002
	Lingual R'	11.24	0.0000	0.0001	Lingual L'	9.16	0.0000	0.0003
	Calcarine R'	9.98	0.0000	0.0001	ParaHippocampal R'	8.83	0.0000	0.0003
	Lingual L'	9.21	0.0000	0.0002	Occipital Inf R'	8.00	0.0000	0.0005
	Cuneus R'	8.73	0.0000	0.0002	Temporal Mid R'	6.35	0.0002	0.0017
	Temporal Inf L'	8.03	0.0000	0.0004	Calcarine L'	6.28	0.0002	0.0017
	Occipital Sup L'	7.26	0.0001	0.0006	Occipital Inf L'	5.34	0.0005	0.0038
	Occipital Inf L'	7.03	0.0001	0.0007	Occipital Mid L'	5.28	0.0006	0.0038
	Occipital Mid L'	5.84	0.0003	0.0019	ParaHippocampal L'	4.99	0.0008	0.0048
	Temporal Inf R'	5.65	0.0004	0.0022	SupraMarginal L'	4.64	0.0012	0.0067
	Occipital Inf R'	4.94	0.0008	0.0044	Temporal Sup R'	4.24	0.0019	0.0100
	Occipital Mid R'	4.48	0.0014	0.0067				
	Temporal Mid R'	4.41	0.0016	0.0067				
	Temporal Mid L'	4.41	0.0016	0.0067				
	Temporal Pol Mid L'	4.36	0.0017	0.0068				
CG1								
	ParaHippocampal L'	13.64	0.0000	0.0001	Temporal Inf R'	8.45	0.0000	0.0019
	Occipital Inf L'	7.97	0.0000	0.0017	Fusiform L'	7.43	0.0001	0.0019
	Fusiform R'	7.43	0.0001	0.0018	Occipital Mid R'	7.35	0.0001	0.0019
	Temporal Inf L'	6.52	0.0002	0.0030	Occipital Inf L'	6.66	0.0001	0.0026
					ParaHippocampal R'	5.65	0.0004	0.0051
					Lingual R'	5.41	0.0005	0.0051
					Occipital Mid L'	5.37	0.0005	0.0051
					Occipital Inf R'	5.31	0.0006	0.0051
					Insula R'	5.04	0.0007	0.0061
					Occipital Sup R'	4.94	0.0008	0.0061
					Lingual L'	4.84	0.0009	0.0062
					Frontal Inf Tri R'	4.55	0.0013	0.0081
					Cuneus R'	4.43	0.0015	0.0085
CG2sham								
	Lingual L'	17.96	0.0000	0.0000	Occipital Inf R'	10.52	0.0000	0.0006
	Lingual R'	12.76	0.0000	0.0001	Occipital Sup L'	8.87	0.0000	0.0007
	Occipital Inf L'	9.37	0.0000	0.0004	Occipital Mid R'	8.44	0.0000	0.0007
	Calcarine L'	8.25	0.0000	0.0007	Lingual R'	8.19	0.0000	0.0007
	Fusiform R'	7.42	0.0001	0.0010	Fusiform L'	7.42	0.0001	0.0011
	Occipital Inf R'	7.23	0.0001	0.0010	Occipital Mid L'	6.51	0.0002	0.0015
	Occipital Sup L'	7.01	0.0001	0.0011	Occipital Sup R'	6.50	0.0002	0.0015
	Occipital Mid L'	6.89	0.0001	0.0011	Temporal Inf R'	6.49	0.0002	0.0015
	Occipital Mid R'	5.55	0.0004	0.0035	Lingual L'	6.19	0.0002	0.0018
	Calcarine R'	5.32	0.0005	0.0040	Calcarine R'	5.16	0.0007	0.0048
	Occipital Sup R'	4.61	0.0012	0.0081	Cuneus L'	4.83	0.0010	0.0063
					Cuneus R'	4.73	0.0011	0.0065

Table 6. Significant connections during FFA self-regulation blocks (Seed: each FG; P-FDR (seed corrected) <0.01; one-sided (positive); AAL Atlas).

