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DIFFERENT TYPES OF DECISION MAKING IMPAIRMENTS IN ANOREXIA NERVOSA

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ABSTRACT

Introduction:

Research on neurocognitive aspects in Anorexia Nervosa (AN) has outlined a cognitive profile characterized by deficiency in the ability to set-shifting (cognitive flexibility) and weak central coherence. A smaller agreement emerges in relation to the compromission of decisional profiles frequently observed in patients with AN since both the complexity of the pathology and the executive function itself make it unclear the nature of these alterations and its relationships with specific or independent clinical and enviornmental variables.

The aim of this study was: to investigate different types of decision-making (DM) ability, veridical and adaptive, in a sample of patients with AN using the Iowa Gambling Task and the Cognitive Bias Task; to analyze test performance using a specific cognitive model for the Iowa Gambling Task (Expectancy Valence Learning Model), and to study the relationship with clinical features, focusing on their relationship with neuropsychological profiles and clinical variables; to explore the neural correlations of the two tasks with functional connectivity; to observe the the impact of the genetic profile on different types of DM.

Materials and Methods:

The sample, consisting of 310 female subjects with AN lifetime and 301 female subjects without diagnosis of lifetime eating disorders, was tested in relation to DM abilities through the Iowa Gambling Task and cognitive Bias Task. All of the participants completed a baseline assessment including the Structured Clinical Interview (SCID) for the DSM-IV, section for eating disorders, and neuropsychological tests including the Wisconsin Card Sorting Test, and Trail Making Test for assessing abilities of abstraction and cognitive flexibility; 10 "and 30" interference memory test for evaluation of working memory, Stop Signal Task for evaluation of inibitory control. The Expectancy Valence Model (EVM) was used to analyze the results obtained in IGT. A genotyping was performed to evaluate the impact of the major polymorphisms implicated in decision-making (158 Val → Met) of the COMT gene and single nucleotide A / G polymorphism (SNP rs25531) of the serotonin carrier gene 5 - HTTLPR. In a smaller subgroup of 35 AN and 34 healthy control, seed based resting state Functional connectivity was explored in networks of interest (executive network, orbitofrontal cortex, accumbens, amygdala)

Results:

Compared to the group of healthy subjects, the decision-making profile of patients suffering from AN was worse in both Iowa Gambling Task (IGT), which evaluates veridical DM, and

Cognitive Bias Task (Cbias), which evaluates adaptive DM, regardless of the diagnostic subtype (restrictive vs. binging/purging), psychopathology severity, scholarity, manual dominance or outcome specific treatment. However in IGT the affective decision-making seems to be independent of IMC, conversely in Cbias the adaptive decisional profile was influenced by underweight. Both types of decision-making in patients were not affected by neurocognitive or clinical variables considered. The unfavorable geotype in AN resulted the homozygous for the met allele of the Comt gene and for the short variant of the serotonin transporter gene. The resting functional connectivity explored on the seeds of interest (executive network, orbitofrontal cortex, accumbens and amygdala) in a subgroup of patients and controls showed significantly different patterns of correlation with the scores of IGt and Cbias. In addition, different resting neural patterns appear to be involved in the two different tasks considered. Only in the AN group a positive correlation between the scores on IGT and the activity of the amygdala resulted. In AN group an higher coactivation within the executive, accumbens and orbitofrontal networks was linked to higher context-independency decisional style assessed with CBias, whereas for the executive network the opposite was true for healthy women**.**

Conclusions:

In summary our results confirm an impairment of different types of decision making in AN and highlitght the importance of assessing decisional processes with different specific tasks in clinical sample. In particular different maladaptative strategies are associated with ineffective decisional profiles in AN, consisting in a “myopia for the future” and “anxiety inhibition” in veridical situations and in a difficulty to update/review one’s own mindset according to new environmental stimuli (context indipendent reasoning strategies) in adaptive decisional framework. The severity of malnurishment seems to influence adaptive decisional style conferring a bias toward a context indipent reasoning, suggesting the need of metacognitive approach to help patients to be more aware of their tendency to automatically use selection bias in DM contexts. Genetic polimorphysms may in part account for the impaired decision making observed in AN patients, with a negative impact of met Comt allele and the short variant of 5HTTLPR polymorphism. Functional connectivity suggests the presence of different dysfunctional decision making networks in AN patients in the two decisional framework, confirming the importance of emotion and anxiety on decisional performance in AN.

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CHAPTER 1

ANOREXIA NERVOSA

Eating disorder (EDs), in their various declinations, constitute a major health problem highly intertwined with the culture of our time. Despite the critical issues emerging in the EDs epidemiological dimension inside the Italian reality (Gigantesco et al., 2010), WHO states that over the past 50 years there has been an apparent global increase in eating disorders, particularly in relation to Anorexia Nervosa (Lukas et al., 1991) where, although the overall incidence has remained stable over the last decades, there has certainly been an increase in the population of high-risk girls aged 15 to 19, (Hoek et al. 2012), even in Italy (Favaro et al ., 2009), although it remains to be clarified whether this reflects a diagnosis increasing or an early onset.

Specifically, according to large population-based studies, the lifetime prevalence of AN in females ranges from 1.2 to 2.2% and that of sub-threshold/atypical AN (aAN) from 2.4 to 4.3% (Wade et al.,2006, Keski-Rakhonen et al., 2007, Bulik et al.,2006).

Bulik at al. 2006, reported the prevalence of AN (according to DSM-IV criteria) in females to be 1.2%, and in males 0.29%, and according to DSM-5 criteria AN prevalence in the population of 14-year-olds was estimated at 3.2% in females, and 1.6% in males (Micali et al., 2015). Although the most common onset age is 15 to 19 years of age (it constitutes the 40% of the newly diagnosis cases), incidence is increasing both in pre-puberty (Nicholls et al., 2011, Favaro et al., 2009) and late-adulthood (Bueno et al., 2014).

According to a literary review,follow-up durations of <4 years, 4–10 years, and >10 years corresponded to AN recovery rates of 32.6±24.3%, 47±15.7%, and 73.2±16.2%, respectively. (Steinhausen, 2002).

The course of AN higly depend on the age of patients: with approximately 70%, and even over 80% of adolescents achieve remission (Steinhausen, 2002, Halvorsen et al.,2004, Herpertz-Dahlmann et al., 2001, Steinhausen et al., 2003, Nilsson et al., 2005). Although most people remitte, about 25% of them experience a chronic and relapsing progression (Berkman et al., 2007). In addition, AN is one of the 10 major causes of disability among young women (Mathers et al., 2000), and has one of the highest rates of mortality among all

psychiatric disorders (Arcelus et al., 2011, Harris et al., 1998). The estimated crude mortality rate (CMR), estimated to correspond to the number of deaths within the population studied in a specific period, was 5.1 deaths per 1000 people per year equivalent to 5.1% for decades or 0.51% per year, and among the patients with AN, one out of five had committed suicide (Arcelus et al., 2011).

Eating disorder have a complex multifactorial etiopathogenesis in which genetic, environmental, psychological, and socio-cultural factors interact with each other, giving them vulnerability to the disorder. To date, however, it is not possible to determine with certainty what causal processes are involved in the development and maintenance of the disease.

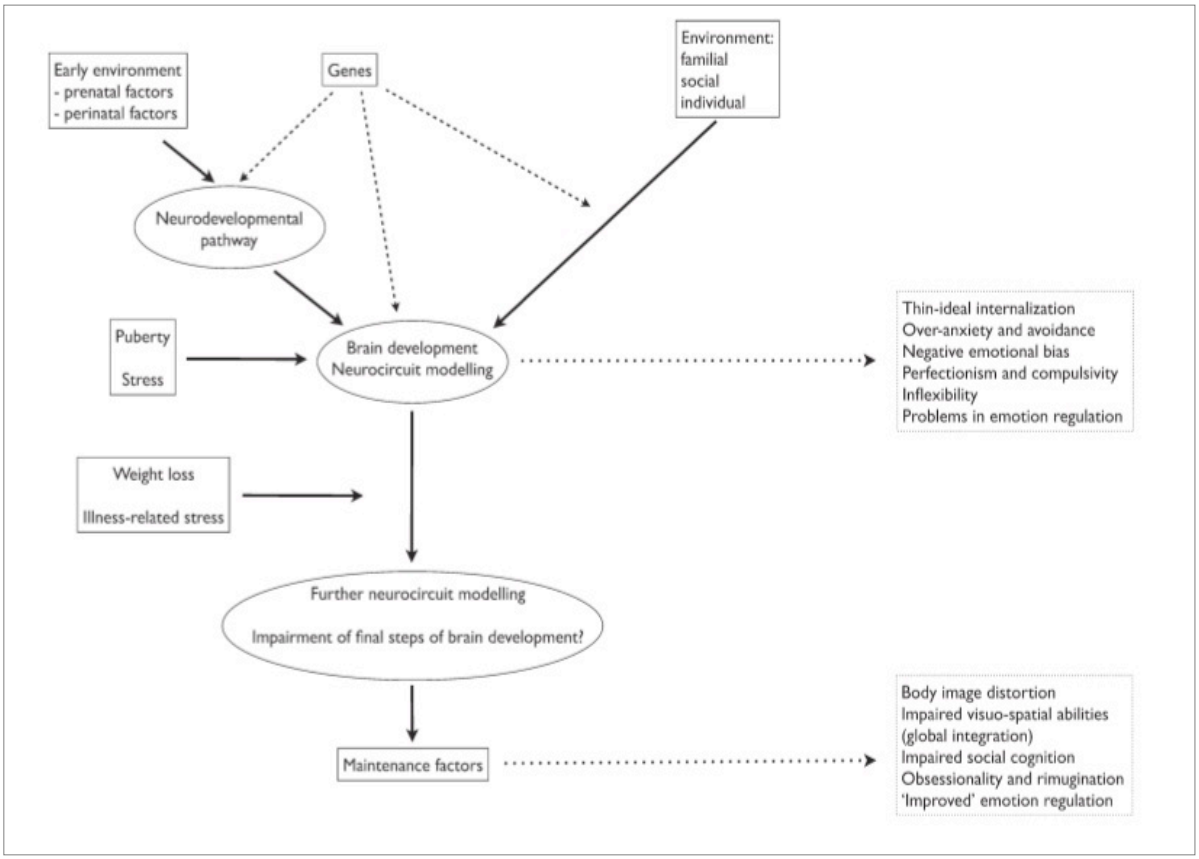
The current challenge, for which there is currently no definitive answer, is to integrate the risk factors identified adding, within the multifactorial etiopathogenetic model proposed for the development of EDs, the role of cognitive functioning as an additional factor of risk / protection. Besides this, there is an increasing need to understand how the specific disorders (AN, BN, BED, and partial syndromes) share each risk factors and cognitive functioning and if and how their etiopathogenetic models differ on the basis of these elements.

The need for a better etiopathogenetic definition is highlighted by the birth of the RDoC project, developed for research by the National Institute of Mental Health (NIMH).

This is a new way of classifying mental disorders based on observable behavioral dimensions and neurobiological measurements, called the Research Domain Criteria (RDoC), which has been applied to EDs too (Elburg & Treasure, 2013). The RDoC underlines the current and increasing need to systematize biological and psychological evidence in order to identify, In light of the increasing of EDs, possible therapeutic implications on the basis of recent neurobiological advances. In this perspective is relevant to improve the understanding of the cognitive functioning underlying or characterizing the different EDs.

Etiopathogenetic predisposing factors of the AN can be identified in the neurodevelopmental alterations linked to genetic and nutritional factors, obstetric complications and infections during pregnancy, besides psychological ones. Like for other mental disorders a multifactorial model composed by predisposing, precipitating and maintenance risk factors was made to explain the disturbance (Garner et al., 1993). Integtrative pathways to eating disorders considering brain modelling as the interface between genetic/environmental risk factors are summarize in figure 1.

Figure 1.



Note. *Pathogenic pathways to eating disorders considering brain modelling as the interface between genetic/environmental risk factors and eating disorder. Solid-line rectangles: at the top of the figure represent risk factors; those at the lower left depict conditions (e.g., puberty, weight loss, etc.) that exert their effects by mediating risk or ''shaping'' the disorder. Ellipses represent the three main stages at which risk factors may cause deviations from normal developmental trajectories: (a) prenatal/perinatal factors which, interacting with genetic liability, may modify and program individual neurodevelopment; (b) adolescence as the period of final neurocircuit modeling, influenced by puberty and stress (in interaction with genetic factors); (c) The period of acute symptoms, in which weight loss, starvation, and disorder-related stress act on the brain. Dotted arrows and rectangles: refer to putative clinical and neuropsychological correlates of vulnerability to EDs (sensitivity to thin-ideal internalization, over- anxiety, cognitive inflexibility, etc.); and those characteristics hypothesized to be determined or worsened by weight loss or starvation (impaired social cognition, specific visuo-spatial ability, body image distortion, etc.). (Based on Favaro, 2013).*

AN is a psychiatric disorder characterized by an intense fear of weight gain as nuclear symptoms, (Table 1 shows DSM-5 AN criteria) resulting in consequent behaviors aimed at achieving a progressive reduction to almost total food rejection. When hungry, anorexic patients progressively chose to avoid calorie intake as to achieve immediate gratification, such as relief from anxiety, ignoring the long-term negative consequences of their choices, such as the progressive and severe decline in physical conditions. Overall, patients appear not to be able to properly guide their eating behavior by showing a sort of "myopia for the future" that lead them to a high resistance to treatment and change (Abbate-Daga et al.,2013). This is in line with the observation in experimental setting of AN poorer decisions than healthy

controls on the Iowa Gambling Task, a task in which individuals incorporate past experience into future decision-making (Reville et al., 2016).
The possibility that these behaviors may be a cognitive dysfunction has been widely explored; several studies have shown that there is a relationship between cognitive processing and certain dietary attitudes, but a greater understanding of the pathophysiology of this disorder is needed (Jauregui-Lobera, 2012).

In this perpective, some authors (Cavedini, Bellodi et al., 2004) have suggested that the disfunctional food behaviors of AN patients may be an expression of their inability to modulate reward and punishment in a long-term perspective, resulting in a deficit in the planning of real life strategies, that helps keep them anchored to their eating symptoms.

Research suggest that some cognitive impairment observed in AN during the acute phase of the disease can be reversible, such as the function of attention and processing speed while other are supposed to be persisting vulnerability trait such as set-shifting and central coherence weakness that can be considered as preexisting factors or a scar of the illness (Tenconi et al., 2010; Jàuregui-Lobera et al., 2013).
The imbalance in the ventral limbic and dorsal executive circuits reported in AN is thought to be implicated in inhibition, decision-making, and reward response (Kaye et al., 2013), and this imbalance may explain the modulation of AN patients to hedonically appealing foods based on pre-defined rules rather than reward drive or hunger state (Eichen et al., 2017).
Furthermore, individuals with AN perform worse on set-shifting tasks such as the Wisconsin Card Sorting Test or the Trail Making Test compared to HCs. This can translate into rigidity, making it difficult for them to change the rules and rituals related to food consumption that maintain AN (Roberts et al., 2016).
The poor set-shifting ability of patients with AN has been observed in both perceptual and cognitive domains (Tchanturia et al., 2004; Holliday et al., 2005; Tchanturia et al., 2012).
Fassino et al. (2002) reported deficits in abstraction and flexibility in patients with restrictive AN and suggested a correlation between body image disorder and abstraction abilities.
Cognitive impairment were also observed in remitted AN (Green et al., 1996; Tchanturia et al., 2002; Tenconi et al., 2010) and in healthy AN patients sisters (Holliday et al., 2005; Tenconi et al., 2010; Rozenstein et al., 2011) suggesting that cognitive inflexibility may be a potential endophenotype for genetic studies of AN. In addition, cognitive inflexibility in AN doesn't seem to be fully explained by the severity of the disease, assessed in terms of body

mass index or duration of illness (Tenconi et al., 2010; Tchanturia et al., 2011). Although a study by Roberts et al. (2010) reports that the poor set shifting is associated with a longer duration of illness and with a greater severity of rituals related to food, but not with the body mass index.

Central coherence refers to the ability to consolidate individual objects or pieces of information into a larger, holistic picture or construct. A meta-analysis shows that individuals with AN perform poorly on tests of central coherence such as the Group/ Embedded Figures Test or Rey-Osterrieth Complex Figure Test compared to HCs (Lang et al., 2014). Weak central coherence could help maintain AN symptomatology as it may cause individuals with AN to focus more on the details of their weight or shape and not on the bigger picture of their overall health (Roberts et al., 2016).

A **poor motor inhibition** measured with the Stop Signal paradigm was observed in AN (Galimberti et al., 2012), while other studies using the go/no-go test didn't found any differencess in comparison to HC (Claes Et al., 2006), although it was observed that the AN subtype with bulimic behaviors along with the BN made more errors (Rosval et al., 2006).
A study (Oberndorfer et al., 2010) showed a lower activation of the prefrontal medial cortex (MPFC) in remissioned patients during the most difficult stop signal testing (when the stop signal appears later than the primary stimulus), suggesting a demand-specific modulation of the inhibitory control circuit of these patients.
Kingston et al., (1996) reported deficits in attention, visu-spatial and mnestical abilities; only attention would improve with weight gain, while the other two deficits tend to persist even after the improvement. In learning tasks AN patients maintain a normal memory level but they show a strong explicit memory bias for anorexia related words (Sebastian et al., 1996; Hermans et al., 1998). An attentional bias toward "fat" and "thin" words as well as more attentional disengagement to food picture (Rieger et al., 1998) has been observed in An patients, they are faster in drawing tasks and tend to show shorter reaction times in copying task (Pieters et al., 2003).
Studies about visual perception and visuo-spatial abilities suggest a visuo-spatial deficit and others showed no differences between AN and healthy control (Mathias et al., 1998; Bradley et al., 1997).

VBM studies conducted in acute patients didn't always show concordant results; Joos et al., (2010) reported a significantly smaller volume in gray matter (GM) (and a higher volume in cerebrospinal fluid (CFS) than healthy controls while no difference had emerged in the volume of white matter (WM). Further regional analyses showed significant reduction of GM in the rostral anterior cingulate cortex (ACC) (at the border of the orbitus cortex), dorsal ACC, right frontal operculum, and left parietal and temporoparietal cortex. Brooks et al. (2011) investigated a small sample of patients with restrictive AN and AN-BP observed small differences in GM volumes at regional (but not global) levels; AN-BP patients reported higher volumes in the left cerebellum, in the bilateral para-hyppocampal regions, in the right anterior pituitary, and in the left orbital cortex. Investigations in AN patients with one year of remission didn't find any significant difference compared to healthy controls in GM, WM and CSF volumes (Wagner et al., 2006) even though in another study (Mühlau et al., 2007) changes in the anterior cingulate cortex remain even after remission. The only longitudinal study in adult AN patients (Roberto et al., 2011) suggested that weight recovery could also result in normalization of GM volume.
In adolescent too a normalization of GM volumes after remission was observed, although some anomalies persisted even after six months of disease improvement (Castro-Fornieles et al., 2009).

Functional MRI studies had shown dynamic alterations in fronto-striatal circuits during the performance of a cognitive flexibility task that may negative impact on the learning of new behaviours and may produce stereotypical and compulsive behaviours to control food intake and weight (Zastrow et al., 2009; Oberndorfer et al., 2011).

AN resting-state functional connectivity (rsFC) experiments have found global cerebral hypofunction, most pronounced in anterior cingulate, frontal regions, and in parietal lobe, as following reported, however studies suggests that some abnormal rsFC patterns found in patients recovered from anorexia nervosa normalize after long-term weight restoration, while distorted rsFC in the frontoparietal network (FPN), a network that has been associated with cognitive control, may constitute a trait marker of the disorder (Boehm et al., 2016). In acutely ill patients has been observed evidence for increased rsFC between the angular gyrus and the FPN that was also associated with self-reported persistence, a personality dimension associated with cognitive control (Boehm et al., 2014). The few rsFC studies in patients

recovered from AN reported heterogeneous results. Cowdrey and colleagues (2014) observed increased rsFC in the Default Mode network (DMN) but no differences in the FPN, (the visual or somatosensory network). In contrast, reduced rsFC in the visual network was reported by Favaro and colleagues, (2012) while McFadden and colleagues (2014) showed reduced rsFC strength in the salience network and sensorimotor network. Using a seed-based approach, Favaro and colleagues (2014) reported that the observed alterations in rsFC of the striatal network in acutely ill patients vanished with recovery.

In summary to gain insight into whether aberrant rsFC is a state or trait marker of anorexia nervosa, further studies with larger samples of recovered patients are needed but it is important to underlie that all these studies mentioned above used a cross-sectional design, and it remains unclear if the observed brain alterations are risk factors, causes, consequences or a "scar" of the disorder (Friedrich et al., 2013).

Taste stimuli studies in AN patients didn't reported an exclusive avoidance motivation to food, but also an higher activation of fear circuitry and reward system with respect to food intake (Vocks et al., 2011; Radeloff et al., 2012). This feature may represent a general avoidance tendency possibly associated with an intolerance of uncertainty and increased anxiety in decision-making context. Investigating avoidance motivation during different stage of the illness (recovered vs. acute), disorder-specific food and taste stimuli primarily indicate a higher responsiveness of the emotional and fear network in acute AN that may produce an avoidance motivation (Friederich et al., 2013). Summarising, no alterations or a hypo-responsive cortico-limbic-striatal network have been observed in response to general emotional stimuli (Zhu et al., 2012), suggesting that patients with AN may display conditioned stimulus-response patterns to food stimuli.

Tab 1. ANOREXIA NERVOSA DSM-5
A. Restriction of energy intake relative to requirements, leads to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight, becoming fat, or persistent behaviour that interferes with weight gain, even though already being at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, inappropriate influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.
Specify whether: *Restricting type:* During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behaviour (i.e., self-induced vomiting, misuse of laxatives, diuretics, enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise. *Binge-eating/purging type:* During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
Specify whether: *In partial remission:* After the whole criteria for anorexia nervosa was previously met. Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of weight gain, becoming fat, behaviours that interferes with weight gain) or Criterion C (disturbance in self-perception of weight and shape) are still met. *In full remission:* After the whole criteria for anorexia nervosa was previously met, none of the criteria have been met for a sustained period of time.
Specify current severity: The minimum level of severity is based, for adults, on current body mass index (BMI) or, for children and adolescents, on BMI percentile. Mild: BMI >17 kg/m2 Moderate: BMI 16-16.99 kg/m2 Severe: BMI 15-15.99 kg/m2 Extreme: BMI < 15kg/m2

CHAPTER 2

DECISION-MAKING

2.1 Decision making processes

The ability to make adequate decisions about possible courses of action is a core cognitive function in daily living, and altered decision-making, for example following damage to the orbitofrontal cortex, may sometimes results in disastrous consequences in life as in the famous patient E.V.R. described by Damasio in 1994, who made poor choices that led to negative consequences being unable to learn from his mistakes, despite an intact neuropsychological functioning on measures of intelligence and executive functions such as flexibility and working memory.

The decision making process is complex and to be effective it requires at one side a remarkable flexibility and future-directedness, which is evident in the ability to rapidly reconfigure the behaviour in response to changing goals, to flexibly adapt to changing contexts and environmental demands, and to pursue long-term goals even if this requires delaying rewards, suppressing habitual responses, or resisting immediate temptations; on the other hand the decision maker needs either to have some logic strategy to make effective inferences at the base of the choice, or that all the reasoning underlying processes are working (Bechara et al, 1994).

From a theoretical ponit of view, at the beginning **decision-making** has been studied broadly as a class of executive function but following models have suggested the differentiation between different types of decison making by identify two substantial classes :

A) *decision under certainty* (referring to the situation involving outcomes that are certain enough);

B) *decision under uncertainty* (in wihich the choice outcome in unknown as in the majority of real-life cases).

Decision making under uncertainty, according to Bechara and colleagues (2005), has been divided into two subtypes :

1) *''decisions involving risk''* (where there is a known probability of each outcome) ;

2) *'decisions involving ambiguity''* (where the outcomes aren't known at all)

In ***decisions involving risk*** the decsion maker must choses between risky and safe choices:

- *safe choices* have a high probability of gaining a reward, but the reward is relatively low in value;

- *risky choices* have a low probability of gaining a reward, though the reward is substantially larger in value.

Two examples of commonly used tasks that use decisions involving risk are the Iowa Gambling Task (Bechara et al., 1994, 1996) and the Cambridge Risk Task (Rogers et al., 1999).

In ***decisions involving ambiguity*** the probability of a specific outcome is either unknown or close to chance but the other and most relevant difference is that the two choices do not differ in reward value.

An example is the two-choice prediction task (Paulus, 1997) in which the decision maker chooses on which side of a house a car will appear and the probability of the car appearing on the right side of the house is identical to it appearing on the left side, with no risk associated with choosing one side or the other.

Goldberg in his recent research activities, highlights a relevant reflection concerning decisional processes and its assessment, noting that most real-life decision making situations are adaptive, rather than veridical as those assesed by the majority of existing decision making tasks, providing a futher decision making distinction:

- ***veridical decision making*** *(*which entails a correct response intrinsic to external situations and is actor-independent, as in experimental situations);

- ***adaptive decision making*** (that is actor-centered and priority-based, as real-world decision making requires).

Veridical decision making is actor-indipendent because the determination of what is ''correct'' and what is ''incorrect'' is inherent in the experimental situation (external milieu) and does not require any knowledge of the organism making the choice (internal milieu). It doesn't give any further information concerning the personal decisional stile or the presence of a possible executive control deficit of the decision maker.

The cognitive control over decisional real life chioices is the consequence of two types of

prefrontal operations: those guiding behavior by internal representations (context-dependent reasoning) and those carrying out exploratory processing of novel cognitive situations (context-independent reasoning) (Aoyagi et al., 2005).

Specifically **context-independent decision-making** is based on the subject's preexistent representations, and reflects an attempt to produce the best possible average responses according to these stable representations, without considering the unique features of the situation at hand. On the contrary **context-dependent decision-making** tries to capture the unique or specific features of the situation, and reflects an attempt to flexibly (Goldberg & Podell 1999). In this theorethical framework Goldberg (1994) developped an adaptive and actor centerd decision making paradigm known as Cognitive Bias Task (CBT or Cbias) to study the contextual reasoning in adults with frontal lobe lesions.

In summury, as we said above, the processes underlying goal-directed action can be classified roughly into decision-making processes where decision making refers to the process of forming preferences, selecting and executing actions, and evaluating outcomes, but in particular the cognitive-affective neuroscience distinguishes *decision making processes* which mediate the selection of goals and the formation of intentions, from the *volitional or cognitive control processes that* support the realization of chosen intentions, especially when they stand in conflict with competing goals, habits, or motivations. (Goschke et al, 2014)

2.2 Neural correlates of decision making

Research on cognitive, affective and neural correlates of decision-making and cognitive control has clearly suggested that the cognitive control of goal-directed action seems not mediated by a unitarian "central executive" system exerting top-down control over subordinate sensory and motor systems, but rather emerges from the interaction of large-scale brain network systems (e.g. Banich, 2009; Gruber and Goschke, 2004; O'Reilly et al., 2010).

Three core large-scale brain network systems involved in decision-making and volitional control have been identified:

1) *"The valuation and motivation network"* including the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), the ventral striatum (VS) and amygdala as a core intersection point;

it mediates the sum of value signal and reward-prediction errors and assign the values to states, goals and actions (Peters and Büchel, 2010).

2) "*The cognitive control network"* which comprises the lateral PFC and parietal cortex (PPC);

that active conciliates the balance between goals and context information, to inhibit overbearing but unwanted responses, and to modulate perceptual, emotional, and response top-down processes (Miller and Cohen, 2001).

3) *"The salience and monitoring network"* including anterior insula, anterior cingulate cortex (ACC), and extended amygdala as a core nodes (Menon and Uddin, 2010; Sridharan et al., 2008);

it regulates the vigilance, arousal and negative affect (Shackman et al., 2011), it's involved in the detection of significant stimuli, the monitoring of response conflicts and the signaling of the demand for enhanced cognitive control (Botvinick et al., 2004; Mansouri et al., 2009).

Other systems directly implicated in the decision-making arise from the interaction between multiple learning, memory and valuation system (Goschke, 2014).
In summary neuroimaging and neuropsychological studies suggest that decision-making is supported by a distributed neural network of brain regions that includes orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), thalamus, parietal cortices, and caudate (Ernst and Paulus, 2005) and in particular converging evidences indicates the prefrontal cortex, and in particular the OFC, as the key region.

2.2.1 The prefontal cortex

The prefrontal cortex (PFC) is widely regarded as the fondamental and critical brain region for the higher cognitive functions such as propositional speech and reasoning, indeed neuroimaging studies suggest that the prefrontal areas do not reach the full maturity until adolescence (Fuster, 2001).
In particular, the PFC is considered to be one of the latest areas in the human brain to develop, reaching the maximum growth until at least the mid-20s (Reichelt, 2016). The PFC it is tought to be the highest level of the cortical hierarchy dedicated to the representation and execution; specifically it's the brain region assign to executive processes "fractionate" into distinct cognitive functions concerned with motivating behavior *(valuation*) and controlling behavior *(cognitive control),* which have been proposed to draw on two partially distinct PFC networks (Stuss, 2011, Miller & Cohen, 2001):

1) *Cognitive control,* which is thought to draw on multiple processes, including response inhibition, error detection and response conflict, named conflict monitoring, switching and working memory (Miyake et al., 2000; Miller & Cohen, 2001; Chase et al., 2008),

has been mainly associated with the dlPFC and the anterior cingulate cortex (ACC) (Badre & D'Esposito, 2009; Koechlin et al., 2003; Bechara & Van Der Linden, 2005)

2) on the other hand *valuation*, reward learning, and decision-making functions have been linked to ventral and medial PFC (vmPFC) activity (Bechara & Van Der Linden, 2005; Rangel et al., 2008 ; Sanfey et al., 2003; Wallis, 2007; O'Doherty , 2004).

In summary it can be said that the general functions of " cognitive control" and "valuation" seem to be the result of the interaction of specific but interacting neural networks, within the PFC to generate adaptive behavior (Stuss, 2011; Kouneiher et al., 2009), however we need to consider that this distinction is framed between various levels of control and motivation (Kouneiher et al., 2009) or between executive functions (monitoring and task setting) and behavioral/ emotional self-regulation (Stuss, 2011). Infact the valuation system is involved to compare among rewards and to set the motivated goals that cognitive control functions will subsequently translate into planning of actions, flexible switching between them, and response monitoring, as notice by Glascher et collegues (2012).

From an anatomical point of view the PFC is the anterior part of the frontal lobe, consisting in the area 8, 9,10, 11, 12, 13, 24, 32, 46 and 47 according to the cytoarchitectonic map of Broadmann (1909); it is functional and anatomical distincts between *ventral PFC* with strong connections to the limbic system and *dorsolateral PFC (dlPFC*) with connections to posterior cortical areas in the parietal lobe (Pandya et al., 1996).

Fuster (2001) in a review of 2001 points out the necessity to understand the function of the PFC to be aware of the vast array of PFC connections with the other cerebral structure since none of its cognitive functions can be understood if taken out of a broad connectionist context. Infact, the areal specialization that can be found in the PFC rather than the topografical distribution of those functions, is thought to derive from the nature of the cognitive information with which they operate.

In particular the PFC can be subdivided in three major areas: orbital, maedial and lateral, of which tis last is maximally developed in the human. The orbital and medial regions are involved in emotional behavior while the lateral region provides the cognitive support to the temporal organization of behavior, speech, and reasoning where the function of temporal organization resoult from a close intertwine with other subordinate functions that are (e.g., temporal integration, working memory, set). (Fuster 2001)

The PFC doesn't receive direct input from the sensory periphery and must obtain all information it processes through its connections with other cortical or subcortical structures , moreover much of that connectivity with subcortical structures is reciprocal. The PFC is

connected with the brainstem, the thalamus, the basal ganglia, and the limbic system and the connections between the PFC and the thalamus are topologically well organized (Fuster, 2001).

Among the *afferent connections* deriving from the brainstem, the diencephalon and the limbic system and conveing to the PFC informations about the internal environment, the level of arousal, and the visceral concomitants of emotion, expecially relevant for the behavioral integrative functions of the PFC are those connections from the amygdala (Ray and Price, 1993) and from the hypothalamus (Jacobson et al., 1978) to the ventral and medial PFC.

These connections infact carry information about, futher than internal states, the motivational significance of sensory stimuli and have a major role in the representation and enactment of emotional behavior (Le Doux, 1993) and certain aspects of memory and motivation. Other prjections of major behavioral relevance are those from the hippocampus (Rosene and Van Hoesen, 1977; Barbas and Blatt, 1995).

The PFC is connected with other cortices of association, but not with primary sensory or motor cortices and some of the *corticocortical connectivity* of the PFC is interhemispheric. The medial, orbital and lateral prefrontal regions are interconnected and each of them is connct with the other two regions (Pandya and Yeterian, 1985, Fuster, 2001).

