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Functional connectivity correlates of response inhibition impairment in anorexia nervosa

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ABSTRACT

Anorexia nervosa (AN) is a disorder characterized by high levels of cognitive control and behavioral perseveration. The present study aims at exploring inhibitory control abilities and their functional connectivity correlates in patients with AN. Inhibitory control – an executive function that allows the realization of adaptive behavior according to environmental contingencies – has been assessed by means of the Stop-Signal paradigm. The study involved 155 patients with lifetime AN and 102 healthy women. A subsample underwent resting-state functional magnetic resonance imaging and was genotyped for COMT and 5-HTTLPR polymorphisms. AN patients showed an impaired response inhibition and a disruption of the functional connectivity of the ventral attention circuit, a neural network implicated in behavioral response when a stimulus occurs unexpected. The 5-HTTLPR genotype appears to significantly interact with the functional connectivity of ventral attention network in explaining task performance in both patients and controls, suggesting a role of the serotoninergic system in mechanisms of response selection. The disruption of the ventral attention network in patients with AN suggests lower efficiency of bottom-up signal filtering, which might be involved in difficulties to adapt behavioral responses to environmental needs. Our findings deserve further research to confirm their scientific and therapeutic implications.

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1. Introduction

In the last decade, the interest in the neuropsychological characteristics of patients with anorexia nervosa has increased and the literature consistently indicates that these patients often exhibit poor decision making skills, high levels of inflexibility and set-shifting impairments, and visuo-spatial problems (Tenconi et al., 2010; Jauregui Lobera, 2013). These findings have both clinical and scientific implications and specific treatments (such as cognitive remediation therapy) are being developed to address those cognitive characteristics that are hypothesized to interfere with a good outcome to treatments (Tchanturia et al., 2014). Few studies to date, however, have specifically explored inhibitory control abilities in this group of patients (Claes et al., 2006; Galimberti et al., 2012), although they are considered key executive functions for flexible and adaptive behavior, and have often been associated with impulsive and compulsive spectrum psychopathology that are typical manifestations in eating disorders (Bari and Robbins, 2013).

The term inhibitory control refers both to cognitive inhibition that controls memory, perceptions, emotions and thoughts, and to behavioral inhibition that includes response inhibition, abilities to delay gratification and reversal learning (Bari and Robbins, 2013). Typically, response inhibition, that is the ability to block an impulsive action and consists of action postponing, action restraint or action cancellation, is investigated through neuropsychological tests such as the Go/No-Go Task (Nosek and Banaji, 2001) and the Stop-Signal Task (SST; Logan and Cowan, 1984).

A response inhibition deficit has been demonstrated in several neuropsychiatric disorders in which there are evident impulsive and compulsive symptoms, such as schizophrenia (Hughes et al., 2012), obsessive–compulsive disorder (Lennertz et al., 2012), alcohol and drug abuse (Loeber and Duka, 2009; Monterosso et al., 2005), autism (Christ et al., 2011) and Attention-Deficit/

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Table 1
Characteristics and stop signal task (SST) performance of the study groups.

	AN underweight ($n=85$)	AN weight-recovered ($n=47$)	Healthy women ($n=106$)	ANOVA
	Mean (SD)	Mean (SD)	Mean (SD)	$F(2, 235)$ (p)
Age (years)	22.7 (7.0)	24.9 (7.8)	23.7 (6.6)	1.64 (0.197)
Education (years)	12.7 (2.8)	13.7 (2.5)	14.5 (2.9)	10.42 (0.001)
Body mass index (kg/m^2)	15.9 (1.5)	21.0 (2.1)	21.5 (3.2)	129.38 (0.001)
Lowest body mass index (kg/m^2)	14.8 (1.9)	16.0 (1.8)	19.6 (2.5)	122.18 (0.001)
Duration of illness (months)	34.3 (50.1)	53.6 (67.0)	=	3.50 (0.064)
Age at onset (years)	18.0 (5.3)	15.9 (2.6)	=	6.09 (0.015)
Edinburgh score	56.8 (33.3)	55.3 (42.4)	60.2 (37.5)	0.36 (0.697)
Depressive symptoms (SCL)	1.4 (0.9)	1.7 (1.0)	0.6 (0.5)	32.4 (0.001)
State anxiety (STAI)	44.0 (12.2)	45.7 (11.4)	34.0 (6.7)	29.0 (0.001)
	N/tot (%)	*N*/tot (%)	*N*/tot (%)	χ^2
Restricting type	67/85 (79%)	14/47 (30%)	=	30.70 (0.001)
5-HTTLPR short allele	63/82 (77%)	34/46 (74%)	74/97 (76%)	0.14 (0.930)
COMT met allele	56/82 (68%)	33/46 (72%)	73/97 (75%)	1.07 (0.585)
	Mean (SD)	Mean (SD)	Mean (SD)	$F(4, 233)$ (p)*
SST errors on no signal trials	3.3 (3.8)	3.8 (4.7)	3.4 (5.4)	0.35 (0.706)
SST probability response signal trials	47.0 (4.8)	47.5 (9.2)	47.8 (4.3)	1.06 (0.349)
SST mean reaction time respond trials	589.1 (129.1)	594.9 (136.0)	575.2 (122.1)	0.53 (0.587)
SST reaction time (ms)	261.7 (53.2)	241.2 (57.0)	242.4 (44.2)	3.09 (0.047)