No differences were found between groups in the connection strength of the right FG (F (2, 36) = 3,224, p = .052, ns.) and of the left FG (H (2).201, p =.904, ns) when all brain areas were evaluated. Group differences were found in the connection strength between the right FG and brain areas of the ventral visual stream (F (2, 33) = 4,81, p = .015), but no group differences were found in the connection strength of the left FG with these brain areas (H (2).265, p =.876, ns). Specifically, the connections of the right FG and brain areas of the ventral visual stream in AG were stronger than the connections in CG1 (p = .012). No differences between CG1 and CG2sham (p = .507, ns), or between AG and CG2sham (p = .143, ns) were found.

6.4 AUTISM CLINICAL CONDITION AND FAA UP-REGULATION

The clinical features and facial processing profiles of the patients with ASD were evaluated to explore correlations between them and FFA up-regulation performance to obtain a better understanding of the rtfMRI-NF process in this population (Spearman correlation, two-tailed, 95% confidence interval, p<.05).

6.4.1 Clinical features and FAA up-regulation performance.

Patients (ADI-R total score) with greater severity of the disease achieved higher activation values on right FFA during all training runs (right FFA: $r_s = 1$, p = .0167/ left FFA: $r_s = 0.6$, p = .0350, ns.). No correlation was found between the up-regulation performance on left and right FFAs and ADOS-2 total score (left FFA: $r_s = -0.667$, p = .267, ns.; right FFA: $r_s = -0.154$, p = .833, ns.), nor Social Communication Questionnaire score (left FFA: $r_s = 0.4$, p = .517 ns.; right FFA: $r_s = 0.7$, p = .233, ns.) nor AQ score (left FFA: $r_s = 0.3$, p = .683 ns.; right FFA: $r_s = 0.4$, p = .517, ns.), nor Social Age of Vineland scale (left FFA: $r_s = -0.8$, p = .133, ns.; right FFA: $r_s = -0.5$, p = .450, ns.), nor chronological Age (left FFA: $r_s = -0.1$, p = .950, ns.; right FFA: $r_s = 0.3$, p = .683, ns.) nor I.Q. (left FFA: $r_s = -0.359$, p = .633, ns.; right FFA: $r_s = -0.154$, p = .833, ns.). No significant relationships between left and right FFA up-regulation performance and facial processing tasks (accuracy of FER, FIR, CFMT and The Eyes task and RT of CFMT) were found (data not shown).

7 DISCUSSION

The present study is the first one to examine the application of real-time rtfMRI-NF as a neuroscientific tool by using FFA up-regulation in subjects with ASD. Both groups that received contingent information from the brain region of interest achieved up-regulation of FFA, albeit with considerable differences.

7.1 FFA UP-REGULATION MAGNITUDE

The results show that neurofeedback based on real-time fMRI can be used to explore the facial processing neural network in participants with ASD. Participants with ASD achieved up-regulation of FFAs guided by rtfMRI-NF in a similar way to participants with typical neurodevelopment who received contingent information of FFAs. Both groups achieved up-regulation of left and right FFAs from the first training session. In contrast, the group that received "sham" feedback (but the same instructions as the other groups) could not self-regulate FFAs in any training session. This suggests that volitional control of the region of interest cannot be learned when there is no contingency between neural activation and the feedback stimulus. This effect has been observed in numerous studies over the last 10 years (deCharms et al., 2005; Lee et al., 2012; Sherwood et al., 2017; J Sulzer et al., 2013b; Zotev et al., 2011b, n.d.). Moreover, the participants who received contingent information we're able to self-regulate FFA bilaterally despite their clinical condition. There was no clinical impediment to achieving up-regulation of FFA in participants with ASD without cognitive or language comorbidity. Numerous studies have shown that this learning is not only dependent on cognitive functions or on higher-level brain areas such as the frontal lobe (Ramot et al., 2016) but occurs as a result of operant conditioning (Birbaumer et al., 2013; Marxen et al., 2016; Ruiz et al., 2014; Sulzer et al., 2013) and recruitment of deeper brain areas such as the insula and striatum (Sherwood et al., 2017; Sitaram et al., 2017). Bearing in mind that this protocol considered verbal instructions, in the future the development of novel rtfMRI-NF protocols could allow participants with ASD but without language or intellectual deficits to participate in rtfMRI-NF training to learn to self-regulate their brain activity to answer other neuroscientific or clinical questions.