Efferent subcortical connections are important for motor control, such as those with the basal gangli and moreover the PFC has further indirect connective access to its closer motor areas through the basal ganglia, the cerebellum and the thalamus.

It is also *reciprocally connected* with the nuclei of diencephalon, mesencephalon and with reticular formations with a diffuse cortical connections (Fuster, 2001).

Neuropsychological studies in the human have been recognized three clusters of symptoms observed after lesions in the three major areas as the orbital, medial and lateral. Harlow described the famous case of Phineas Gage who had a lesion of orbital prefrontal cortex that had lead him to an abrupt changes of personality (Damasio et al., 1994), and other changes consisted in the appearance of a series of instinctual behaviours becoming impulsive and disinhibited, besides severe disorder of attention.

Patients with lesion in medial prefrontal region, which include the most anterior portion of the cingulate gyrus, may show problems in general motility, attention and emotions and loss of spontantaneity. (Cummings, 1993).

Including the most anterior portion of the cingulate gyrus, studying of normal participants

with positron emission tomography (PET) and functional magnetic resonance (fMRI) have lead to formulate the existence of an "anterior attentional system" (Petersen et al., 1989), due to its essential contribute in task that demand sustained effort and concentrated attention (Posner et al., 1988; Raichle, 1994).

Lesions of the lateral region resulted in inability to formulate and to carry out plans and sequences of actions; this deficit in planning is extended to the representation and construction of sequences of spoken and written language.

The DLPFC, the striatum at the dorsolateral caudatum, the dorsomedial globus pallidus and the thalamus constitute a **frontostriatal circuit called dorsolateral circuit**, that is thought to be fundamental for " classical" executive function such as working memory, selective attention planning, set-shifting and reasoning (Alvarez 2006).

The OFC, striatum at the ventromedial caudatum, dorsomedial globus pallidus and the thalamus constitute a **frontostriatal circuit called orbital circuit**. (Manes 2002).

2.2.1.1 The Orbitofrontal cortex

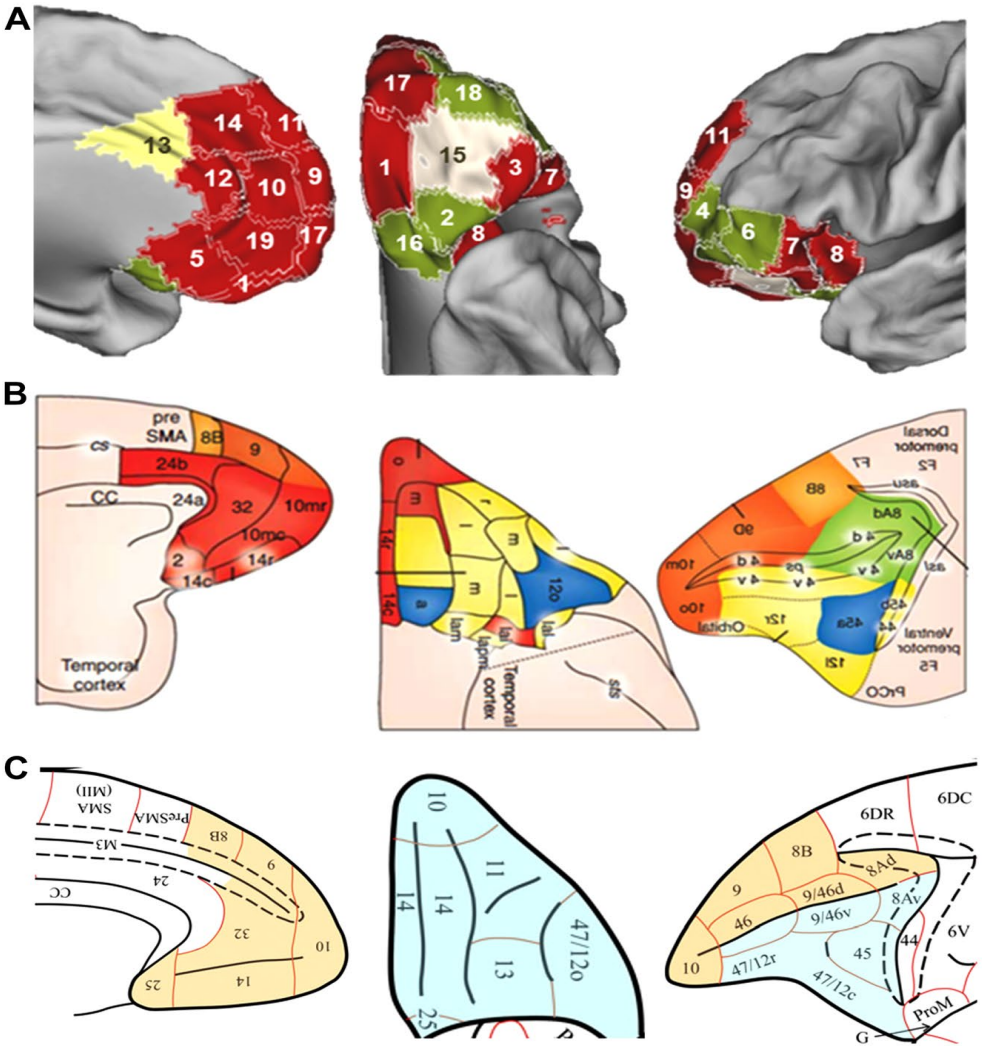
The orbitofrontal region of the prefrontal cortex (OFC) includes the rectus gyrus and orbital gyri, and represents the inferior surface of the frontal lobes lying immediately above the orbital plates. Lesions of this region are not usually restricted to the OFC, but they extend into neighboring cortex and involve different size sectors of the ventromedial prefrontal (VMPFC) region. The VMPFC region includes the medial and sectors of the lateral orbitofrontal cortex, encompassing Brodmann's areas (BA) 25, lower 24, 32, and medial aspect of 11, 12, and 10, and the white matter subjacent to all of these areas. Patients with bilateral lesions of the VMPFC develop severe impairments in personal and social decision-making, in spite of otherwise largely preserved intellectual abilities (Bechara 2004)

The ventromedial cortex, to which the OFC belongs, - even if the anatomical distinction is still debated (Manes 2002, Dunn 2006), further than limbic connections with amigdala and ipotalamo, is reciprocally connected with nucleo accumbens, differentely from the DLPFC that doesn't. The accumbens has a major role in reward and punishment processing (Wickens 2007).Have been demonstrated that the orbital and medial PFC are organized in separate networks (Samara et al., 2017) such as the **basoventral and mediodorsal** according to the cytoarchitectonic trends described by Barbas and Pandya (1989) and **the medial and orbital prefrontal systems** of Carmichael and Price (1996) and Ongür and Price (2000) (see Fig. 1) and, further than corticocortical connections, the medial and the orbital prefrontal systems are characterized by distinct connections with the rest of the brain (Öngür and Price 2000).

Noteworthly human neuroimaging studies revealed a preferential neural activation according to the stimulus value (Sugrue 20051 Kringelbach 2005), with the medial and lateral OFC answering respectively to positive results (rewards) the former and negative ones (punishment), the latter.

For this reason the ventromedial PFC can be considered as " the accounant" that support the DLPC in the execution of complex behaviour (Fellows 2007) by valuating the corrent value of a stimulus and representing its corresponding future value (Wickens 2007). In so doing this area drives the decisional process ofthe subject by establishing how a certain choice will be more or less advantageos in comparison to others.

Figure 1.



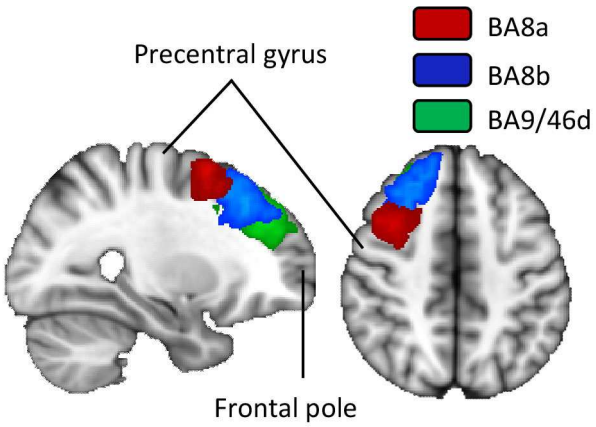
Note. *Cortical surface representation of the results of the hierarchical clustering analysis. OMPFC clusters belonging to the medial group are shown in red; clusters belonging to the orbital group are shown in green; singletons are uniquely colored.* ***b Medial (red) and orbital (yellow) networks*** *proposed by Carmichael and Price (1996) and Öngür and Price (2000) (in Price and Drevets 2010). Areas connected to more than one network and believed to act as interfaces for information exchange are seen in blue.* ***c. Mediodorsal (orange) and basoventral (light blue) cytoarchitectonic trends*** *described by Barbas and Pandya (1989) (in Yeterian et al. 2012).(Adpted from Samara et.al 2017)*

2.2.1.2 The dorsolateral prefrontal cortex

The dorsolateral prefrontal cortex (DLPFC) is a functionally and structurally heterogeneous region and a key node of several brain networks, implicated in cognitive, affective, and sensory processing.

The DLPFC includes the Brodmann areas (BA) 9, 8a, 8b and the dorsal part of 46 82 and span the middle frontal gyrus and the lateral aspects of the superior frontal gyrus. It is banked by the inferior frontal sulcus on the lateral side, the precentral sulcus on the posterior bank, and the frontal polar cortex (FPC, BA10) on the anterior bank as the best delineation since the anterior bank is inconsistently defined across the literature (Koechlin et al., 2011; Ongur, Ferry et Price, 2003; Ongur & Price 2000) (see Figure 2).

Figure 2.



Note. *Regions of the brain comprising the dorsolateral prefrontal cortex (DLPFC), including Brodmann Area 8, 9 and the dorsal part of 46. The three clusters shown represent subregions of the DLPFC based on a parcellation scheme by Sallet and colleagues (Sallett et al., 2013)*

The DLPFC is generally associated with maintenance and regulation of top-down modulation, and driving appropriate behavioral responses O'Reilly 2010; Sallett et al., 2013) and it is involved in cognitive processes (Cieslik et al., 2013;Nee & D'Esposito 2016) and emotional regulation (Etkin et al., 2015; Okon-Singer et al., 2015,).

Interestingly the DLPFC is thought to be, further than a key node in the cognitive control network (Cole et al. 2007), also a region of switch and interface between two brain networks (Seeley et al., 2007). The extrinsic mode network (EMN) (Hugdahl et al., 2015) and the default mode network (DMN) (Fox et al., 2005; Raichle et al., 2001) perhaps also for its advantageous anatomical position since it sits between the interface of the EMN and DMN. In

particular the EMN is thought to be a generalized network allocating cognitive resources to any cognitive task or sensory processing of the external milieu while the DMN is active in the absence of any overt stimulus (or task), and is thought to be related to monitoring of the internal milieu and introspection. (Seeley et al., 2007).

2.2.2 Neural correlates of different decisional processes: Hot vs cold, veridical vs non veridical decision making

A voxel-based lesion-symptom mapping study on a large sample of subjects with focal lesion assessed with a battery of neuropsychological task, indicates that decision-making require functional-anatomical networks of ventral region of PFC including the orbitofrontal, ventro-medial, and frontopolar cortex (Glascher 2012), altough recent evidences suggest that the neural substrate of decision-making may vary depending on the nature of the decision being made .

The group of Kraine (2006) hypothized a neural dissociation between risky and ambigous decision making, in the wake of the theoretical model of hot and cold Executive function of Zelao and Muller developped in 2002. In particluar Zelao and Muller theorized that executive functions (EF) as well as decision-making, can be divided into ‘‘hot’’ and ‘‘cool’’ subtypes.

Hot EF are considered to be linked to affective, emotional, and visceral inputs and to be associated with the **OFC**, whereas *cool EF,* beeing characterized by more purely cognitive and rational processes, are tought to relie to the **DLPFC** activity (Zelao & Muller 2002).

Hot decision making paradigms are considered those *involving risks and rewards*, such as gambling tasks (Kerr and Zelazo, 2004), and the Hot EF theory has been confirmed by lesion and neuroimaging studies involving these tasks that demonstrated the *role of the OFC* in making risky decisions (Bechara, 2001; Ernst et al., 2002).

On the contrary, may be considered **cold decision making** the paradigms which don’t involve risk, (Krain at al., 2006) as in *ambiguous decision-making* tasks occurs since, as we prevously said, they involve selections from among responses of equal valence, and neuroimaging studies reported *DLPFC activation* when subjects are making a choice from among several responses without an explicit risk or reward (Hyder et al., 1997; Frith et al., 1991).

The meta-analysis of Krain and collegues reported, in line with the hot and cold FE theorization a dissociable patterns of neural activity in frontal and parietal cortices between **decisions involving risk and** those **involving ambiguity**, showing a neural dissociation in

OFC and DLPF, anterior and posterior subregions of ACC with a specific activation of the subcallosal cingolate region and the lateralization of parietal activity.

Specifically the activity of orbitofrontal cortices ***OFC*** *increases more likely during tasks involving risk* while the invovment of ***DLPFC*** *is more likely to occur during tasks involving ambiguity* (Krain et al., 2006).

Moreover they also demonstrated the presence of functionally differentiated sub-regions within ***ACC****,* in particular even if *both risky and ambiguous decision-making activate ACC, risky decisions were associated with activity in a more rostral portion of BA 32 and in nearby areas of pre-supplementary motor area (BA 8/9).* Effectively the involvement of rostral ACC areas is greater in affective processes (e.g., error-related processing, conflict detection), while that of more caudal portions is prevlent in pure cognitive processes (e.g., response facilitation/inhibition) (Kiehl et al., 2000; Milham and Banich, 2005; van Veen et al., 2001).

Another interesting point is the activation of a **sub-callosal region of cingulate** in ambiguos but not in risky decisions. This regionis thought to be involved in emotional disregulation observed in some psychiatric disorders and is thought to be connected to OFC, a region that, as we said, doesn't appear to be consistently activated in ambiguous decisions. This result has suggested to the authors two rfeflections: 1) the cingulate sub-callosal region may act independently of OFC despite their intimate connections and 2) the possible presence of an affective component also in ambiguous decisions, even though markedly less than in risky decisions.

The significant **parietal activation** in both types of decision-making was attributed to its importance (and in particular of the BA 7) in attentional processes, further than its implication in many cognitive and sensory stimuli (Culham and Kanwisher, 2001). However a laterlization of the parietal activation was detected ,in particular risky decision-making was associated with greater activity in the left inferior parietal lobe, while ambiguous decision-making showed greater activation on the right. This dissociation may reflect the need for numeric evaluation and comparison in the risky tasks ,which are processes associated with left parietal activity (Pesenti et al., 2000; Sandrini et al., 2004) while the ambiguous decision-making tasks don't require explicit numerical computations.

An fMRI study published on Science revealed that activity **in risk** vs ambiguous situation was localized in the **dorsal striatum (caudate nucleus).** They suggest that the orbitofrontal cortex and the amygdala may represent a "vigilance"/evaluation-system which responds rapidly to the degree of uncertainty while a second system that includes the *dorsal striatum is associated with reward-anticipation* and reacts more slowly and later than the first system. In

addition the level of ambiguity in choices correlated positively with activation in the amygdala and orbitofrontal cortex, and negatively with the striatal system, moreover the striatal activity correlates positively with *expected reward* (Hsu et al., 2005).

The **amygdala** is thought to have a role in the reaction to emotional information (Bechara et al., 2003), and it is modulated by the DMPFC. Both amygdala and OFC are likely involved in detecting salient and relevant stimuli of uncertain value but the amygdala in particular (Adams et al., 2004) is thought to also provides a reward-related signal that can motivate behavior, throughtout the connections between the amygdala/OFC and the striatum.

In summary both two types of decision-making, hot and cold, can have an adaptive or maladaptive value depending on the situation. For example, implementation of reflective processing as a strategy to avoid the repetition of performing errors or, on the other hand, a quick visceral response may be more effective if there is an oncoming danger (Séguin et al., 2007).

Evidences from developmental studies suggest that the development of decision making skills follows, along with the maturation of frontal areas, a path in which **veridical decision making** skills reaches mature performance levels earlier than **non-veridical, ambiguous choice abilities** (Aihara et al. 2003).

A dicothomy between veridical and non-veridical decision making has been supported by lesion studies reporting selective impairments of either type of decision making, such as in substance abusers that show impaired decision making in unstructured, self-regulated situations, but not in veridical scenarios (Verdejo-Garcia et al. 2006).

Goldberg and colleagues (1994) reported in a sample of right-handed female patients with bilateral frontal lesions, a strong context-dependent reasoning in the Cognitive Bias Task (CBT or Cbias), a **non-veridical subject-centered ambigous task** as previous told. Moreover a functional MRI (fMRI) study demostrated that CBT triggers significant *bilateral activations in **DLPFC*** relative to a veridical decision making control task (Vogeley and colleagues 2003).

In addition this emerging hypothesis that prefrontal cortical mechanisms involved in non-veridical decision making do not overlap with those of veridical decision making has been tested with a recent repetitive transcranial magnetic stimulation (rTMS) study. Transcranial magnetic stimulation (TMS) applied to the *left and right dorsolateral prefrontal cortex (DLPFC*) using 1 Hz and 10 Hz (intermittent) rTMS and sham protocols triggered a *shift* towards a *more context-independent, internal representation* driven non veridical selection *bias* (Tulviste et.al , 2016).

Developmental and lesions neuroimaging studies demonstrated a left lateralization of the context-dependent reasoning and a right lateralization of context-independent reasoning in right handed male (Goldberg et al., 1994; Aihara et al., 2003; Shimoyama et al., 2004).

Consisting with Goldberg's findings in patients with frontal lobe lesions (Goldberg & Podell, 1999) and Vogeley (2003) another fMRI study demonstrated a *robust dorsomedial as well as dorsolateralfrontal lobe activation in subjective decision task*. Specifically this last study analized the cerebral activation in a veridical baseline decision task (EVD) and in two subjective situation : an "internal subjective decision " (ISD) of *color preferer condition* involving an inward or self-referential context, and an "external subjective decision " (ESD) of *subjective color similarity condition* where the choice between two equivocal alternatives was based on the external color properties of the color stimuli rather than on self-preference. In particular the authors conclude that the greater activation in the anteriormedial PFC **(AMPFC), the retrospenial cortex (RSC) and the caudate nucleus** during ISD may suggest that ***self-referential processing***, rather than subjective judgments among ambiguous response alternatives, *accounted for the AMPFC and RSC response* (Jhonson at al., 2005).

2.3 THE ASSESSMENT OF DIFFERENTS DECISION MAKING:

IGT AND CBT

2.3.1 The Iowa Gambling Task and the Somatic marker Hypothesis

The Iowa Gambling Task (IGT) developed by Bechara, Damasio A., Damasio R., and Anderson (1994) is one of the most frequently used neuropsychological tasks to assess decision-making in uncertinity situations and was initially ideated, with the aim to analyze the putative impairment of decisional prcessing in patients with ventromedial prefrontal lesion. Infact the very initial findings in decision-making mechanism derive from systematic examination of well-defined brain lesions (Bechara, 2005).

The aim of the task is to gain the maximum by chosing card from four decks, named A, B, C, D. Each selection can be associated to a reward and a earnt of a certain amount of money, or to a punishment that leads to a certain amount of loss. The participants, who do not know after how many choices the experiment will end, receive initially a counterfeit money sum and they need to try to gain the most possible, and lose the least they can. The total of money owned is constantly updated at each try. Each deck has a fixed card sequence, the A and B are disadvantageous, the C and D are advantageous. For each selctions of the first two decks there

are a fixed reward of 100 dollars, whereas for the advantageous ones each card presents a 50 dollars reward. The frequency of cards with punishment is different across the four decks and it is set to be higher in the high-paying decks A and B incurred in a total loss of $1250 every 10 cards, and to be low-paying in C and D with a total loss of $250 every 10 cards. Therefore A and B decks are disadvantageous in the long term because they entail a $250 loss every 10 card, on the contrary the C and D decks are advantageous because they provide a net gain in the long term (Bechara et al., 2000). Moreover, another differences within the two category of decks consist in the fact that in the deck A the punishments are more frequent but the amount of loss are lower compared to B and this is even the same with the C deck compared to D.

Figure 3a.

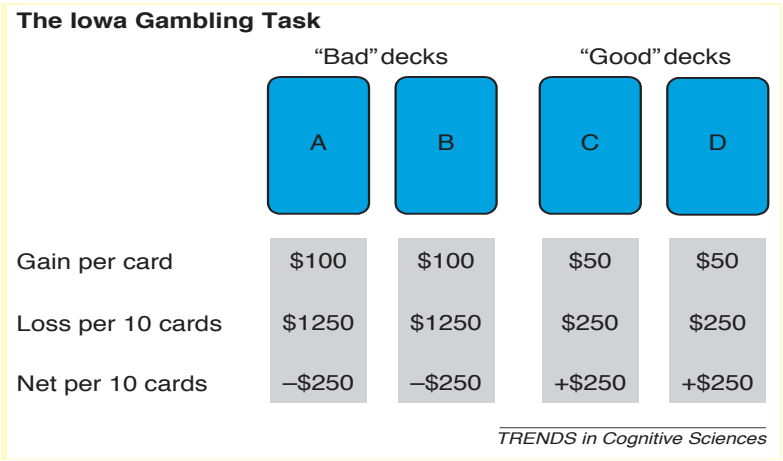


Figure 3b.

Card number	Deck A (+$100)[a]	Deck B (+$100)[a]	Deck C (+$50)[a]	Deck D (+$50)[a]
1				
2				
3	—$150		—$25	
4				
5	—$300		—$75	
6				
7	—$200		—$25	
8				
9	—$250	—$1250	—$75	
10	—$350		—$50	—$250
11				
12	—$350		—$25	
13			—$75	
14	—$250	—$1250		
15	—$200			—$250
16				
17	—$300		—$25	
18	—$150		—$75	
19				
20			—$50	
21		—$1250		—$250
22	—$300			
23				
24	—$350		—$50	
25			—$25	
26	—$200		—$50	
27	—$250			
28	—$150			
29			—$75	
30			—$50	
31	—$350			
32	—$250	—$1250		—$250
33	—$250			
34			—$25	
35			—$25	
36				
37	—$150		—$75	
38	—$300			
39			—$50	
40			—$25	
41		—$1250	—$50	—$250
42	—$300			
43				
44	—$350		—$50	
45			—$25	
46	—$200		—$50	
47	—$250			
48	—$150			
49			—$75	
50			—$50	

Note. *The Iowa gambling task and **fig. 3 b** representation of a score card from the original gambling task of Bechara (1994).The negative numbers correspond to the amount of money lost when the card is chosen. The empty spaces correspond to cards with money gain and without loss ($100 for A and B deck and $50 for C and D deck) (*Bechara *et al., 2000a)*

The original experiment conducted with real cards was later substituted by a computerized version, described in Bechara, Tranel, and Damasio (2000).

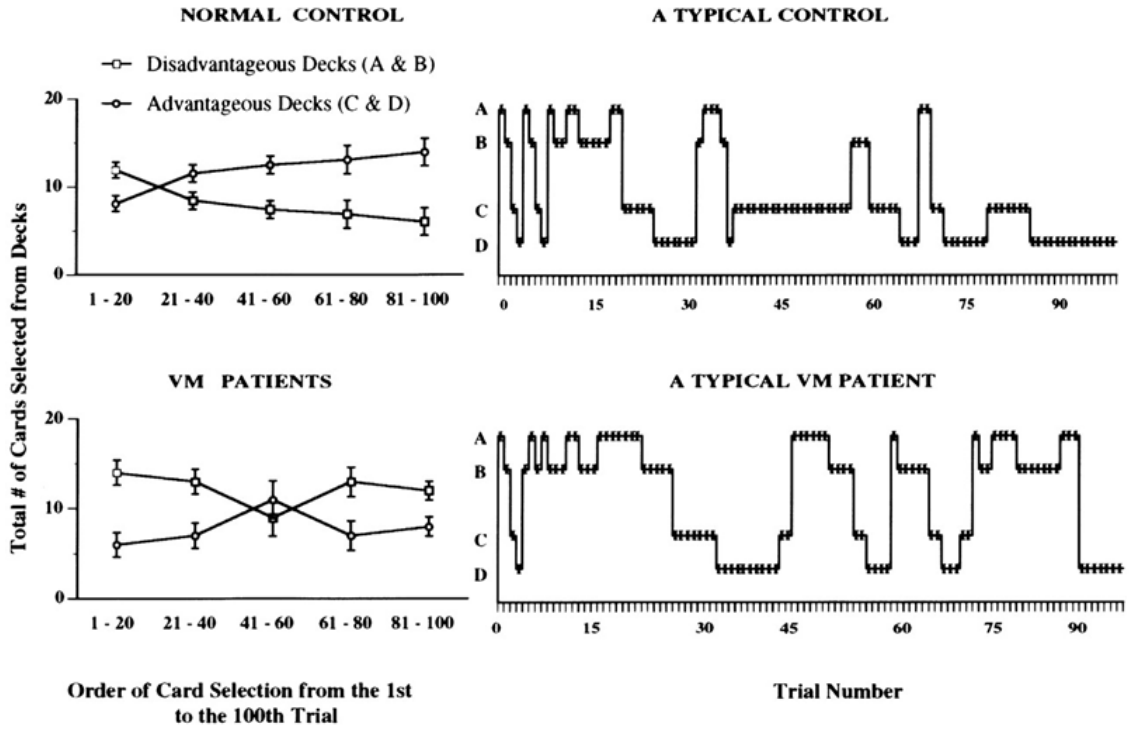
To solve the task successfully, subjects have to figure out the rules implicitly by using the feedback they get after each choice. “Implicitly” means that it is quite difficult for decision maker to keep track and remember the gains and losses from previous trials but individuals have to follow their own feelings and hunches, in accordance with the **“Somatic marker hypothesis“ (SMH)** developed by Damasio (1994, 1996). With the “Somatic Marker Hypothesis’’, Damasio and collegues provide a neuroanatomical and cognitive framework for decision-making highlitghting that the decisional processing depends in many important ways on neural substrates that regulate homeostasis, emotion, and feeling. In particular this theory derived from decision making studies on neurological patients with an impairment of emotional information processing, which lead Damasio to consoder that people make choice not only by evaluating the consequences and their probability of occurring, but also and even sometimes primarily at a gut or emotional level Specifically the result suggested that lesions of the VMPFC (which includes the orbitofrontal) interfere with the normal processing of ‘‘somatic’’ or emotional signals, while sparing most basic cognitive functions result in a impairment of decisional prcessing that compromise the quality of decisions in daily life

The theoretical framework of the SMH recognized to the VMPFC an important role in the regulation of both parasimpatic and stress reactivity through the foloowing suppression of affective responces to negative emotional signals (Gjedde & Geday 2009; Hansel & von Kanel 2008: Lyons, Parker, Katz & Schatzberg 2009) and a successful physiological correlate of the Somatic marker hipotesis was also identified in the Skin Conductance Respone (SCR) (Bechara et al., 1996).

During the IGT patients with OFC damage fail to perform change and continue to choose from risky decks even when this lead to negative consequences while normal unaffected controls, gradually focus their choices on the advantageous decks avoiding disadvantageous selections (Tomassini et al., 2009).

In particular at the very beginning of the task healty controls (HC) and patients withVMPFC lesion (VM) perform similarly sampling all decks even with a preference for immediate reward as shown by the repeated selection from bad decks, but after the first two blocks, HC switched to pick from good decks C and D and only occasional returns to bad A and B, while VM patients return more frequently and more systematically to the bad decks, or perhaps they remain attached to their previous preferences (Bechara et al., 1994; Bechara et al., 2000b), as shown in Fig.4. In re-test situations bad performance of VM didn’t change positively or negatively intead HC control improved their performance over time.

Figure 4.



Note. *Left panel shows cards selection on IGT in the two groups (normal controls and VM patients) according to deck type (disadvantageous vs advantageous) and trial block. Right panels shows the profile of card selections observed in a typical control and a typical VM patient (from Bechara et al., 2000b).*

In another experimental situation Bechara and collegue (1997), as previous said, isolated a physiological correlate of the SMH. They collected behavioral, psychophysiological, and self-account measures paralleling to the performance at IGT of Healty control and patients with bilater demage of VMPFC. In particular a Skin conductance responce (SCR) was registerd within the 5 seconds immediately preceding and following the card selection. The researcher registered 3 different type of responce:

1) **Reward SCR** generated immediately after a rewarding selection;

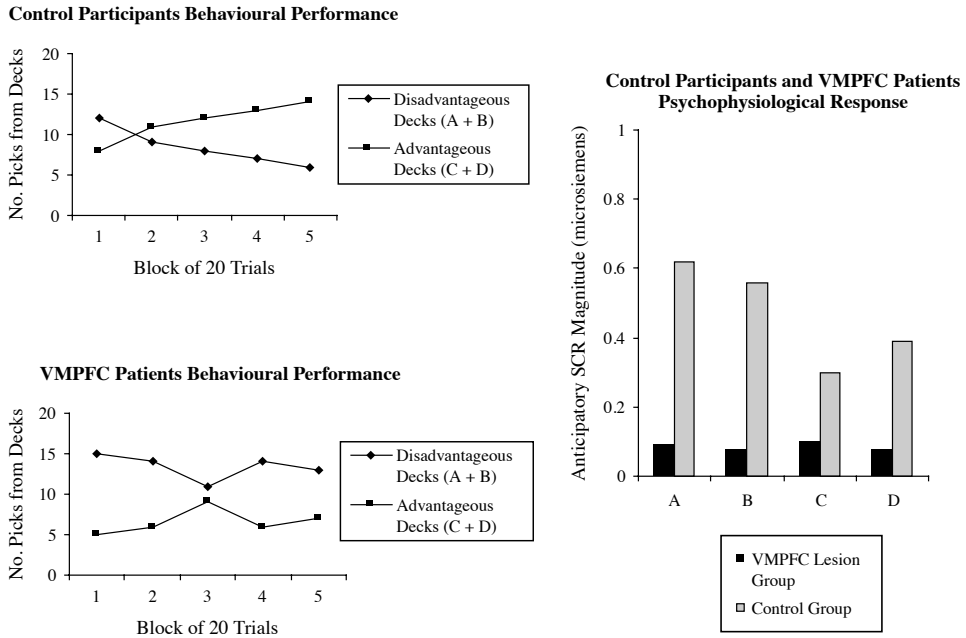
2) **Punishment SCR** generated after a rewarding selection immmediately followed by the selection of a card associated to a loss;

3) **Anticipatory SCR** generated in the period of choice card immediately preceding the selection of the card;

Both HC and VM patients generated reward and punishment SCR but only healty decision maker, with the task proceding acquired experiences and developped an anticipatory SCR, while patients do not (see Fig. 5). Moreover HC group began to choose advantageously before they realized which strategy worked best, whereas VM patients continued to choose disadvantageously even after they knew the correct strategy. In addiction normals began to

generate anticipatory SCRs whenever they pondered a choice that turned out to be risky, before they knew explicitly that it was a risky choice, whereas patients never developed anticipatory SCRs, although some eventually realized which choices were risky. The authors concluded that in normal individuals, nonconscious biases using neural systems other than those that support declarative knowledge, guide behavior before conscious knowledge does and that without the help of such biases, overt knowledge may be insufficient to ensure advantageous behavior. motional experience of similar situations . The ventromedial frontal cortices are among the structures candidated to hold such dispositional knowledge, and its activation in turn may activates autonomic and neurotransmitter nuclei. (Bechara et al., 1997)

Figure 5.



Note. *Anticipatory SCR and IGT performance in normal cotrol and VM patients.*

Bechara and his colleagues postulated three hypothesis to explain these results: 1) VM patients might be more sensitive to rewards compared to punishments even if this involves an initial gain but a higher future loss; 2) they may be insensitive to punishment focusing attention exclusively toward rewards; 3) their behaviour is possibly guided by immediate rewards so they might be insensitive to future consequences (Bechara et al., 1994). To test these hypothesis, another version of the basic IGT was developed, this task was almost the same except for the order of the cards and that the schedule of rewards and punishments was reversed (Bechara et al., 2000a). In this variant task the four decks of card were named E, F, G, H, and unlike the basic task in this the punishment was immediate and the reward was delayed since every card was associated to a punishment and several cards presented even a

reward. The good decks were E and G associated with immediate higher losses (100$) but a net in the long term was secured, the considered bad decks were the F and H with modest immediate losses (50$) and a net of lower gain in the long term, revealing therefore to be disadvantageous. Similarly to the original IGT, normal controls subject choose mainly from advantageous decks, instead VM lesion patients, evidently discouraged by high punishment of E and G decks, chose more frequently cards from the disadvantageous ones, revealing so an inability to modify the selections with the progress of the game. These results may indicate that VM lesion patients were more influenced by immediate punishment than by delayed reward, indicating neither a insensitivity to punishments nor a hypersensitivity to rewards.