SST=Stop signal task; STAI=State trait anxiety inventory; SCL=Hopkins Symptoms Checklist.

* Statistics are adjusted for age and education.

Hyperactivity Disorder (Senderecka et al., 2012). In eating disorders, only one study have demonstrated significant impairments in inhibitory control (Galimberti et al., 2012) and one has correlated inhibitory control with levels of impulsiveness (Rosval et al., 2006). Neurofunctional investigations in a group of patients recovered from AN have found decreased activation of the medial prefrontal cortex in comparison to healthy women during the execution of a task that requires inhibitory control (Oberndorfer et al., 2011).

An impairment in response inhibition has usually been considered as a sign of prefrontal cortex dysfunction (Konishi, 2011) particularly in the ventral prefrontal region, which seems to be involved in controlling impulsiveness and instinctual drives. Functional neuroimaging studies have identified several brain areas implicated in modulation of response inhibition, not only among cortical regions such as the pre-supplementary motor area (pre-SMA; Mostofsky et al., 2003), the premotor area (Watanabe et al., 2002), the parietal area (Rubia et al., 2001), the ventrolateral prefrontal cortex (Swick et al., 2008), but also among subcortical regions, such as the basal ganglia (Greenhouse et al., 2012) and the subthalamic nucleus (Aron, 2007). The anterior cingulate cortex also has a possible role in response inhibition (Casey et al., 1997), particularly because of its connections with the basal ganglia and with the pre-SMA (Devinsky et al., 1995).

Two attention networks are involved in the processing of tasks of response inhibition: the bilateral dorsal attention system, which allows attention to be focused on a baseline specific task (a visual stimulus in the SST), and the right-lateralized ventral attention system, which reorients attention in response to salient stimuli, such as the stop signal in the SST (Chica et al., 2013; Corbetta and Shulman, 2002). In addition, pre-SMA activation is specifically associated to successful motor inhibition (Sharp et al., 2010).

Dopaminergic system has been consistently implicated in response inhibition (Congdon et al., 2009), whereas the implication of serotoninergic pathways appears less established (Clark et al., 2005; Chamberlain et al., 2006; Drueke et al., 2013). Attentional systems mainly rely on dopaminergic neurotrasmission and a significant positive correlation has been found between stop signal reaction time and DA release in the left orbitofrontal cortex, right middle frontal gyrus, and right precentral gyrus (Albrecht et al., 2014). In AN, the COMT genotype seems to have a peculiar effect on cognitive performance and prefrontal cortex functional connectivity in starving AN patients (Favaro et al., 2013). However, also variations in serotoninergic tone – such as those associated with 5-HTTLPR polymorphism – are likely to modulate response inhibition processes (Fallgatter et al., 1999; Landro et al., 2015) and the prefrontal serotoninergic pathways mediate inhibitory signals through GABA receptors both on prefrontal cortex itself (Yan, 2002) and on raphe nuclei (Jankowski and Sesack, 2004).

The aim of the present study was to investigate response inhibition in a sample of patients with AN, exploring the resting-state functional connectivity of networks implicated in this cognitive function, and considering the possible effects of 5-HTTLPR and COMT polymorphisms.

2. Methods

2.1. Participants

The study sample consisted of 238 Caucasian women, 132 of whom with a lifetime diagnosis of anorexia nervosa, and 106 healthy controls. In the AN group, the mean age at assessment was 23.5 years (SD=7.3) and mean level of education 13.1 years (SD=2.7). All AN subjects met DSM-IV criteria for AN in their lifetime: 81 belonged to restricting subtype (no binge-eating or purging behavior in their lifetime); 51 had an AN episode that was either preceded or followed by a BN episode (Table 1). At the time of neuropsychological assessment, AN subjects were at different stages of their illness: 85 were acutely underweight (mean BMI=15.9 ± 1.5) and 47 were weight-recovered (mean BMI=21.0 ± 2.1).

The healthy control group consisted of 106 women with no history of eating disorders, with a mean age at assessment of 23.7

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