Whether participants with TD or with ASD could show further improvement in their FFA up-regulation performance with a longer training protocol is an open question. Longer protocols may be useful to achieve higher values of FFA up-regulation and translate that learning outside the scanner (Auer et al., 2015; J Sulzer et al., 2013b). Transferring it to a natural setting could be useful to explore both the association between FFA up-regulation performance and actual face processing improvement, and this method's potential as an enhancement of usual therapies, as proposed for ASD (Caria and de Falco, 2015b) and for other psychiatric disorders (Buyukturkoglu et al., 2015; Hanlon et al., 2013; Mehler et al., 2018; Ruiz et al., 2013b).

7.2 VARIABILITY OF THE FFA UP-REGULATION MAGNITUDE

A large variability (standard deviation of the BOLD signal) was found in rFFA values during the training sessions. This concurs with the high intra-subject and inter-subject variability frequently reported in the fMRI literature (Gaxiola-Valdez and Goodyear, 2012; Lund et al., 2005). Despite the small group size in this study, findings on the variability of the BOLD level were significant. In particular, in the case of participants with TD, the contingent neural information contributed to producing less variability in the control of BOLD activity of both FFAs. There is literature that associates BOLD signal variability with the maturation and specialization process of some brain areas (Nomi et al., 2017), which suggests a possible use of this novel approach to explore the maturation and specialization process (for example of face processing (Meng et al., 2012)) in typical and ASD development. However, longer rtfMRI-NF protocols could serve that aim better (Sulzer et al., 2013).

7.3 FUNCTIONAL ANALYSIS OF THE BRAIN AND FFA UP-REGULATION

7.3.1 Whole Brain analysis

One important finding of the study is the hypoactivation profile of the ventral visual stream - mainly of the right hemisphere – observed in persons with ASD as a consequence of FFA up-regulation guided by real-time fMRI neurofeedback. This finding is in line with the literature showing a specific FG hypoactivation profile when individuals with ASD participate in visual processing tasks with faces as stimuli (i.e. FFA hypoactivation) (Nickl-

Jockschat et al., 2014; Pierce et al., 2004a) but not with non-social stimuli (Humphreys et al., 2008; Scherf et al., 2010). Moreover, the literature shows that the level of FG activation elicited by non-social stimuli increases with motivational relevance or specialization level, both in the case of individuals with TD (Adamson and Troiani, 2018; Bilalić et al., 2016; Gauthier et al., 2000) and individuals with ASD (Foss-Feig et al., 2016; Grelotti et al., 2005). Hence, whether up-regulation of another specialized brain area (e.g. the Parahippocampal place area) can recruit the ventral visual stream to the same level as FFA-up-regulation is an open question. We do not know, either, if individuals with ASD can reach the same level of ventral visual stream activation as individuals with TD by self-regulating other specialized FG areas. Answers to these questions could lead to a deeper understanding of the face-processing deficit of people with ASD from a developmental perspective (for example, a facial processing deficit resulting from a lack of specialization in early development). A possible explanation of FG Hypoactivation in participants with ASD may have to do with high variability in the location of FFA obtained in this (Table 3) and other studies with participants with ASD (Scherf et al., 2010).