Therefore the first two hypotheses were excluded because patients chose more frequently from the disadvantageous decks associated with an immediate high rewards but higher long term punishments. The authors inferred that patients were anchored to a strategy of choice, because the OFC damage prevents them from integrating information about past outcomes in order to identify the "good" decks (Bechara et al., 2000a). This may be linked to two defferent but overlapping deficits: the inability to retain in the working memory information useful for the choice and the inability to label the decks representation with a positive or negative valence.

Evidence suggests that the IGT assesses **"hot" decision** making processes, as emotional processing is associated with performance on the task, consistently with the somatic marker hypothesis. However risky decision making component of the IGT is more apparent in the last trials of the task than in earlier trials. In particular it is thought that during the first block (1-20) of trials IGT might represent a decision making under ambiguity task, because has not been time for a participant to experience any of the win/loss contingencies for the deck choices. Instead selections during the last block of trials (41-100) were referred to as decision making under risk, because after many plays, participants should have experienced the different win/loss contingencies enough to know which decks are risky and which are not; thus, decisions to play a risky deck at that point would reflect a different decision process than a play of a risky deck early in the 100 trials. (Brand et al. 2007. Recent studies are consistent with this characterization as cards 1–20 representing ambiguity and trials 41–100 representing risk (Brand et al. 2007; Gendle and Golding, 2010; Stoltenberg and Vandever, 2010); the second block (card 21-40) may represent a transition phase of decision making that represents a state of knowing prior to certainty (Stoltenberg et al., 2011).

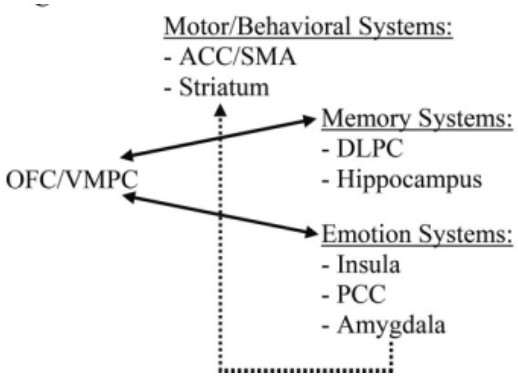
- **Neural correlates of IGT and SMH**

Northoff (2006) in an fRMI study explored the link in healthy subject between the VMPFC activity and the elaboration emotional and cognitive responces during IGT, reporting a

positive correlation between the activity in VMPFC (implicated in emotional responce) and the good performance at IGT, providing a neural correlates of the Somatic marker Hipotesis.

Also the results of an fMRI study of Li and collegues (2010) exploring the pattern of brain activities during performance of the IGT support the general theoretical framework of the SMH. Infact they found to be engaged during the performance at IGT a neural circuitry involving the dorsolateral prefrontal cortex (for working memory), the insula and posterior cingulate cortex (for representations of emotional/somatic states), the mesial orbitofrontal and ventromedial prefrontal cortex (for coupling the two previous processes), the ventral striatum and anterior cingulate/SMA for implementing behavioral decisions (see fig.6). However and unexpectedly this study didn't reveal any significat activity in two key regions: the amygdala, in contrast with the SMH previous study of Bechara (Bechara, 2004) and the Hippocampus, a region also thought to be important for decision because complex decisions require the ability to remember certain information for more than 40 seconds, which is the limit of the working memory capacity of the dlPFC. The authors expalined this last results as caused by the experimental procedure used, and in particular they suggest that the lack of amygdala activity may reflect a combination of the functional properties of the amygdala (e.g., rapid neuronal firing and habituation) and the experimental procedures designed.

Figure 6



Note. *Schematical representation of brain regions involved in decision makin according to SMH: target regions include OFC/VMPFC, DLPFC, anterior insula, posterior cingulus, striatum (including ventral striatum) , sopracallosum anterior area of cingulus and the nereby supplemental motor area (adapted from Li et al., 2010)*

Similarly a structural magnetic resonance study on Parkinson Disease (PD) patients in a initially stage that didn't find any correlation between gambling score and Grey Matter (GM) loss in amygdala even if GM volume loss in left lateral OFC was to decision-making impairment in PD (Ibarretxe-Bilbao et al., 2009). The authors have interpreted this lack of correlation, as a different and distinct contribution of OFC and amygdala in decision-making

process based on the findings that monkeys with amygdala lesions were able to flexibly change stimulus-reward associations (Rudebeck & Murray, 2008).

Concerning the more specific role of the **right lateral OFC in IGT** performance previous reported (Tranel et al. 2002) other studies contested this functional specificity and suggested that also more widespread prefrontal lesions in dorsolateral (Manes et al. 2002; Clark et al. 2003; Fellows and Farah 2005) and dorsomedial (Manes et al. 2002) regions negatevely impact on IGT performance, even though via different underlying mechanisms (Manes et al. 2002; Fellows and Farah 2005). Conversely in sample of AN, (Bodell et al., 2014) the decrease of **left medial OFC brain volume**, further than the lower BMI, was significantly associated with worst IGT performances but only in acute actively ill patients; while this association was no longer significant after weight restoration even though the increase in brain volume and BMI may not have been sufficient to improve decision making in all patients, suggesting that it may represent a trait-like cognitive vulnerability for AN.

Despite the above mentioned properties, the neural underpinning of the IGT has not yet been fully clarified, do to the complexity of the task further than the experimental prcedures used or even the subjects of the study.

For example **sex differentiation in IGT** peerformance has been widely reported (van den Bos et al., 2013) and PET data confirmed that men and women show differences in regional activation during IGT performance (Bolla et al. 2004), with a grater men activation of the right lateral OFC (BA 10, 47) in compairison to women, and a women greater recruitment of left DLPFC, left medial frontal gyrus and temporal lobe than men. These sex differences in task-related activation might explain some reported male advantage on the IGT (Reavis and Overman 2001; Bolla et al. 2004; Overman et al. 2004; Lawrence et al. 2006).

In summary neuroimaging evidences even though with some inconsistences are complexively agree in recognizing a central role to the PFC in decision making (Li et al., 2010, Northoff et al. 2006, Windmann et al., 2006; Ernst et al., 2002; Tucker et al., 2004; Bolla et al., 2005; Bolla et al., 2003; Fukui et al., 2005). In partcular the activation of both prefrontal and posterior regions (mOFC, VMPFC, ACC, DLPFC, insula and the nearby inferior parietal cortics) during the IGT have been demonstrated with both PET (Ernst et al., 2002) and fMRI studyes (Fukui et al. 2005).

It is important to note that the IGT has encountered numerous criticisms for its complexity and the implication of several auxiliary processes for successful performance.However the use of simpler tasks more specific to target different cognitive processes of decision-making may lack in clinical validity being closer to a experimental decion making context than a real

life situation. Therefore a modeling approaches may be useful to desentangle the complexity IGT by decomposing behavioural performance into more specific cognitive processes including the relative impact of rewards and punishments on evaluations, the rate that the contingent payoffs are learned, and the consistency between learning and responding. In this line the application of the expectancy valence learning model help to analyze IGT performance according to three parameters: a motivationl, a learning and a choice consitency one (Busemeyer & Stout., 2002).

2.3.2 The "cognitive modeling" and the Expectancy valence model

The "cognitive modeling" has been used in several neurocognitive tasks to deconstruct task performance into more defined underlying processes based on formal cognitive models. Formal cognitive models can provide a theoretical basis for the analysis of the multiple processes involved in cognitive tasks allowing a quantitative evaluation of the theorized underlying processes.

The expectancy valence learning model (EVL or EVM), developped by Busemeyer e Stout in 2002, is a validated formal cognitive model of IGT and represents a theoretical starting point for the evaluation of cognitive versus motivational processes emerged in risky decision making tasks.

The EVL analyses three theorized processes involved in IGT performance: motivational, learning, and response processes with three corresponding parameter: a motivational, a learning and a choices consistency parameter. The basic theorical assumption is that the decision maker would make its card selection in a given trial basing on his own "**expectation of valence**" (i.e., an affective feeling, positive or negative, associated with a given deck or an implicit association between a given deck and good/bad outcomes). The expectation of valence is formed through learning/memory of the experiences of gains and losses received following choosing a given deck (adaptive learning mechanism) in preceding trials. This expectancy is finally utilized as inputs into a probabilistic choice mechanism that selects the choice on each trial.

The formation of the expectation of valence *is a function of one's sensitivity*; for example a person with a higher sensitivity to losses than gains will form an negative expectation valence for a given deck that has given equal amounts of gains and losses. In the EVL model the individual difference in sensitivity to gain as opposed to loss is represented by the **motivational parameter (W).**

As prevuious said, the formation of expectancy is based on an adaptive learning mechanism and individuals with a memory or learning functions deficts are less able to use information from preceding trials to guide their decisions. The individual difference in this process is represented by a **learning/ memory parameter (Φ or a**) that representing the attention to recent outcomes as opposed to the persistence of initial choices, indexes how much experiences in past trials are discounted (memory decay),

The **response consistency parameter *(C)*** represents the degree of consistency in making decisions with respect to the expectancies of valences *(exploitation)* as opposed to making random choices *(exploration)*.

The Exploitation is a strategy used by an organism to provide an option that is associated with the highest possibility of reward while *the Exploration* involves deviations from this behaviour to seek for new and previously unexplored options. The balance between exploitation and exploration is critical in real life because exploitation is the most adaptive strategy where the environment is stable and contingencies between options and outcomes are fixed, while exploration is more adaptive where the environment is unstable and contingencies between options and outcomes are uncertain. The group of ~~Ohira (2013)~~ suggested that the degree of exploration could be liked to a tonic (and not phasic) sympathetic activity. In particular the PET study of the group reveals a positive correlation between an increase of epinephrine concentration in peripheral blood and both exploration during decision making and cerebral activity in brain regions including the somatosensory cortices, right anterior insula, dorsal ACC, and dorsal pons. Suggesting that the activity in the right anterior insula could specifically mediated the association between sympathetic activity and exploration in decision making.

The EVL model has been used in several clinical populations and has identified specific impairments in each disorder such as a motivational bias in substance abusers (Fridberg et al., 2010) or in adolescent with recent schizofrenia onset (Kester 2006), an impairment of lmemory/learning in Hungtington disese (Busemeyer et al., 2002), a choice inconsistency in autistic specrtum diseases (Yecham et al., 2010) an in bipolar diroder (Yecham et al., 2008). In eating disorders instead seems to be major involved the learning parameter in AN and the motivational parameter (an higher attention to reward) in BN patients (Chan et al 2014).

2.3.2.1 The Expectancy valence model parameters

As previous said the EVL analyses three cognitive processes involved in IGT motivational, learning, and response processes with three corresponding parameter: a motivational, a

learning and a choices consistency parameter.

1) The motivational parameter (W) (attention to gains and losses):

The experience after a payoff on the selected deck during the task is assumed to produce an affective reaction called valence that is at the base of this first attention weight parameter (W). The valence of the payoffs experienced on a trial t is denoted v(t), and is represented as a weighted average of the gains and losses in trial t:

$$v(t) = W \cdot win(t) - (1\text{-}W) \cdot loss(t),$$

where ***win*(*t*)** stands for the amount of money **won** on trial *t*,
***loss*(*t*)** is the amount of money **lost** on trial *t*,
and ***W*** is the parameter indicating the **weight given gains versus losses**.
The ***W*** parameter **ranges from 0 to 1**, thus small value (close to 0) denote an attention to losses, as opposite to higher value (close to 1) with an attention to gains which can increase the preference for the high-gain identifiable in the disadvantageous decks.

2) **The learning/ memory parameter (Φ)** (the updating of expectancy of value):

The second parameter represents the attention to recent outcomes as opposed to the persistence of initial choices. It is hypothesised that decision makers learn expectancies about the valence that represent the anticipated consequences of choosing cards from each deck, these expectancies improve through an adaptive learning mechanism.
When the subject chooses a deck *j*, the expectancy for that deck, Ej, is updated as a function of its previous value which reflect past experience, as well as the newly experienced payoffs on the current trial:

$$Ej(t) = Ej(t\text{-}1) + \phi \cdot [v(t) - Ej(t\text{-}1)]$$

This learning model produces expectancies that are weighted average of the past valences. The dimension of the adjustment from the prediction error, [v(t) – Ej(t)], is controlled by the learning-rate parameter, ϕ.

This parameter **ranges from 0 to 1,** *smaller values produced less discontinuity* compared to past results on the contrary, *high values* of ϕ produce *rapid adjustments with strong recency effects, but with high discontinuity compared to past outcomes and a greater influence than those recent ones.* This rapid discounting may be the reason for a tendency to select from disadvantageous decks, because these decks produce infrequent losses ~~(Yechiam et al., 2005).~~

An higher value of the updating rate parameter was found in older adults compared to younger adults (Wood et al., 2005), suggesting th that older adults show relatively large recenty effects and exhibit more rapid memory loss (Wetzels et al., 2010).

3) **The response-sensitivity parameter (C)** (choice concistency, amount of exploration):
The last third parameter explains the **choices consistency** during the task, not only on the expectancies produced by the decks, but also on the coherence with which decision maker applies those expectancies when making choices. The probability of choosing a deck, according to this model, is determined by the strength of that deck relative to the sum of the strengths of all decks:

$$\Pr[Gj(t+1)] = \frac{e^{\theta(t)*Ej(t)}}{\sum_k e^{\theta(t)*Ek(t)}}$$

Pr[G*j*(t+1)] is the probability that the model will select deck *j* on trial *t*.

The variable that determines the consistency between choices and expectations is the ɵ(*t*) and it is assumed that changes with experience (the more the experience, the more the consistency of selection).
This assumption is formalised by this function:

$$\theta(t) = \left(\frac{t}{10}\right)^c$$

where *c* is the response sensitivity parameter (Yechiam et al., 2005). When this parameter *value is higher*, *choices are focused in the high expectation decks*, if the *value is lower*, the *choices become incoherent and independent from expectations*.

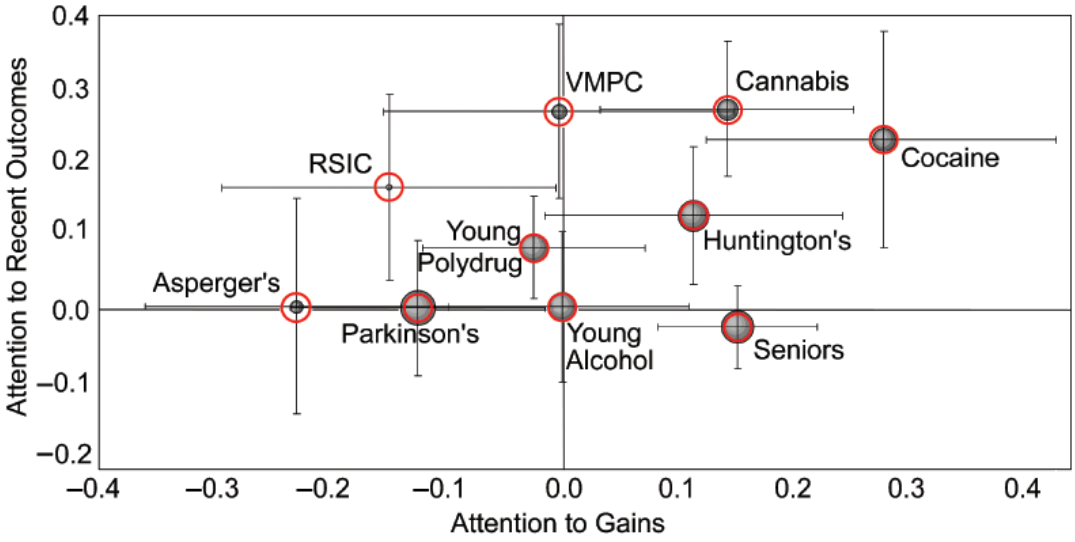
In the modelling analyses of the expectancy-valence model, the parameters were optimized separately for each decision maker individually, this occurs by maximizing the probability of the observed sequence of the 100 choices produced by the individual during the task. In this optimization process, the fit of the cognitive model is compared with a baseline model, in which the parameters assumed determine values based on the optimized proportion of choices from each decks. The measure of how the expectancy valence model adequacy is better compare to that of the basic model is represented by ***G2,*** which *is a model-fit statistic analogous to the chi-square*; a *positive value* of this parameter means that *the cognitive model performs better than the baseline model, while negative value indicate the opposite.*

2.3.2.2. The Application of the model

An example of the EVL model application is the study of Yechiam et al. (2005), conducted on a sample of 10 diffrent populations of subjects. The analyzed polupations were composed

by subjects affected by: 1) Aspergers syndrome; 2) Parkinson's disease; 3) a VMPFC lesion, 4) right somatosensory and insular cortex lesion (RSIC); 5) Huntington's disease; 6) young polydrug abusers; 7) alcohol abusers; 8) chronic cannabis; 9) cocaine abusers; 10) cocaine abusers ; the control group was composed by healthy subjects aged between 65 and 88.

Figure 6.



Note. *The figure show the mapping of the 10 populations examining by IGT according to the expectancy valence model. The circle location represents the degree of deviation between the groups and their respective control, in attention to loss versus gain and in attention to recent outcomes. The diameters of the circle are based on the proportion of the difference between the examined group and the control, in respect to the parameter that indicates choices coherence. The red rings show the limits that, if reached, indicate the absence of differencse, circles smaller than rings indicate low values of consistency parameter (from Yechiam et al., 2005).*

The results found that young polydrug abusers and young alcohol abusers showed parameters value very similar to their associated control groups while the other populations showed a variety of significant different performances compared from their controls

In particular chronic drug abusers and subjects affected by Huntington's disease were characterised by a higher attention to gains the most recent trials compared to healthy controls while normal senior subjects (average age =77), showed a significant higher attention to gain in compairison to their control group between the ages of 18 and 34.

On the contrary Parkinson's disease patients, Aspergers syndrome and RSIC patients showed a hight sensitivity for punishment. VMPFC lesion patients reported a profile characterised by both high impulsivity and cognitive rigidity showing a low adaptive learning behaviour.

TABLE 1

Percentage of Positive G^2 Values, Indicating an Improvement of the Adaptive Learning Model Over the Baseline Model, and Results of Significance Tests for the Parameters

Sample	Sample *n*	Control *n*	$G^2 > 0$ (sample + control)	Parameters significantly different between groups[a]
Asperger's syndrome	15	14	66%	W[b], c
RSIC lesion	22	12	62%	c
Parkinson's disease	20	33	75%*	—
Young polydrug abusers	39	37	49%	—
Young alcohol abusers	27	32	67%*	—
VMPC lesion	21	12	76%*	ϕ, c
Normal seniors	63	87	61%*	W, c
Huntington's disease	14	33	75%*	—
Chronic cannabis abusers	25	16	24%	ϕ, W
Chronic cocaine abusers	12	14	69%*	W

Note. RSIC = right somatosensory and insular cortex; VMPC = ventromedial prefrontal cortex.
[a]A significance level of $p < .05$ was adopted. [b]This parameter became significant after 150 trials.
*$p < .05$ in a binomial test.

Note. *The table shows the percentage of positive G2 values, indicating an improvement of the Adaptive Learning model over the baseline ones, and results of significance tests for the parameters.*

The use of expectancy-valence model for the analysis shows that an impairment at IGT, rather than reflecting a single common decision-making deficit, tend to be associated with different processes that reflect the continuous influence of attention to gains and losses, recently effects, and response sensitivity (Yechiam et al., 2005).

2.4 Impact on IGT of AGE, STRESS, GENOTIPE AND GENDER on DM

2.4.1 Impact of serotoninergic and dopaminergic system on DM

The influence of DM on dopaminergic and serotoninergic systems on decision making, both individually and in their interaction, is now consolidated by various evidence widely discussed by Rogers in a 2011 review.

In particular, the effects of dopamine at the very beginning appeared to be confined to the first part of IGT when decisions are still driven by "hidden knowledge" (that is, the phase in which the subject is guided by physiological activation instead of conscious choice) (Damasio et al., 1994), while the effects of serotonin affected only the last part of the task, when decisions are

primarily driven by conscious knowledge of which choices are advantageous and which ones are not.
As clearly stated by Bechara in 2003, these findings suggest that the "hidden" bias of the choices can be dopaminergic, whereas the conscious one may be serotoninergic.

To notice that a different genetic architecture between different type of DM (ambigous vs risky) has been shared by other authors but following evidences suggested an opposite pattern concerning the IGT (Stoltenberg & Vandever, 2010). In particular individual differences in decision-making under ambiguity (the first block of IGT choice, not the last ones) have been found to vary according with genetic polymorphism of SLC6A4, where long-allele carriers showed impairment on early trial blocks (Gu et al., 2013; Stoltenberg & Vandever, 2010; Stoltenberg et al., 2011).
Further evidence regarding the role of dopamine in DM led to the theorization of a more robust and shared model of Michael Frank in 2009. Frank focused on the involvement of the dopaminergic system in learning and in particular on the role that expression of D2 receptors has in influencing "exploitation" based on learning after choices outcomes, and that of COMT expression, has in the enancement of exploratory behavior after a negative outcome, by influencing the dopaminergic prefrontal activity.
The expression of striatal density of D1 and D2 receptors is thought to affects learning as follow: homozygous for the allele A / A of DARPP-32 gene polymorphisms (that increase striatal synaptic plasticity), shows greater learning from the positive results than the allele G carriers) while there is evidence that D2 postinaptyc receptors density, that is linked to the DRD2 gene, is implicated in learning from negative outcomes) (Santesso 2009). In this regard, studies on Parkinson's disease show that a state of dopaminegration depletion in non-medicated patients led to altered learning from the positive outcomes of choices and an increase in learning from the negative consequences of errors, while the passage to one Medicated condition overturned this model facilitates learning from the positive results (Frank 2004).
In summary the receptor activity of D1 and D2 seems therefore to have a complementary influence on learning from the positive or negative consequences of the choices, although it is not yet clearly defined whether the effects are presynaptic or post-synaptic and how D1 And D2 influence the subsequent selection of options in pallidum-thalamic patwahy. Conversely, the activity of dopamine at the prefrontal areas, probably due to its interaction with striatal dopamine, seems to play a role in shifting to a more strategic decision-making style, for example by favoring exploration behaviors also mediated by interaction with medial prefrontal sites (Ullsperger 2010). Frank's model theorizes that genetic variations of D1 expression (linked to the DARPP-32 gene) and D2 receptor (linked to the DRD2 gene) would

warrant the use, in assessments, of known behaviors derived from learning from positive and negative consequences ("exploit"); conversely, carriers of MET COMT allele (associated with a decrease in synaptic dopamine uptake) would show an increased ability to shift to alternative attitudes (as expressed by the learning rate parameter "), as a result of negative choice outcome, supporting the hypothesis that the COMT genotype could regulate exploration based on uncertainty about the consequences of a choice a (Frank 2009). However, the latter data, contradicts the study by Van den Bos of 2009 that reported that female subjects carrying the Met/Met polymorphisms of the COMT Val158Met chose more frequently disadvantageous than the Val/Val carriers at IGT (Van De Bos et al., 2009).

Probably this difference could be linked to gender differences (as described below) and to experimental setting. It has been noted that the Met/Met homozygous gives an advantage in memory cognitive tasks and in WCST (Egan et al., 2001; Malhotra et al., 2002; Rosa et al., 2004), while in emotional tasks Met/Met carriers reported greater activation of limbic areas (amygdala and PFC) after negative (but not positively) connotated stimuli (Drabant et al., 2006; Smolka et al., 2005, 2007). This mat results in a poorly processed affective stimulation, and IGT is a task that requires adequate emotional processing to develop adptive behavioral responses, in line with the somatic marker hypothesis.

There are various evidences of the influence of the serotoninergic system on DM both in clinical and healthy populations, even though they seems to be are less strong than dopaminergic ones.

The influence of a triallellic polymorphism (Lg, La, S) of the promoter region (5-HTTLPR) of the serotonin transporter gene (SLC6A4), where variant S is associated with lower availability of serotonin, has been especially explored.

Healthy SS women, opted for more disadvantaged options than other LL variants (Homberg et al., 2008) and showed a DM altered in ambiguity situations (Stoltenberg 2010). Moreover also in risky decision making has been evidenced a genetic contribution by the observations that carriers of the ss allele of the 5-HTTPLR gene made 28% less risky choices than carriers of the s/l and l/l allele whereas carriers of the 7-repeat allele of the DRD4 gene took more risks than individuals without this allele, (Kuhnen & Chiao, 2009).

It has been observed that men and women show performance differences in the IGT (van den Bos, 2013) and that in parallel the impact of the S allele of the 5HTTPLR gene on decision making is greater in women, but it remains to be understood whether this reflects more a gender difference in DM or in the functionality of the serotoninergic system (Nishizawa 1997).

Infact decisional sex differences have been related to variation in activity of the OFC and PFC as well as in serotonergic activity and left–right hemispheric activity. Sex differences in orbitofrontal cortex activity may be due to organisational effects of gonadal hormones early in life and the behavioural and neurobiological differences in the IGT between men and women

may be an expression of a more general sex differences in the regulation of emotions (van den Bos 2013).

Indeed, various studies on neurological patients and on healthy subjects show a preferential lateralization of decision making in the left hemisphere in women and the right one in men (Bolla 2004, Tranel 2005, Van den Bos 2013). It was hypothesized that this may reflect the use of different cognitive strategies between the sexes (holistic-gestaltic vs. analytic and verbal processing style) (Tranel 2005).

Concerning the interaction between the two neurotransmitter systems in Ha et al., in 2009, evaluated the influence on DM of the interaction between the 5-HTTLPR promoter gene triallich polymorphism (Lg, La, S) and the gene polymorphism of the receptor D4 dopamine (DRD4). As S and Lg are associated with a comparable level of serotonin transporter expression, two groups were considered: 'S'S' (including SS, SLg and LgLg genotypes) and non-S'S '(including genotypes SLa, LaLa, LaLg). For the DRD4 gene, two distinctly functional allelic variants have been considered (the 4R variant reduces the cAMP more than the 7R allele) for the different ability to reduce the cAMP mediator level to the limbic regions. In this area it has been seen that a substantial presence of cAMP has a dopaminergic effect (Lynch 2005). The results showed that in the presence of the S'S' 5-HTTLPR variant, patients with the 7R variant of the DRD4 gene had a better IGT performance than those with the 4R variant, suggesting that a different genotype of the serotonin transporter may affect the impact that gene variants for D4 dopamine receptor may have in the IGT's performance. Finally, independent of genotype, COMT activity is higher in males than in females (Chen et al., 2004). This implies that IGT performance of females may be generally worse compared to males (Van den Bos et al., 2013).

Even the brain derived neurotrophic factor (BDNF) seems to affect performance at DM. BDNF affects the proliferation of neurotransmitter systems, including dopaminergic and serotoninergic, neuronal survival, neuronogenesis, synaptic plasticity (Lu, 2003) and cognitive processes such as learning, memory, and decision making (Gasic et al., 2009; Yamada et al., 2002). It has been seen that BDNF (Met / Met or Val / Met) polymorphisms are associated with impaired perfomances at IGT (Kang et al., 2010) and in tests evaluating memory and executive functions (Gong et al., 2009; Rybakowski et al., 2003).

2.4.2 Impact of Stress, Adolescence and Sex in DM Modulation

During adolescence the significant changes occuring in affective neurobiology provide a plasticity to prepare the individual for independence but they also make the system highly vulnerable to the effects of environmental stress exposures. The associations between stress-

exposure and developmental changes in amygdala, prefrontal cortex, and ventral striatal dopaminergic systems during the adolescent period have been observed despite the vast differences in types of adverse exposures. (Totthenam & Galvan, 2016). These neurobiological systems appear consistently vulnerable to stress experienced during development, providing putative mechanisms to explain why affective processes that emerge during adolescence are particularly sensitive to environmental influences.

Since, as with many other psychiatric disorders, ED and in particular AN also show a high incidence rate in adolescence, in this perspective it's interestng a literary review of Gàlvan & Rahdar (Gàlvan & Rahdar, 2013) that widley discuss the effects of stress on Decision making in adolescence .

The cognitive and neural development of PFC in adolescents is still incomplete and subjected to a series of maturation processes. Moreover, after a stimulus associated with a reward an exaggerated neural response in dopaminergic prevalence regions, such as ventral striatum (also known as accumbens nucleus), has been identified; this would inevitably leads to negative repercussions in the decision-making process.

Eshel and colleagues (2007) showed that immature activity in the OFC correlated with greater risk-taking performance compared to adults (Eshel et al., 2007) and in adolescents was observed a significantly more left nucleus accumbens activity than adults during winning trials (Ernst et al., 2005).

Adolescents, then, having a great neural activation following a reward without being ready at the neural level to regulate reward-related behaviors, tend to show bias against risk behaviors and immediate rewards showing a highly dysfunctional decision style. At the same time, teenagers show an hypersensitivity to stress over children or young adults. In several studies, a marked response to stress was reported, with an increases in salivary cortisol in response both to traditional stressors (public speech or academic excellence, or experiences of peer refusal) (Stroud et al., 2009; Adams et al., 2006, Klimes-Douganet al., 2001; Gunnar et al., 2009). Considerably they also reported a greater cortisol reactivity in everyday activities such as playing video games, doing homework or doing sports (McHale et al.,2012).

Today it is believed that **stress** can potentially exacerbate behavioral bias or subjective behavioral tendencies, leading, for example, to more conservative choices in people who tend to avoid risk and favoring risky choices in risk-seeking individuals (Porcelli Delgado et al., 2009). Even if whitout decision-making tasks, numerous fMRI studies have provided additional support for the notion that brain regions commonly implicated in decision-making

(including the PFC, striatum, hippocampus and amygdala) are sensitive to stress-induced changes.For instance, under conditions of acute stress, have been reported an increased activation of the DLPFC, the ACC and the ventral striatum (Pruessner et al., 2004), a decreased activation of the OFC, hippocampus and hypothalamus (Pruessner et al., 2008), and mixed results (either increased or decreased activation) in the amygdala, thalamus and insular cortex (Wang et al., 2005; Pruessner et al., 2008; Dedovic et al., 2009).

On stressed mice, there was an induction of atrophy in the medial areas of PFC, dorsomedial and dorsolateral striatum and lateral portions of the OFC, this changes resulted in a shift in the behavior of mice from goal-directed towards habitual directed (Dias-Ferreria et al., 2009). Similarly, a human fMRI study observed that the group of stressed subjects did not choose according to the consequences of their behavior but rapidly developed abitual behavioral responses, that means that stressed individuals are unable to adapt their behaviors in relation to their needs and the information (impairment of updating). (Soares et al., 2012)

-**Gender variation** was also observed in the effects of stress on decision making, as well as a variability in the basic decision-making processes between men and women. A separate study showed that being acutely stressed during a risk-taking task increased activation in both the insula and putamen for men, but activation in these regions decreased for women (Lighthall et al., 2012).

Van den Bos summarized all gender differences in relation to DM in a 2013 review; (Van den Bos., 2013). Specifically concerning to stress, elevated stress levels indicated by cortisol levels induce IGT performance in men while women show improved performance at IGT (Van den Bos et al., 2009b). Parallel in the presence of great stress while men show an increase in risk taking, women show a decrease. These evidences may be related to a different decision-making speed in the presence of stressful conditions, with a male tendency to show greater decisional speed and a feminine characterized by longer times (Lighthall et al., 2009).

2.5 The Cognitive Bias Task

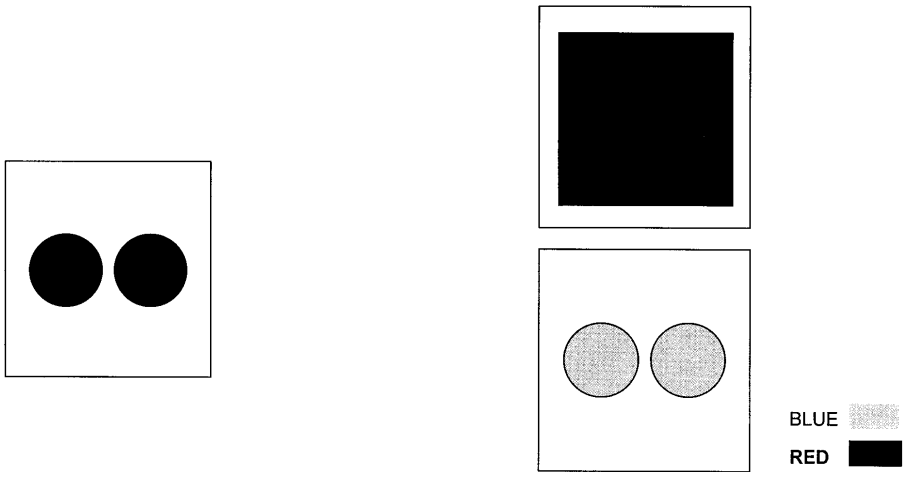
As previous said, the cognitive process controlling over daily life decisions depends upon two types of prefrontal operations: those guiding behavior by internal representations (context-dependent reasoning) and those carrying out exploratory processing of novel cognitive situations (context-independent reasoning). Specifically **context-independent decision-making** is based on the subject's preexistent representations, and reflects an attempt to produce the best possible average responses according to these stable representations, without considering the unique features of the situation at hand. On the contrary **context-dependent decision-making** tries to capture the unique or specific features of the situation, and reflects an attempt to flexibily (Goldberg & Podell 1999).

The role of the prefrontal cortex, as previous said, is thought to be particulary important further than for veridical decision making, also for decision processing in ambiguous, conflicting situations even if the two different types of decision making are based on distinct mechanisms.
Most of real life decision making situations can be considered adaptive rather than veridical; only for memory veridical decision making entails finding the correct response intrinsic to external situations (as the majority of neuropsichological experimental context require, including the IGT) and for this is considered as "actor-independent" while adaptive decision making is actor-centered and priority-based because doesn't involve a veridical but a neutral scenario in which the subject don't need to search for an advantageous option as the choice outcomes are free of rewarding or punishing values and the Goldberg's Cognitive Bias Task was designed to target this specific type of decision making.
Specifically the Cognitive Bis Task (CBT) was developped by Goldberg and collegues (Goldberg et al., 1994) to study contextual reasoning in adults with frontal lobe lesions. In this task, patients with left frontal lobe lesions showed context-independent reasoning while those with right frontal lobe lesions reported a context-dependent reasoning. The authors concluded that extreme context-dependent and context-independent response selection biases were linked, respectively, to left and right prefrontal systems in right-handed male subjects.

The Cognitive Bias Task consists of visual stimuli representing simple geometric figures characterized along five binary qualities: color (red/blue), contour (outlined/ filled), number (one/two), shape (circle/square), and size (larger/smaller). Based on the binary dimensions a

total of 32 possible geometric designs are available. All geometric designs can be related to each other based on the five binary dimensions and for each trial a similarity index is calcuated (the **similarity index** range is 0–5, depending on the overlap of the five binary dimensions). Each trial consisted of three stimuli (one target card+two selection cards) being presented on the computer screen in a vertical alignment. The target card is presented alone for two seconds, followed by the presentation of two selection cards below it (see Fig.7). Subjects were instructed to observe the target card carefully and then to select one of the two selection cards. The subject was instructed to pick the card "you liked the best; there is no correct or incorrect choice".

Figure 7.



Note. *Simple trial from the cognitive bias task (from Goldberg et al., 1999).*

The similarity indices, representing the dimensional concordance between the subject's choice and the target, are summed across trials. This generated a **cumulative score ranging** from **80 to 220.**

- a **low cumulative score** indicates that the subject consistently *chose the more different choice relative to the target*.
- an **high cumulative score** indicates that the subject consistently responded *by choosing the more similar choice relative to the target*.
- A **middle-range score** (closer to the midpoint 150) indicates that *the subject's choices are unrelated to the target or that the subject makes a relatively equal number of similar and different choices.*

Each session comprised of 60 fully counter balanced trials and the stimuli were presented in such a way that the similarity index (ranging 0–5) between the target card and each of the two selection cards was always dissimilar, forcing the subject to make a choice that is either more similar to, or more different from the target. The CBT is structured in a way that the frequency representation of each binary dimension, similarity indices, and the presentation order, are fully counter balanced.

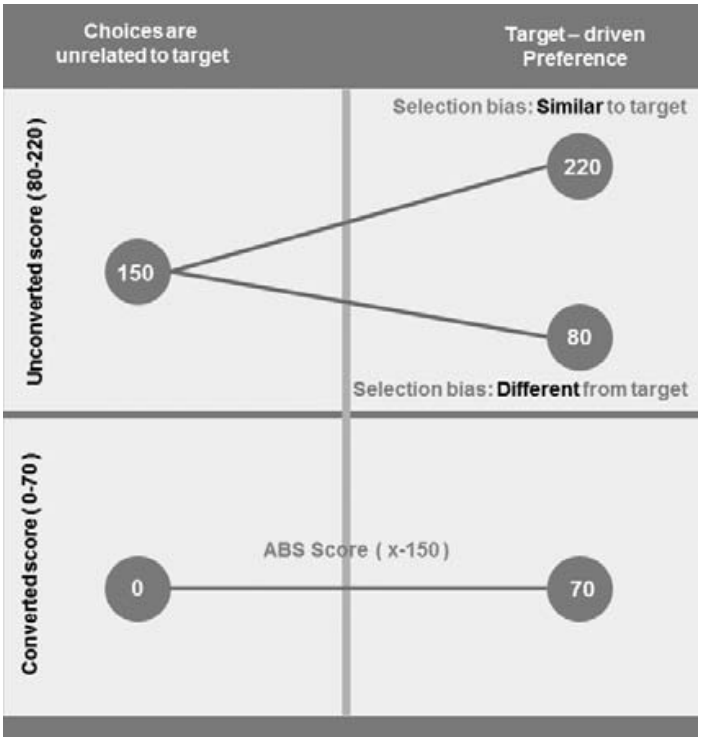
The **CBT score** is derived by summing up the similarity index between the subject's choice and the target card for all trials. The final **converted CBT score (range: 0–70)** (see Fig. 8) represents the absolute deviation of the subjects' choices from a score midpoint of 150.

-A **low converted score** indicates that the subject shows a *context-independent* decision-making bias (does not use the target card as context);

-an **high converted score** indicates a *context-dependent* decision-making bias (consistently chooses similar/different relative to the target, indicating guidance by the properties of the target).

- A **middle converted score**, (closer to 35) is the best and indicates that individuals decide considering both context and internal representations

Figure 8.



Note. *The sum of the similarity indexes (ranging 0-5) across trials provides a CBT unconverted score ranging from 80 to 220, representing the degree of dimensional concordance between the subject's choice relative to the target.*
A converted CBT score (0–70) is the absolute deviation of the unconverted score from the midpoint (150). (adapted from Tulviste et al., 2016)

2.5.1 Neural correlates of Cognitive Bias task

As discussed previous in this chapter converging neuroimaging and neuromodulatory (Goldberg et al., 1994; Aihara et al., 2003; Aoyagi et al., 2005; Shimoyama et al., 2004) evidences have confermed a lateralization of the context-dependent and context-independent reasoning hypothesized that in right-handed adult males they are respectively associated with the left and right frontal lobe. Infact patients with left frontal lobe lesions show context-independent reasoning in a cognitive bias task (CBT), while those with right frontal lesions show context-dependent reasoning.

A SPECT investigations demonstrated that context-dependent reasoning in CBT requires not only activation of both prefrontal regions, but also dynamic changes in activation from the

right to left prefrontal regions: the right prefrontal cortex (BA 9/10/46) is activated during the early portion of 30-CBT trials, followed in later trials by left prefrontal (BA 9/10/46) activation, which is associated with working memory (Shimoyama et al., 2004).

Sexual and **aging differences** have been also found in adapting decision making. In a modified CBT (mCBT), young children show more context-independent responses while adolescents and adults show more context-dependent responses suggesting that the locus of frontal cortical control would shifts from the right to the left frontal lobe as cognitive contextual reasoning develops (Aihara et al., 2003).

Concerning the **sexual differentiations** the response bias in healthy right –handed subjects at CBT is more context-dependent in males and more context-independent in females (Goldberg et al., 1994).

Considering that the PFC volume increases slowly until 8 years of age, and presents a rapid growth between 8 and 14 years of age (Kanemura et al., 2003) with the prefrontal-to-frontal volume ratio increasesing with age in a sigmoid shape, developmental studies have suggested that the timetable for the development of lateralized frontal lobe function might depends upon biologic factors, as seen in sexual dimorphism of human brain (extending beyond the systems directly linked to reproductive behavior), handedness, and lesion evidence (Aoyagi et al., 2005).

The undisputed role of the DLPFC in non veridical task and in particular a major role of the left DLPFC has been suggested as both non veridical and visuospatial working memory performances are supposed to share demand for the right DLPFC resources (Tulviste et al., 2016). In this rTMS study the stimulation of bilateral DLPFC regions resulted in a bias towrd context indipendet reasoning that was considered characteritic of rather posterior (parietal) than frontal lesions. This result lead the authors to speculate that the stimolation of the left and right DLPFC may trigger posterior lesion-mimiking effects in decision making in healty subjects by exerting suppressing effects on the parietal lobes. This result infact are in line with the parietal cortex lesion effects documented by Goldberg (1994). The parietal cortex infact is connected to the DLPFC through the superior longitudinal fasciculi from which it receive inputs and in this study the effect of treatment was major in the left hemisphere, consistency with the lateralized parietal lesion effects (Goldberg et al. 1994), in addition dorsolateral prefrontal and posterior parietal regions are part of the large-scale Central Executive Network known to activate together (Toro et al. 2008).

CHAPTER 3
DECISION MAKING IN ANOREXIA NERVOSA

3.1 DM IN ANOREXIA NERVOSA

The study of decisional processes in Anorexia nervosa (AN) is relatively recent; the first group which explored this research path was the Cavedini et collegues' one (2004), starting from the neuropsychological similitudes observed between AN and obsessive-compulsive disorders (OCD) spectrum, assuming that AN could have belonged to this disease spectrum.
AN group showed worse decisional performances at IGT in comparison to healty group (HC) and the scores weren't correlated with illness severity, BMI or subjects age. In addiction the analysis of decisional strategies, revealed that rather than a specific strategy, patients seemed to randomly select decks perhaps because of an inability to performe the task or for a lack of cooperation with the test. Restrictive AN patients performed worse than binging/purging AN (ANbp) ones, with a clear predilition for disadvantageous decks in AN and the absence of a specific strategy in ANbp. The authors pointed out a parallelism between test results and behavior shown by AN patients in everyday life since they appeared of being unable to modulate food choices on the basis of long-term consequences, preferring immediate gratification and the reward derived from the reduction in caloric intake. Similarly **OCD** patients seemed unable of choosing on the basis of a future perspective, remaining trapped in the need to immediately resolve the anxiety caused by their obsessions. Actually, a common or overlapping neural substrate of the two disorder have been suggested by findings of familiar co-occurrence of eating disorders and obsessive compulsive disorder (Halmi et al., 2003).
Further research by **Cavedini et al. (2006)** examined (with the IGT) if the evaluation of decision making in patients with AN might be useful to predict the efficacy of the treatment of the disease. This connection was born from the hypothesis of the existence of a correlation between anorexia nervosa and obsessive-compulsive disorders, since patients with OCD with poor performance at Gambling Task seemed to respond poorly to therapy with serotonin reuptake inhibitors (Cavedini et al., 2002). The authors of that study reported that AN patients with a preserved decision making benefited from a cognitive-behavioral therapy programme based on operanting conditioning, while AN patients with a poor IGT performance had shown a worse prognosis; moreover they didn't detected significant outcomes differences between patients treated with SSRIs and those who hadn't undergone drug therapy. This study also observed that the worsening in decision making remained stable regardless of the cinical outcome of the treatment. This result suggests that the decision-making ability can be

considered as independent of the primary etiopathogenetic mechanisms of AN and that it can rather specifically correlate with the individual characteristics of affected subjects, influencing the expression of the disorder (restrictive vs. purging) and treatment outcomes. **Tchanturia et collegues (2007)** were the first to investigate decision making in anorexia nervosa using the Iowa Gambling Task and skin conductance responces (SCR) measurements in a group of patients of both sexes with AN, a group of long term recovered AN and a group of healthy subjects, showing results in line with the somatic marker hypothesis. In fact, acute AN group showed both worse performance at IGT than the other two groups, and a low cutaneous anticipatory response before card selection compared to controls. In addition, the skin response after selecting a card associated with a loss was reduced in relation to healthy subjects, suggesting a reduction in the ability to modulate appropriate emotional stimuli for gains and rewards. An interesting data emerging from the same study and contradicting what Cavedini and colleagues (2004) highlighted is that long term recovered AN patients didn't show the characteristics of the diseased subjects, behaving as HC both in the test results and in the amplitude of SCRs developed. In addition, the study showed an important correlation between depression level in the examined subjects and their performance at the test, and it was therefore impossible to determine with certainty the relative contribution of affective and cognitive symptoms to the IGT. However, the relationship between depression and performance at IGT remains broadly debated; for example Dalgleish and collegues (2004) and Garon and collegues (2006) report that depression has no effect on the of the IGT performance. In addition, the authors explain the decreases seen in both anticipatory and response to loss SCR in AN as a reflection of a centrally mediated low sensitivity to punishment, in line with the Rolls (1996) and Hornak (2004). According to their model AN patients would have an impaired association between the reinforcement properties of the stimulus and their action in the IGT. This theoretical framework would thus explain the apparent insensitivity to harmful stimuli (high threshold for pain, hunger, health risks associated with malnutrition) shown by patients with AN as mediated as a centrally mediated low sensitivity to punishment. Interestingly, subsequent fMRI studies on AN patients have shown an increased neural activation in right anterior insula and DLPFC during pain anticipation, further than and exaggerated responses to punishment (pain and monetary losses) in the DLPFC, and the anterior, mid-, and motor cingulate (Bischoff-Grethe et al., 2013; Strigo et al., 2013).

The only other study that analyzed the **SCR** associated with IGT in Eating Disorders is that of **Liao et al., (2009)** in a group of people with BN, one with AN and one of healthy controls (HC). The results showed an IGT impairment in both patient groups compared to HC; in this case the performance of AN was comparable to those of BN and the performance of the three groups diverged between the 41st and 60th selection, showing how only the HC group was able to learn with the preceding of the task. Furthermore, there was **no correlation between**

performance at IGT and BDI depression levels while a strong correlation with even a predictive value over the performance at IGT was that of obsessive symptomatology mesured with OCI (Obsessive Compulsive Inventory). SCR data, on the other hand, seems to be supportive of the Somatic Marker theory.

Indeed, although the IGT performance of both EDs group were worse than HC, only the AN group showed a decrease in the anticipatory SCR while the BN group behaved as the HC. The authors, therefore, attribute the AN decrease of SCR as due to low BMI-related metabolic factors and causing, for example, for example, a lower temperature or lower skin conductivity. This result was in line with Tchanturia's work (2007) who observed in long term recovered AN an increasing in SCR as well as an improvement on the IGT. Finally, concerning to the sensitivity to punishment or gain, the evidence of a greater SCR in response to losses observed in all the three groups and the positive correlation between its amplitude and the amount of loss indicates that both AN and BN are equally sensitive to punishment, even though they seem unable to learn. This result suggests that even in HC the responses to loss are more unpleasant than how responses to winning can be more pleasing as stated by the broad tenet of neuroeconomics.

The results of the work published by **Brogan et al. (2010)**-analyzing the performance of IGT of 22 patients with AN, comparing with those of 17 patients with BN, of 18 obese patients and 20 healthy controls, showed instead even worse performances of the test in the three clinical groups than the group control.

Guillaume (2010) has published aninteresting study exploring the relationship between DM and the possible role of its confounding factors by analyzing the performance of a group of 49 AN patients divided into two subtypes: restrictive and purging, 38 BN patients and 83 HC. The sample was entirely made up of euthymic patients not in pharmacological treatment.The results reported the absence of significant differences between the performance of AN vs HC and Purging vs restrictive AN in contrast to the results of previous studies. Moreover, no significant correlations emerged between any clinical dimension in AN (such as perfectionism or body dissatisfaction or overall EAT score), and performance at DM, although correlations with any coexisting obsessive-compulsive symptoms or alterations of other executive functions such as as attention and memory (thought to have a negative impact on the performance at the IGT), were assessed. BMI didn't even affect IGT scores. In contrary, HC group performance resulted broadly overlapping with those presented in previous studies, leading the authors to believe that the basis of inconsistency between studies could be a sample difference in relation to the confounding factors considered **(depression and pharmacotherapy).**

The **Abbate-Daga study (2011),** including exclusively restrictive subtype of acute AN, shows results in line with previous studies. In particular, the patient group had significantly worse performance at IGT than the HC group and regardless of the severity of the depressive

state. Patients showed the tendency to select from disadvantaged decks in the first 50 choices, with predilection for high-rewarding cards, irrespective of whether subsequent losses would be greater, and this feature has been considered by the authors as a further proof of cognitive inflexibility in Verbal domain (inscribed in the difficulty of inhibiting wrong responses). This executive function have been tested in this study with Hayling Sentence Completion Task (HSCT). In the second part of the task (after the 50th selection), after adjusting the data for BMI, the differences in IGT performance don't remain significant**, highlighting as decision making is only partially independent of the level of malnutrition.**

The study design of **Danner et al., (2012)** was focused on investigating the presence and the relationship between weak central coherence and cognitive inflexibility (the two executive function (FEs) probably more related to the rigid processing style identified in a subgroup of patients with AN), and decision-making, even in the hypothesis that cognitive rigidity could interfere with learning and thus explain in part the weakening of decision-making. Another purpose was to clarify the relationship of these FEs with the state of the disease, so as to identify them as state or trait alterations. The sample consisted of 16 women with acute acute AN (duration of illness of at least 2 years),15 patients who had been treated for at least one year (at least 12 continuous menstrual cycles and BMI recovery), and 15 healthy controls. The results actually showed the presence of a set-shifting and decision-making impairment in patients compared to controls but not of central coherence. The latter, however, was significantly weakened in a subset of patients, (both acute and remitted), which also showed cognitive inflexibility, in line with clinical observations that some, but not all, patients with AN show cognitive rigidity. Decision-making, on the other hand, was unrelated to the other two FEs impairment, thus disconfirming the hypothesis that a rigid cognitive processing style, interfering with implicit learning processes, may reflect on a dysfunction of decision- making processes. Finally, the evidence that alterations in Dm and cognitive flexibility were present in both acute and remitted patients, supported the hipotesis that both the FEs could represent **more a trait alterations, and therefore stable in time, than a status one.** However other two studies have investigated DM in acute and remission (Cavedini et al., 2006 and Tchanturia et al., 2007) and show discordant results (the first in line with the hypothesis of DM alteration as a trait alteration and The second that disconfirms it).

To investigate the presence of a common pattern of FEs impairment among the so-called **"Extreme Weight Conditions" (EWCs)** such as AN and Obesity (OB) (according to the recent theory that would see in the EWCs a continuum of pathologies that share both biological risk factors and intermediate neurocognitive phenotypes) ,the **Fagundo** group **(2012)** compared the performance of a large acute AN, OB and healthy control (HC) group, in relation to cognitive flexibility (WCST), response inhibition (Stroop color and world test) and decision making (IGT). The results actually appeared in the direction of an impairment of executive profile in EWCs . Which could be linked to the development and maintenance of

these pathologies. Specifically by deepening the performance of the IGT, the results showed an improvement in the HC group during the task and absent in the other two groups that showed a similar tendency to seek immediate gratification to future gains though the mechanisms implicated by the authors may be different. Specifically by analyzing IGT performance, the results showed an improvement during the task only an in HC but not in the other two groups. that showed a similar tendency to seek immediate. The latter two groups showed a similar tendency to seeking instant reward regardless of future losses, even though the mechanisms involved are different between groups.

The OB performance would seem more impulsivity related, as confirmed by both the stroop results and self-administered questionnaires, with a consequent difficulty in delaying gratification. The authors suggest intead that in AN behind the dysfunction reported at IGT there is more an attitude of rigidity and inflexibility that prevents them from adapting to change. WCST also showed a common dysfunctional profile between An and OB, unlike the HC group. Finally, the absence of correlation with BMI suggested exclude a role of malnutrition in the observed dysfunctions.

Galimberti (2013) confirmed and replicated the concomitant alteration of set-shifting and DM in AN, providing new perspectives for the endophenotypes search. The sample was composed of 29 AN patients (without concomitant depressive episode orundergoing antidepressant drugs), with their relative first-degree relatives (mothers or sisters) and 29 control subjects with their first healthy family members degree. The FEs assessed were Decison Making (IGT), set-shifting (WCST) and planning (Tower of Hanoi). The findings identified impairments at both IGT and WCST in AN patients and their family members, while planning was preserved. As in other studies, these results were **independent of BMI. Concordance analysis strongly suggested that these impairment at IGT and WCST aggregate in AN families**. The identified dysfunctional executive profile shared by women with AN and their unaffected relatives, supported the hypothesis that they may constitute biological markers for AN and then possible vulnerability factors. By analyzing the genetic effect through the inheritability index, there was no evidence of genetic influence on the WCST, while the IGT's inheritance index suggested the presence of genetic effects that affect this measure, by making DM, as already previously set-shifting was considered, to be an AN candidate endophenotype.

Garrido et al (2013) specifically investigated the relationship between Dm and impulsivity measured with BIS (Barratt Impulsiveness scale) within the two restrictive and bulimic/purging (B/P) subtypes (both AN and BN) of a group of 71 ED patients, comparing them with a healthy control group (HC). In line with findings of the two previuos studies exploring the difference between the two subtypes of AN (Cavedini et al., 2004 and 2006), in this study, patients with a restrictive subtype had the worse IGT performance in comparison to both controls and bulimic /purgative subtype. This latter group in this work also showed,

differently from the restrictive one always choosing from the disadvantaged decks, a minimal, though not meaningful, effect of learning, highlighting a difference between the mechanisms driving decision making processes in the restrittive and b/p patients. This evidence is reported by the authors as supportive to Liao data (1999) of the absence of a reduction in SCR anticipatory in a BN group (which showed behavior similar to the control group), opposed to the evidence that in the AN, (in association with alteration to IGT), there is a reduced skin advance response in high risk choices (Tchanturia 2007, Liao 2009).
The Garrido results also showed an independence between the performance of the IGT and the severity of the disease (BMI), illness duration (in years) or early onset. Impulsivity was negatively correlated with the IGT performance only in the B/P group, thus demonstrating that more impulsive ANBP or BN patients show a worse decision-making.
Lindner (2012) compared the performance at IGT in a 100 An remitted patients (at least one year , BMI between 18.5 and 26 kg/m^2 with regular menstrual cycle and no significant cognitive nutrition such as fear of weight gain, body distortion or self-esteem based on weight/body shapes) and 100 healthy controls. Remitted patients performed at IGT better than healthy control group, while planning (investigated through the Tower of London test) was worse in the patient group. These results contrast with those reported by Tchanturia (2007) and **Bosanac (2007),** (which, however, didn't identify any significant difference between remitted and HC group), and with Cavedini study (2006) that had revealed worse performance in patients perduring also after treatment (is Remarkable that also Tchanturia reported a better IGT performance trend in An patient group, even though not statistically significant). The authors argue as a possible explanation of these incongruity of results, the definition of remission, which in this study is defined both in physiological, behavioral and psychological terms, as well as the number of the sample size larger in this study. The interpretation of the observed best IGT performance in patient group and in particular in the 5th block (consisting in the last 20 selections, where game conditions should be more transparent due to implicit learning of the lower risk asocciated with the first two deck in comparison to the other two) is that best patient performance can reflect a less risk-oriented attitude than controls, in line with other evidence (Fahy 1993, Kaye 1995) and with an higher harm-avoidance. Finally, there was an effect of BMI and obsessive symptomatology on IGT performance but not of depressive symptoms, impulsivity or severity of eating symptoms on IGT. **Tchantura in 2012,** focused on finding **gender differences in DM** in AN by analyzing the performance of two-sex AN versus a healthy control group. The results showed that both AN women (AN f) and male patients (AN m) had worse performance at IGT vs HC and no difference was detected between AN m vs AN f. The only difference between the two groups was a greater impulsivity measured whit BET (Barrett Impulsiveness Scale) in AN m, but impulsivity didn't correlate with the performance at IGT.
The only study published so far that used a cognitive modeling called Prospect Expletance

Valence Model (**PVL),** an Elaboration of the EVL in the analysis of the performance of IGT in ED, is the **Chan study of 2014** that compares patients with AN, BN and Healthy controls, with the aim tof identifying differences in the mechanisms underlying DM in these groups. The results reported in AN group revealed an impairment in the learning/memory parameter, indicating that patients tended to choose on the basis of more recent experiences.

The use of the cognitive model, however, doesn't make it clear whether the impairment concerns explicit or implicit learning (which happens in a non-conscious way), the latter considered to be the probably more involved at the moment.
The other interesting aspect was that BMI was positively correlated with the learning/memory parameter, therefore the authors suggest **that malnutrition may in part affect the learning / memory capacity and thus negatively impacts on decision-making process**.
In BN group, instead, the perfromances at IGT were characterized by a greater sensitivity to rewards than to losses compared with the in comparison with HC.
In relation to performance at the IGT, the AN group showed marginal impairing in performance compared to the control group whereas those of the BN group were significantly impaired.It was therefore concluded that these differences between groups could derived from different mechanisms such as memory/learning deficts in AN and alteration of reward and sensitivity to punishment in BNs.
In the longitudinal study of **Bodell et al. (2014),** aside from IGT, AN patients completed a battery of assessment including demographic information, self- report questionnaires, interviews, neuropsychological tests and MRI scans.
This study found an impaired decision-making of low-weight women with AN compared to control group, besides they not found significant improvements with weight restoration in overall AN sample. The impairment in decision-making during the acute phase of the illness was associated with lower BMI and a reduced medial left OFC volume and, the majority of poor performing patients did improve the performance on IGT with weight restoration, thus authors hypothezise that decision-making dysfunction in AN might be an impairment consequent to the malnutrition. The limitation of this study is a very small sample size that cannot allow to reach a representative distribution of the population and the data to be generalised on AN population.
The third longitudinal sturdy **(Steward et al.,2016)** support the hypothesys that impaired DM in An might depend on clinical state rather that contituting a trait vulnerability since enduring remission from AN (after one year of follow up) can reverse DM impairment.

In the same year **Perpina et al.,2016** replicate the deficitsat IGT in a group of both ED (AN, BP and EDNOS for AN) and Obese patients regardless of age, gender, BMI, year of education mood, obsessive symptoms and severity of eating symptoms even though anxiety

and depression reported a significant associations with the neuropsicological measures (IGt and WCST).

In 2015 Danner and collegues **(Danner et al., 2015)** focused on the influences of negative affect on decision making in a goup of An patient and healty controls; the resultes revealed a DM impairment only in ANBP group while ANR and Healthy group were both able to improve learning in the procedinig of the task, highlighting the importance of considering different AN subtypes when examining DM; moreovere they observed that **differences in negative affect didn't influences DM performances.**

Matsumoto et al., 2015, observed ad impaired DM only in BN group in compairison to HC but not in An group; they also found that an increasment of anxiety, depression and eating/weighting concerns would predict poorer decision making.

Aloi et collegues too **(Aloi et al., 2015)** found that BED and not AN, worse performed at IGT further than WCST.

In summary, there are many evidence supporting an impairment in decision-making in the AN but at this time is still unclear the relationship with the disfunctions of any further executive functions, the role of malnutrition, and therefore if altered decision-making can be considered or not a pre-existing and favoring element in the development of EDs, and the role of depressive symptoms, serotoninergic function that is genetically dependent or induced by concomitant use of SSRIs

Other studies have also shown that performance in decision making is influenced by genetics, (Jollant 2007 a and jollant 2007 b) but no study had calculated the Heritability Index, except that of Galimberti.

Data on performance in DM in patients with AN are still contradictory, some studies report a impairment of this executive function studied through IGT (Cavedini et al 2004, Cavedini et al 2006; Tchanturia et al 2007; Brogan et al 2010; Abbate Daga et al., 2011) while others hadn't identified any significant differences in performance between patients with AN and healthy controls (Guillame et al, 2010; Lindner et al 2012).

Guillame (2010), suggested that impairment in decision-making identified in the previous ones could be attributed exclusively to the presence of **potential confounding factors** such as significant **depressive symptoms or drug presence**, conversely Adoue (Adoue et al.,2014) concludes that the decisional impairment in AN seem unrelated to potential co-occurrent major depressive-disorders.

Tchanturia et al 2007 hadn't identified any SSRI influence on IGT performance in AN

patients. Indeed, there is evidence of **involvement of the serotonin system** in decision making (Jollan et al., 2007 A) and 2007 b), suggesting that SSRIs can affect these neurocognitive functions.

Concerning to the **effect of weight-recovery** on AN decision-making performance, studies have analyzed this executive function in AN patients with weight recovery or remission (Tchantura et al 2007; Jollant et al., 2007 and 2007 b), identify an absence of significant difference in IGT performance among patients with weight gain and healthy controls. This results contrasts with those of the Galimberti study 2013 where poor performance was independent of BMI.

This inconsistency could be explained as a difference in the study designs used in the previous literature.

Lidner (2012) has suggested that the cross-sectional study design used in these studies does not allow to explore whether the improvement in decision making performance in remitted or weight recovery patients **may be pre-existing** for treatment as well. Only one study evaluated DM's performance before and after treatment (Cavedini et al., 2006) and the results revealed that decision-making impairment was stable over time and independent of physical or clinical changes achieved after treatment.

Even the evidence of a decision-making **inheritance** seems to favor a pre-existing impairment to a consequence of the disease. However, further studies are needed to attest and confirm this hypothesis.

Few studies have investigated **SCR** in AN, actually showing a SCR decreasing but its relationship with BMI seems to be more likely to be caused by metabolic factors (decrease in temperature / skin conductance) than to find support in the somatic marker.

The only metanalyses on IGt in ED conducted in 2015 by Guillaume et al., 2015 concludes that in comparison to HC, IGT perfomance are worse in ED An, BN or BED) and that An restrictive type revealed the worse perfomance . Even though poor DM was more pronunced in acute phase of the illness than in recovered state (AN recovered showed a decisional profile similar to HC), the nutritional status during the acute phase wouldn’t seem to influences DM skills .

The study assessing decision making with IGT in AN published at today are summarized in Appendix 1.

CHAPTER 4
THE RESEARCH

4.1 Study aims

The aim of this study is:

1) To asses different subtype of Decision-making in a very large sample of patients affected by anorexia nervosa (AN) and Healthy control (HC);
2) To better understand whether age, demographic features, BMI, illness duration, AN subtype (restrict vs Binge-purging) and neuropsychological profile in particular cognitive inflexibility are associated with differences in decisional profile in AN en HC groups;
3) To explore the putative role of decisional assessment in An outcome after treatment;
4) To explore the impact of the genetic profile on decisional performance in AN and HC;
5) To apply cognitive modeling to deeper analyze the IGT performance in both An and HC ;
6) To explore the correlation between Resting State connectivity and the different subtype of decision making object of the study .

Our hipotesys is that AN group would show a decisional and neuropsychological impairment indipendent of the features mentioned above.

4.2 Materials and methods

The sample

The participants of the study were 310 Caucasian female patients with a lifetime diagnosis of anorexia nervosa (AN), and 301 healthy women. Patients were recruited among those in outpatient treatment at the Eating Disorders Unit of Padua Hospital, Italy, in the period between January 2009 and April 2017 according to inclusion/exclusion criteria and willingness to participate.

For patients, criteria for participation were: a lifetime diagnosis of AN according to the *Diagnostic and Statistical Manual of Mental Disorder (Fourth Edition, DSM-IV,* and *Fifth Edition, DSM 5,* American Psychiatric Association, APA, 1994, 2013); more than 14 years of age; written informed consent from patients and, in the case of patients younger than 18, from

one parent. All the patients had to meet lifetime criteria for the diagnosis of AN according to both DSM–IV and DSM–5 (APA, 1994, 2013).

Exclusion criteria were: traumatic brain injury, lifetime presence of any neurologic or systemic illness independent from the eating disorder; lifetime presence of a psychiatric diagnosis (except for depressive and anxious disorders), presence of alcohol or substance abuse, psychoactive medication, except for the use of antidepressants, moderate mental impairment (Intelligence Quotient <60), any contraindication for MRI.

According to the evidences regarding the different decisional profile observed in early adolescents and characterized by impulsivity and major sensivity for reward of gains, thought to coincide with asymmetric neural development with overactive striatal regions and a slower developing of the inhibitive frontal cortex (Smith, Xiao and Bechara 2004), we divide the whole sample into a group aged between 14 and 18 and defined "adolescent" and a group aged more than 18 define as "adult".