A hypoactivation profile of the inferior frontal gyrus was apparent in participants with ASD unlike those with TD who received contingent information from their FFAs. Inferior frontal gyrus is a brain area associated with the cognitive control network, and with different aspects of volitional cognitive functions (Della Rosa et al., 2018; Swick et al., 2008), as a substrate of the working memory of faces (Courtney et al., n.d.; Druzgal and D'Esposito, 2003) and part of the imitation and mirror system (Buccino et al., 2004; Molenberghs et al., 2009). In all these specific cognitive functions individuals with ASD tend to show specific deficits associated with hypoactivation of inferior frontal gyrus (Bookheimer et al., 2008; Dapretto et al., 2006; Rogers and Bennetto, 2000). This might be explained by an inferior frontal gyrus hypoactivation profile is a result of deficits in these specific cognitive functions during the elaboration of a mental strategy for thermometer control. However, successful neurofeedback training is considered to be disassociated from cognitive effort (Emmert et al., 2016a) or any specific mental strategy (Kober et al., 2013). Thus, the inferior frontal gyrus hypoactivation profile shown by participants with ASD could be explained as a specific dysfunction of the facial processing neural network, which is observable as a consequence of FFA up-regulation. In fact, participants with TD who achieved FFA up-regulation showed a

significant ipsilateral functional connection between the FFA and inferior frontal gyrus, but this was absent in ASD individuals and participants in CG2sham (who received the same instructions as CG1 and AG).

In addition, the insula and caudate nucleus were only recruited by those subjects with TD who achieved FFA up-regulation. Both brain areas are considered to be part of the extended network of face processing, in particular of emotional aspects (Haxby and Gobbini, 2010). The Insula plays a role in detecting other's emotions (Thom et al., 2014), in interoception (Critchley et al., 2004) and emotional awareness (Craig, 2009; Gu et al., 2013). In fact, an acquired Insula lesion results in impaired facial recognition of emotion. The caudate nucleus is associated with motivation, reinforcement learning, and reward (Daniel and Pollmann, 2014; Kasanova et al., 2017; Liljeholm and O'Doherty, 2012; Morita et al., 2013; Schultz, 2016). It has been associated, specifically, with social behavior reinforcement (Báez-Mendoza and Schultz, 2013; Bhanji and Delgado, 2014) and giving relative valence to the aspects of faces (Aharon et al., 2001; Lin et al., 2012). A hypoactivation profile of the insula and caudate nucleus have been reported in persons with ASD when performing different social cognition tasks (Dichter et al., 2012; Odriozola et al., 2016; Pierce et al., 2004b; Scott-Van Zeeland et al., 2010) which could explain the lack of activation of the insula and caudate nucleus in our participants with ASD. In addition to the emotional processing of faces, these brain areas have been consistently reported to be part of the neural network that is recruited in rtfMRI-NF (Sitaram et al., 2017). Specifically, the insula has been associated with interoceptive body awareness and cognitive control. The striatum has been associated with motivation and procedural learning in rtfMRI-NF training, independently of the ROI targeted (Emmert et al., 2016b) and even when no feedback awareness is present (Ramot et al., 2016). In fact, the participants with TD in CG2sham did not show activation of either of these brain areas despite the given instructions. Therefore, the non-activation of the caudate and insula as a consequence of FFA up-regulation training could be better explained as a focal dysfunction of these brain areas. Whether or not FFA up-regulation in ASD subjects could be provided by an alternative neural mechanism in rtfMRI-NF training - disassociated from the reward system and interoceptive awareness - needs to be explored in further studies.

The findings give some insight into the role of the cerebellum. As known, the cerebellum plays a key role in the development and modulation of the motor system (Salman and Tsai, 2016), but also of the higher social cognitive function (Riva and Giorgi, 2000) and reward system (Carta et al., 2019). In typical development, its connections extend to different brain areas, such as the inferior frontal gyrus (Watson et al., 2014), insula (Dobromyslin et al., 2012; Kaufman et al., 1996), ventral tegmental area, and caudate (Carta et al., 2019; Fox and Williams, 1970). In ASD, a disruption of long-range cerebrocerebellar circuits has been reported (Rane et al., 2015). In particular, the lack of correlation between cerebellar activation and caudate activation in ASD may explain the lack of social motivation (Crippa et al., 2016). On the other hand, recruitment of the cerebellum may be a compensatory mechanism to obtain better social adaptive behavior (Crippa et al., 2016; D'Mello and Stoodley, 2015). This compensatory mechanism seems to be more effective in ASD individuals with fluent language and normal or high I.Q. (Livingston et al., 2018; Livingston and Happé, 2017a). Therefore, recruitment of the cerebellum without activation of the striated/caudate nucleus in participants with ASD may be the result of atypical/ specific development in individuals with ASD.