Table 1. *Characteristics of adolescent and adult samples*

	ADOLESCENT GROUP (n=141)		ADULT GROUP (n=470)	
	Adolescent girls with AN (n=109)	Adolescent girls (n=32)	Adult women with AN (n=201)	Adult women (n=269)
Age (years)	16.8 (1.2)	16.5 (1.3)	26.2 (6.6)	26.8 (5.5)
Body mass index (kg/m^2)	17.1 (2.5)	21.0 (2.4)*	18.1 (3.0)	21.5(2.9)*
Lowest BMI	15.4 (1.7)	19.5 (2.1)*	15.2 (1.8)	19.3 (2.1)*
Duration of illness (months)	16.4 (13.3)	-	67.71 (66.7)	-
Age of onset	14.87 (1.4)	-	18.69 (4.7)	-
Edinburgh	54.5 (35.0)	61.1 (27.3)	54.9 (40.6)	62.0 (35.4)
Education (years)	10.3 (1.4)	10.3 (1.5)	14.7 (2.2)	15.9 (2.3)*
HSCL Depression	1.4 (0.9)	0.7 (0.6)*	1.6 (0.9)	0.6 (0.5)*
Trait anxiety	51.9 (12.8)	42.2 (11.0)*	54.9 (11.2)	39.3 (8.7)*
State anxiety	43.0 (12.0)	36.2 (8.8)*	43.1 (11.5)	33.7 (7.0)*
Current underweight status (BMI<18.5)	84 (77%)	0%	121 (60%)	0%
Restricting type	86 (79%)	0%	112 (55.8%)	0%
Amenorrhea	81 (74%)	0%	90 (48%)	0%

* $p<0.001$

The healthy controls were recruited from the general population; exclusion criteria were: a lifetime history of eating disorder, BMI below 18, presence of a first degree relative with a lifetime eating disorder, traumatic brain injury, presence of any neurologic, psychiatric or systemic illness; presence of alcohol or substance abuse; psychoactive medication, any contraindication for MRI.
The study obtained the approval of the local ethics committee and all the participants gave informed written consent for the use of data in an anonymous form; an informed consent signed by parents was required for participants under 18. Table 1 shows the clinical and sociodemografical variables of the sample.

A subgroup of 69 subjects (35 patients with AN, 34 healthy controls) participated in the resting-state functional connectivity study. In this subsample, all patients with AN were underweight (mean BMI =15.8 ± 1.8; range 10.4–17.5). Table 2 shows the Characteristics of participants to the MRI study

Table 2. *Characteristics of participants to the MRI study*

	AN patients (n=35)	Healthy women (n=34)	
	mean (SD)	mean (SD)	t (p)
Age (years)	26.6 (7.3)	25.5 (6.0)	0.61 (0.544)
Education (years)	14.37 (2.2)	15.47 (2.4)	-1.97 (0.052)
Body mass index (kg/m2)	15.8 (1.8)	21.7 (3.07)	-9.87 (0.000)
Lowest body mass index (kg/m2)	14.0 (1.8)	19.8 (2.6)	-10.65 (0.000)
Age at onset (years)	18.5 (5.0)	-	-
Edinburgh score	58.7 (37.8)	54.5 (44.3)	0.42 (0.675)
Depressive symptoms (SCL)	1.4 (0.7)	0.7 (0.6)	3.93 (0.000)
State anxiety			
STAI S	44.5 (12.3)	35.1 (7.4)	3.8 (0.000)
STAI T	56.43 (9.86)	39.88 (9.42)	7.12 (0.000)

4.2.1 Clinical assessment

All participants (patients and controls) were measured in weight and height and underwent a routine baseline assessment that included the administration of the following battery:

- the eating disorders section of the Structured Clinical Interview for DSM-IV (**SCID**; First, Spitzer, Gibbon, & Williams, 1995);

- the Italian Questionario per i Disturbi dell'alimentazione (**Q.D.A.;** Santonastaso, 1995), a self report questionnaires exploring the weight history, body image, eating behaviour, traumatic events, clinical and medical personal and familiar history and sociorelational situation; weight suppression was defined as the difference between highest ever body mass index and current body mass index

- The validated Italian version of the Eating Disorder Inventory (**EDI**; Garner et al., 1983), to assess the eating psychopathology misuring the following subdimension (drive for thiness, body dis- satisfaction, bulimia, ineffectiveness, interoceptive awareness, perfectionism, maturative worry);

- The general psychopathological features were investigated through the Hopkins Symptoms Check List (SCL-90 Derogatis, Lipman, Rickels, Uhlenhuth, & Covi,1974) a self report questionnaire which investigates the presence and severity of psychiatric symptoms, using a Likert scale (ranging from 0 to 4) . The following subscales were analyzed in the present study:

- Somatization (SOM): riflette disturbi che insorgono dalla percezione di disfunzioni corporee;
- Obsessivity-Compulsivity (O-C): Thoughts, impulses, actions experienced as incoherent and unwanted by the subject;
- interpersonal sensivity (IS): Feelings of inadequacy and inferiority towards other people
- Depression (DEP): Summarizes a broad spectrum of concomitant symptoms with a depressive syndrome;
- Anxiety (ANX): A set of symptoms and behaviors related to a high manifest anxiety;
- Anger/Hostility (HOS): Thoughts, feelings and actions characteristic of a state of anger and irritability
- Phobic Anxiety (PHOB): Persistent response to irrational and unproportionate fear concerning people, places, and specific situations, leading to avoidance / flight;
- Paranoid thought (PAR): Disturbance of thought characterized by suspicion and fear of a loss of autonomy mixed with hostility
- Psycoticism (PSY): Even though including the primary symptoms of schizophrenia (hallucinations, extraneous thought), is to be considered as a continuous dimension of human experience, characterized by schizoid retreat, isolation and lifestyle;
- Sleep Disorders (SLEEP): Insomnia, Sleep Disorder, Early Awakening

- the State-Trait Anxiety Inventory (**STAI**; Spielberger, Gorsuch, & Lushene, 1970), which measures both state and trait anxiety, consisting in two short sub-tests of 20 items, whith a four-level scale of intensity:

1) The STAI-S subtest refers to the "anxiety state" at the administering time and was constructed by choosing items that obtained the highest average scores in a stressful situation and lower average scores in a relaxing one

2) The STAI-T subtest measures anxiety as a trait, (ie the subject's tendency to produce anxious reactions under specific conditions). This part was built by selecting highly correlated items with Taylor's Anxiety Manifest scale and IPAT Anxiety Scale.

- Tridimensional Personality Questionnaire (**T.P.Q.;** Cloninger, 1987); Self-evaluation tool consisting of 100 dichotomous items (true / false) to investigate the temperamental aspects of personality

a. Novelty seeking: exploratory excitability / stoic stiffness (NS1), impulse / reflection (NS2), extravagance / confidentiality (NS3), disorder / regimen (NS4)

b. Harm avoidance: anxiety / uninhibited optimism (HA1), fear of uncertainty / safety (HA2), mistrust of strangers / sociability (HA3), fatigue and asthenia / energy (HA4);

c. reward dependence: sentimentality / insensitivity (RD1), obstinacy / indecision (RD2), attachment / detachment (RD3), dependency / independence (RD4);

d. Persistence

- Edinburgh Handedness Inventory (Oldfield, 1971): for handedness assession ;scores ranged between - 100 (fully left-handed) and + 100 (fully right-handed).

4.2.2 Decisional process assessment

- Iowa Gambling task (Bechara et al., 1994) The participants have to make a series of choices from a set of four computerized decks of cards (A, B, C and D) trying to achieve the goal of maximizing a monetary gain starting with a credit of 2000 $. Every selection is associated with an immediate reward and with an occasional penaltywhich differs in frequency and magnitude across the decks. In particular, the first two decks (A and B), associated with high reward but with even higher unpredictable losses, are disadvantageous decks, resulting in a negative long-term outcome. On the other hand, decks C and D are advantageous decks since they are associated with lower immediate rewards but with even lower occasional losses. Players are not given any information about the decks and must learn from experience to select advantageously; they performed a single block of 100 trials, divided into five blocks of 20 trials. IGT was used to measure the decisional process under uncertainty: after the 40th selection it's supposed to switch from the assessment of under ambiguity to the under risk ones (Brand, Labudda, & Markowitsch, 2006).

We analyzed the IGT performance using several indices:
(1) **the IGT net score,** that is the difference between the total number of selected cards from the advantageous decks (C e D) and from the disadvantageous ones (A e B);
(2) **the net score for each successive block of 20 cards.** Moreover, IGT performance was dichotomize into "poor" and "good" according to different cut-off as following: IGT net < 10 (Bechara et al., 2001).
To better understand the different psychological processes that underlie performance on the IGT we used the **EVL model,** designed by Busemeyer and Stout (2002). This model uses three parameters to formalize its assumptions about participants' performance on the IGT.
-The first is the **motivation parameter *("w")*** that reflects the attention to gains or losses, and it ranges from 0 to 1. Attention to losses is indicated by smaller values, while values closer to 1 reflect attention to gains.
-The second parameter, the **expectancy learning (updating expectation) ("*a*")** refers to the attention that the subject poses on the more recent result experienced in contrast with those that he poses on results of past selections and it ranges from 0 to 1, according to the expectancy of each deck derived from the outcome of previous experience of choosing such deck. Smaller value suggests a lower updating, while higher value shows a major influence of recent choice's outcome rather than past outcome.
-The third parameter, **choice consistency (response–sensitivity parameter) ("*c*")** determines the sensitivity of the choice probabilities to the expectancies and it ranges from - 5 (random choices) to + 5 (consistent choices that are highly dependent on expectancy).

- **Cognitive Bias Task.** (Goldberg et al., 1994) The computerized version of the CBias was adopted. Participants are asked to sit in front of a computer screen and look at the first stimulus (one card appears at the top of the screen). When the next two stimuli appear (two more cards appear just below the first), participants are asked to choose one of the two last cards, the one they prefer. Participants are told that there is no correct or incorrect choice, but they were invited to answer quickly because the choice was supposed to be instinctive. The target-card (first card) consists of a card showing simple geometric stimuli. Each stimulus is characterized along five binary dimensions: color (red/blue), shape (circle/square), number (1/2; one/two), size (large–larger/small–smaller), and contour (outlined/filled with a homogeneous color). The next two cards (choice-cards) differ from each other in their greater or lesser similarity to the target-card. The target-card is presented alone for 2 s and is then followed by the simultaneous presentation of the two choice-cards. The target-card remains on the screen with the two choice-cards to remind the subject of the relative context. The target-card is considered to represent the cognitive context that subjects use to make their response choices. The task is very easy (e.g., "Choose the card you like best"), and there are no external constraints or rules (e.g., "Choose only the red stimulus") and no correct or

incorrect answers (the task does not involve veridical DM processes). Two types of scores can be computed from the CBias. First, for each of the 60 trials a "**similarity index"** is calculated, ideally ranging from 5 (identical) to 0 (differing along all five dimensions). However, there are no trials in which one of the two choice-cards is identical to the target-card, so participants must choose the one more similar or dissimilar to the target-card.

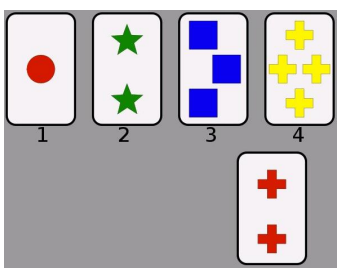
- The **CBias raw score** is the sum of each "similarity index" across trials and ranges from 80 to 220, representing the degree of agreement with the target-card, in view of the cognitive context. High cumulative raw scores imply consistently similar target choices (context-dependent response selection bias); low cumulative raw scores imply consistently different choices, and so, vice versa, they also represent a context-dependent selection bias. Lastly, midrange raw cumulative scores imply that choices are unrelated to target-card characteristics (context-independent response selection bias). On this scale, high or low scores indicate a context-dependent response bias, while mid-range scores indicate a context-independent selection bias.

- the **CBias converted score** is an alternative scoring is computed as the absolute deviation of the raw score from the raw-score midpoint of 150. On this scale, ranging from 0 to 70, high scores represent a context-dependent selection bias, while low scores represent a context-independent response selection bias. A mid- range score, in this case, falls between the two extreme cognitive selection strategies.

4.2.4 Neuropsychological assessment

A. **The Wisconsin Card Sorting Test** (Berg, 1948) to investigate set shifting abilities; the execution of the WCST presupposes a multitude of executive functions including abstraction, the appeal to functional strategies of problem solving, the ability to switch strategy when the situation requires a change of rule and the skill to learn and to memorize functional rules. In this study the following performance indices were considered: number of completed categories, number of perseverative responses, total number of errors and a measure of global efficiency called global score (global score = [number of trials - number of achieved categories × 10]; Laiacona et al., 2000). Fig 1.

Figure 1. *The Wisconsin Card Sorting Test*



B. The **Trail making test A e B,** (TMT; Reitan, 1958) a visuo-motor task to measure attention and mental tracking, visual search, speed of processing.

- In the Trail Making Test A (**TMT-A)** the individual is required to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper; this task particularly investigates selective attention and visuo-spatial abilities.
_The Trail Making Test B **(TMT-B)** is similar to A version except that individuals must alternate and shift between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). This second task looks for set-shifting abilities, selective and alternate attention and requires some cognitive flexibility. The score of each part is obtained by the amount of time (in seconds) required to complete the task. Moreover the time difference in the two tasks (B-A) is considered an index of cognitive flexibility.

C. **Memory with interference** (Mondini, Mapelli, Vestri, Arcara, & Bisiacchi, 2011), based on the Brown–Peterson paradigm, was employed to assess working memory. Participants are asked to memorize a triplet of consonants for 10" and 30" (three trials each) after which the subject is distracted with an interference task, (to perform an addition with the aim of preventing rehearsal of material held for short-term retention). The score range is from 0 to 9.

D. **The Stop-Signal paradigm (SST)** to measure motor response inhibition. In the present study, reaction times were estimated using the median method described in Verbruggen and Logan (2009). SST involves two concurrent tasks: a go task, which is a choice reaction time task (i.e. the primary task, a shape judgment task), and a random stop task, which involves an auditory stop signal that tells participants to inhibit their responses to the go task and to stop. The test is based on the "dual race model" (Logan and Cowan, 1984), which uses interleaved staircase functions to generate an estimate of stop signal reaction times, giving a measure of an individual's ability to inhibit an ongoing motor response (Stop Signal Reaction Time, SSRT). In the present study, we used as outcome variables: the SSRT, that is the time (ms) to internally suppress a motor response that has already been initiated;

- the **Brief Intelligence Test** (Colombo, Sartori, & Brivio, 2002) (the Italian version of the National Adult Reading Test, a measure of premorbid intellectual ability) when their age was 18 years or higher; the 'Information' subscale of the Wechsler Intelligence Scale for Children (age below 16 years) or Wechsler Adult Intelligence Scale (age between 16 and 18 years) when age was below 18 years, to exclude mental impairment.

4.3 Statistical Analyses

One-way analysis of variance were used to compare independent groups. For Ordinal variable Mann-Whitney U-test was used. Comparisons between group were performed with general linear models (GLM) accounting for the effects of covariates (age and education). Spearman's correlation coefficient was used to explore the relationship between demographic variables, clinical variables and neuropsychological test scores.
Considered the explorative nature of the study, a probability threshold value of 0.05 was assumed for statistical significance.
All analyses were implemented with Statistical Product and Service Solutions software, version 22.0 (SPSS Inc, Chicago, IL).

4.3.1 Genotype analysis

DNA samples were collected at the time of the neuropsychological assessment. Participants were genotyped for the presence of the polymorphism 158 Val → Met of the COMT gene, the short variant of the 5-HTTLPR gene, and the A/G single-nucleotide polymorphism (SNP rs25531) of the 5-HTTLPR gene, according to standard protocols described below. For the 5-HTTLPR gene, samples were split on the basis of the presence or absence of the short variant (S) of the 5-HT transporter, and polymorphism G were included in this short group variant. Genetic data concerning COMT gene were available for 163 patients and 152 healthy women and for 5HTTLPR for161 patients and 201 healty control.

a) Genotype analyses protocol: COMT

PCR primers were designed with open-source Primer3 software (http://frodo.wi.mit.edu/primer3/): FOR 5'-CATCACCATCGAGATCAACC-3' and REV 5'-CCTTTTTCCAGGTCTGACA-3'; the polymerase chain reaction (PCR) and HRM analysis were carried out using Takara Ex Taq R-PCR custom (Takara Bio Europe S.A.S., Saint.Germain-en-Laye, France). The PCR was performed in a 25 µL total volume containing 1X PCR buffer, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 300 nM of each primer, 1.5 µM of Eva Green, 1.25 IU Taq DNA polymerase and $3x10^9$ copies/µL DNA; amplification conditions were 95°C 3min, 40 cycles of 95°C 10s, 56°C 20s, and final step of 72°C 5min. HRM analysis was performed with the temperature ramping (81°C to 91°C, rising by 0.1°C). Three different melting profiles were obtained: one for heterozygotes Val158Met, one for homozygotes Val158Val and one for homozygotes Met158Met. In HRM analyses, homozygote and heterozygote curves were confirmed by sequencing as reference for genotype analysis of unknown samples. PCR products were sequenced by Big Dye

Terminator kit (Applied Biosystems Inc., Carlsbad, CA) and resolved on an ABI-PRISM 3100 Genetic Analyzer (Applied Biosystems Inc.).
Melting curves were normalised throughout calculation of "line of best fit" of two normalisation regions, before and after major fluorescence drop, corresponding to melting of PCR product, with software provided with Rotor-Gene 6000 (Corbett Research, Cambridgeshire, UK).

b) Genotype analysis protocol: 5-HTTLPR

The 5-HTT promoter region was amplified from genomic DNA to discriminate between the L- and S- allele (rs4795541). Primer sequences were designed using Primer3 software (http://frodo.wi.mit.edu/) (forward: CAACTCCCTGTACCCCTCCT and reverse: GTGCAAGGAGAATGCTGGAG). This reaction produced a fragment of 297-bp for the long L allele and a fragment of 254-bp for the short S allele. 200ng of genomic DNA were amplified using 12.5µl of prealiquoted ReddyMixTM PCR Master Mix (Thermo Fisher Scientific, Milan, Italy), 10X DMSO and 0.4µM of each primer, in a total volume of 25µl. Cycling conditions were: 1 cycle at 94° C for 4 minutes, followed by 37 cycles at 94° C for 1 minute, at 61° C for 1 minute and at 72° C for 1 minute.
To genotype the rs25531 the amplification was followed by a restriction digestion. 7µl of PCR product were digested at 37° C for 2 hr with 5U of MspI (New England BioLabs, Celbio, Milan, Italy), which recognizes the sequence 5'-C/CGG-3'. Fragments were separated on acrylamide gel at 10% (45min at 200V). The LA allele produces fragments of 257-bp and 39-bp while the LG allele fragments of 174-bp, 84-bp and 39-bp.

4.3.2 fMRI image analysis

Data were collected on a Philips Achieva 1.5 T scanner equipped for echo-planar imaging. A resting-state fMRI scan entailed 250 continuous functional volumes (repetition-time=2009 ms, echo- time=50 ms, flip angle=90°, 21 slices, matrix=128x128, acquisition voxel size=1.8x1.8x6 mm, acquisition-time=8 min; field of view=23 cm). Participants were instructed to rest with their eyes closed during the scan. High-resolution 3D T1-weighted anatomical images were also acquired in a gradient-echo sequence (repetition-time=20 s, echo time=3.78 ms, flip angle=20°, 160 slices, acquisition voxel size =1x0.66x0.66 mm, field of view=21–22 cm).
All functional and anatomical images were visually inspected for quality. The first five volumes of every scan were discarded, to remove any stabilisation effects. Preprocessing was

performed using the Analysis of Functional NeuroImages (version AFNI_2010_10_19_1028; http://afni.nimh.nih.gov/afni; NIMH, Bethesda, Maryland) and FM-RIB Software Library (version FSL 4.1.6; http://www.fmrib.ox.ac.uk; FMRIB, Oxford, UK) tools as described in Biswal et al. (2010). It consisted of motion correction using Fourier interpolation (volume registration using least squares alignment of three translational and three rotational parameters), spatial smoothing with a 6-mm FWHM Gaussian kernel, mean-based intensity normalisation of all volumes by the same factor, linear and quadratic detrending, and spatial normalisation via estimation of a linear transformation (affine with 12 degrees of freedom, using FLIRT, FSL) from the individual functional spaces to MNI152 standard brain space using each individual's high-resolution anatomic image. A high-pass filter setting of 200 sec (0.005 Hz) was used to reduce very-low frequency artefact such as scanner draft and a low-pass filter to remove any components in the high-frequency spectrum (0.1 Hz). Nuisance signals (6 motion parameters, white matter, cerebrospinal fluid, and the global signal) were removed by multiple regression before performing functional connectivity analyses.

- **A seed voxel correlation approach** was used to explore functional connectivity within the networks implicated in DM.

The spherical seeds (diameter = 12 mm) were:

1) ***Dorsal attentional network*** **(DAN)** : Inferior parietal sulcus (IPS)/superior parietal lobule (SPL); MNI coordinates: -25, - 53, 52 and 25, -57, 52 (Woodward et al., 2011);

2) ***Executive network (ECN)*** :left and right DLPFC; MNI coordinates −42, *34, 20 and 44, 36, 20*), (Woodward et al., 2011);

3) Amygdala (anxiety) MNI coordinates *:* left, -19, -4, -18 and right, 27, -3, -15 (Steffens et al. 2011);

4) ***Orbitofrontal cortex (lateral OFC)***: MNI coordinates *:* left, -31, 42, -8 and right, 31, 42, 8 (Steffens et al. 2011);

5) ***Accumbens network (reward):*** ventral caudate/nucleus accumbens or inferior ventral striatum (VSI): MNI coordinates ±9, 9, -8; (Di Martino et al., 2008);

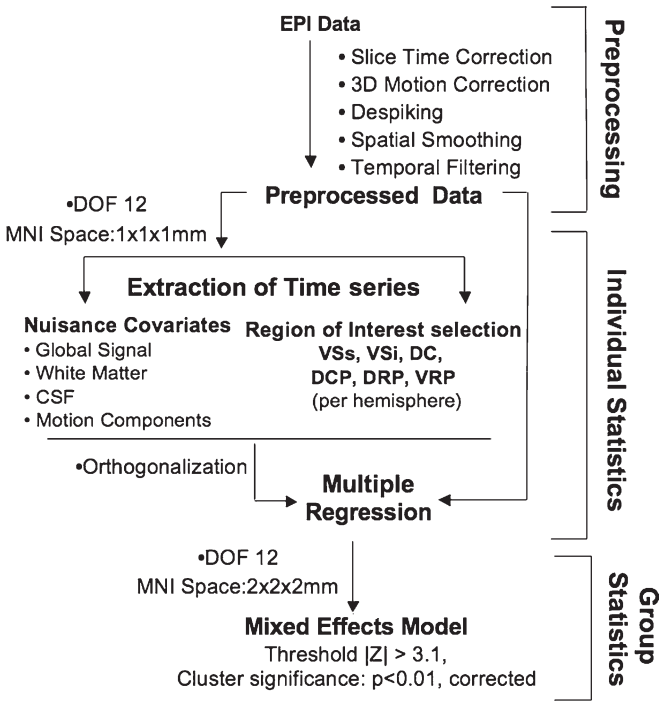
6) ***Ventromedial Prefontal cortex (VMPFC)*** MNI coordinates *:left -6, 50, -9 and right 7, 54, -9. (*Steffens et al., 2011).

Nuisance signals were removed by multiple regression before functional connectivity analyses. Each individual's 4D time series were regressed on nine predictors, consisting of white matter, cerebrospinal fluid, the global signal and six motion parameters (three cardinal

directions and rotational movement around three axes). The time series of the nuisance signals were extracted by: a) averaging all voxels in the brain (global signal) across the time series; b) segmenting each individual's high-resolution structural image (FAST, FSL; Zhang et al., 2001), applying a threshold at 80% tissue type probability, and averaging all voxels within the thresholded mask (white matter and cerebrospinal fluid) across each time series; c) using the residuals obtained after motion correction by MCFLIRT (FMRIB, Oxford, United Kingdom). Each subject's residual 4D time series was transformed into Montreal Neurological Institute space by means of a linear affine transformation implemented in FSL (FLIRT) and the time series extracted for each seed. Time series were averaged across all voxels in the seed ROI and then, for each subject, the correlations between the time series of the seed ROI and of each voxel in the brain were determined. *Lastly, correlation maps were converted to Z-value maps*. The resulting standardised maps were then used to perform group comparisons and correlations using age and hand lateralization as nuisance variables. Non-parametric permutation testing (5,000 permutations) was used for correlational analyses of spatial maps, according to the TFCE method (Threshold-Free Cluster Enhancement) (Smith & Nichols 2009), with correction for multiple comparisons across space, threshold $p<0.05$.

Graph data were obtained by extracting the average z-value in the brain area of interest for any individual map, and managing data using Statistical Product and Service Solutions software (SPSS, Inc., Chicago, IL).

Figure 2.



Note. *MRI Resting State data analysis overview. Summary sketch of an example data analysis steps included in preprocessing, and individual and group statistics. Abbreviations from the top: DOF- degrees of freedom. (adapted from De Matino et al., 2008)*

4.4 RESULTS

4.4.1 Sociodemografical characteristics of the sample

Table 1. *Characteristics of adolescent and adult groups*

	ADOLESCENT GROUP (n=141)		ADULT GROUP (n=470)	
	Adolescent girls with AN (n=109)	Adolescent girls (n=32)	Adult women with AN (n=201)	Adult women (n=269)
Age (years)	16.8 (1.2)	16.5 (1.3)	26.2 (6.6)	26.8 (5.5)
Body mass index (kg/m^2)	17.1 (2.5)	21.0 (2.4)*	18.1 (3.0)	21.5(2.9)*
Lowest BMI	15.4 (1.7)	19.5 (2.1)*	15.2 (1.8)	19.3 (2.1)*
Duration of illness (months)	16.4 (13.3)	-	67.71 (66.7)	-
Age of onset	14.87 (1.4)	-	18.69 (4.7)	-
Edinburgh	54.5 (35.0)	61.1 (27.3)	54.9 (40.6)	62.0 (35.4)
Education (years)	10.3 (1.4)	10.3 (1.5)	14.7 (2.2)	15.9 (2.3)*
HSCL Depression	1.4 (0.9)	0.7 (0.6)*	1.6 (0.9)	0.6 (0.5)*
Trait anxiety	51.9 (12.8)	42.2 (11.0)*	54.9 (11.2)	39.3 (8.7)*
State anxiety	43.0 (12.0)	36.2 (8.8)*	43.1 (11.5)	33.7 (7.0)*
Current underweight status (BMI<18.5)	84 (77%)	0%	121 (60%)	0%
Restricting type	86 (79%)	0%	112 (55.8%)	0%
Amenorrhea	81 (74%)	0%	90 (48%)	0%

** $p<0.001$*

Sociodemografical and clinical characteristics of the two subgroup of adults and adolescents are shown in table 1. In both subgroups AN patients and healthy controls differ for BMI, lowest BMi, anxiety and depressive symptoms. Adult An patients show a lower schooling profile in comparison with healty women.

4.4.2 Neuropsychological and clinical features

Table 2. *Neuropsychological performance in adolescent sample*

	Adolescent girls with AN (N=109) Mean (SD)	Adolescent girls (N=32) Mean (SD)	t	p
WCST	*n=109*	*n=32*		
Global score	51.3 (37.75)	47.7 (32.9)	-0.49	0.623
Number of categories§	4.94 (1.74)	5.38 (1.51)	1.36	0.210
Total errors	32.32 (23.34)	30.78 (19.38)	-0.34	0.733
Total answer	100.8 (23.27	101.47(21.49)	0.14	0.886
Perseverative responses	18.08(15.12)	16.63(12.26)	-0.5	0.619
Number of correct answers	68.49(9.95)	70.69(10.34)	1.09	0.277
TMT	*n=108*	*n=32*		
Trail Making Test A	29.6 (10.6)	26.7 (7.8)	-1.47	0.144
Trail Making Test B	61.32(19.73)	55.26 (17.04)	-1.56	0.120
Delta trail	31.67(16.6)	28.53(16.70)	-0.94	0.350
	n=104	*n=32*		
Memory with interference 10”	7.61 (1.6)	7.25 (1.6)	-1,07	0.285
Memory with interference 30”	7.0 (1.9)	7.4 (1.5)	1,24	0.286
	n=86	*n=27*		
SSRT	258.5 (58.8)	263.1 (52.2)	0.39	0.387
	n=54	n=28		
WISC	11.20(2.35)	10.07 (3.11)	-1.843	0.069

§Ordinal variable (Mann-Whitney U-test was used, z not adjusted for age and educational level)

Table 2 reports cognitive functioning in AN adolescents group and healthy girls that doesn’t reveals significant differences even after correction for age and education.

In adult subsample, as showed in Table 3, AN patients have reported an impairment of set-shifting and cognitive flexibility further than lower QIT score.

Table 3. Neuropsychological performance in adult sample

	Adult women with AN (N=201) Mean (SD)	Adult women (N=269) Mean (SD)	t	p
WCST	*n=201*	*n=248*		
Global score	48.67 (35.50)	35.78 (28.79)	*-4.157*	***0.000***
Number of categories§	5.10 (1.54)	5.58 (1.12)	*3.702*	***0.000***
Total errors	29.79 (21.81)	22.20 (16.94)	*-4,040*	***0.000***
Total ansewer	99.72 (22.69)	91.63 (20.01)	*-3.957*	***0.000***
Perseverative responses	16.79 (14.54)	12.47 (10.83)	*-3.498*	***0.001***
Number of correct answers	69.94 (9.58)	69.43 (7.61)	*-0.606*	*0.545*
TMT	n=199	n=254		
Trail Making Test A	30.27(9.83)	29.01(9.04)	*-1.388*	*0.166*
Trail Making Test B	60.80(22.65)	56.43(20.13)	*-2.170*	***0.030***
Delta trail	30.52(20.68)	27.41(17.63)	*-1.727*	*0.085*
	n=163	*n=240*		
Memory with interference 10”	8.03(1.31)	8.15(1.30)	*0.895*	*0.371*
Memory with interference 30”	7.33(1.71)	7.32(1.644)	*-0.025*	*0.980*
	n=120	*n=114*		
SSRT	255.67	250.84	*-0.509*	*0.611*
	n=88	*n=108*		
QIT	*105.39(4.86)*	*107.11(2.69)*	*2.976*	***0.003***

§Ordinal variable (Mann-Whitney U-test was used, z not adjusted for age and educational level)

Both adults and adolescent AN patients have reported higher scores in all EDI dimensions, with the exception of body dissatisfaction and perfectionism in girls that doesn’t significantly differs from their affected peers (see tables 4 and 5). AN women also showed greater psychiatric symptomatology at all SCL and STAI dimensions; the temperamental traits most frequent in adults AN are harm-avoidance and persistance while reward dipendence and novelty seeking are those in adult women. AN adolescent girls have revealed too an higer general psychiatric symptomatology but only depressive, anxiet, obsessive-compulsive and interpersonal sensivity dimensions are significantly higher in comparison to the control group.

Concerning the temperamental traits healthy and AN girls differ for novelty seeking, higher among healthy girls and persistance higher among AN girls.

Table 4. *Clinical assessment in adolescent sample*

	Adolescent girls with AN (N=109) Mean (SD)	Adolescent girls (N=32) Mean (SD)	t	p
EDI	*n=101*	*n=31*		
drive for thiness	10.76(7.27)	3.23(3.62)	-7.746	**0.000**
interoceptive awareness	8.25(6.72)	3.13(4.36)	-4.971	**0.000**
bulimia	3.56(5.0)	1.32(2.1)	-3613	**0.000**
body dissatisfaction	11.73(7.16)	9.48(7.09)	-1.533	0.128
ineffectiveness	7.80(7.03)	3.39(4.43)	-4.166	**0.000**
maturative worries	8.56(4.59)	5.90(3.82)	-2.932	**0.004**
perfectionism	4.56(3.65)	3.19(2.41)	-2.423	0.052
Body checking	*n=54* 37.98 (24.62)	*n=29* 24.62(14.4)	-3.118	**0.003**
STAI	*n=104*	*n=32*		
STAI T	51.9(12,8)	42.28(10.97)	*-4.182*	***0,000***
STAI S	42.9(11.96)	36.25(8.86)	*-3.401*	***0.001***
SCL90	*n=99*	*n=30*		
SCL tot	1.09 (0.70)	0.68(0.52)	*-2.195*	***0.005***
SOM	0.98(0.78)	0.74(0.58)	*-2.867*	*0.135*
OC	1.20(0.83)	0.83(0.66)	*-2.225*	***0.028***
IS	1.33(1.027)	0.89 (0.61)	*-2.911*	***0.005***
DEP	1.36(0.9)	0.69(0.60)	*-4.695*	***0.000***
ANX	1.06(0.8)	0.70(0.72)	*-2.191*	***0.030***
PSY	0,77(0.66)	0.45(0.49)	*-2.452*	*0.016*
TPQ	*n=100*	*n=30*		
N-S	14.41(4.75)	17.57(5.42)	*3.085*	***0.002***
H-A	18.53(16.17)	16.17(5.66)	*-1.694*	*0.093*
R-D	11.79(3.82)	13.67(3.12)	*2.453*	*0.016*
PERS	6.13(2.13)	4.57(2.27)	*3.467*	***0.001***

Table 5. *Clinical assessment in adult sample*

	Adult women with AN (N=201) Mean (SD)	Adult women (N=269) Mean (SD)	t	p
EDI	*n=194*	*n=204*		
drive for thiness	11.54 (6.85)	1.31 (2.86)	*-19253*	***0.000***
interoceptive awareness	9.15 (6.51)	1.18 (6.51)	*16.117*	***0.000***
bulimia	5.26 (5.59)	0.47 (1.27)	*-11.670*	***0.000***
body dissatisfaction	12.02 (7.60)	5.51 (5.43)	*-9.770*	***0.000***
ineffectiveness	9.75 (7.24)	1.59 (2.99)	*-14.561*	***0.000***
maturative worries	7.44 (3.70)	3.70 (3.147)	*-8.904*	***0.000***
perfectionism	5.49 (3.97)	3.02 (2.73)	*-7.187*	***0.000***
Body checking	*n=48* 36.42 (22.52)	*n=95* 17.12 (12.69)	*-5.513*	***0.000***
STAI	*n=188*	*n=230*		
STAI T	54.95(11.30)	39.30(8.70)	*-15.587*	***0.000***
STAI S	43.12(11.55)	33.69(7.06)	*-9.799*	***0.000***
SCL90	*n=190*	*n=256*		
SCL tot	1.3 (0.71)	0.45 (0.35)	*-14.838*	***0.000***
SOM	1.20 (0.87)	0.43 (0.37)	*-11.352*	***0.000***
OC	1.54 (0.91)	0.64 (0.57)	*-11.745*	***0.000***
IS	1.49 (0.86)	0.51 (0.50)	*-13.832*	***0.000***
DEP	1.66 (0.92)	0.59 (0.51)	*-14.070*	***0.000***
ANX	1.36 (0.84)	0.52 (0.44)	*-12.385*	***0.000***
PSY	0.99 (0.69)	0.22 (0.31)	*-13.899*	***0.000***
TPQ	n=189	n=256		
N-S	14.67 (5.30)	16.77 (4.81)	*4.370*	***0.000***
H-A	21.40 (6.06)	16.34 (5.73)	*-8.968*	***0.000***
R-D	12.56 (3.95)	14.39 (3.08)	*5.485*	***0.000***
PERS	6.13 (1.9)	5.06 (1.9)	*-5.865*	***0.000***

4.4.3 Decision Making

Decisional performances at Iowa Gambling Task (IGT) and Cognitive Bias Task (Cbias) in the Adolescent subgroup are shown in table 6. AN girl have reported a negative trend in all IGT measures even though without a statistical power (see fig.6, fig 1).

Table 6. *Decisional performances in Adolescents girls*

	Adolescent girls with AN (n=109)	Adolescent girls (n=32)	t	p
Iowa 0-20	-2.79 (4.78)	-0.56 (3.63)	2.43	0.730
Iowa 21-40	0.84 (7.08)	1.31(5.39)	0.34	0.712
Iowa 41-60	2.99 (8.04)	3.56 (6.31)	0.37	0.282
Iowa 61-80	2.26 (7.48)	3.84(6.64)	1.08	0.254
Iowa 81-100	1.82 (9.02)	3.38 (6.02)	0.91	0.259
			F (1,138)*	p
Net score	5.03(26.58)	11.5 (19.38)	1.61	0.206
Iowa learn	6.02 (14.14)	6.47 (9.82)	0.02	0.888
a	0.320 (0.38)	0.418 (0.43)	1.56	0.214
w	**0.449 (0.36)**	**0.622 (0.37)**	**5.46**	**0.021**
c	0.321 (1.86)	0.090 (1.78)	0.39	0.535
	(n=74)	(n=30)	t	p
CBias	29.99 (23.04)	38.93 (23.79)	1.78	0.079

* corrected for the effects of age and education; *p<0.005*

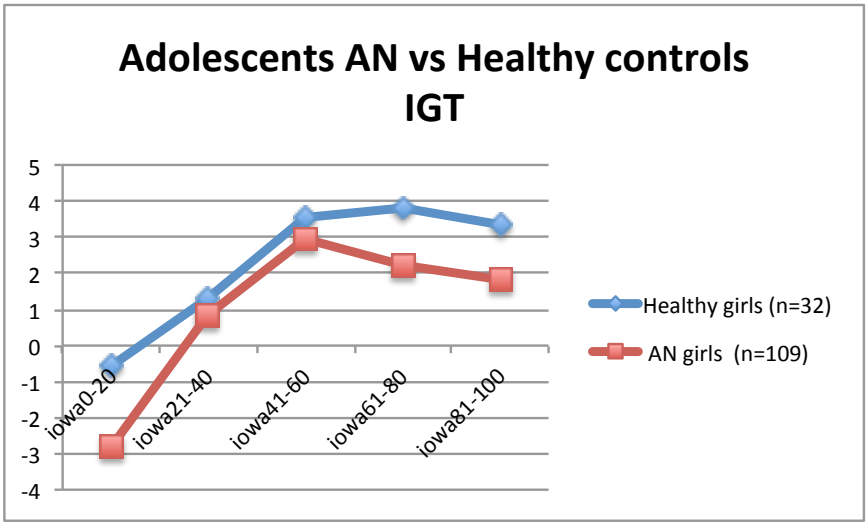
To further characterize the cognitive and decision-making profile of subjects, the performance of the IGT was analyzed with the Expectancy Valence Model.

The comparison between the Healthy and AN girls was significant only for the motivational parameter w, which indicates the attention to winnings and losses. It is assumed that after making a choice, depending on the payout or the loss, the participant attributes a different weight to each of the two possibilities; the meaning attributed to the two possibilities is called "valence" (v (t)) and is the combination of reward experience and loss experience. This parameter varies from 0 to 1; a proper decision-making should be made by giving equal weight to wins and losses (w = 0.5), high values pay more attention to wins, lower values more attention to losses. The AN girls score significantly lower at w EVL parameter indicative of a grater attention to losses than winnings in comparison of the healthy peers.

The second parameter, *a*, is the learning rate and indicates the ability to update or, on the contrary, keep up with the own choices in the game. This parameter varies from 0 to 1; high values, as the trend in healthy girls and women, are indicative of quick adjustments, a higher

discontinuity than the past results and a greater influence on recent results. Low values, as in AN subjects, are indicative of slow changes and greater persistence in changing the choices.
The third parameter, *c*, indicates the consistency of choice during the task and assumes that it changes with the experience (the greater the experience and the greater the consistency in the selections). When the value of this parameter is high, the choices converge toward the deck where the highest expectation is given, when the choices are low, the choice is inconsistent and independent of expectations.
No significant differences in the other EVL parameter, with the exception for the w, have risulted in Adolescent subgroup.

Figure 1. *Block selection trend at IGT in Adolescent subgroup.*



The results of adolescent adaptive decision making indicated by CBias converted score (value ranging from 0 to 70), that is the computed as the absolute deviation of the raw score from the raw-score midpoint of 150, are shown in table 6. Healthy girls reported higher scores (less context-independent) than AN patients, but differences were not statistically significant. On this scale infact high scores represent a context-dependent selection bias, while low scores represent a context-independent response selection bias. A closer value to 35, representing the mid- range score, is the best and indicates that individuals decide considering both context and internal representations.

Table 7. *IGT performances in Adult women*

	Adult women with AN (n=201)	Adult women (n=269)	t	p
Iowa 0-20	-0.02 (6.07)	-1.40 (5.86)	1.12	0.262
Iowa 21-40	**2.38 (7.02)**	**3.70 (6.92)**	**2.04**	**0.042**
Iowa 41-60	**3.34 (7.96)**	**6.06 (7.56)**	**3.76**	**0.000**
Iowa 61-80	**2.41 (8.60)**	**6.13 (8-83)**	**4.57**	**0.000**
Iowa 81-100	**2.04 (9.56)**	**6.12 (9.06)**	**4.73**	**0.000**
			F (1,464)*	p
Net score	**8.25 (26.13)**	**20.7 (26.0)**	**18.66**	**0.000**
Iowa learn	**4.09 (18.50)**	**9-95 (15.57)**	**11.78**	**0.001**
a	0.334 (0.41)	0.341 (0.41)	0.03	0.867
w	0.405 (0.32)	0.454 (0.31)	3.39	0.066
c	0.508 (1.78)	0.777 (1.62)	2.36	0.125
	(n=93)	(n=109)	t	p
CBias	28.24 (22.97)	35.13 (23.66)	2.09	**0.038**

* corrected for the effects of age and education $p<0.005$

A significant decisional impairment at all IGT scores have been reported in AN adult subgroup in comparison with healthy women. Scores obtained in all block selections, with the esclusion of the first one, show differences between the experimental group and the control group Further than by analyzing the card selection profile in blocks of 20, (0-20, 21-40, 41-60, 61.80, 81-100), for each of which has been subtracted the number of choices that are advantageous from the number of disadvantageous choices, two other parameters were then used to evaluate the decisional processing: the Net score, which is calculated as the difference between the total advantageous choices and total of disadvantageous selectionsand, and the Iowa Learn, which is calculated as the difference between total performance in the last 40 selections and total performance in the first 40 selections. The results indicate a significantly inferior net score and learning index (Iowa Learn) for the AN group in comparison to the control group. (see table 7, figure 2,3). The parameters EVL analyses didn't reveal any significant results in adult subgroup between healthy and control subjects.

Adult AN group reported significantly lower scores (more context-independent) than healthy women on Cbias converted score; remarkable healthy subjects Cbias converted score mean value resulted very closer to the mid point of 35 (see Fig.4).

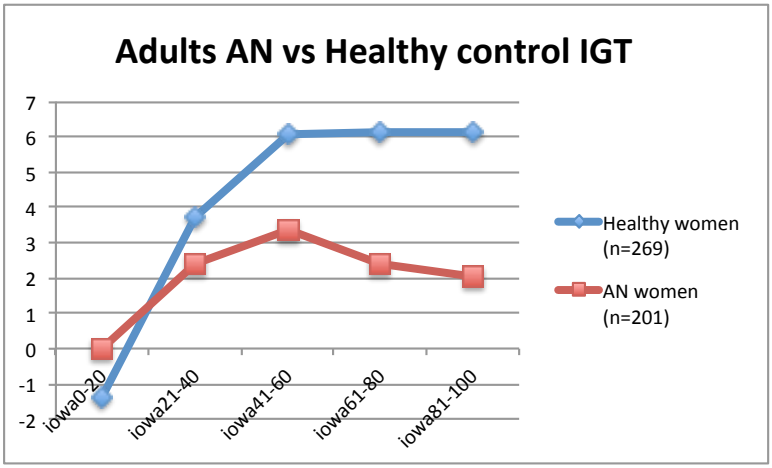


Fig 2 Block selection trend at IGT in Adult women ($p<0.005$)

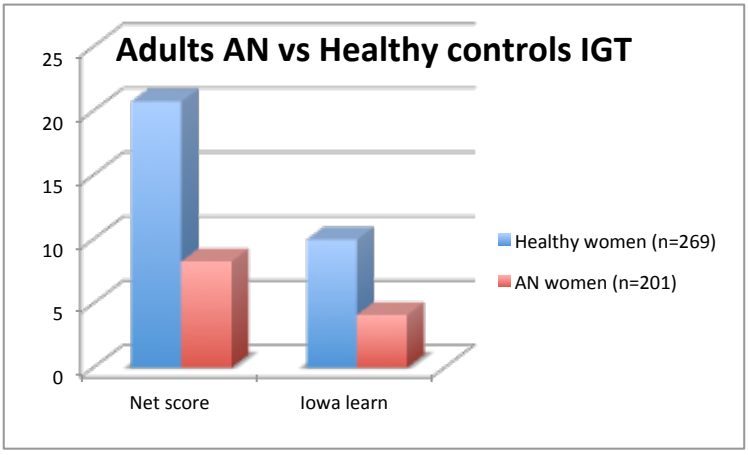


Fig 3 IGT performances in Adult women ($p<0.005$)

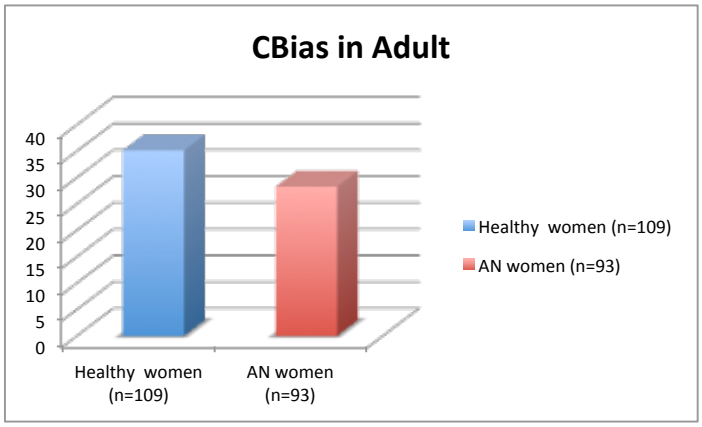


Fig 4. Cbias converted score in Adult women ($p<0.005$)

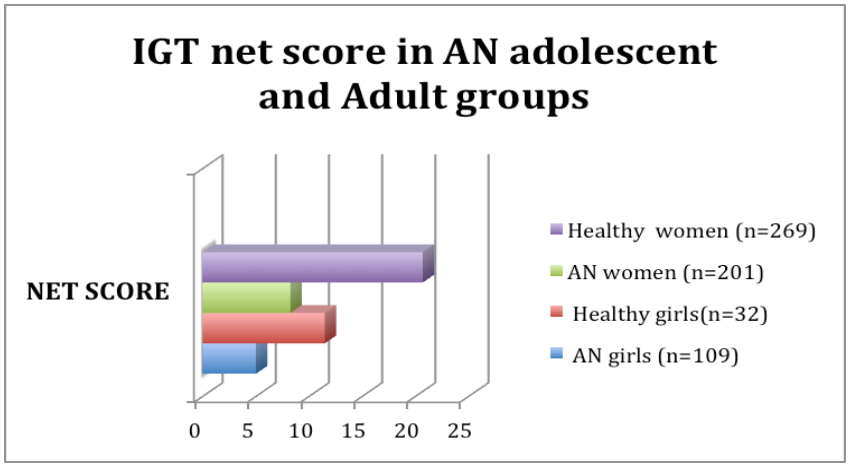


Fig 5 IGT Net Score in Adolescent and Adult Samples

4.4.3.1 Comparison of clinical characteristics with decisional profile:

a) impact of the diagnostic subtype on decision making

Since the different putative mechanisms involved in DM performance in AN and BN may engage different underlying patterns (Chan et al., 2014), we analize the decision making in AN restrictive and binging/purging (who at any stage of their life developed binging/purging or had a previous BN) subtype.

1) **AN Adolescent girls Restrictive vs AN Binging/Purging subtype:**

The characteristics of the two groups Acute AN Restrictive girls vs AN Binging purging in adolescent sample are shown in table 9.

Table 9. *Acute AN adolescent girls Restrictive vs AN Binging/purging subtype girls*

Adolescents:	AN R girls (n=86)	AN BP girls (n=23)	t	p
Iowa0-20	1.44 (7.11)	-2.39 (6.67)	*-1.172*	*0.244*
Iowa21-40	3.49 (7.64)	1.13 (9.31)	*-1.718*	*0.089*
Iowa41-60	2.53 (7.30)	1.22 (8.19)	*-1.253*	*0.213*
Iowa61-80	1.56 (8.71)	2.78 (10.22)	*-0.749*	*0.456*
Iowa81-100	1.56 (8.71)	2.78 (10.22)	*0.577*	*0.565*

Adolescents:	AN R girls (n=86)	AN BP girls (n=23)	t	p
Net score	6.40 (25.32)	-0.09 (30.91)	*-1.039*	*0.301*
Iowa learn	5.16 (14.24)	9.22 (13.61)	*1.224*	*0.224*
a	0.334 (0.39)	0.265 (0.31)	*-0.768*	*0.444*
w	0.470 (0.37)	0.36 (0.32)	*-1.198*	*0.223*
c	0.314 (1.99)	0.349 (1.32)	*0.080*	*0.937*
CBias	(n=59) 26.51 (21.43)	(n=15) 43.67 (24.75)	*2.682*	***0.009***

P<0.05

Adolescent An B/P reveals a significant higher contex-dipendent decisional style in adaptive task as shown in table 9, fig .5 in comparison to restrictive AN peers. The IGT scores didn't reveal any significant differences in adolescent or adult group (see table10). In adult group neither Cbias score risulted significant in the comparison between the different AN subtype groups.

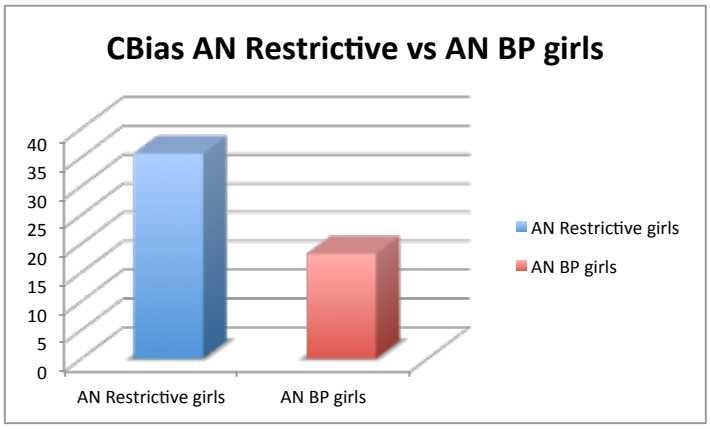


Fig 6. Adolescent AN restrictive vs AN BP subtype Cbias converted score (p<0.05)

2) AN adult women Restrictive vs AN Binging/Purging subtype:

The characteristics of the two groups AN Restrictive women vs AN Binging purging in women sample are shown in Table 10

Table 10. *Acute AN adult women Restrictive vs AN Binging/purging subtype women*

Adults:	AN R women (n=112)	AN BP women (n=89)	t	p
Iowa0-20	-1.79 (5.95)	-2.31 (6.22)	*-0.602*	*0.548*
Iowa21-40	2.27 (6.81)	2.52 (7.31)	*0.249*	*0.803*
Iowa41-60	2.93 (7.99)	3.87 (7.94)	*0.827*	*0.409*
Iowa61-80	2.32 (8.21)	2.52 (9.11)	*0.160*	*0.873*
Iowa81-100	1.36 (9.4)	2.90 (9.51)	*1.149*	*0.252*
Net score	6.83 (25.11)	10.04 (27.40)	*-0.866*	*0.388*
Iowa learn	3.21 (18.45)	5.21 (18.61)	*0.764*	*0.466*
a	0.324 (0.41)	0.346 (0.40)	*0.370*	*0.711*
w	0.405 (0.31)	0.407 (0.32)	*0.045*	*0.964*
c	0.640 (1.73)	0.342 (1.83)	*-1.179*	*0.240*
CBias	(n=55) 27.85 (23.85)	(n=38) 28.79 (22.58)	*0.193*	*0.848*

P<0.05

b) impact of weight on decision making

Given that the malnutrition state negative impacts on cognitive processing and perhaps on decisional processing too (Tchanturia et al., 2007, Bosanac 2007, Bodell 2014) we define two subgroups of patient according to the BMI at the time of assessment. A subgroup of 25 adolescent and 121 adult AN patients, although still in treatment, were weight-recovered at the time of the neuropsychological assessment (BMI ≥ 18,5).

Patients with AN lifetime were defined as **"acute"** when DSM-5 diagnostic criteria were all fulfilled at the time of assessment and the BMI was <18,5 and **"weight-restored'"** when eating and cognitive symptoms were still present, but the weight was in the normal range (BMI ≥ 18,5) at the time of assessment.

1) ***Acute AN adolescent girls (BMI<18.5) vs AN weight restored girls (BMI ≥ 18.5)***

The characteristics of the two groups Acute AN girls (BMI<18.5) vs AN weight restored girls

(BMI ≥ 18.5) in adolescent sample were: Mean weight at time assesment: M(SD)= *16.0(1.41) vs 20.50(2.16); t=-12,046 p(0.016)*; Lowest BMI M(SD)= *15.81(1.77) vs 15.22(1.65); t=-1,524;(p=0.000)*; Mean age :*M(SD)=17.34(1.22) vs 16.64(1.22); t=-2.525;(p=0.013).*

Table 11. *Acute AN adolescent girls (BMI<18.5) vs AN weight restored girls (BMI ≥ 18.5)*

Adolescents**:**	AN (BMI ≥ 18.5) girls (n=25)	AN (BMI <18.5) girls (n=84)	t	p
Iowa 0-20	*-2.96 (4.47)*	*-2.74 (4-89)*	*0.203*	*0.840*
Iowa 21-40	*0.64 (6.94)*	*0.90 (7.17)*	*0.163*	*0.871*
Iowa 41-60	*3.04 (7.57)*	*2.98(8.21)*	*-0.036*	*0.972*
Iowa 61-80	*2.72 (6.9)*	*2.12 (7.68)*	*-0.351*	*0.726*
Iowa 81-100	*0.56 (9.46)*	*2.19 (8.90)*	*0.792*	*0.430*
			t	*p*
Net score	*3.88 (27.01)*	*5.37 (26.60)*	*0.245*	*0.807*
Iowa learn	*5.60 (13.39)*	*6.14 (14.43)*	*0.168*	*0.867*
a	*0.265 (0.34)*	*0.336 (0.39)*	*0.813*	*0.418*
w	*0.36 (0.32)*	*0.475 (0.37)*	*1.473*	*0.173*
c	*0.723 (1.76)*	*0.201 (1.88)*	*-1.234*	*0.220*
CBias	*(n=15) 39.40 (26.01)*	*(n=59) 27.59 (21.82)*	*-1.799*	*0.076*

Results at IGT and Cbias scores suggest worse decisional profile in weight recovered group of AN lifetime adoelscent in comparison with underweight AN, even though whitout reaching a statistical significance (Table 11). AN weight recovered adolescent also showed a more context-dipendent decisional style in adaptive decision making and a decisional pattern chacterized by less rapid changes and higher sloweness, tendency to persist in choices (lower *a* parameter) and greater focus on negative outcomes (low *w* parameter) than underweight AN patients, that prove to be more efficient in learning (higher IGT learn) ,more versatile (greater a parameter) and focused on positive outcomes (w greater).

2)Acute AN Adult women (BMI<18.5) vs AN weight restored women (BMI ≥ 18.5)

The characteristics of the two groups Acute AN women (BMI<18.5) vs AN weight restored women *(BMI ≥ 18.5)* in adult sample were; mean weight at time assessment***:*** *M(SD)=*

16.30(1.56) vs 20.86(2.54); t=-15.739; p=(0.000); Lowest BMI: M(SD)=*15.84(1.62) vs 14.80(1.81); t=-4.127 ;(p=0.000);*Mean age:*M(SD)=26.96(6.55) vs 25.77(6.55); t=-1.256; (p=0.212).*

Table 12. *Acute AN Adults women (BMI<18.5) vs AN weight restored women (BMI ≥ 18.5)*

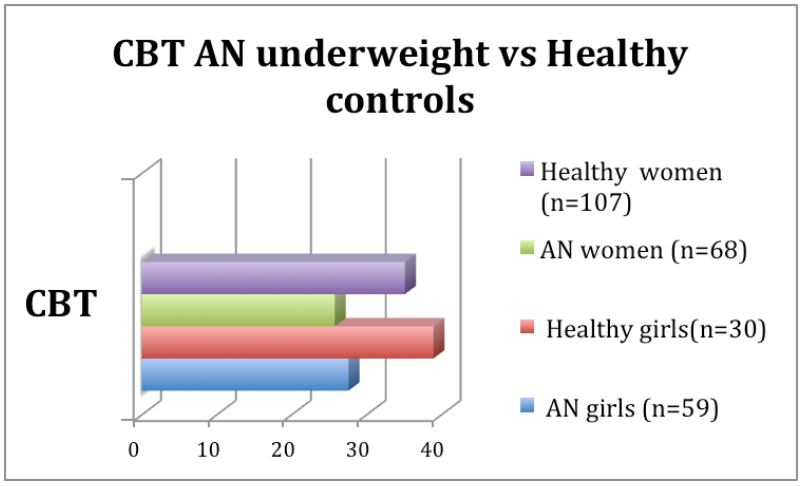
Adults:	*AN (BMI ≥18.5) women (n=80)*	*AN (BMI < 18.5)women (n=121)*	*t*	*p*
Iowa0-20	*-2.43 (6.06)*	*-1.76 (6.09)*	*0.759*	*0.449*
Iowa21-40	*3.10 (7.43)*	*1.90 (6.72)*	*-1.186*	*0.237*
Iowa41-60	*3.25 (8.28)*	*3.40 (7.78)*	*0.135*	*0.893*
Iowa61-80	*3.50 (9.22)*	*1.69 (8.12)*	*-1.467*	*0.144*
Iowa81-100	*2.80 (9.95)*	*1.54 (9.12)*	*-0.926*	*0.355*
			t	*p*
Net score	*10.50 (27.82)*	*6.77 (24-97)*	*-0.99*	*0.323*
Iowa learn	*5.63 (19.84)*	*3.08 (17.57)*	*-0.953*	*0.342*
a	*0.343 (0.41)*	*0.329 (0.41)*	*-0.243*	*0.808*
w	*0.414 (0.32)*	*0.400 (0.33)*	*0,306*	*0.760*
c	*0.465 (1.78)*	*0.536 (1.79)*	*0.273*	*0.785*
CBias	*(n=25) 34.96 (24.14)*	*(n=68) 25.76 (22.19)*	*-1.730*	*0.087*

Even if without statistical power, the decisional results in adult group suggest a reverse trend in comparison to acute vs weight recovered group in adolescent sample since adult acute AN have reported a worse trend in IGT selection blocks with a lower net and learn score, and a decisional stile more influenced mostly from recent outcome vs past (higher a) and most focused on reward vs punishment (higer w) even if the numeric value difference is lower than in adolescent group and equally not significant. On the contrary the weight seems to impact mostly on adaptive decision making since Cbias share a common profile in both adults and adolescents with an higher context-dipendent decisional style in acute underweight patients (lower Cbias converted score). To explore this hipotesys, since the CBias score has actually resulted correlated with weight (see correlation analyses paragraf), we compare AN patients of the two age different groups with the corrispectively healthy controls (see table 13), excluding from the analyses the patients witth a recovered weight.

Table 13. CBias in AN underweight (BMI <18.5) vs Healty controls

		CBias converted score Mean (SD)	F(1,86); F(1,172)	p
ADOLESCENT GROUP (n=89)	Adolescent girls with AN BMI<18.5 (n=59)	27,59 (21,82)	4,903	***0,029***
	Adolescent girls (n=30)	38,93 (23,79)		
ADULT GROUP (n=177)	Adult women with AN (n=68)	25,76 (22,19)	5,054	***0,026***
	Adult women (n=107)	35,13 (23,66)		

Figure 7. *Cbias score in AN uderweight vs healty control in adolescent and adult groups.*



Analyses results confirmed that in both adolescent and adults group underweight An patient shows a significant higher context-dipendent reasoning in comparison to control groups.

No significant differences have resulted in IGT measures between An underweight and Healthy controls.

c) impact of genetic polymorfisms on decision making

We found a significant impact of COMT polymorfism on decisional syle in adolescent group only in healthy sample (see table 14), where the absence of met (A) allele was associated with

higher EVL *a* and lower *c* parameter in IGT. This results are suggestive of a decisional profile carachterized by rapid adjustments, by higher discontinuities than past results and a greater influence on recent results (a higher) and a lower coherence of choices toward the decks with the highest expectations resulting in the absence of a clear decisional strategy (very lower c parameter) and a less efficient (though not statistically significant) decisional profile. In adolescent subgroup neighter significant COMT genotype effect was found for adaptive decision making nor 5HTTLPR polymorfism significant effects have resulted in all IGT and Cbias scores in healthy and AN girls.

Table 14. *IGT measures in different COMT genotypes in adolescent girls.*

ADOLESCENTS girls**:**	AA/AG met-met/ met-val (n=8)	GG val-val (n=15)	t	p
IGT net M(SD)	15.00 (22.62)	13.73 (20.02)	0.138	0.891
a	**0.146 (0.22)**	**0.592 (0.41)**	***-3.346***	***0.003***
w	0.546 (0,37)	0.685 (0,37)	-0.820	0.422
c	**1.167(1.15)**	**-0.768 (0.39)**	**2.294**	**0.008**
CBias	*45.38 (23.27)*	*39.5 (23.71)*	0.551	0.588

In adult subgroup we found a significant impact of both COMT and 5HTTLPR poliformisms in AN women but not in healthy women (see tables 15 and 16).

Table 15. *IGT measures in different COMT genotypes in adult women.*

AN ADULTS**:**	AA/AG met-met/ met-val (n=38)	GG val-val (n=125)	t	p
Iowa 0-20	-2.05 (6.69)	-1.61 (6.12)	*-0.38*	*0.705*
Iowa 21-40	1.11 (6.65)	2.86 (7.45)	*-1.30*	*0.194*
Iowa 41-60	**0.32 (6.52)**	**4.32 (8.60)**	***-2.64***	***0.009***
Iowa 61-80	**-0.58 (7.67)**	**3.02 (8.834)**	***-2.27***	***0.025***
Iowa 81-100	0.63 (8.86)	2.34 (9.7)	*-0.96*	*0.335*
Net score	**-1.0 (24.31)**	**11.21 (27.02)**	***-2.49***	***0.014***

AN ADULTS:	AA/AG met-met/ met-val (n=38)	GG val-val (n=125)	t	p
Cbias	*23.94 (23.66)*	*24.26(21.63)*	*-0.52*	*0.961*

Adults AN homozygotes for Val (G) COMT allele have reported a significant more efficient decisional profile after the 40th seclections in IGT (fig. 8) with higher net score values (fig. 9) while no differences resulted for adaptive decision making in all adult groups.

Fig 8 *Block selection trend at IGT in Adult AN according to COMT genotype (p<0.05)*

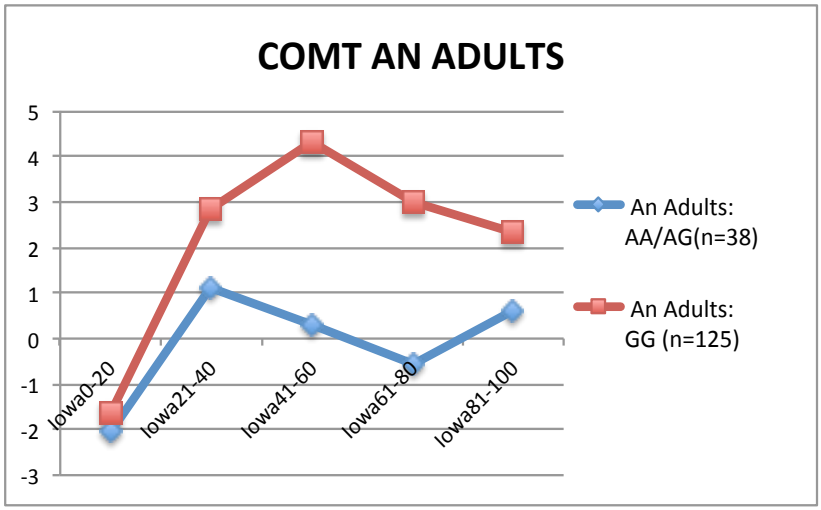
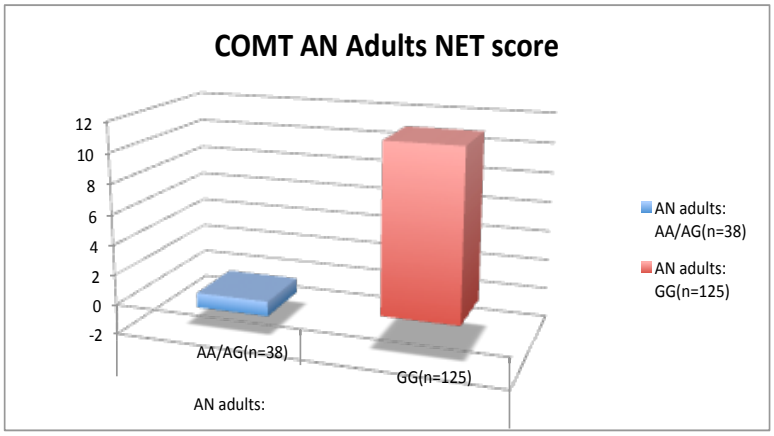


Fig 9 *IGT Net score score in Adult AN according to COMT genotype ((p<0.05).*



Only in AN women *5HTTLPR* SS genotype have resulted significantly associated with worst IGT performances, while no differences in Cbias score were found.