7.3.2 Functional connectivity analysis

Up-regulation of FFA in participants with TD resulted in a typical functional connectivity pattern observed previously with different visual tasks aimed at evaluating aspects of the visual processing of faces. Specifically, the connectivity profile in these participants was characterized by connections between the occipital lobe and the right FG, but not with the left FG. The left FG had only an ipsilateral functional connection with the inferior occipital gyrus. This finding can be explained by the typical right lateralization of visual processing of faces (Meng et al., 2012), and by a hierarchical organization of the information (Zhen et al., 2013), whereby the support of the right hemisphere is required to process the representation of faces in the left occipital lobe (faces presented on right visual field) (Verosky and Turk-Browne, 2012)). In addition, participants with TD showed significant functional connectivity between the FG and the insula and inferior frontal gyrus as a result of successful FFA up-regulation. As described above, both brain areas have been widely reported to be part of the face-processing network (Haxby and Gobbini, 2010; Zhen et al., 2013). In contrast, participants with ASD showed neither this typical right neural

lateralization of functional connectivity in the temporo-occipital cortex, nor functional connectivity between the FG and the insula, or the inferior frontal gyrus. On the other hand, unlike the TD participants, those participants with ASD presented functional connectivity between the FG and areas responsible for higher-order visual processing of faces but of the temporal lobe (the anterior temporal pole and middle temporal gyrus) (Collins and Olson, 2014; Von Der Heide et al., 2013; Zhen et al., 2013).

This atypical functional connectivity pattern could be due to a lack of the typical neural specialization of facial processing (Dawson et al., 2005; Nass and Gazzaniga, 2011), or long-distance brain underconnectivity (Aoki et al., 2013; Courchesne and Pierce, 2005), or it may reflect compensatory/ atypical mechanisms for facial processing (Joseph et al., 2015; Pierce et al., 2001). If so, it may configure a functional connectivity profile associated with FFA up-regulation that is specific for the development of individuals with ASD. In fact, as a reflection of lack of specialization and/or the use of atypical/compensatory mechanisms for FP, participants with ASD in this study showed adequate precision in recognizing and remembering faces, but without the comparative advantage demonstrated by participants with TD.

In addition, participants with ASD showed more and stronger connections than individuals with TD between the FG and the brain areas of the ventral visual stream with rtfMRI-NF training. Hyper-connectivity of short-distance connections have been widely reported in ASD (Barttfeld et al., 2011; Courchesne and Pierce, 2005) and have been correlated with symptom severity, social impairment (Chien et al., 2015; Supekar et al., 2013) and savant abilities (Loui et al., 2011).

7.4 CLINICAL FEATURES AND FAA UP-REGULATION

This study included ASD subjects without cognitive or language disability for two main reasons. First, because in this protocol participants were required to follow some instructions inside the scanner, which could present difficulty to those with cognitive or language comorbidity. Second, with ASD symptoms a more homogenous sample permits a better interpretation of the results.

Although one participant was unable to complete the training protocol due to sensory discomfort, the other five participants with ASD finished it without inconvenience. However, given the high prevalence of Sensory Processing Disorder in this population (Marco et al., 2011), a fuller sensory profile evaluation than ADOS-2 and ADI-R seems highly recommended for participants in rtfMRI-NF protocols. Nevertheless, five participants with ASD guided by the rtfMRI-NF managed to self-regulate FFAs and achieve similar activation values to participants with TD who received contingent feedback.

Interestingly, higher values of FFA up-regulation were found in participants with more severe core symptoms of ASD in their childhood (ADI-R total score), despite no correlation was found between the up-regulation performance and the severity of current core symptoms (evaluated by ADOS-2). An explanatory hypothesis might be that FFA self-regulatory ability is currently higher in those who developed more communicative and social skills throughout their childhood and adolescence by developing better skills to process information from faces (e.g. individuals with more severe symptoms on their childhood). No correlations between chronological age of ASD participants and self-regulation performance were found (self-regulation performance values were similar through adolescence and adulthood). Moreover, no correlations were apparent between the performance of the different facial processing tasks and FFA self-regulation performance. This can be explained by the absence of important differences in the results of these tasks between all individuals (probably because these tasks were evaluated at later stages of the development of visual processing when compensatory mechanisms had already been incorporated).