Table 17. *IGT measures in different 5HTTLPR genotypes in AN adult women.*

AN ADULTS:	LL/LS (n=116)	SS (n=45)	t	p
Iowa 0-20	-1.12 (6.21)	-3.04 (6.71)	*1.741*	*0.084*
Iowa 21-40	3.07 (6.76)	1.07 (8.51)	*1.565*	*0.120*
Iowa 41-60	3.88 (7.58)	2.22 (10.03)	*1.133*	*0.259*
Iowa 61-80	2.60 (8.79)	1.33 (8.58)	*0.828*	*0.409*
Iowa 81-100	2.60 (9.63)	0.22 (9.28)	*1.421*	*0.157*
Net score	**11.34 (24.75)**	**1.40 (31.04)**	***2.125***	***0.035***
a	0.350 (0.41)	0.303 (0.41)	*0.664*	*0.519*
w	*0.450 (0.34)*	*0.350 (0.33)*	*1.68*	*0.095*
c	*0.436 (1.94)*	*0.622 (1.59)*	*-0.57*	*0.569*
CBias	*15.06 (15.71)*	*27.49 (23.089*	*2.06*	*0.043*

L= La or Lg

Figure 10. *IGT net score in different 5HTTLPR genotype in AN adult women.(P<0.05)*

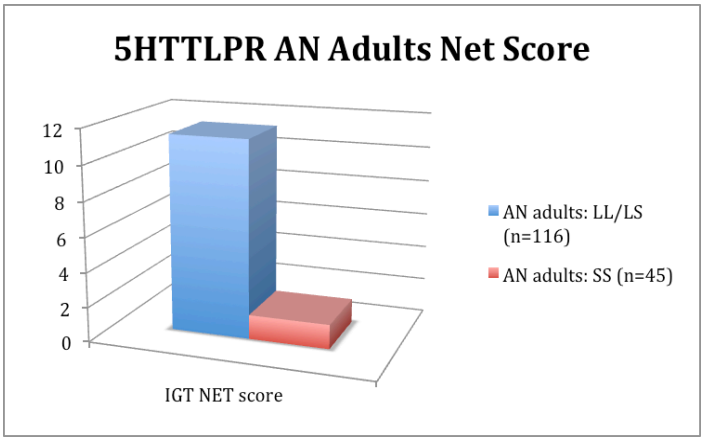
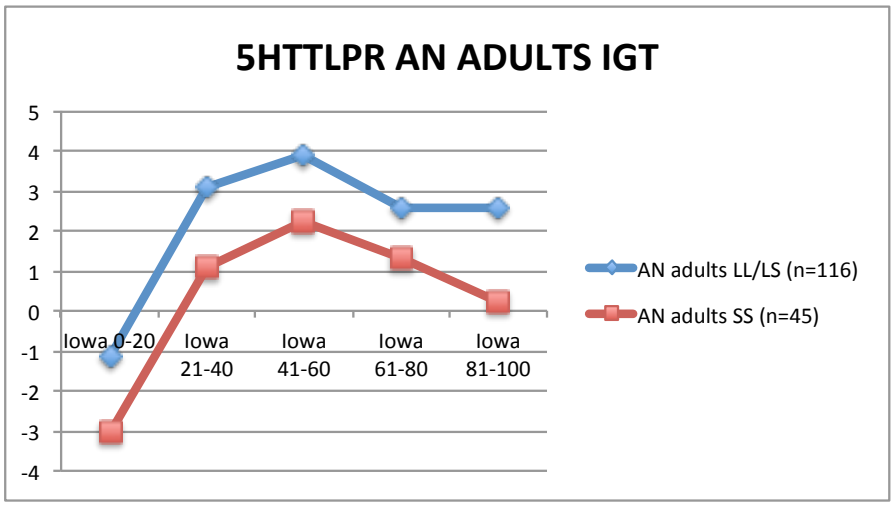


Figure 11. *Block selection trend at IGT in Adult AN according to 5HTTLPR genotype (p<0.05)*



4.4.3.2 Analysis of correlations between neurocognitive, clinical characteristics and decisional profile

Through the Spearman correlation coefficient, non-parametric correlations between the performance of the IGT and Cbias (respectively assessed with net and Learn score and coverted score) and the results at neuropsychological and clinical assessment were investigated. Only significant results are shown in table 17.

-eating symptoms: in adolescent group CBT positive correlates with body cecking (rho=0.368, p=0.049) and in adolescent AN with motivational parameter w (rho=0.330,p=0.015); in adult healty IGT net and desire for thinnes at EDI are negative correlated (rho=-0.146, p=0.038) while in AN women EDI ineffectiveness e negative correlates with w parametr (rho= -0.146,p=0.043); in adolescent AN also IGT net and EDI bulimia resulted positive associated (rho=0.208,p=0.037).

-temperamental trait: only in adolescent girls we found a positive correlation between IGT net and **noveltly seeking** trait (rho=0,483;p<0.007) in adolescent An girls instead IGT learn is negative associated with reward dependence (rho=-0.220; p=0.028); persistance at TPQ is negative correlated with IGT net (rho=-0.189; p=0.003) and learn(rho=-0.14; p=0.024) in healthy adults but the opposite is true in the adolescent AN girls and IGT net (rho=0.387; p<0.000); any significant correlations emergent between temperametal trait and IGT.

-psychiatric sympthoms: any significant correlations resulted between depressive, anxiosus or

OCD symptoms and IGT net and score while CBT is negative correlated with Stai S-rho=0.208,P=0.030) and Anxiety at SCL 90 (rho= -0.246,p=0.011);

-***neurocognitive functioning:*** TMT B negative correlates with both IGT net and learn in AN groups (repsectively AN adolescents: IGT net rho=-0.223, p=0.020; igt learn rho=-0.19,p=0.048; An women: IGT net rho=-0.150,p=0.034; igt learn rho= -0.171,p=0.016).
In An adolescent group TMTB is negative associated with w motivational parmeter (rho= -0-198; p=0.040) and with Cbias (rho= -0.245, p=0.035); TMT A also negative correlates in AN girls and women with IGT net (AN girls rho= -0.224, p=0.020). In AN women, further than the negative association with IGT NET (rho=-0.240, p=0.001), TMTA also resulted negative correlated with IGT Learn (rho= -0.158, p=0.026), a parameter (rho= -0.212, p=0.003) and w EVL parameter (rho=-0.232, p<0.001).
-Memory with interference 10" resulted only positive associated in adults healthy women with Igt learn (rho=0.160, p=0.0139); moreover only in this group memory with interfernce at 10''resulted negative associated with w parameter (rho=-0.2134, p=0.030). In AN women Memory with interference at 30" negative correlates with c parameter (rho= -0.232, p=0.003).
-Worse performances at WCST (higher global scores, number of errors and perseverative responces) are associated with worse decisional profile at IGT scores in healthy woman and adolescent girls (respectively in AN girls: WCST total error and IGT net : rho= -0.217, p=0.024; WCST and IGT learn rho=-0.244,p=0.011; WCST global score and IGT net (rho= -0.218, p=0.023), WCST global score and with learn rho= -0.214 p=0.25);(in healthy women: WCST total errors and IGT net (rho=-0.262p<0.000); and IGT learn (rho=-0.210; p=0.001), and e c parameter (rho = -0.141, p=0.026); WCST global score with IGT net(rho= -0.305,p<0.000) and IGT learn (rho=-0.240,p<0.000), and e a parametr 8rho=0.340,p<0.000), and e c parameter (rho= -0.136,p=0.033); and WCST perseverative responces with IGT net (rho=-0.271, p<0.000), and IGT learn (rho= -0.230,p<0.000), and e c parameter (rho=-0.131, p=0.040).
-In both adult groups QIT and IGT net are positive associated (AN (rho= 0.239, p=0.025), healthy (rho=0.340, p<0.000); in healthy also QIT negative correlates with c parameter (rho= -0.209, p=0.030).
-SSRT resuted negative associated with *a* parameter in AN women a (rho=-0.187, p=0.042), and positive correlated with c parameter in healthy women (rho=0.191, p=0.041).

- ***scholarity:*** In particular CBias signifantly correlates with scholarity only in adolescent subgroup (healty girls: rho=0.412, p=0.024; AN girls rho=0.244, p=0.036). Scholarity positively impacts on IGT learn only in AN adolescent girls (rho=0.240, p=0.012) and on IGT net (rho=0.142, p=0.020) in adults healthy women.
-***handedness:*** Only in adolescent affected girls handedness and Iowa scores are correlated

(Edinburgh and net score (rho=-0.229, p=0.017; Edinburgh and IGT learn (rho=-0.226,p=0.019); Edinburgh and w parameter (rho= -0.240,p=0.012)

-***BMI***: The only correlation between IGT mesures and BMI was found in AN girls where the IGT net and lowest BMI were positive correlated (rho=0.192; p=0.046), and the BMI at the end of treatment was positive correlated with a parameter (rho= 0.275,p=0.024); in adolescent girls moreover the highest BMI was negative associated with c parameter (rho=-0.357,p=0.045). On the contrary several significant correlation between weight and adaptive decision making emerged: in particular Cbias was positive correlated with the BMI at the time of assessment in adolescent AN girls(rho=0.385, p<0.001) and healthy adults (rho=0.203, p=0.034) the lowest BMI (rho=0.365, p<0.001) and with the highest too (rho=0.244, p=0.036).

-***IGT and Cbias mesures:*** In all adolescent and adults groups net score positive correlates with the motivational w paramete (table 17A-D) and so Iowa learn does with the only exceptions of the adolescent girls (rho=0.29;p=0.104). The motivational w parameter and the udating a parameter also resulted positive correlated in all groups with the exception of adolescent girls (rho=0.15 p=0.117). A negative correlation between a and c parameters and w and c parameters resulted in all adolescent and healty groups. Only in adult both An and healty subjects, net score is positive associated with the c value.Iowa learnis positive correlated with c parameter only in adult groups and significantly negative correlated with a parameter only in healthy women. IGT learn and Net score are significantly and positively correlated each others in all groups as shown in Table 18 A-D; on the contrary it is rilevant that IGT and Cbias didn't correlates each other.

Table 18 (A-D) *Correlations between decisional IGT and cbias measures.(* ρ=rho Spearmann coefficient)

Adolescent girls (n=32)	Net score ρ;(p)	Iowa Learn	a	w	c
a	0.28 (0.116)	-0.14(0.446)	-	**0.50 (0.003)**	**-0.93 (<0.001)**
w	**0.42 (0.017)**	0.29(0.104)	**0.50 (0.003)**	-	**-0495(0.004)**
c	-0.25 (0.172)	0.21(0.234)	**-0.93 (<0.001)**	-0495(0.004)	-
Iowa learn	**0.535(0.002)**	-	-0.14(0.446)	0.29(0.104)	0.21(0.234)
Cbias	-0.03 (0.839)	-0.23 (0.222)	0.12 (0.514)	0.286 (0.125)	-0.1 (0.603)

A

AN girls (n=109)	Net score ρ;(p)	Iowa Learn	a	w	c
a	-0.00(0.924)	-0.12(0.222)	-	0.15 (0.117)	**-0.77 (<0.001)**
w	**0.42 (<0.000)**	**0.27(0.005)**	0.15 (0.117)	-	**-0.33(<0.000)**
c	0.12 (0.198)	0.19(0.052)	**-0.77 (<0.001)**	**-0.33(<0.000)**	-
Iowa Learn	**0.47 (<0.000)**	-	-0.12(0.222)	**0.27(0.005)**	0.19(0.052)
Cbias	-0.03 (0.769)	-0.12 (0.310)	0.22 (0.053)	0.97 (0.410)	-0.9 (0.433)

B

Adult women (n=269)	Net score ρ;(p)	Iowa Learn	a	w	c
a	0.11 (0.065)	**-0.14(0.017)**	-	**0.23 (<0.000)**	**-0.75 (<0.001)**
w	**0.40 (<0.000)**	**0.37(<0.000)**	**0.23 (<0.000)**	-	**-0.288(<0.000)**
c	**0.20 (0.001)**	**0.35(<0.000)**	**-0.75 (<0.001)**	**-0.288(<0.000)**	-
Iowa learn	**0.67(<0.000)**	-	**-0.14(0.017)**	**0.37(<0.000)**	**0.35(<0.000)**
Cbias	-0.04 (0.687)	-0.11 (0.248)	-0.86 (0.372)	-0.05(0.602)	0.05 (0.598)

C

AN Adult women (n=201)	Net score ρ;(p)	Iowa Learn	a	w	c
a	0.08 (0.240)	-0.10(0.149)	-	**0.216 (0.002)**	**-0.76 (<0.001)**
w	**0.48(<0.000)**	**0.43(<0.000)**	**0.216 (0.002)**	-	**-0.296(<0.000)**
c	**0.14 (0.044)**	**0.214(0.002)**	**-0.76 (<0.001)**	**-0.296(<0.000)**	-
Iowa learn	**0.56(<0.000)**	-	-0.10(0.149)	**0.43(<0.000)**	**0.214(0.002)**
Cbias	-0.78 (0.459)	-0.110 (0.295)	-0.95 (0.368)	-0.04(0.676)	-0.69 (0.516)

D

4.4.3.3 Decisional profile and outcome treatment

In order to explore the relationship between decisional processing and outcome AN treatment, we compared the IGT and CBT performance at baseline in different An group according to the clinical diagnosis after a 12 months of specialized treatment.
In both adults and adolescent subgroups, any differences emerged from the comparison between AN subjects with clinical improvEment but without a full psychological or phisical remission (adolescents :n=47; Adults: n=100)and those with a persistent AN full diagnosis (Adolescents; n=17; Adults:n=43) in the two different decision tasks.
In the comparison between remitted AN, where full recovery was defined as: at least 3 years of normal weight, regular menses, no eating symptoms, and good social and interpersonal outcome (an adapted version of the Morgan–Russell criteria have been used for definition of recovery; Morgan & Hayward, 1988) an not remitted AN, we found a significant results only in Cbias converted scores at baseline in adolescent subgroup. In particular we found a higher score in remitted girls group (n=28) (very closer to mid Cbias converted score values) and a lower score (suggestive of a contex-independent decisionl style) in not remitted girls (n=36); respectively CBias M(SD)=35.62 (24.04) vs 18.18 (16.51); t=-2.356; p=0.0368 (Fig 12).

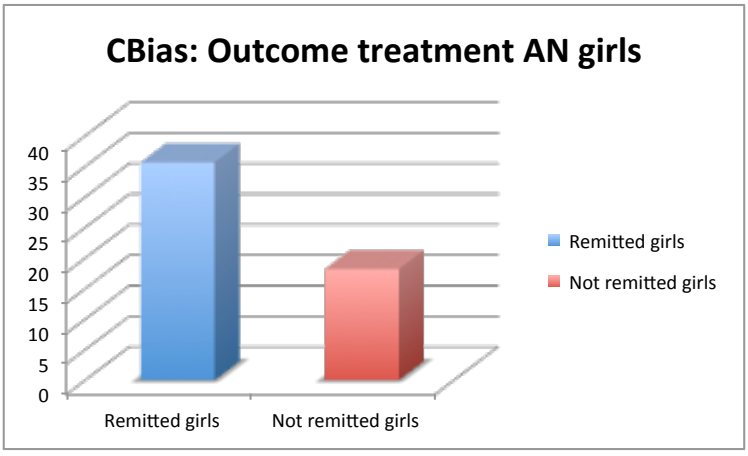


Fig. 12 *Baseline Cbias converted score in AN girl with or without remission after treatment ($p<0.05$)*

4.5 Functional connectivity correlates of decision making

Given the differences resulted between the two decision making tasks IGT and Cbias, and considered the observed absence of correlation between this two, we decided to explore their functional connectivity correlates at rest in a subsample of adults AN (mean BMI =15.8 ± 1.8) healthy controls (HC).

The clinical and demografical charactheristics of the sample investigated with resting state RMI (rsRMI) are reported in table 19; decisional performance at IGt and Cbias were both significantly worse in An women with lower Cbias scores suggestive of a more context-indipendent decisional style (see fig.13)

Table 19 - *Characteristics of participants to the MRI study*

	AN patients (n=35)	Healthy women (n=34)	
	mean (SD)	mean (SD)	t (p)
Age (years)	26.6 (7.3)	25.5 (6.0)	0.61 (0.544)
Education (years)	14.37 (2.2)	15.47 (2.4)	-1.97 (0.052)
Body mass index (kg/m2)	15.8 (1.8)	21.7 (3.07)	-9.87 (0.000)
Lowest body mass index (kg/m2)	14.0 (1.8)	19.8 (2.6)	-10.65 (0.000)
Age at onset (years)	18.5 (5.0)	-	-
Edinburgh score	58.7 (37.8)	54.5 (44.3)	0.42 (0.675)
Depressive symptoms (SCL)	1.4 (0.7)	0.7 (0.6)	3.93 (0.000)
State anxiety			
STAI S	44.5 (12.3)	35.1 (7.4)	3.8 (0.000)
STAI T	56.43 (9.86)	39.88 (9.42)	7.12 (0.000)
Net score	2.69 (26.74)	24.74 (28.89)	-3.29 (0.002)
a	0.351 (0.44)	0.46 (0.44)	-1.01 (0.316)
w	0.447 (0.36)	0.51 (0.36)	-0.77 (0.445)
c	0.814 (1.84)	0.081 (1.99)	1.59 (0.117)
	(n=24)	(n=28)	
CBias	12.13 (11.19)	27.46 (21.34)	-3.31 (0.002)

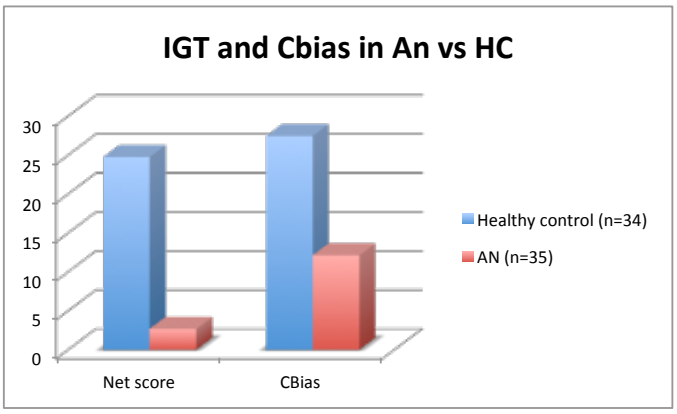


Fig 13*: decisional performances at IGT and Cbias in AN and Healthy control partecipants to the MRI study (p<0.005).*

A seed voxel correlation approach was used within the networks implicated in DM as previous described.

The seed of interest were: *Dorsal attentional network* (DAN): Inferior parietal sulcus (IPS)/superior parietal lobule (SPL); MNI coordinates: -25, - 53, 52 and 25, -57, 52 (Woodward et al., 2011); *Executive network (ECN)* :left and right DLPFC; MNI coordinates −42, *34, 20 and 44, 36, 20*); (Woodward et al., 2011); *Amygdala* MNI coordinates *:* left, -19, -4, -18 and right, 27, -3, -15 (Steffens et al. 2011); *Orbitofrontal cortex (lateral OFC)*: MNI coordinates *:* left, -31, 42, -8 and right, 31, 42, 8 (Steffens et al. 2011); *Accumbens network :* ventral caudate/nucleus accumbens or inferior ventral striatum (VSI): MNI coordinates ±9, 9, -8; (Di Martino et al., 2008); *Ventromedial Prefontal cortex (VMPFC)* MNI coordinates *:left -6, 50, -9 and right 7, 54, -9. (*Steffens et al. 2011).

The analysis of the correlation between the values of two different decisional mesures (Igt net score and Cbias), and the brain regions that had revealed a significant between-group different connectivity at resting state was performed.

The Cbias converted score **significantly** correlated with resting state functional connectivity of those between group difference areas as following described:

1) ***within the executive network*** we found opposite patterns in AN and Healty control (HC) group with a significant **negative** correlations between CBias and positive coattivation of the executive network with **OFC** and **insula cortices in AN group** while a significant and **differently positive correlation resulted in HC group** within this network; (see fig 14 A-B);

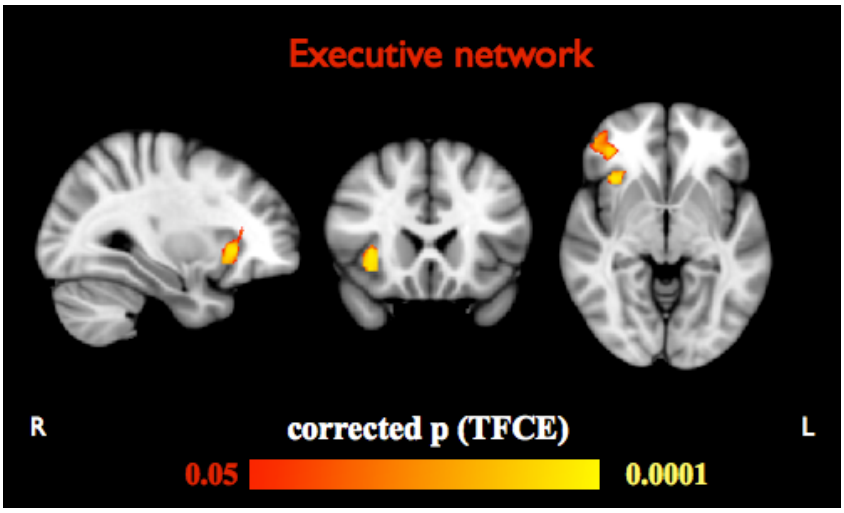


Fig 14 A

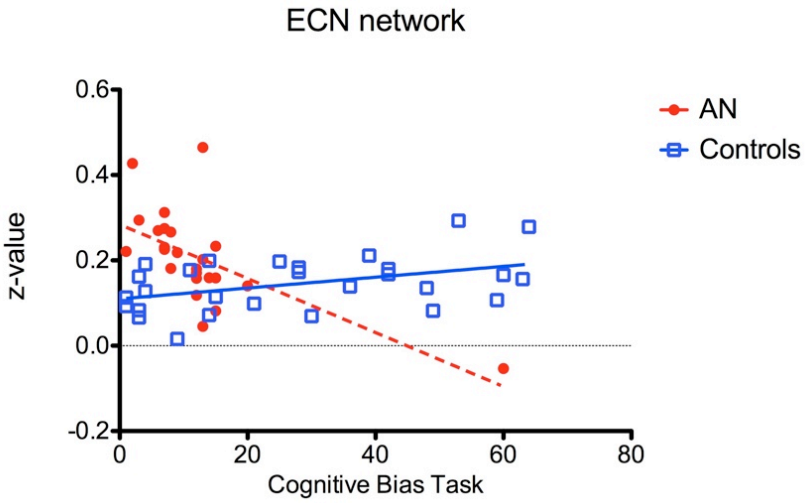


Fig 14 B

Fig. 14.(A-B) Differences in correlation with Cbias converted score for seed-based analysis of *Executive network (ECN)* (left and right DLPFC; MNI coordinates −42, *34, 20 and 44, 36, 20*); (A) Area of significant correlation in the AN group for positive connectivity (2 peaks: Right OFC and Right insula cortex).B). Graphs show individual values of connectivity in the brain areas that exhibited significant differences in AN and HC. Analyses by non-parametric permutation test, with age, education, and hand lateralization (Edinburgh score) as covariate.

2) within **the orbitofrontal** network *(lateral OFC*: MNI coordinates *:* left, -31, 42, -8 and right, 31, 42, 8) only in **AN group** CBias significantly negative correlateed with **the positive**

OFC connectivity with the **right middle frontal cortex** while no significant correlation emerged between Cbias and connectivity of OFC in whole brain analysis (fig 15 A-B)

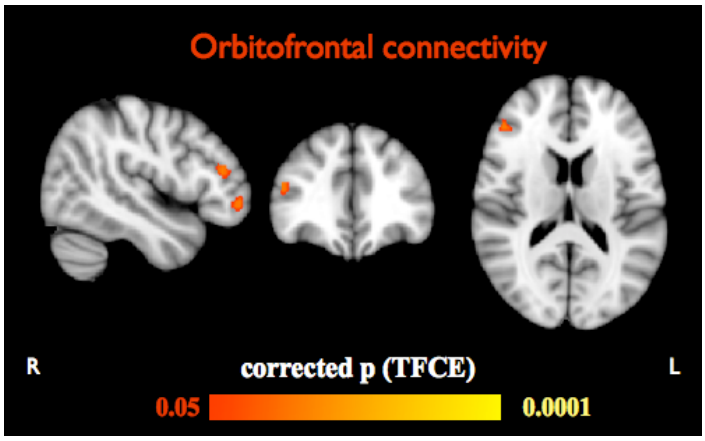


FIG 15 A

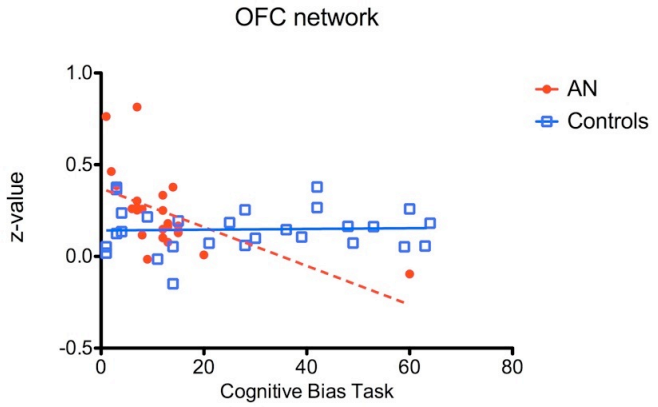


FIG 15 B

Fig. 15.(A-B) Differences in correlation with Cbias converted score for seed-based analysis of *lateral OFC: MNI coordinates : left, -31, 42, -8 and right, 31, 42, 8);* (A) Area of significant correlation in the AN group for positive connectivity (peaks: right middle frontal cortex .B). Graphs show individual values of connectivity in the brain areas that exhibited significant differences in AN and HC. Analyses by non-parametric permutation test, with age, education, and hand lateralization (Edinburgh score) as covariate.

3) ***Accumbens connectivity*** (inferior ventral striatum (VSI): MNI coordinates ±9, 9, -8); we found a significant **negative** correlations between CBias converted score and positive connectivity with **right accumbens** and the **subcallosal cortex (**BA25) while no significant correlation emerged between Cbias and connectivity of accumbens in healthy group (fig 16 A-B).

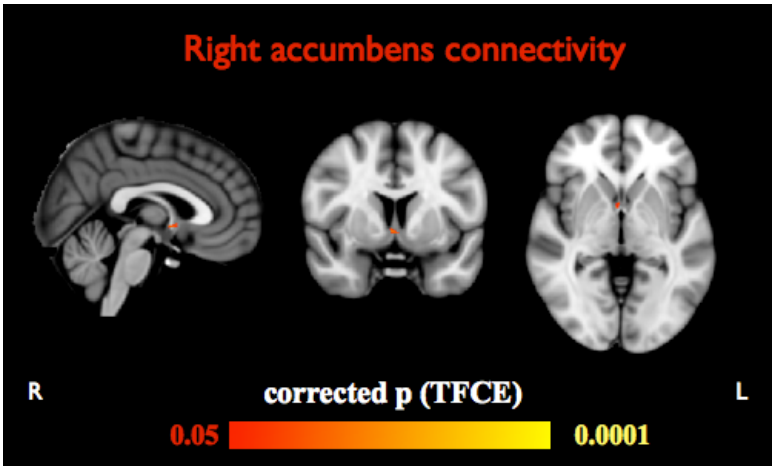


FIG 16 A

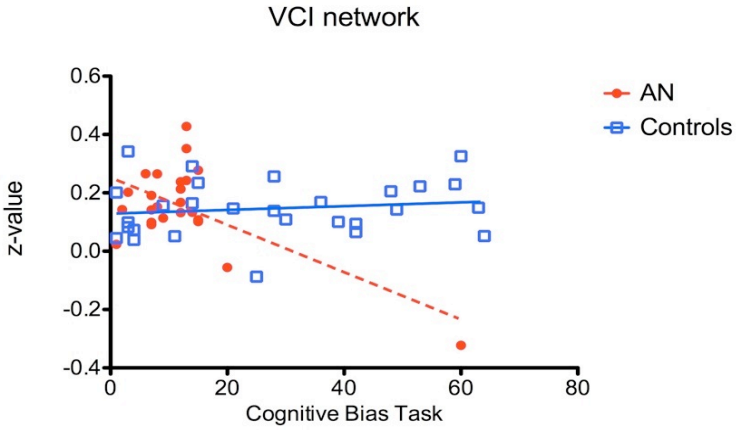


FIG 16 B

Fig. 16 (A-B) Differences in correlation with Cbias converted score for seed-based analysis of *right inferior ventral striatum* (*VSI):* MNI coordinates ±9, 9, -8); (A) Area of significant correlation in the AN group for positive connectivity (peaks: subcallosal cortex).B). Graphs show individual values of connectivity in the brain areas that exhibited significant differences in AN and HC. Analyses by non-parametric permutation test, with age, education, and hand lateralization (Edinburgh score) as covariate

No other significant correlations with Cbias scores were found within all the other network explored.

In the brain regions that have revealed significant differences in connectivity at resting state between AN group and patients, we found a significant correlations with IGT only in **Amigdala connectivity** (*Amygdala* MNI coordinates *:* left, -19, -4, -18 and right, 27, -3, -15) and only in AN group.

In particular the coattivation between **left amigdala** and **right putamen** resulted **significantly positive with IGT net** score in **AN patients** while no correlations was found in the HC group neither other significant result emerged whithin oll the other networks of interest in both groups.

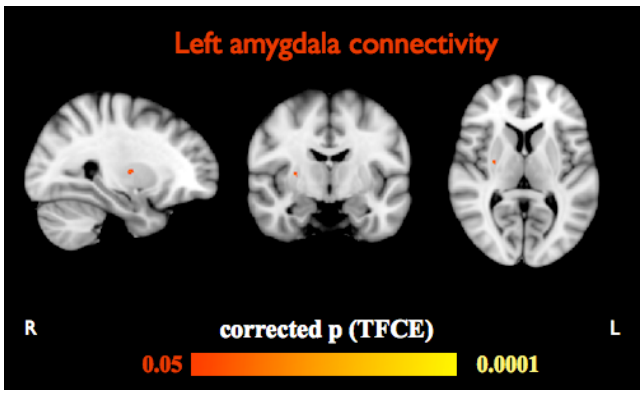


Fig 17 A

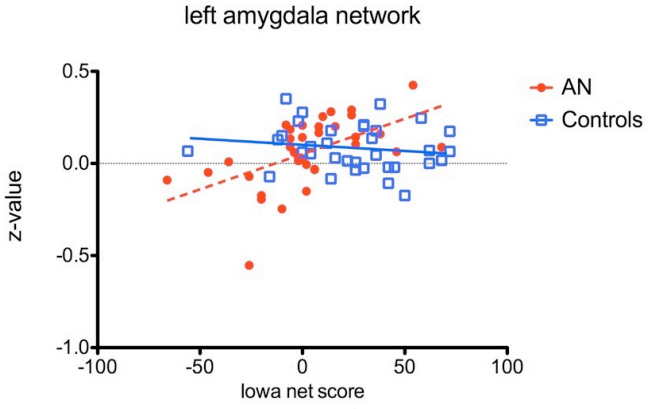


Fig 17 B

Fig. 17.(A-B) Differences in correlation with Cbias converted score for seed-based analysis of (*Amygdala* MNI coordinates *:* left, -19, -4, -18 and right, 27, -3, -15); (A) Area of significant correlation in the AN group for positive connectivity (peaks: Right putamen .B). Graphs show individual values of connectivity in the brain areas that exhibited significant differences in AN and HC. Analyses by non-parametric permutation test, with age, education, and hand lateralization (Edinburgh score) as covariate.

4.6 DISCUSSION

Some clinical features of AN seem to reflect a compromised decision-making processing, however, because of the complexity of underlying decision-making mechanisms and the problematic in the global exploration of neuropsychological features of complex psychiatric disorders such as anorexia nervosa, it is difficult to accurately identify which type of decisional processes are implicated and what exactly cause this impairment.

In particular the clinical evidence of the tenacity showed by AN patients in remaining ancorated to their illness despite the clear logic awarness of the physical risks and social consequences may reflect a preference for immediate reward despite the long-term adverse consequences (e.g. maintaining behaviour restriction and starvation despite the negative physical and psychosocial consequences).

Starting from this clinical feature and evaluating the evidences suggesting a dysfunction in reward mechanisms in AN (Wagner et al. 2007; Zink & Weinberger, 2010; Kaye et al. 2013), we decided to assess decision making with Iowa gambling task (IGT), which measures the preference for risky and disadvantageous choices in a context of uncertainty (the participant is unable to assess the long-term risk associated with each option).

But even if the IGT is the most used decision making task under uncertainty, it assess this executive function in a veridical situation in which the subject need to search a correct answer in the experimental framework in wich are supposed to be right and wrong answers and for this reason it may fail to exactely target the type of decision making required in everyday life. Therefore considered the differences in experimentnal setting and real-life, we decided to assess in parallel also the adaptive decision making that analyze the decisional style in an neutral and not rewarding/punishing decisional framework in which there arent any right or wrong choices but the subject is completely free to decide in coherence whith his own internal rapresentation or to follow the external environmental context. The task that we used for adaptive decision making assessment is the Cognitive bias task (Cbias) (Goldberg et al.1994)

In addition to neuroimaging, also the possibility to apply analytical models (such as the Expectancy Valence Model), that divide the performance at the IGT in specific cognitive processes, may provides advances in approaching this issue.

In our study, we have therefore sought to analyze different types of uncertainty decision-making performances (risky and ambigous or hot and cold), in different decisional

frameworks (veridical and adaptive), in a very large sample of AN patients and healthy control to deepen the mechanisms underlying its impairment, focusing in particular on the relationship between them and some peculiar neuropsychological (as cognitive rigidity), clinical (underweight, age of presentation) and genetic aspects of the of disease.

AN often has its onset during adolescence (Smink et al., 2012, Herpertz-Dahlmann., 2015, Micali et al., 2013), a challenging age characterized by somatic, psychological as well as social changes alongside the proceding of the neurocognitive maturation.

Adolescents exposed to stress, for example, are susceptible to changes in affective/motivational circuits involved in DM such as amygdala, prefrontal cortex, and ventral striatum (Tottenham & Galvan, 2016). More over, in contrast to the typical linear development of executive functions, the affective decision-making abilities, progressed in a J-shaped curve: the younger, more developmentally naive children, performed better on the IGT than older and early-adolescent individuals; the performance became advantageous again toward the end of the teenage years, as observed in a sample of children and adolescents from 8 to 17 years old using the IGT, (Smith et al., 2012). This trajectory, continue the author , is thought to coincide with asymmetric neural development in early adolescents.

We decided to analyze separately the decisional processes in adolescent and adults subjects because of the wellknown differences in the overall executive functioning (Tymula et all. 2013, Smith et., al 2012), including DM, in early adolescents, that is thought to reflect the asymmetry of neural development, consisting in a relatively overactive striatal regions but a slower development of inhibitory frontal functioning.

Our data analysis reveals different **decisional profiles** between patients with An and controls in the two task, characterized by worse AN performance (as indicated by lower scores in IGT net), with a predilection for long term disadvantaged decks and a difficulty to update/review one's own mindset according to new environmental stimuli (context indipendent strategies) in Adaptive decision making (as indicated by lower Cbias converted score), even though with a statistical power only in adults subgroup.

In detail the veridical decisional profile in adult women significantly resulted impaired in both the first (before the 40th selection) and second (after the 41th selection) part of IGT, suggesting a compromission of both hot affective and cold cognitive domain.

Some authors have previuos suggested that the first blocks of the trial may involve prevalently the decision making in ambigous situation because the subject has not yet figured out the rules of the task and at the very beginnig (the first block selections) he tries to guess

the rewarding outcome, (it is remarkable that the first block of trials hasn't resulted correlate with any of the other IGT blocks (Brand et al., 2007). With the proceding of the task, only after that the rules have been figured out, it has been suggested that IGT would preferentialy have measured decision under risk (Brand et al., 2006). The boundary between the transition from one type of decision-making to the other is nuanced as it greatly depends on reversal learning mechanisms and reward sensitivity as well as it happens gradually in the preceding of the task, anyway it has been suggested that 40th selections would approsimately represent this transitions.

However, being also a monetary gambling task, the IGT has overall been considered as a behavioural indicator of risky decision making in most studies (Kraine et al., 2006, Guillaime et al.2016)

This classification issue may be the reasons of some research inconsistences as well as explain our partly unexpected neuroimaging results.

Performance at IGT is the result of a balanced interaction between executive functions, (Cold FEs) reward sensitivity, and emotional aspects (hot FEs) to more optimally weigh short term gains against long term losses or probable outcomes of the choices. The modulation of emotional responses and the inhibition of impulses directed at the reward provided by "hot" EF capacities allow a more efficient evaluation of rational and cognitive determinations of risks and gain associated with outcomes and on the other side, the enactment of "cool" EFs involved in the abstract reasoning and problem solving, would reinforce the efficiency of reward anticipation processes (Giancola et al., 2012; Brevers et al., 2013)

The analyses of EVM parameter reveal that AN girls score significantly lower at the w parameter indicative of a grater attention to losses than winning in comparison of the healthy peers. An higher sensivity to reward in adolescents is supported from literature evidences showing that adolescents generally present a worse decision-making profile in comparison to adults, since they are more closely related to immediate reward, (Galvan & Rahdar 2013) as healthy girls in our study seems to be. Adolescents, in fact, having a great neural activation following a reward without being ready because of the neural immaturity, to regulate reward-related behaviors, tend to show bias against risk behaviors and immediate reward, showing a highly dysfunctional decision-making style (Gàlvan & Rahdar 2013). However in presence of Anorexia nervosa the tendency to focus on winnings in adolescents girls is replaced by a greater focus on losses and punishment, and we found this trend also in adults affected women (lower w value). This is in line with Bischoff-Grethe et al finding of an exaggerated

striatal response to losses compared to wins in a group of An adolescent patients, which could be related to sensitivity to punishment typically seen in this patient group (Bischoff-Grethe et al., 2013).

It is possible that this focus on negative aspects can partly explain the difficulties of patients in relieving their eating symptoms, failing to fully appreciate or to take advantage of positive experiences such as those related to transient and benefical behavioral changes.

Regarding **the role of inhibitory control ability**, literature reported that a deficit of it is associated with worse performance at IGT. In a group of patients with vmPFC lesion, subjects defined as "poor stopper" at SSRT showed worse performance at IGT than "good stopper" subjects (Blakemore 2012). However, in our sample no significant differences were observed in SST signal stop response time between patients and controls, but while affected adults reported longer reactions time in comparison to healthy woman, (suggestive of a lower inibitory control), the opposite pattern resulted in adolescent sample were affected girls instead showed a higher inibitory control in comparison to healthy girls. Interestingly only in AN adult group, while a lower inibitory control (higher SSRT reaction time) is significant associated with higher c value suggestive of major choice inconsistency with the expectation formed and a lack of decisional strategy with also random selection , in the healthy adults a higher inibitory control (low SSRT reaction time) is significantly associated with higher a value, suggestive of a decisional style characterized by more rapid updating, less persitance or rigidity with a higher discontinuities of past results with a greater influence on recent outcome (a higher) .

Summing up our data therefore show that teenagers with AN lose their peers' ability to be more careful about winnings but seem to be more influenced in their decisions by previous negative outcomes; in addition they present a higher inibitory control tendency in comparison to healthy subjects. Teenagers tend to have a hypersensitivity to stress over children or young adults; (Stroud et al., 2009; Adam et al., 2006; Klimes-Dougan et al., 200;1 Gunnar et al., 2009), at today it is believed that stress can potentially exacerbate behavioral bias or subjective behavioral tendencies (habit based responses) by for example making more conservative choices in people who tend to avoid risk and favoring risky choices in risk-seeking subjects (Dias-Ferreira et al., 2009; Porcelli & Delgado, 2017).

No difference between the groups has emerged in relation to parameter **c** or the consistency of choice for which it can be stated that the state of malnutrition does not compromise the ability of patients to develop less coherent or more random decision-making strategies than controls.

However, it is understandable that malnutrition, due to associated organic sequences, may somehow affect the decision-making profiles of subjects with AN. At present, this topic is widely debated in literature with conflicting positions on it. While on the one hand, it is commonly shared that the underweight may be considered as a confounding factor in the analysis of the ineffective decision-making of patients, on the other it is unclear whether they are pre-existing to AN and thus facilitating or following the pathology and hence Strictly dependent on organic and metabolic factors.

It is not known therefore whether dysfunctional decision profiles of patients with AN can be attributed specifically or exclusively to underweight or has to be sought in a genetically determined and distinctly cognitive functioning possibly predisposing to the pathology.

Few studies compared decision-making before and after **weight** recovery of patients with An and some reported improvement in IGT results with remission (Tchanturia et al 2007; Danner et al 2012) other no difference between patients treated with AN lifetime and controls (Tchanturia et al 2007) and others even best performances of patients with AN lifetime remittes compared to control group (Lindner et al 2012), as if achieving both physical and psychological remission could be peculiarities of those patients having a more effective decision-making profile than the healthy population and which allowed them to overcome the disease.

To shed light on this point we tried to figure out whether weight gain in An lifetime patient could have been associated with improved decision-making performance, by analyzing the performance of two subgroups divided according with the weight recovery (BMI $\geq$18.5) at the time of assessment. We didn't find any significant differences between groups but we observed an opposite trend in adults and adolescent group with lower IGT net in adolescent weight recovered AN in comparison to underweight patients while the opposite was true for adults women. Neither the adaptive decision making reveal any significant differences between the two groups.

However the correlation analyses revealed a stastical effect of weight on Cbias performance, since it have resulted positive correlated with weight and BMi, therefore we compare AN patients of the two age different group with the corrispectively healthy controls only in underweight AN patients and in both adolescent and adults repored a significant bias toward a context indipendent resoning in adaptive decision making and no significant differences for veridical decision making.

Overall this results suggest that veridical decision making could represent more specifically a **trait of the disease**. This last result is absolutely in line with most of the results published so far in the literature that have not found a correlation between BMI and performance at IGT (Cavedini et al 2004, Cavedini et al 2006, Guillame et al 2010, Fagundo et 2012; Galimberti et al 2013; Garrido & Subirà 2012, Guillame et al., 2015). The only studies that reported positive correlation between BMI and performance at IGT were two studies that compared remitted and acute patients (Tchanturia et al 2007, Lindner et al., 2012) and another who had interestingly found a correlation between these two Variables only in the second part of the IGT, the most specific one for decision making under risk (after the 50th selection) (Abbate-Daga et al 2011). The only three longitudinal studies avilable (Cavedini et al., 2006; Bodell et al., 2014, Steward et al., 2016) showed inconsistent results: one study support the hypothesys of a trait impairment (Cavedini et al., 2006), a second suggest that lower BMI and OFC volume may represent a trait-like cognitive vulnerability for AN and the last study (Steward et al., 2016) support the hypothesys that impaired DM in An might depend on clinical state rather that contituting a trait vulnerability since enduring remission (after one year of follow up) from AN can reverse DM impairment.

Our results are partially in line with the only adptive decision making study on AN (Tenconi et al., 2016), because we haven't found a trend for performance on the CBias to improve (to be less context independent) in weight recovery patients, even if we found and a significant correlation between CBias performance and BMI.

Since the different putative mechanisms involved in DM performance in AN and BN may engage different underlying patterns (Chan et al., 2014), we analize the decision according to clinical subtypes. There are not many studies that have analyzed DM performance based on the diagnostic subtype and our findings are in line with those evidence that had not found difference between veridical decision-making performance according on the diagnostic subtype (Guillame et al 2010, Galimberti et al., 2013, Tenconi et al., 2016). In our sample, patients with restrictive AN lifetime do not differ from the binging/purging subtype (who at any stage of their life developed binging/purging or had a previous BN), neither in adolescent nor in adult group, in contrast to Cavedini et al., 2004 and Garrido & Subirà 2012, although in this second study were included in the BP sample also patients with only diagnosis of BN lifetime whitout previous AN.

On the contrary we found a significant context indipendent resoning only in restrictive subtype adolescent AN in comparison to B/P peers which presented a bis toward contex

dipendent reasoning (higher Cbias score), and in opposition to previous results (Tenconi et al., 2016) .

Various studies have highlighted the presence in patients with anorexia nervosa of cognitive inflexibility as well as a poor central coherence index and poor performance of IGT and in the study of 2013 Galimberti highlighted a family aggregation of impaired decision-making and set-shifting performance.

Our sample showed negative correlations between **cognitive inflexibility** and IGT performance in a different way between patient and of controls in both adults and adolescent subsample .In particularly in the adult control group, the scores on IGT net and learn were negatively correlated with WCST scores as well as with persistence at TPQ, so in healthy subjects an increase in persevering responses and cognitive inflexibility interfering with learning , may compromise the effectiveness of decision-making perfomance. In the AN women, although there was no negative correlation with WCST scores, the analyses reported a negative correlation with another test that measures set shifting: the TMT A and TMT B. However, WCST and TMT are two different tests, and probably TMT, especially A is most affected by any compromission of attention and organic aspects, being also a measure of the speed of performance. Similarly, two studies (Galimberti 2013; Danner 2012) had not reported any correlation between the scores at the IGT and WCST set shifting and the Berg's card sorting test in AN patients, assuming that the absent association between cognitive inflexibility and performance at DM could support the idea of a DM trait alteration rather than constituting a predisposing mechanism to the illness.

Similarly, in our study, we did not find any positive correlations between the cognitive inflessibility of WCST and performance at IGT in healthy women. Although correlations are not indicative of a cause-effect relationship, however, it is possible that in healthy adults cognitive rigidity may play a role compromising decision-making by affecting it negatively, while in adults patients the coexisting impairment of both of these two FEs and the co-absence of their association could indicate a basic impairment of each of them separately that may enance the vulnerability to develop AN.

In adolescent group instead we observed in AN girls the same pattern of negative correlation emerged between IGT and WCST in Healthy women.

Interestingly the contex indipendet decisional bias emerged in AN patients hasn’t resulted associated with an impairment of set shifting at WCST, even though the rigidity and the

cognitive and behavioral inflexible attitude observed further than the attentional set-shifting difficulties (Holliday et al., 2005; Roberts et al., 2013) could have suggested it.

In order to explore the relationship between decisional processing and **outcome AN treatment** , we compared the IGT and CBT performance at baseline in different An group according to the clinical diagnosis after a 12 moths of specialized treatment.

In the comparison between remitted, and not remitted AN, we found that remitted girls group showed a higher Cbias score at baseline (very closer to mid Cbias converted score values) while a contex-independent decisionl style chacterized the baseline assessment ot those patients who wouln't have achieved a remission after the treatment. This may suggest that at least adolescent patients with a negative Cbias baseline assessment may required intensive or more customize treatment.

Evidences have suggested an influence of **5HTTLPR and COMT Val158Met polymorphisms** on performance at IGT (Kang et al., 2010, van der Bos et al., ,2009, O'Brien et al., 2014;) with individuals homozygous for the low-activity short allele showing poorer performance on the IGT (Homberg et al., 2008; van den Bos et al., 2009; Verdejo-García et al., 2013) and Met allele homozygote participants show better performance on cognitive tasks, such as measures of working memory, although healthy Met-Met subjects have been found to have inflexible processing of affective stimuli and poorer performance on the IGT (van den Bos et al., 2009).

Our results are partially according with previous findings since we a found a significant impact of both COMT and 5HTTLPR poliformisms in adult subgroup but in AN women and not in healthy subjects.

In particular only in AN women 5HTTLPR SS genotype have resulted significantly associated with worste IGT performances, while no differences in Cbias score were found.

Even though 5-HTTLPR low-activity allele carriers have been shown to have impaired performance on the IGT (Homberg et al., 2008; van den Bos et al., 2009; Verdejo-García et al., 2013), has been hypothized that decisions making under ambiguity may involve a different genetic architecture than decision making under risk (Stoltenberg & Vandever, 2010) **.** In particular individual differences in decision-making under ambiguity in female (the first block of IGT choice) may vary according with genetic polymorphism of SLC6A4, where long-allele carriers showed impairment on early trial blocks (Gu et al., 2013; Stoltenberg and Vandever, 2010; Stoltenberg et al., 2011).

In our study adults AN homozygotes for Val (G) COMT allele have reported a significant more efficient decisional profile in the two middle block selection (after the 40th seclections) in IGT with higher net score values while no differences resulted for adaptive decision making in all adult group.

According with the hypothesis of Fank (2009), the COMT genotype would regulate exploration based on uncertainty about the consequences of a choice and the carriers of MET COMT allele (associated with a decrease in synaptic dopamine uptake) would show an increased ability to shift to alternative attitudes (as expressed by the "learning rate parameter a"), as a result of negative choice outcome (Frank 2009). Conversely has been reported that female subjects carrying the Met/Met polymorphisms of the COMT Val158Met chose more frequently disadvantageous decks than the Val/Val carriers at IGT (Van De Bos et al., 2009), as in line with our results in AN women.

Further than gender or experimental setting differences, It has been noted that the Met/Met homozygous gives an advantage in memory cognitive tasks and in WCST (Egan et al., 2001; Malhotra et al., 2002; Rosa et al., 2004), while in emotional tasks Met/Met carriers reported greater activation of limbic areas (amygdala and PFC) after negative (but not positively) connotated stimuli (Drabant et al., 2006; Smolka et al., 2005, 2007). Being IGT a task requiring adequate emotional processing to develop adptive behavioral responses, we support the idea that ah higher limbic activation may results in a poorly processed affective stimulation and thoug may negativ impact on decisional perfomances

In our adolescent healthy group too, our result don't support the theory of Frank (2009) since the absence of met allele was associated with higher EVM "a" and very lower "c" parameter in IGT, suggestive of a dysorganized an caothic decisional profile carachterized by rapid adjustments, higher discontinuities than past results with a greater influence on recent results (a higher) and a lower coherence of choices toward the decks with the highest expectations resulting in the absence of a clear decisional strategy (very lower c parameter).

While the considered genetic polymorfism haven't reveald any impact on adptive decision making.

In summary our results in AN woman group are in line with the hipothesis of a protective role of val allele for flexibility in emotional hot process and of COMT Met allele, thought to be protective for cognitive cold functions such as working memory (van den Bos et al., 2009). And with a negative effect of low functioning 5-HTTLPRS polymorphism on decision making.

A further interesting point is that IGT and CBias score, did not appear to be correlated with each other and this result support the hypothesis that these tasks target may actually target different aspects of DM (Tenconi et al., 2016 ; Verdejo-García et al., 2006), and our results, of their functional connectivity correlates, seem to move on this direction.

Several evidences of neural dissociation in different type of decision making have been reported either for the differnent types of veridical decisional processes assessed with IGT (Krain et all., 2006) or for thore of adaptive decision making assessed through the Cbias.

The IGT performance derive from the interaction of emotional (limbic) system and cognitive control (associative) system (McClure et al., 2004; Bechara, 2005; van den Bos et al., 2006b; van den Bos et al., 2014; de Visser et al., 2011a; Gläscher et al., 2012) that work in parallel, with a predominace in the early part of the task of the emotional system, and of the cognitive control system in the late phase, involved in an eventually suppressive activity of the emotional system. In particular the emotional system may encompass the orbitofrontal cortex (OFC) and the ventromedial prefrontal cortex (VMPFC), while the cognitive control system encompasses the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC; e.g., McClure et al., 2004; Northoff et al., 2006; Lin et al., 2008; Lawrence et al., 2009; Li et al., 2010; de Visser et al., 2011a; Gläscher et al., 2012).

The VMPFC has a key role in IGT decisional performances, since it is involved in what has been defined as the "affective meaning" of the choice (Roy et al., 2012, van den Bos et al., 2014), consisting in the anticipatory signaling of good versus bad options, fondamental to directing the decision-making behavior toward the best long-term option (Bechara et al., 1999). The orbitofrontal cortex and the amygdala may represent a "vigilance"/evaluation-system which responds rapidly to the degree of uncertainty while a second system that includes the dorsal striatum is associated with reward-anticipation and reacts more slowly and later than the first system; of notice the activity in risk vs ambiguous situation was localized in the dorsal striatum (caudate nucleus) (Hsu et al., 2005).

Leaving behind the classification issues concerning the complexity of IGT, as previuosly discussed, it is overall thought that hot decision making paradigms are considered those involving risks and rewards, such as gambling tasks (Kerr and Zelazo, 2004) and in line with the hot and cold FE theorization has been reported a different patterns of neural activity in frontal and parietal cortices between decisions involving risk and those involving ambiguity, consisting in neural dissociation in OFC and DLPFC (respectively in the two different decisional situations). Overall IGT performance is the result of interaction between cold

executive functions, hot components involved in reward sensitivity and emotional aspects but also of automatic component involved in learning and reversal learning abilities.

However unexpectedly, in our rsMRI results, IGT net score did not correlate with functional connectivity within the executive, orbitofrontal and accumbens networks. Only in AN patients a significant positive correlations emerged between net score and the connectivity of L amygdala with R putamen . This results could indicate at one side that the performance at IGT is the result of a complex process that is only partially described by the net score but on the other side also confirms the importance of emotions and anxiety in conditioning the performance of AN patients.

The amygdala is thought to have a role in the reaction to emotional information (Bechara et al., 2003), and it is modulated by the DMPFC. Both amygdala and OFC are likely involved in detecting salient and relevant stimuli of uncertain value but the amygdala in particular (Adams et al., 2004) is thought to also provides a reward-related signal that can motivate behavior, throughtout the connections between the amygdala/OFC and the striatum. The amygdala also represent the core structure of the fear circuitry which playing a central role in fear conditioning, togheter with the medial prefrontal cortex ,the rostral anterior cingulate cortex (rACC) and dorsal anterior cingulate cortex (dACC), hippocampus, insular cortex and striatum (Shin et al., 2010).

In AN patients the association between higher score whith a greater co-activation of amigdala-putamen may indicates an emotional disregulation of the patients in the direction of avoidance of potentially anxiety situations and suggest that neural regulation of decision-making processes mediated by the amigdala striatal connections may be altered in AN subjects.

Interestingly decision making involves this same regions (amygdala, ventromedial prefrontal cortex, and anterior cingulate) (McClure et al., 2004), whose functional coupling among each other is associated with variation in the 5-HTTLPR polymorfism. In particular a low-activity allele carriers have reduced functional coupling between the amygdala and rostral anterior cingulate cortexas as well as the amygdala and prefrontal cortex (Pezawas et al., 2005; Roiser et al., 2009). with a negative impact on decisional performances.

On the contrary, Cbias score seems to be a less complex measure reflecting a general impairment of decision making in AN patients.

In our study AN patients revealed a difficulty to update/review one's own mindset according to new environmental stimuli, consisting in a more context indipendent decisional style

(lower Cbias score), in comparison to healthy women. We found an opposite pattern of correlation between Cbias and the connectivity within the Executive network between patients and controls.

A lateralization of the context-dependent (associated with the left) and context-independent (associated to the right) frontal lobe reasoning have also beed suggested (Goldberg et al., 1994; Aihara et al., 2003; Ayoagi et al., 2005; Shimoyama et al., 2004) while the undiscussed involment of DLPFC in adaptive decision making have been whidely confermed. (Tulviste et al., 2016), This lateralization of contex-indipendent decisional style is confirmed in our results.

In An patients we found a correlation between a contex indipendent reasoning and a stronger synchronous activity between the right OFC and insular cortex in AN patients withinn the executive network while in healthy women the direction of correlation was significant different. We also found only in patients that lower values at Cbias correlated with the coattivation of the right middle frontal cortex within the OFC connectivity and of the right accumbens and suballosal cortex within the accumbens connectivity. It is possible that this Higher coactivation within the executive, accumbens and orbitofrontal networks is linked to higher context-independency an therefore less efficient adaptive decision making in AN patients.

4.6.1 Conclusion

In summary our result confirm an impairment of different type of decision making in both adult and adolescent AN, and highlitght the importance of assessing decisional processes with different specific tasks in clinical sample.

In particular different maladaptative strategies are associated with poor decisional profile observed in AN, consisting in a “myopia for the future” and “anxiety inhibition” in veridical situations and in a difficulty to update/review one’s own mindset according to new environmental stimuli (context indipendent reasoning strategies) in adaptive decisional framework. The severity of malnurishment seem to influence adaptive decisional style conferring a bias toward a context indipent reasoning in adaptive situation. highlighting the need of metacognitive approach to help patients to be more aware of their tendency to automatically use selection bias in DM contexts.

The impairment of affective decision making in AN regardless illness status, BMI, clinical subtypes or outcome treatment suggests a trait cognitive vulnerability dimension.

Genetic polimorphysms may in part account for ineffective decisional style observed in AN patients, with a negative impact of met Comt allele and short variant of 5HTTLPR polymorphism.

AN patients showed worse neuropsychological profile in both adolescent and adult group, even though poor performance on the IGT and other cognitive tasks seems to be more pronunced in adult AN; this difference may reflect a sample size issue in adolescent group, or a scar effects of malnourishment in adults subgroup or may be the result of the ongoing neurodevelopment of frontal areas in comparison to the basal ones.

The analyses of EVL parameter reveal no difference between the groups in relation to parameter **c** or the consistency of choice for which it can be suggest that the state of malnutrition does not compromise the ability of patients to develop less coherent or more random decision-making strategies than controls.

AN girls score significantly lower at «w» parameter, indicative of a grater attention to losses than winning in comparison of the healthy peers. This trend was also found in adults AN women (lower w value). It is possible that this focus on negative aspects can partly explain the difficulties that patients have in relieving their eating symptoms, failing to fully appreciate or to take advantage of positive experiences such as those related to transient and beneficial behavioral alterations.

Functional connectivity suggests the presence of different dysfunctional DM networks in AN patients in the two decisional framework, confirming the importance of emotion and anxiety on decisional performance in AN.

Since the cross sectional design of our study, further and longitudinal studies with recovered and at risk subjects are necessary to confirm our results.

- **Limits and future directions:**

Some limitation of the present study need to be kept in mind reading our results.
First of all the imbalance between the number of adolescent and adults subjects; this is one of the reason why, further than the neural developmental issue, we have decided to analyze separately the two group avoiding to compare each other. However, considering the small adolescent sample and the differences between AN and HC girls, it would be necessary to collect further evidences of our result in a larger sample.
Moreover since our data have been retrieved for a very long time, there are some tools corresponding to old versions of the most frequently used tests at present to assess the eating disorder psychopathology and personality (i.e. EDI and TPQ):

Potential gene-environment interactions on affective decision making have been suggested (He et al., 2012) but they still remain largely unkown in healthy subjects and completely unexplored in AN, despite the advances in pathogenic hypothesis of eating disorders (see Favaro et al., 2013). In this direction it would be interesting to analyze the impact of both enviornmetal risk or protective variable and its combined effects with genetic polymorphism in AN .

It would be interetsing to explore the influences of different types of stress (cronic, acute, perinatal, early life or adolescents) on decision making in An patients since no study at today have controlled for this rilevant aspect which are known to be associated with alterations in the development of volumetric and connectivity changes between core DM areas such as the amygdala and PFC regions (Favaro et al., 2015; Totthenam & Galvan, 2016).

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Authors	Design	Sample	IGT Performance	Performance and others tests	IGT Relations - variables
Cavedini et al. 2004	Cross sectional Hospitalized patients Age(22-40)	59 AN (26 ANR; 33ANBP) 82 HC	AN<HC ANR<ANBP	AN=HC WST AN=HC OAT AN=HC WCST	No IGT/BMI No IGT/severity*(Y-Cornell)
Cavedini et al. 2006	Longitudinal Hospitalized patients Age (21-26)	38 AN 30 HC	AN<HC	AN= HC WST AN=HC OAT	+ (IGT /treatment response) No IGT/BMI No IGT/severity*(YBC-EDS)
Tchanturia et al. 2007	Corss sectional Acute phase vs healing from 1 aa(=BMI 20-25) Age (26-29)	29 AN 29 HC 14 AN rec	AN < HC and AN rec AN rec=HC	SCR AN rec = HC SCR AN ↓ anticipatory and↓ after losses compared to SCR HC and AN rec	+ IGT/depression (BDI) + IGT/BMI
Liao et al. 2009	Cross sectional Age(16-55)	29 AN 26 BN 51 HC	AN-e-BN<HC-	**SCR** BN=HCSCR AN ↓ anticipatory and after losses compared to SCR HC	No-IGT/depression (BDI) +IGT/obsessive symptoms (OCI) predictors of IGT
Brogan et al. 2010	Cross sectional Age (27-52)	22 AN 17 BN 18 Obese (OB) 20- HC	AN=BN=OB<HC		
Guillaume et al. 2010	Cross sectional Euthymic sample Drug-free Age (23-28)	49 AN (37 ANR, 13 ANBP) 38 BN 83 HC	ANBP=ANR AN=BN=HC		No IGT/BMI No IGT/EDI
Abbate-Daga et al. 2011	Cross sectional Age 24	30 ANR 30 HC	ANR<HC	AN < HC in TMT, WCST, HSCT	No IGT/BMI before the 50th selection + IGT/BMI after the 50th selection
Danner et al. 2012	Cross sectional Acute phase vs remitted From 1 y (=BMI>18,5 with mestrual cycle) Age 25.3	16 AN 15 AN rec 15 HC	AN<HC AN≈ ANrec	AN and ANrec <HC in-BCST, AN and ANrec=HC in ROFT	+IGT/depression- (BDI) +IGT and severity- No IGT/set-shifting No IGT/cognitive rigidity
Fagundo et al. 2012	Cross sectional Age(18-60) Age (28-40)	35 AN 52 OB (no BED) 137 HC	AN<HC OB<HC	AN and OB < HC WCST OB<AN and HC in SCWT	No IGT/BMI
Galimberti et al. 2013	Cross sectional Euthymic sample Drug-free Age (24-28)	29 AN + respective family member (1st grade, F, healthy) (AN F) 29 HC + respective family member (1st grade, F, healthy) (HC F)	AN<HC AN F < HC F and HC ANR=ANBP	WCST: AN<HC and AN F<HC F TOH: AN=HC and AN F = HC F	No IGT/BMI No IGT/severity No IGT/set shifting + IGT-ereditabily Index (No WCST ereditabily Index)
Garrido & Subirà 2012	Corss sectional Age (23-38)	27 ANR 44 BP (20 ANBP, 24 BN) 38 HC	ANR<HC BP<HC ANR<BP		No IGT/BMI NO IGT/depression (BDI) NO IGT:Severity (-) IGT/impulsivity only in BP
Lindner et al. 2012	Cross sectional 1 year remission (BMI> 18,5 + menstrual cycle . no psychological and behavioral symptoms) Age 35	100 AN rec 100 HC	ANrec >HC	TOL: ANrec <HC	+ IGT/BMI + IGT/obsessive symp. NO IGT/depression NO IGT/severity

Tchanturia et al. 2012	Cross sectional Age (22-27)	48-AN-- (29 AN f; 19 AN m) 61 HC (41 f; 20 m)	(fAN =mAN)<HC	BSI: mAN>fAN	NO IGT/impulsivity
Chan et al. 2014	Cross sectional Age (25-27)	94 AN 63 BN 67 HC	AN<HC BN<<HC	**PVLM**: AN memory alteration/learning; AN Memory correlates (+) with BMI BN>attention to gains rather than losses vs HC	No IGT/depression (BDI)
Bodell et al. 2014	Longitudinal	AN=22 HC=20	IGT didn't improve with weight restoration but AN baseline poor performers improve with weight restoration	MRI	ONLY in ACUTE AN: + BMI/IGT LmOFC/IGT
Fornasari et al. 2014	Cross sectional adolescent	An = 15 HC = 15	AN< HC		IGT related to anxiety
Adoue et al. 2014	Cross sectional	AN = 63 HC= 49	An <Hc AN dep=AN not dep		IGT unrelated to depressive state
Aloi et al. 2015	Cross sectional	An= 45 BED = 45 HC = 45	BED < AN BED< HC	WCST BED<AN	
Matsumoto et al, 2015	Cross sectional Only adults (age 18-38)	An =22 BN=36 HC=51	BN<HC		
Guillame et al., 2015	Meta-analysis		AN, BN or BED < HC Rec An ≈ HC ANR<ANBP ANR, ANBP<HC		Age and BMI did't explain result
Danner et al., 2015	Cross sectional	ANR= 32 ANBP=32 HC=40	ANBP impaired learning ANR ≈ HC improve learning		+ BMI/IGT only in ANBP IGT not influenced by negative affect
Tenconi et al., 2016	Cross sectional	An=91 HC=98	An<HC	CBT: An <HC SS 5HTTLPR: contex indipendentat CBT	+ CBT/BMI SS HTLLPR: no diff IGT No IGT/BMI
Perpiñá et al., 2016	Cross sectional An: age 13-47 OB: age 19-65	OB=27 HC=39 86 ED (ANR=18, ED.AN=21, BP=47)	ANR,ED.AN,BP, OB<HC	WCST: OB < HC ED <HC; OB< ED	- IGT/ depression (SCL) - IGT/anxiety no IGT/BMI, no IGT/education
Steward et., al 2016	Longitudinal T0: baseline T1: follow up after 3 months of DH Only Adults (age>18)	42 AN 46 HC	T0: AN<HC T1: -AN remitted ≈ HC (p=0,56) -AN partial/no remitted <HC (p=0,8)	Adjusted for depression	**IGT state vulnerability**

+ = positive correlation; - = negative correlation; LmOFC= left medial orbitofrontal cortex; CBT= Cognitive Bias Task; IGT=Iowa Gambling Task;BDI= Beck Depression Inventory; TOL= Tower of London; OCI= Obsessive-Compulsive Inventory SCR= Skin Conductance Response ;EDI= Eating Disorders Inventory