Among the study's limitations is the small size of the sample of participants. However, a strict statistical analysis with correction for multiple comparisons applied during our analyses contributed to the consistency of our analysis. The absence of a group of ASD patients trained with sham feedback could be another potential limitation. However, for ethical considerations we decided, to use instead of a TD control group trained with sham feedback because of two reasons. First, literature shows that up-regulation of a ROI guided by a rtfMRI-NF probably entails behavioral improvement regarding the functions of the respective trained ROI (Buyukturkoglu et al., 2015; Li et al., 2013; Linden et al., 2012; Ruiz et al., 2013a; Shih et al., 2012; Sitaram et al., 2007b; J Sulzer et al., 2013b; Weiskopf, 2012b).

Second, effective rtfMRI-NF training could bring emotional improvements in the participants due to the experience of successful up-regulation (Mehler et al., 2018). Therefore, it has been preferred to avoid the use of sham feedback in a clinically vulnerable population. Another possible limitation of the study is the difference in age between the groups. Although it was preferred to use subjects with an age (late adolescence or beyond) at which the neural development of face processing is considered done (de Heering et al., 2012; Pelphrey et al., 2009), part of the results of the ASD group may be due to a lag in the neural development of visual processing of faces and not to the ASD condition (Golarai et al., 2010). However, significant results are not expected from the immature TD, thus being better explained by an atypical development (e.g. short-range hyperconnectivity between occipitotemporal brain areas or absence of long-range functional connectivity with insula or inferior frontal gyrus) as previously discussed. Despite that, further studies using this technique to assess changes throughout the development, i.e. at different ages, seems to be useful to obtain a better understanding of the neurodevelopment in ASD. Finally, women were under-represented in the study, a tendency of other studies on ASD (Halladay et al., 2015) despite the quadrupled prevalence of ASD in males compared to females. Behavioral and neural network differences have been found between males and females (Alaerts et al., 2016; Coffman et al., 2015; Werling and Geschwind, 2013), so future use of rtfMRI-NF to explore the facial processing neural network will be useful to study sex differences (Haney, 2016; Kreiser and White, 2014).

7.5 CONCLUSIONS AND FUTURE APPLICATIONS

This is the first research to show that the neural networks involved in the visual processing of faces (one of the most important neural substrates affected in ASD) can be studied using FFA up-regulation with rtfMRI-NF training. Consistent differences in facial processing neural networks were found between individuals with typical development and individuals with ASD. Even though there were no group differences in face processing tasks (measured at the beginning of the study), participants with ASD showed atypical functional connectivity and brain activation during FFA up-regulation. They showed a hypoactivation of the ventral visual stream, absence of lateralization of early visual cortex, and atypical features such as stronger short-range connections to the FG with a lack of long-range connections to the insula

and inferior frontal gyrus. This raises new possibilities of gaining further neuroscientific and potential clinical insights that may benefit persons with ASD and their relatives. For example, the neural study of gender differences and of the neurodevelopmental process in ASD are two areas in which this novel tool could play an important role. Moreover, at a neural level, participants with ASD achieved FFA up-regulation without recruit caudate and insula. Both brain areas have been described as necessary for different aspects of rtfMRI-NF training (Sitaram et al., 2017). Additional research work is needed to explore the role of these brain areas in successful up-regulation in clinical populations. At a clinical level, it seems possible that rtfMRI-NF could aid clinicians in complex diagnostic scenarios. Biomarker or classifier rtfMRI-NF-based tools could boost the diagnostic process in adolescents and adults with normal I.Q. and fluent speech in whom there is a suspicion of ASD. They could be also used to classify ASD subpopulations as a basis for providing individualized clinical support. Finally, in the light of these results, it would be useful to explore the possible benefits of rtfMRI-NF training during the early stages of development as augmentation therapy for social and adaptive improvement in persons with ASD.

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